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Total Synthesis of (−)-Dihydrosporothriolide Utilizing an Indium-Mediated Reformatsky−Claisen Rearrangement

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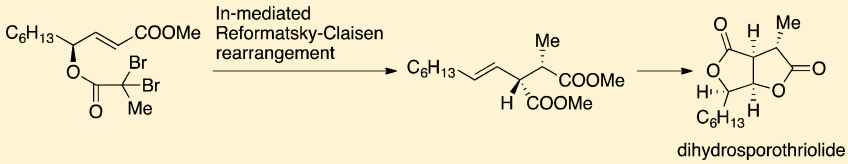
Supporting Information



ABSTRACT: The asymmetric synthesis of (−)-dihydrosporothriolide (**1**), a biologically active bis-γ-butyrolactone, is described, that proceeds through a D-proline-catalyzed asymmetric aminooxylation, indium-mediated Reformatsky−Claisen rearrangement of an α,α-dibromoacetate derivative, and diastereoselective dihydroxylation. The route requires no protective group manipulation and allows the concise seven-step synthesis of **1** from *n*-octanal.

The fused bis-γ-butyrolactones have attracted considerable attention in the synthetic and biological communities over the years due to their highly oxygenated compact structures and wide ranging biological activities.[1,2] For example, avenaciolide exhibits potent antifungal and antibacterial activities[3] and inhibits glutamate transport in rat liver mitochondria.[4] The intriguing bis-γ-butyrolactone skeleton is also found in isoavenaciolide,[3] ethisolide,[5] and canadensolide,[6] numerous syntheses of which have been reported over the past decades (Figure 1).[7−10] In

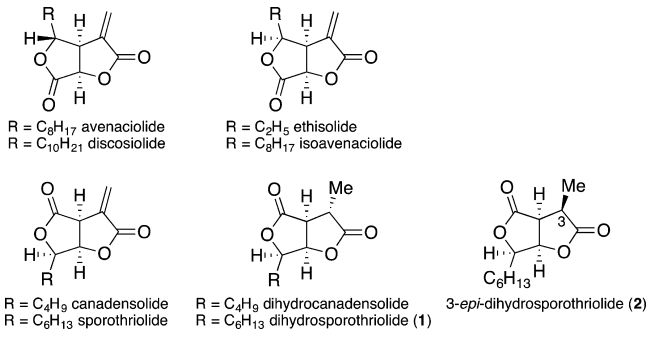
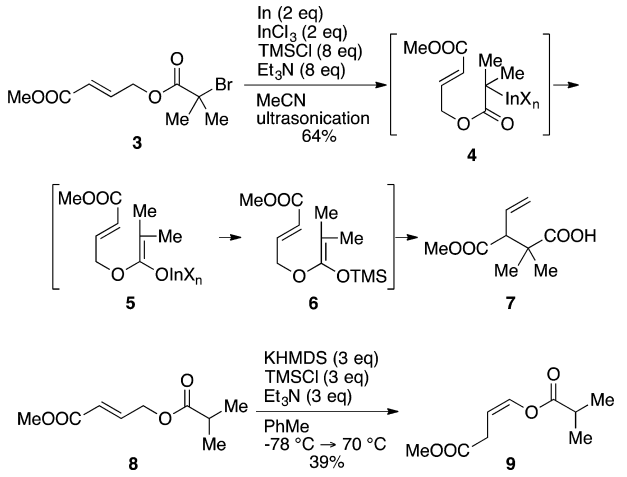


Figure 1. Bis-γ-butyrolactone natural products.

1994, Schulz et al. isolated sporothriolide and discosiolide from fungi, *Sporothrix* sp.[11,12] Sporothriolide bears a striking resemblance to canadensolide that differs simply in the length of the alkyl chain and shows significant antibacterial, fungicidal, algicidal, and herbicidal activities. It was also revealed that its hydrogenated product, namely, 3-*epi*-dihydrosporothriolide[13] (**2**), possesses remarkable antibacterial and herbicidal activities. In 2010, dihydrosporothriolide (**1**) was isolated from *Xylaria* sp[14] and well-characterized by Isaka et al. Before the isolation of this natural product, the synthesis had appeared in a literature;[15] however, the spectral data of natural dihydrosporothriolide were completely different from those reported for the synthetic sample. To clarify the structural ambiguity, we planned to synthesize dihydrosporothriolide (**1**) and confirm its structure and absolute configuration.

Recently, we have developed the indium-mediated Reformatsky−Claisen rearrangement of α-bromoacetate derivatives that are applicable to base-sensitive substrates, as exemplified by Scheme 1.[16] We assumed that α-bromoacetate derivative **3** would be initially transformed to α-indium species **4** and then converted to an indium enolate **5**, which would react with a silylating agent to form silyl ketene acetal **6**. Finally Claisen rearrangement of the silyl ketene acetal **6** would furnish the product. The feasibility of this method for base-sensitive substrates makes it complementary to the Ireland−Claisen

Scheme 1. Reformatsky−Claisen Rearrangement vs Ireland−Claisen Rearrangement



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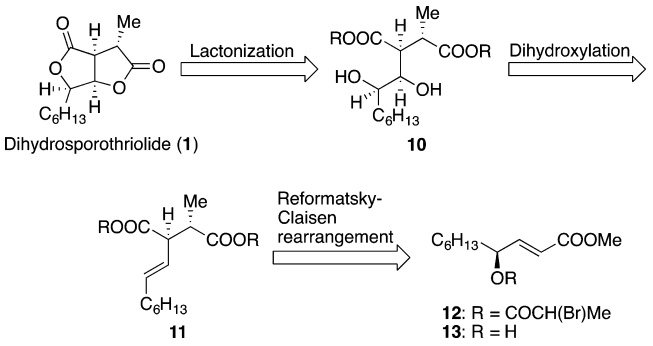
rearrangement and allows a simple access to valuable building blocks for the synthesis of complex natural products. For example, Reformatsky−Claisen rearrangement of **3** afforded carboxylic acid **7** in 64% yield, whereas the reaction of **8** under Ireland−Claisen conditions did not afford the rearranged product **7** but the isomerized product **9** (Scheme 1).[16b] These results clearly represent a marked advantage of the indium-mediated Reformatsky−Claisen rearrangement over the common Ireland−Claisen rearrangement in the reaction of base-sensitive substrates.

Scheme 2 illustrates the retrosynthetic analysis that relies on our Reformatsky−Claisen protocol. Dihydrosporothriolide (**1**)

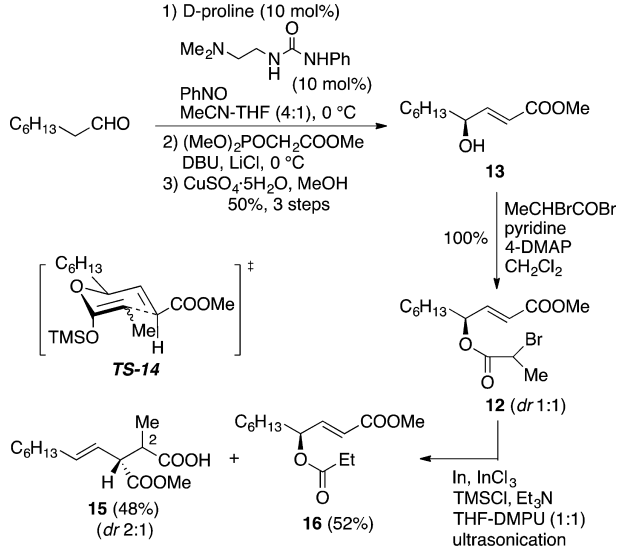
Scheme 2. Retrosynthetic Analysis of 1



would be synthesized by bislactonization of acyclic compound **10**, which could be prepared by dihydroxylation of olefin **11**. Compound **11** would be secured by Reformatsky−Claisen rearrangement of **12** readily available by acylation of allylic alcohol **13**.

Our synthesis of **1** commenced with the enantioselective preparation of alcohol **13** (Scheme 3). Thus, *n*-octanal was first

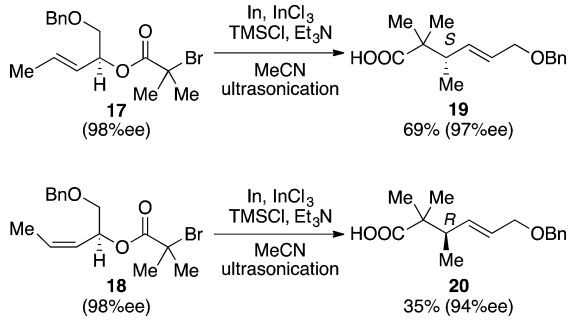
Scheme 3. Attempted Reformatsky−Claisen Rearrangement



subjected to D-proline-catalyzed asymmetric aminooxylation[17] with nitrosobenzene using 1-(2-(dimethylamino)ethyl)-3-phenylurea[18] in MeCN−THF (4:1), followed by Horner−Wadsworth−Emmons olefination[19] in one pot. The subsequent $CuSO_4$-mediated fission[20] of the resulting N−O bond afforded **13**[21] of 95% ee in 50% yield for 3 steps.[22] Acylation of **13** with bromopropionyl bromide using pyridine and 4-DMAP afforded quantitatively compound **12** as a 1:1 mixture. Next, we focused on the Reformatsky−Claisen rearrangement. When **12** was exposed to In and $InCl_3$ in the presence of TMSCl and Et_3N in THF−DMPU (1:1) under ultrasonication, the rearranged product **15** was obtained as a 2:1 diastereomeric mixture in 48% yield, along with debrominated product **16** in 52% yield. Although the stereochemistry of **15** at the C-2 position was unclear at this stage, the major isomer of **15** later turned out to have the desired *S*-configuration at C-2 based on the X-ray analysis of **1**. It is assumed that compound **15** would be produced via chairlike transition states (**TS-14**) of the corresponding silyl ketene acetals.

We previously reported that the Reformatsky−Claisen rearrangement of enantiomerically pure *E*-compound **17** (98% ee) and *Z*-compound **18** (98% ee) provided compounds **19** and **20** in 97% ee and in 94% ee, respectively (Scheme 4).[16b] Since

Scheme 4. Reformatsky−Claisen Rearrangement or Chiral Substrate[16b]



the significant loss of the enantiomeric purity of the substrates was not detected in these cases, we proposed that the indium-mediated Reformatsky−Claisen rearrangement would proceed through a chairlike transition state.

On the basis of the aforementioned results, we assumed the stereochemical course of the rearrangement of **12** as shown in Scheme 5. Compound **12** would initially react with indium species to generate α-indium intermediate **21**. In the transformation of **21** to indium enolates *Z*-**22** and *E*-**22**, conformer **21-B**, convertible to *E*-**22**, would be disfavored due the steric repulsion between alkoxy and methyl groups. In contrast, another conformer **21-A** experiences less repulsion so that *Z*-**22** would be favorably generated. After silylation of *Z*-**22**, the resulting *Z*-**23** would undergo the rearrangement via a chairlike transition state to afford *S*-**15** as a major product.

The production of debrominated product **16** can be explained by facile protonation of the corresponding α-indium intermediate with the acidic α-proton of **12**. Since the Reformatsky−Claisen rearrangement of **12** provided a considerable amount of undesired **16**, we next selected α,α-dibromopropionate **24** as a substrate (Scheme 6). To our knowledge, the Reformatsky−Claisen rearrangement of an α,α-dibromoacyl compound is unprecedented. Compound **24** was easily available by the esterification of **13** with α,α-dibromopropionic acid[23] using EDCI and 4-DMAP. Gratifyingly, the rearrangement of **24** proceeded smoothly to provide a 2:1 mixture of carboxylic acids **15** in 80% yield, along with debrominated product **16** in 14% yield. The mixture of carboxylic acids **15** were esterified with trimethylsilyl diazomethane in THF−MeOH to afford the desired ester **25** and its epimer **26** in 56% and 29% yields,

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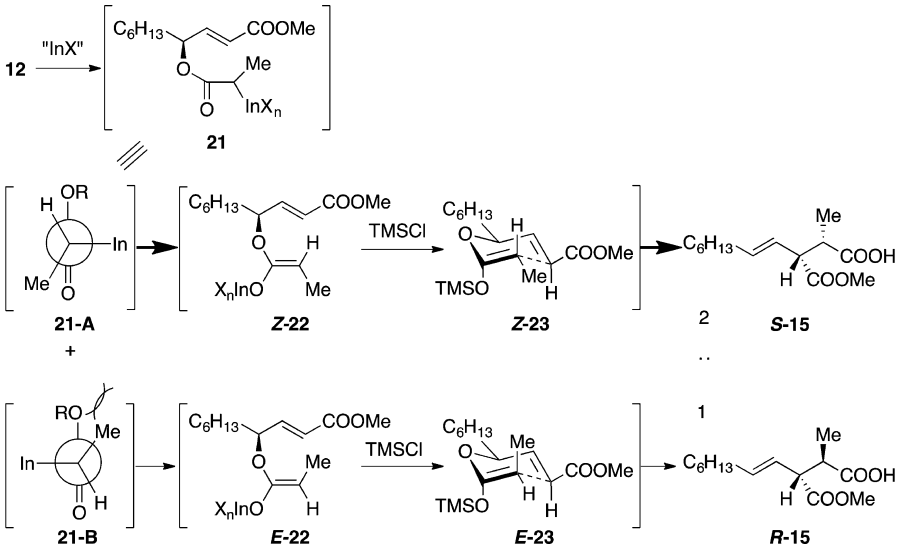
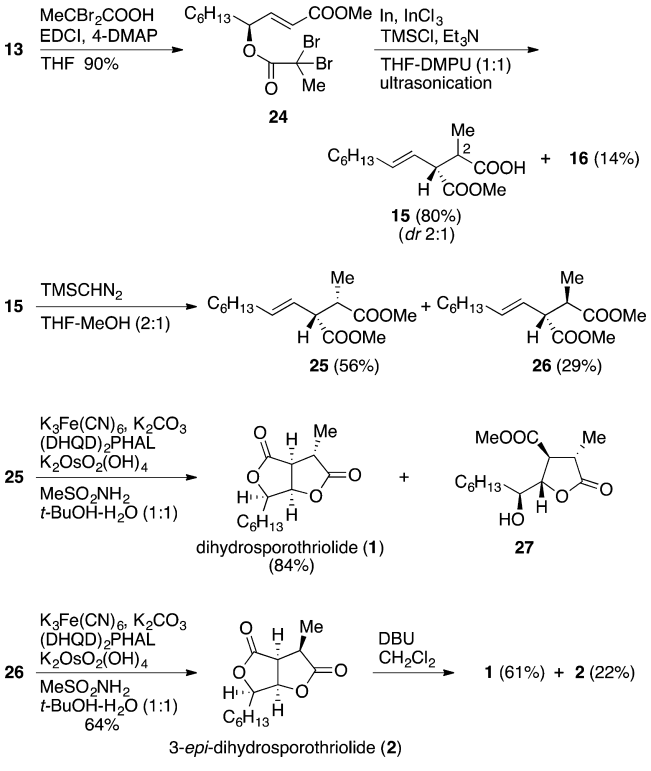
Scheme 5. Plausible Mechanism of Reformatsky−Claisen Rearrangement of 12



Scheme 6. Synthesis of Dihydrosporothriolide 1



respectively. The reaction of α,α-dibromo compound **24** afforded clearly a better result than the reaction of α-monobromo compound **12**. It is assumed that, compared to the α-bromo enolate derived from **12**, the lower nucleophilicity of the enolate generated from **24** would retard the protonation to decrease the yield of undesired product **16**. It is also assumed that ester **12** containing an acidic α-proton can serve as a proton donor, leading to the production of **16**, whereas compound **24** has no such acidic proton at the α-position. It should be noted that the corresponding α-bromocarboxylic acid was not detected as a rearranged product in this particular case. This result shows that the rearranged α-bromocarboxylic acid would be rapidly transformed to indium enolate, which affords a mixture of **25** and **26** in the presence of an excess amount of indium species.[24]

With compound **25** in hand, dihydroxylation of **25** was next investigated. When **25** was treated with a catalytic amount of OsO_4 and NMO in THF−H_2O, dihydroxylation and subsequent lactonization proceeded to furnish dihydrosporothriolide **1** in 63% yield and monolactone **27** in 35% yield, which was derived from the minor diastereoisomer of the dihydroxylation products. On the other hand, the Sharpless asymmetric dihydroxylation led to more satisfying results. Thus, upon reaction of **25** with Super-AD-mix[25,26] using $(DHQD)_2PHAL$ as a chiral ligand in aqueous *t*-BuOH at 0 °C, diastereoselective dihydroxylation occurred preferentially to give **1** and **27**[27] in 84% and 11% yields, respectively. The characterization data of the synthetic material matched the reported data for natural dihydrosporothriolide in all respects. In addition, recrystallization of synthetic sample from hexane and ethyl acetate provided crystals suitable for X-ray analysis, which clearly indicates its stereostructure. At this stage, we unambiguously confirmed the absolute structure of dihydrosporothriolide to be **1** as demonstrated by Isaka et al.[14]

In the case of minor rearranged product **26**, the dihydroxylation with super-AD-mix β provided 3-*epi*-dihydrosporothriolide **2** in 64% yield along with other unidentified compounds. The structure of **2** was determined by NMR spectra (COSY, and NOESY).[28] It was found that treatment of **2** with DBU in CH_2Cl_2 at room temperature for 24 h furnished a 3:1 mixture of **1** and **2** that was chromatographically separable. This result shows that epimer **2** can be also converted to dihydrosporothriolide.

In summary, we have achieved the concise asymmetric synthesis of (−)-dihydrosporothriolide (**1**) in 17% overall yield in seven steps starting from *n*-octanal, thereby confirming its absolute structure. The synthesis illustrates the synthetic utility of our indium-mediated Reformatsky−Claisen rearrangement applicable to base-sensitive substrates. It should be highlighted that the synthetic route requires no protecting group manipulation.

EXPERIMENTAL SECTION

General. Tetrahydrofuran was purified by filtration through a column of activated alumina under an argon atmosphere.[29] Dichloromethane (CH_2Cl_2), pyridine, and triethylamine (Et_3N) were distilled

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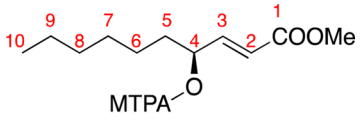
from calcium hydride. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) was distilled under reduced pressure from calcium hydride. Methanol (MeOH) was distilled from sodium. Unless otherwise noted, reagents were commercially available and used without further purification. Normal reagent-grade solvents were used for flash chromatography and extraction. $InCl_3$ was flame-dried for 1 min under reduced pressure prior to use. The ultrasonic cleaner with 120 W, 38 kHz, was used for ultrasonication. All reactions were monitored by TLC with precoated silica gel plates (0.25 mm thickness). Visualization was achieved via UV light, a 5.6% ethanolic *p*-anisaldehyde solution containing 5.6% of concentrated H_2SO_4-heat, and 10% ethanolic phosphomolybdic acid solution-heat. Column chromatography was performed using silica gel (particle size 100−210 μm), and flash chromatography was performed using silica gel (particle size 40−50 μm). Melting points were measured in open capillary tubes and are uncorrected. IR spectra were measured on a Fourier transform infrared spectrometer in neat state. The ^{1}H NMR and ^{13}C NMR spectra were measured using $CDCl_3$ as solvent, and chemical shifts are reported as δ values in parts per million (ppm) based on internal $(CH_3)_4Si$ or solvent peak (^{1}H NMR 7.26 ppm, ^{13}C 77.0 ppm). Splitting patterns were designated as "s, d, t, q, m, and br", indicating "singlet, doublet, triplet, quartet, multiplet, and broad", respectively. Optical rotations were recorded on a digital polarimeter using $CHCl_3$ as solvent. HRMS spectra were taken in EI (dual focusing sector field). All reactions were carried out under anhydrous conditions and an argon atmosphere, unless otherwise noted.

Methyl (*S*,*E*)-4-hydroxydec-2-enoate (13). To a solution of D-proline (166 mg, 1.44 mmol) and nitrosobenzene (1.03 g, 9.63 mmol) in MeCN (20 mL) and THF (5 mL) were added 1-(2-(dimethylamino)-ethyl)-3-phenylurea (298 mg, 1.44 mmol) and octanal (2.25 mL, 14.4 mmol) at 0 °C, and the mixture was stirred for 12 h. To the mixture were added trimethyl phosphonoacetate (3.5 mL, 21.6 mmol), LiCl (916 mg, 21.6 mmol), and DBU (2.5 mL, 16.9 mmol) at 0 °C. After stirring for 6 h, the mixture was diluted with saturated aqueous NH_4Cl (30 mL) and extracted with AcOEt (30 mL × 3). Organic extracts were washed with brine (20 mL), dried over Mg_2SO_4, and concentrated. The residue was diluted with MeOH (40 mL), and $CuSO_4\cdot 5H_2O$ (479 mg, 1.92 mmol) was added. After stirring at room temperature for 10 h, $CuSO_4\cdot 5H_2O$ (480 mg, 1.92 mmol) was added again. The mixture was diluted with saturated aqueous NH_4Cl (20 mL), extracted with AcOEt (30 mL × 3), and washed with brine (20 mL). Drying over Mg_2SO_4, concentration, and flash chromatography (SiO_2 100 g, hexanes−AcOEt, 5:1 to 3:1) afforded compound **13** (952 mg, 4.75 mmol, 50%) as a colorless oil; $[\alpha]_D^{28}$ +22.3 (*c* 1.00, $CHCl_3$) {lit. for the enantiomer, $[\alpha]_D^{20}$ −20.2 (*c* 1.0, $CHCl_3$), 93% ee;[21a] $[\alpha]_D^{20}$ −22.4 (*c* 1.03, $CHCl_3$)[21b]}; R_f = 0.25 (hexanes−AcOEt, 4:1); IR (neat): 3439, 2936, 2858, 1731, 1689, 1437, 1313, 1173, 1042, 981, 927, 862, 724, 610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (dd, *J* = 4.9, 15.6 Hz, 1H), 6.04 (dd, *J* = 1.7, 15.6 Hz, 1H), 4.32 (q, *J* = 4.9 Hz, 1H), 3.75 (s, 3H), 1.73 (dd, *J* = 1.7, 15.6 Hz, 1H), 1.61−1.55 (m, 2H), 1.43−1.24 (m, 8H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 150.7, 119.4, 70.9, 51.5, 36.5, 31.6, 29.0, 25.0, 22.4, 13.9; MS (EI): *m*/*z* (%) = 200, 171, 115, 87; HRMS−EI: *m*/*z* calcd for $C_{11}H_{20}O_3$: 200.1413; found: 200.1413 (M^+).

MTPA Esters of 13. To a solution of **13** (5 mg, 0.025 mmol) in CH_2Cl_2 (1.0 mL) were added pyridine (0.5 mL), 4-dimethylaminopyridine (2 mg, 0.018 mmol), and (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride (14 μL, 0.0748 mmol). After stirring at rt for 10 h, the mixture was evaporated and the residue was subjected to chromatography (SiO_2 1 g, hexanes−AcOEt, 10:1) to furnish (*S*)-MTPA ester (11 mg, 0.025 mmol, ∼100%) as a colorless oil. Analogously, (*R*)-MTPA ester was also prepared. ^{1}H NMR difference in ppm ((*S*)-Mosher ester − (*R*)-Mosher ester, 400 MHz, $CDCl_3$): δ H_3; 6.86−6.80 = +0.06, H_2; 5.99−5.86 = +0.13, H_4; 5.61−5.59 = +0.02, H_3; 3.75−3.73 = +0.02, H_5; 1.69−1.74 = −0.05.



Mosher ester of 13

Methyl (4*S*,*E*)-4-((2-Bromopropanoyl)oxy)dec-2-enoate (12). To a solution of compound **13** (202 mg, 1.01 mmol) in CH_2Cl_2 (5 mL) were added pyridine (0.19 mL, 2.35 mmol), 4-dimethylaminopyridine (12.2 mg, 0.100 mmol), and 2-bromopropionyl bromide (0.12 mL, 1.15 mmol). The reaction mixture was stirred at 0 °C for 13 h. The mixture was diluted with brine (10 mL), extracted with Et_2O (10 mL × 3), dried, and concentrated. The residue was subjected to chromatography (SiO_2 15 g, hexanes−AcOEt, 10:1) to furnish a 55:45 diastereomeric mixture of **12** (347 mg, 1.01 mmol, ∼100%) as a colorless oil; R_f = 0.63 (hexanes−AcOEt, 5:1); IR (neat): 2929, 2858, 1729, 1665, 1435, 1312, 1273, 1219, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (dd, *J* = 5.5, 15.9 Hz, 0.55H), 6.86 (dd, *J* = 5.5, 15.9 Hz, 0.45H), 6.05 (dd, *J* = 1.6, 15.6 Hz, 0.55H), 6.04 (dd, *J* = 1.7, 15.6 Hz, 0.55H), 6.00 (dd, *J* = 1.7, 15.6 Hz, 0.45H), 5.43 (q, *J* = 6.4 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 0.55H), 4.39 (q, *J* = 6.9 Hz, 0.45H), 3.75 (s, 3H), 1.85 (d, *J* = 7.1 Hz, 1.65H), 1.84 (d, *J* = 6.9 Hz, 1.35H), 1.76−1.70 (m, 1H), 1.40−1.24 (m, 8H), 0.88 (d, *J* = 6.8 Hz, 3H; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 144.8, 144.7, 121.4, 121.3, 73.9, 73.8, 60.3, 51.7, 51.7, 39.8, 39.8, 33.6, 33.6, 31.5, 31.5, 28.8, 28.8, 24.7, 24.6, 22.6, 22.4, 21.5, 21.5, 14.1, 14.0; MS (EI): *m*/*z* (%) = 336, 334, 255, 199; HRMS−EI: *m*/*z* calcd for $C_{14}H_{23}{}^{81}BrO_4$: 336.0759; found: 336.0746 (M^+).

(2*R*,*S*,3*R*,*E*)-3-(Methoxycarbonyl)-2-methylundec-4-enoic Acid (15) and Methyl (*S*,*E*)-4-(Propionyloxy)dec-2-enoate (16) from 12. A mixture of TMSCl (0.5 mL, 3.9 mmol) and Et_3N (0.5 mL, 3.5 mmol) was centrifuged at 3000 rpm for 5 min. The supernatant (0.23 mL, containing 1.4 mmol of TMSCl and 1.3 mmol of Et_3N) was added to a mixture of dried $InCl_3$ (100 mg, 0.454 mmol) and In (52 mg, 0.454 mmol) in THF (1.0 mL). To a stirred mixture was added a solution of **12** (76 mg, 0.227 mmol) in DMPU (1.0 mL), and the reaction mixture was stirred at 10−30 °C for 2 h under ultrasonication. The stirring mixture was diluted with AcOEt (20 mL × 2) and washed with 3 M HCl (10 mL × 3) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (SiO_2 5 g, hexane−AcOEt, 5:1 to 3:1) to afford a diastereomeric mixture **15** (28 mg, 0.109 mmol, 48%) as a 2:1 diastereomeric mixture as a colorless oil and **16** (30 mg, 0.117 mmol, 52%) as a colorless oil; **15**: R_f = 0.15 (hexanes−AcOEt, 3:1); IR (neat): 2928, 2856, 1737, 1711, 1458, 1435, 1164, 970, 411 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70−5.58 (m, 1H), 5.45 (dd, *J* = 9.0, 14.9 Hz, 0.67H), 5.27 (dd, *J* = 9.3, 15.1 Hz, 0.33H), 3.70 (s, 2H), 3.68 (s, 1H), 3.17 (t, *J* = 9.0 Hz, 1H), 2.94−2.86 (m, 1H), 2.06−1.98 (m, 2H), 1.40−1.25 (m, 8H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 173.2, 137.0, 136.3, 125.0, 124.1, 124.1, 52.0, 52.0, 51.9, 51.6, 42.1, 40.9, 32.4, 32.3, 31.6, 28.9, 28.7, 28.6, 22.5,15.0, 14.6, 14.0, 14.0; MS (EI): *m*/*z* (%) = 256, 183; HRMS−EI: *m*/*z* calcd for $C_{14}H_{24}O_4$: 256.1671; found: 256.1669 (M^+); **16**: $[\alpha]_D^{29}$ −13.0 (*c* 0.35, $CHCl_3$); R_f = 0.58 (hexanes−AcOEt, 5:1); IR (neat): 2930, 2858, 1731, 1665, 1462, 1435, 1310, 1274, 1176, 1082, 851, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (dd, *J* = 5.2, 15.6 Hz, 1H), 5.92 (dd, *J* = 1.5, 15.6 Hz, 1H), 5.40 (q, *J* = 5.7 Hz, 1H), 3.74 (s, 3H), 2.37 (q, *J* = 7.6 Hz, 2H), 1.85−1.63 (m, 2H), 1.30−1.26 (m, 8H), 1.16 (t, *J* = 7.6 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 166.5, 146.0, 120.9, 72.2, 51.6, 33.8, 31.5, 28.9, 27.7, 24.6, 22.5, 14.0, 9.0; MS (EI): *m*/*z* (%) = 256, 199, 183; HRMS−EI: *m*/*z* calcd for $C_{14}H_{24}O_4$: 256.1675; found: 256.1659 (M^+).

Methyl (*S*,*E*)-4-((2,2-Dibromopropanoyl)oxy)dec-2-enoate (24). To a solution of compound **13** (125 mg, 0.625 mmol) in THF (6 mL) were added EDCI (356 mg, 1.86 mmol), 4-dimethylaminopyridine (22.5 mg, 0.186 mmol), and 2,2-dibromopropionic acid (427 mg, 1.86 mmol). After the reaction mixture was stirred at room temperature for 6 h, EDCI (128 mg, 0.67 mmol) and 4-DMAP (11.3 mg, 0.093 mmol) were added, and stirring was continued at room temperature for an additional 6 h. The mixture was diluted with sat. NH_4Cl (10 mL), extracted with Et_2O (10 mL × 3), dried, and concentrated. The residue was subjected to chromatography (SiO_2 10 g, hexanes−AcOEt, 20:1) to furnish **24** (232 mg, 0.560 mmol, 90%) as a colorless oil; $[\alpha]_D^{27}$ −0.4 (*c* 1.06, $CHCl_3$); R_f = 0.66 (hexanes−AcOEt, 4:1); IR (neat): 2930, 2857, 1736, 1665, 1436, 1378, 1261, 1173, 1119, 1068, 977, 593 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (dd, *J* = 4.9, 15.6 Hz, 1H), 6.13 (dd, *J* = 1.7, 15.6 Hz, 1H), 5.47 (q, *J* = 5.9 Hz, 1H), 3.76 (s, 3H), 2.66 (s, 3H),

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1.80−1.75 (m, 2H), 1.44−1.24 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 165.9, 144.1, 121.5, 51.7, 51.6, 37.1, 33.5, 31.5, 29.8, 24.6, 22.4, 14.0; MS (EI): m/z (%) = 416, 414, 412, 385, 383, 381, 263, 261, 183; HRMS−EI: m/z calcd for $C_{14}H_{22}{}^{81}Br_2O_4$: 415.9844; found: 415.9835 (M^+).

Dimethyl (2*S*,3*R*)-2-Methyl-3-((*E*)-oct-1-en-1-yl)succinate (25) and Dimethyl (2*R*,3*R*)-2-Methyl-3-((*E*)-oct-1-en-1-yl)succinate (26). A mixture of TMSCl (0.5 mL, 3.9 mmol) and Et_3N (0.5 mL, 3.5 mmol) was centrifuged at 3000 rpm for 5 min. The supernatant (0.25 mL, containing 0.98 mmol of TMSCl and 0.89 mmol of Et_3N) was added to a mixture of dried $InCl_3$ (112 mg, 0.506 mmol) and In (52 mg, 0.506 mmol) in THF (2.0 mL). To a stirred mixture was added a solution of **24** (104 mg, 0.253 mmol) in DMPU (2.0 mL), and the reaction mixture was stirred at 10−30 °C for 1.5 h under ultrasonication. The stirring mixture was diluted with 2 M HCl (10 mL), extracted with Et_2O (10 mL × 3), and washed with brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (SiO_2 5 g, hexane−AcOEt, 10:1 to 2:1) to afford a diastereomeric mixture of **15** (51.9 mg, 0.202 mmol, 80%) and **16** (9.2 mg, 0.036 mmol, 14%).

To a solution of **15** (51.9 mg, 0.202 mmol) in THF (1 mL) and MeOH (2 mL) was added timethylsilyldiazomethane (2.0 M solution in hexane; 0.3 mL, 0.6 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The mixture was concentrated and purified by flash chromatography (SiO_2 5 g, hexanes−AcOEt, 20:1) to give compound **25** (30.5 mg, 0.113 mmol, 56%) as a colorless oil and compound **26** (15.6 mg, 0.058 mmol, 29%) as a colorless oil; **25**: $[\alpha]_D^{28}$ +63.4 (c 0.81, $CHCl_3$); R_f = 0.62 (hexanes−AcOEt, 4:1); IR (neat): 2953, 2927, 2856, 1735, 1458, 1434, 1259, 1192, 1157, 1067, 970 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.58 (d, J = 15.1, 6.8 Hz, 1H), 5.41 (dd, J = 9.5 15.1 Hz, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 3.19 (t, J = 8.8 Hz, 1H), 2.89 (ddd, J = 7.0, 8.8, 13.9 Hz, 1H), 2.04−1.97 (m, 2H), 1.31−1.25 (m, 8H), 1.15 (d, J = 6.8 Hz, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6 173.1, 135.7, 124.6, 52.5, 51.8, 51.5, 42.5, 32.3, 31.6, 29.0, 28.8, 22.5, 15.2, 14.0; MS (EI): m/z (%) = 270, 256, 238, 210, 183; HRMS−EI: m/z calcd for $C_{15}H_{26}O_4$: 270.1831; found: 270.1825 (M^+); **26**: $[\alpha]_D^{28}$ +103.0 (c 0.38, $CHCl_3$); R_f = 0.57 (hexanes−AcOEt, 4:1); IR (neat): 2954, 2928, 1736, 1459, 1434, 1195, 1165, 970, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 (d, J = 15.1, 6.8 Hz, 1H), 5.26 (dd, J = 9.6 15.1 Hz, 1H), 3.67 (s, 3H × 2), 3.22 (t, J = 9.5 Hz, 1H), 2.88−2.80 (m, 1H), 2.03 (q, J = 7.2 Hz, 2H), 1.36−1.26 (m, 8H), 1.13 (d, J = 7.1 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 173.9, 136.7, 124.3, 51.9, 51.9, 51.8, 41.1, 32.4, 31.6, 28.9, 28.7, 22.5, 14.7, 14.0; MS (EI): m/z (%) = 270, 256, 238, 210, 183; HRMS−EI: m/z calcd for $C_{15}H_{26}O_4$: 270.1831; found: 270.1830 (M^+).

(3*S*,3*aS*,6*R*,6*aR*)-6-Hexyl-3-methyltetrahydrofuro[3,4-*b*]furan-2,4-dione (Dihydrosporothriolide) (1) and Methyl (2*S*,3*S*,4*S*)-2-((*S*)-1-Hydroxyheptyl)-4-methyl-5-oxotetrahydrofuran-3-carboxylate (27). To an ice-cooled solution of **25** (27.0 mg, 0.10 mmol) in *t*-BuOH-H_2O (1:1, 1.0 mL) were added super-AD-mix-β prepared by mixing $K_3Fe(CN)_6$ (98 mg, 0.3 mmol), K_2CO_3 (41 mg, 0.3 mmol), $(DHQD)_2PHAL$ (8 mg, 0.01 mmol), $K_2OsO_2(OH)_4$ (0.4 mg, 0.001 mmol), and $MeSO_2NH_2$ (9.5 mg, 0.1 mmol). After stirring at room temperature for 16 h, $Na_2S_2O_3{\cdot}5H_2O$ (150 mg) was added, and stirring was continued for 30 min. Then, the mixture was diluted with 1 M HCl (5 mL) and diethyl ether (5 mL), and the mixture was stirred for an additional 90 min. The reaction mixture was filtered through Celite cake, and the filtrate was concentrated to half volume. The mixture was extracted with AcOEt (5 mL × 3), dried, and concentrated. The residue was subjected to flash chromatography (SiO_2 5 g, hexanes−AcOEt, 4:1) to provide dihydrosporothriolide (20.1 mg, 0.084 mmol, 84%) as a colorless solid and compound **27** (2.9 mg, 0.011 mmol, 11%) as a colorless oil.

Dihydrosporothriolide (1). mp 90−91 °C (recrystallized from hexanes−AcOEt, 1:2); (lit. 92−93 °C); $[\alpha]_D^{27}$ −29.2 (c 0.375, $CHCl_3$) {lit. $[\alpha]_D^{25}$ −33 (c 0.13, $CHCl_3$) }; R_f = 0.25 (hexanes−AcOEt, 2:1); IR (neat): 2927, 2857, 1789, 1458, 1361, 1326, 1302, 1207, 1129, 1077, 1015, 966, 902, 789, 682, 634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.12 (dd, J = 4.2, 5.9 Hz, 1H), 4.56 (dt, J = 4.2, 7.1 Hz, 1H), 3.15 (d, J = 6.1 Hz, 1H), 3.07 (q, J = 7.6 Hz, 1H), 1.97−1.78 (m, 2H), 1.51−1.24 (m, 8H), 1.45 (d, J = 7.6 Hz, 3H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 174.7, 82.4, 78.3, 49.0, 38.3, 31.5, 28.9, 28.8, 25.3, 22.5, 17.1, 14.0; MS (EI): m/z (%) = 240, 222, 194; HRMS−EI: m/z calcd for $C_{13}H_{20}O_4$: 240.1362; found: 240.1343 (M^+).

27. $[\alpha]_D^{27}$ +16.8 (c 0.33, $CHCl_3$); R_f = 0.55 (hexanes−AcOEt, 2:1); IR (neat): 3460, 2929, 2857, 1772, 1738, 1437, 1378, 1262, 1176, 1005, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (d, J = 9.1 Hz, 1H), 3.78 (s, 3H), 3.67 (brs, 1H), 3.19 (t, J = 9.1 Hz, 1H), 3.01−2.94 (m, 1H), 1.75 (brs, 1H), 1.67−1.60 (m, 2H), 1.57−1.44 (m, 2H) 1.37 (d, J = 7.0 Hz, 3H), 1.30−1.26 (m, 6H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 171.4, 80.9, 70.9, 52.6, 48.7, 39.1, 34.0, 31.6, 29.0, 25.5, 22.5, 14.6, 14.0: MS (EI): m/z (%) = 272, 238, 210, 183, 158: HRMS−EI: m/z calcd for $C_{14}H_{24}O_5$: 272.1624; found: 272.1632 (M^+).

(3*R*,3*aS*,6*R*,6*aR*)-6-Hexyl-3-methyltetrahydrofuro[3,4-*b*]-furan-2,4-dione (3-*epi*-dihydrosporothriolide) (2). To an ice-cooled solution of **26** (27.0 mg, 0.10 mmol) in *t*-BuOH-H_2O (1:1, 1.0 mL) were added super-AD-mix-β prepared by mixing $K_3Fe(CN)_6$ (98 mg, 0.3 mmol), K_2CO_3 (41 mg, 0.3 mmol), $(DHQD)_2PHAL$ (8 mg, 0.01 mmol), $K_2OsO_2(OH)_4$ (0.4 mg, 0.001 mmol), and $MeSO_2NH_2$ (9.5 mg, 0.1 mmol). After stirring at room temperature for 25 h, $Na_2S_2O_3{\cdot}5H_2O$ (160 mg) was added, and stirring was continued for 30 min. Then, the mixture was diluted with 1 M HCl (5 mL) and diethyl ether (5 mL), and the mixture was stirred for an additional 90 min. The reaction mixture was filtered through Celite cake, and the filtrate was concentrated to half volume. The mixture was extracted with AcOEt (5 mL × 3), dried, and concentrated. The residue was subjected to flash chromatography (SiO_2 5 g, hexanes−AcOEt, 4:1) to provide 3-*epi*-dihydrosporothriolide (15.4 mg, 0.064 mmol, 64%) as a colorless solid.

3-*epi*-Dihydrosporothriolide (**2**): mp 77−78 °C (recrystallized from hexanes−AcOEt, 1:2); $[\alpha]_D^{23}$ +15.4 (c 0.48, $CHCl_3$) {lit. $[\alpha]_D$ −22.06 (c 0.5, $CHCl_3$)[15,28]}; R_f = 0.21 (hexanes−AcOEt, 2:1); IR (neat): 2927, 2860, 1785, 1459, 1344, 1200, 1020, 946, 896, 787, 680, 579, 405 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.02 (dd, J = 4.2, 6.0 Hz, 1H), 4.51 (dt, J = 4.2, 6.4 Hz, 1H), 3.45 (dd, J = 6.2, 10.0 Hz, 1H), 3.06 (dq, J = 10.0, 7.6 Hz, 1H), 1.94−1.78 (m, 2H), 1.56−1.26 (m, 8H), 1.47 (d, J = 7.6 Hz, 3H), 0.89 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 172.0, 81.5, 77.9, 44.6, 36.6, 31.5, 28.9, 28.7, 25.3, 22.4, 13.9, 10.9: MS (EI): m/z (%) = 240, 194, 98: HRMS−EI: m/z calcd for $C_{13}H_{20}O_4$: 240.1362 ; found: 240.1364 (M^+).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray analysis of dihydrosporothriolide and ^{1}H and ^{13}C NMR spectra of synthetic intermediates and dihydrosporothriolide. X-ray crystalllographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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