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Synthesis of the C1–C12 acid fragment of amphidinolide T marine macrolides via SmI_2-mediated enantioselective reductive coupling of aldehydes with a chiral crotonate

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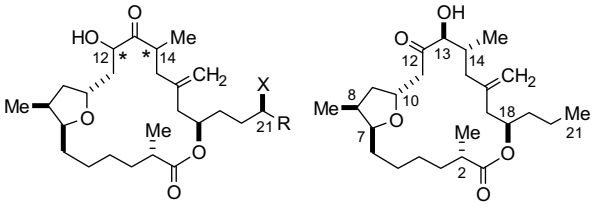
ABSTRACT

A new strategy for enantioselective assembly of the trisubstituted tetrahydrofuran ring has been established for synthesis of the C1–C12 acid fragment of amphidinolide T series marine macrolides. The key steps involve the SmI_2-mediated highly enantioselective reductive coupling of an aldehyde with the (1*S*,2*R*)-*N*-methylephedrine-derived crotonate to form the *cis*-3,4-disubstituted γ-butyrolactone and the subsequent BF_3-mediated 1,3-*anti*-selective allylation of the five-membered-ring oxocarbenium ion with allyltrimethylsilane. The desired C1–C12 acid fragment was obtained in >25% overall yield via a 9-step sequence.

1. Introduction

Amphidinolides are a large family of bioactive macrolides from symbiotic marine dinoflagellates *Amphidinium* sp. and the amphidinolide T congeners consist of five structurally related 19-membered macrolides (Fig. 1).[1,2] They commonly possess a trisubstituted tetrahydrofuran (THF) ring and a C16-*exo*-methylene group. Their structural differences are reflected on the relative position of the α-hydroxy ketone subunit at C12 and C13 and the absolute configurations of the C12/C13-hydroxy and the C14-methyl groups. Moreover, amphidinolide T2 is the only homologue which has an extra chiral hydroxy group at C21. Up to date amphidinolide T1 and T3–T5 have been synthesized by Fürstner,[3] Ghosh,[4] Jamison,[5] Zhao,[6] and Yadav.[7] Ring-closing metathesis (RCM),[3,8] Yamaguchi macrolactonization,[4,6,7,9] and nickel-catalyzed alkyne–aldehyde reductive macrocyclization[5] have been applied in the formation of the 19-membered ring macrocycle.[10] Another focus of these total syntheses is on the strategies toward stereoselective assembly of the trisubstituted THF ring. The *syn* aldol intermediates **1a**–**c** were prepared by the diastereoselective Brown allylation[3] and crotylation,[5] and the diastereoselective aldol reaction[4] of the titanium enolate of a chiral propionate (Scheme 1). It was followed by the cyclization reactions of the advanced intermediates derived from **1a**–**c** to afford the γ-butyrolactone[4,5] and the lactol **2b**,[3,5] which could be transformed into the sulfone **2a**.[3,4] Under the Lewis acid catalysis, the sulfone **2a**, the lactol **2b** and the lactolether **2c**[7] can serve as the precursors of the five-membered-ring oxocarbenium ions to undergo alkylation reactions with allyltrimethylsilane,[5,7] silyl enol ethers,[3,4] and allenylsilane or allenylstannane,[5] resulting in the formation of the C8/C10-*trans* **3a**–**c** in a highly stereoselective manner.[11] Zhao et al. established an intramolecular O-alkylation of the C10-alkoxide generated in situ from the acetate **4b** which was derived from the *anti*-aldol **4a**.[6] The desired trisubstituted THF product was obtained with inversion of the configuration at C7.[6]



T2: 12β-OH, 14α-Me, R = Me, X = OH
T3: 12β-OH, 14α-Me, R = X = H
T4: 12α-OH, 14α-Me, R = X = H
T5: 12α-OH, 14β-Me, R = X = H

amphidinolide T1

Figure 1. Structures of the 19-membered marine macrolides amphidinolide T1, T2, T3, T4, and T5.

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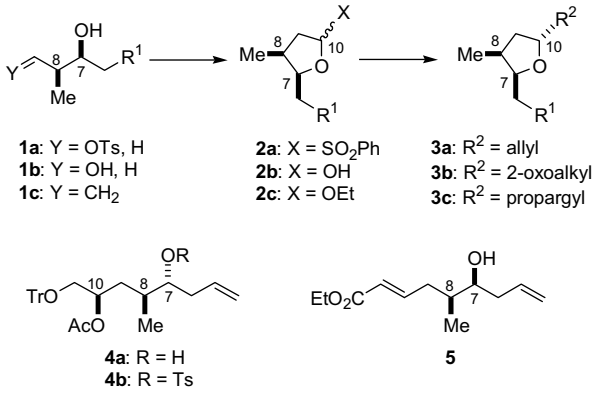
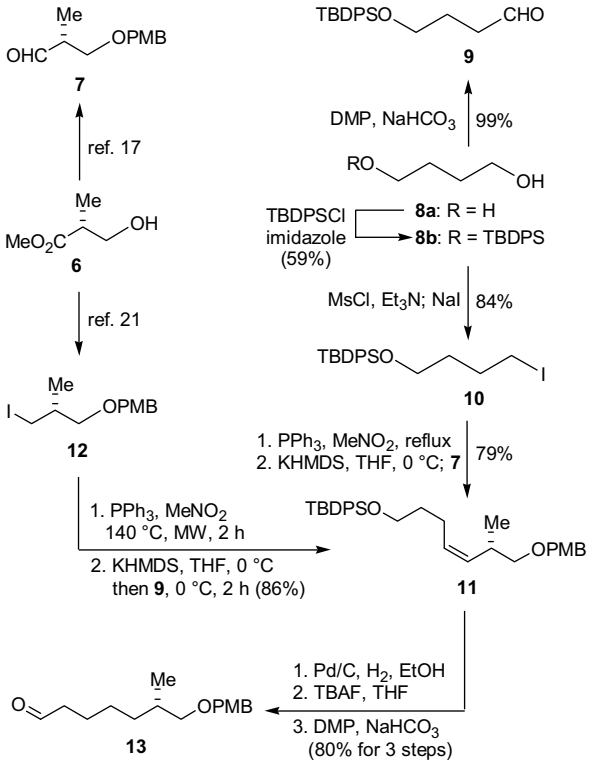
Iqbal et al. used an intramolecular oxy-Michael addition within **5** to construct the THF ring with a 82:18 diastereomeric ratio.[12] In our previous total synthesis of amphidinolide X and Y, we employed a 5-*endo* epoxide ring-opening cyclization to build up the 1,1,4,5-tetrasubstituted THF subunit.[13] We report here on synthesis of the C1–C12 acid fragment of amphidinolide T macrolides by utilizing an enantioselective reductive coupling of an aldehyde with the (1*S*,2*R*)-*N*-methylephedrine-derived crotonate[14–16] to install the requisite absolute configurations at C7 and C8 in the trisubstituted THF ring.



Scheme 1. Stereoselective formation of the trisubstituted THF ring of amphidinolide T macrolides.



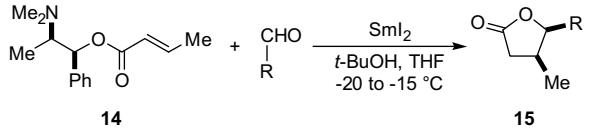
Scheme 2. Preparation of the C1–C7 aldehyde **13**.

2. Results and discussion

The chiral aldehyde (*R*)-**7**,[17] easily derived from (*R*)-methyl 3-hydroxy-2-methylpropionate **6**, and its antipode have been used in diastereoselective reactions such as aldol[17a,c,d] and crotylation[17b] and the TBDPS- and Tr-protected analogues[18] have been subjected to the reaction with Takai's (γ-methoxyallyl)chromium reagent. Racemization at the stereogenic center of these aldehydes was not revealed in the above reactions. We initially carried out the Wittig olefination of (*R*)-**7** for the synthesis of the aldehyde **13** (Scheme 2). The iodide **10**,[19] prepared from 1,4-butanediol **8a**, was reacted with PPh_3 in refluxing $MeNO_2$ for 21 h to give the phosphonium salt (92%), which was deprotonated using KHMDS to form the requisite ylide. The latter, without isolation, reacted with (*R*)-**7** in THF at 0 °C for 1 h, providing the (*Z*)-alkene **11** {$[\alpha]_D^{22}$ +0.77 (*c* 3.80, acetone)} in 86% yield. The optical rotation of **11** is rather lower but we could not realize loss of stereochemistry during the Wittig olefination till **11** was transformed into the known C1–C12 acid fragment **18** {$[\alpha]_D^{20}$ −0.3 (*c* 4.44, CH_2Cl_2); lit.[5b] $[\alpha]_D^{23}$ +8.4 (*c* 4.5, CH_2Cl_2)} (vide infra). At that stage, we decided to prepare the alkene **11** via the Wittig reaction starting from the achiral aldehyde **9**[20] and the chiral iodide **12**.[21] The alkylation of PPh_3 with **12** was first carried out in refluxing $MeNO_2$ for 23 h followed by washing the residue with Et_2O, giving a yellow oil with ca. 75% conversion of **12** presumably due to steric hindrance of the iodide **12**. When the oil was used for the Wittig reaction with **9** the alkene **11** was produced in 32% yield. Fortunately, under microwave heating[22] for 2 h in a closed vial at 140 °C in $MeNO_2$ the iodide **12** was mostly reacted with PPh_3 to form the phosphonium salt. The latter was then deprotonated by KHMDS and the resultant ylide reacted with **9** to furnish the alkene **11** {$[\alpha]_D^{20}$ +29.8 (*c* 3.75, acetone)} in 86% overall yield from **12**. Hydrogenation of **11** over Pd/C in EtOH (rt, 1 h; 99%) and removal of the TBDPS protection group by TBAF in THF (rt, 1 h; 95%) gave the saturated primary alcohol, which was oxidized to the aldehyde **13** by DMP–$NaHCO_3$ (rt, 0.5 h; 85%).

With the aldehyde **13** in hand, we next investigated the SmI_2-mediated reductive coupling reactions of aldehydes with the (1*S*,2*R*)-*N*-methylephedrine-derived crotonate **14** (Table 1).[14] We first performed the known reaction of **14** with cyclohexanecarbaldehyde at different temperatures (Table 1, entries 1–3). The desired *cis*-3,4-disubstituted γ-butyrolactone **15a** was obtained in high diastereomeric selectivity as reported[14] but the yield was low. By applying the conditions we established for the reactions of the crotonates derived from atropisomeric 1-naphthamides,[15c] **15a** was obtained in 56% yield (entry 3). Use of 3 equiv of SmI_2 was found beneficial in the reaction of octanal as well and the product **15b** was produced in 45% yield (entries 4 and 5). Similarly, the reaction of the chiral aldehyde **13** with **14** afforded the product **15c** in 53–67% after shortening the reaction time to 3 h between −20 to −15 °C on small scales (entry 6). The yield of **15c** dropped slightly to 46% on average for the preparative scales (entry 7). These results suggest that the

Table 1
SmI_2-Mediated enantioselective reductive coupling



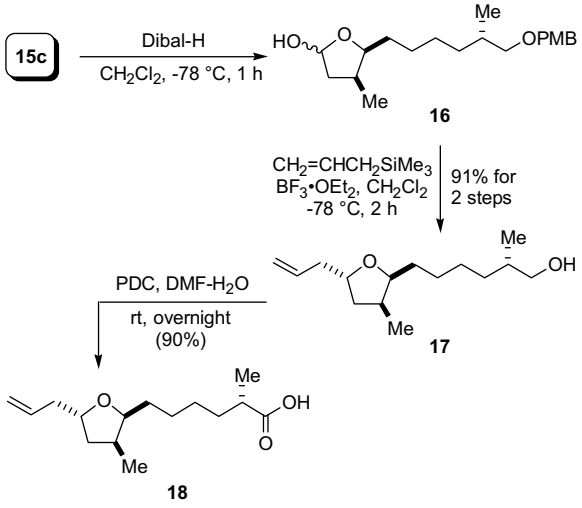
Entry	RCHO	SmI_2 (eq)	*T* (°C); *t* (h)	**15**; Yield (%)
1	CyCHO	2	−78; 1 and then −78 to rt; 2–3	**15a**; 34[a]
2	CyCHO	2	−20 to −15; 6	**15a**; 45
3	CyCHO	3	−20 to −15; 6	**15a**; 56
4	Octanal	2	−20 to −15; 6	**15b**; 33
5	Octanal	3	−20 to −15; 6	**15b**; 45
6	**13**	3	−20 to −15; 3	**15c**; 53–67[b]
7	**13**	3	−20 to −15; 3	**15c**; 46[c,d]

[a] A GC yield of 74% was reported for formation of **15a** at −78 °C and a 71% isolated yield was given for **15a** prepared at 0 °C (Ref. 14).
[b] For the runs of 0.2–0.25 mmol.
[c] Average yield for three runs of ca. 3 mmol of **13**.
[d] A 97.1:2.9 diastereomer ratio was obtained by HPLC analysis over a chiral stationary phase (see Supplementary data for details).

SmI_2-mediated reductive coupling reaction is sensitive to the reaction conditions. The byproduct of the reaction seems related to the reduced aldehyde but the exact structure has not been deduced yet. Nevertheless, the straight-chain aldehydes gave low yields of 55–59% by GC analysis in Fukuzawa's work.[14] Our results for the reductive coupling reactions of octanal and **13** are consistent with this trend.[15b,d]

The *cis*-3,4-disubstituted γ-butyrolactone **15** prepared from **14** is expected to have ≥97:3 cis:trans ratio with ≥94% ee for the cis isomer according to Fukuzawa's work.[14] Due to lack of stereochemical communication with the remote chirality in the aldehyde **13**, the stereochemical course of the reductive coupling reaction of **13** is controlled by the chiral crotonate **14**, preferentially affording the cis diastereomer **15c**. However, the pair of cis diastereomers of **15c**, being different at the C3 and C4 stereogenic centers on the γ-butyrolactone ring, are not distinguishable by ^{1}H NMR spectroscopy. By using HPLC analysis over a chiral stationary phase, we were able to estimate a diastereomer ratio of 97.1:2.9 for **15c** (see Supplementary data). Moreover, the corresponding *trans* isomers of **15c** were not detected by ^{1}H NMR spectroscopy, indicating that the reductive coupling of **13** with **14** offers high diastereoselectivity.

As depicted in Scheme 3, **15c** was first reduced by Dibal-H at −78 °C to give the lactol **16**, which was subjected to the allylation with allyltrimeyhlsilane in the presence of $BF_3{\cdot}OEt_2$ at −78 °C.[5b,7] The 3,5-*trans*-2,3,5-trisubstituted THF product **17** was formed in 91% overall yield from **15c**. Under the Lewis acidic conditions, the PMB protecting group was cleaved spontaneously. The primary alcohol **17** was finally oxidized to the known carboxylic acid **18**[5b] in 90% yield by treating with PDC in DMF–H_2O.[23] All spectral data and optical rotation {$[\alpha]_D^{17}$ +11.9 (*c* 4.3, CH_2Cl_2); lit.[5b] $[\alpha]_D^{23}$ +8.4 (*c* 4.5, CH_2Cl_2)} of our sample **18** are consistent with those reported by Jamison.[5b]



Scheme 3. Synthesis the C1–C12 acid fragment **18**.

3. Conclusion

In summary, we have established a one-step stereoselective synthesis of the *cis*-3,4-disubstituted γ-butyrolactone **15c** via the SmI_2-mediated reductive coupling of the chiral aldehyde **13** with the know chiral crotonate **14**.[14] The reaction is reproducible on preparative (sub-gram) scales in the average yield of 46%, which is comparable to those multiple-step approaches reported in the literature.[3–7,10] Improvement over the product yield of the reductive coupling is considered by using the chiral crotonates derived from other chiral auxiliaries.[15c,d] Research toward this goal is in progress in our laboratories.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ (400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively) with $CHCl_3$ as the internal reference. IR spectra were taken on a FTIR spectrophotometer. Mass spectra (MS) were measured by the $^+$ESI or $^-$ESI method at 70 eV. High-resolution mass spectra (HRMS) were measured by the $^+$ESI. Optical rotation data were recorded on a polarimeter with a cylindrical quartz cell (thermostattable, 3.5 mm ID×10 mm). Silica gel plates pre-coated on glass were used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel and petroleum ether (PE; bp 60–90 °C) were used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Anhydrous Et_2O, THF and PhMe were freshly distilled from sodium benzophenone ketyl under N_2. Anhydrous CH_2Cl_2 and $MeNO_2$ were freshly distilled from CaH_2. Dess–Martin periodinane (DMP) was prepared according to the literature procedure.[24] (1*S*,2*R*)-*N*-Methylephedrinyl crotonate **14** {$[\alpha]_D^{23}$ −2.8 (*c* 1.35, $CDCl_3$)} was prepared according to Fukuzawa's procedure.[14] The solution of SmI_2 (0.1 M in THF) from a commercial source was used in this work. The reductive coupling reactions using in situ prepared SmI_2 from Sm metal and diiodoethane[25] gave similar results. The microwave reactions were carried out in closed pressurized process vials on a technical microwave reactor (Emrys™ creator from Personal Chemistry AB, Uppsala, Sweden) with the reaction temperature measured by an IR sensor. The reaction time is the holding time after reaching the set reaction temperature. Other reagents were obtained commercially and used as received. Ambient temperature ranges from 10–30 °C.

4.2. Preparation of known intermediates

*4.2.1. Synthesis of (R)-(−)-3-(4-methoxybenzyloxy)-2-methylpropanal (**7**)[17]*

To a solution of (*S*)-(−)-3-(4′-methoxybenzyloxy)-2-methylpropan-1-ol[26] (3.88 g, 18.47 mmol) in CH_2Cl_2 (370 mL) at rt was added solid $NaHCO_3$ (15.5 g, 185 mmol) followed by carefully adding a solution of Dess–Martin periodinane (DMP)[24] in CH_2Cl_2 (0.3 M, 74 mL, 22 mmol). The resultant mixture was stirred at room temperature for 0.5 h followed by treating with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (3×200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 20% EtOAc in PE) to give the aldehyde (*R*)-**7** (3.77 g, 98%) as a colorless oil. R_f=0.56 (20% EtOAc in PE); $[\alpha]_D^{20}$ −27.8 (*c* 1.9, $CHCl_3$); lit.[17d] $[\alpha]_D^{25}$ +29.4 (*c* 9.06, CH_2Cl_2; ca. 95% purity) for (*S*)-**7**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.24 (d, *J*=8.0 Hz, 2H), 6.88 (d, *J*=7.6 Hz, 2H), 4.46 (s, 2H), 3.81 (s, 3H), 3.67–3.58 (m, 2H), 2.69–2.61 (m, 1H), 1.12 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 159.2, 129.9, 129.2, 113.8, 72.9, 69.8, 55.2, 46.7, 10.7.

*4.2.2. Synthesis of 4-[(tert-butyldiphenylsilyl)oxy]butan-1-ol (**8b**)[19b,20]*

To a solution of 1,4-butanediol **8a** (8.86 mL, 100.0 mmol) and imidazole (8.850 g, 130.0 mmol) in dry CH_2Cl_2 (300 mL) was added *t*-$BuPh_2SiCl$ (52.0 mL, 200.0 mmol) dropwise under a nitrogen atmosphere at room temperature followed by stirring at same

temperature for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (eluting with 9% EtOAc in PE) to give, along with the bis-silylated byproduct, the monoalcohol **8b**[19b,20] (18.50 g, 59%) as a colorless oil. R_f=0.17 (9% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.72 (m, 4H), 7.48–7.39 (m, 6H), 3.76 (t, J=6.0 Hz, 2H), 3.68 (t, J=6.0 Hz, 2H), 2.68 (br s, 1H), 1.77–1.65 (m, 4H), 1.12 (s, 9H).

4.2.3. Synthesis of 4-(tert-butyldiphenylsilyloxy)butanal (**9**)[20]

To a solution of the alcohol **8b** (12.56 g, 40.2 mmol) in CH_2Cl_2 (200 mL) at room temperature was added solid $NaHCO_3$ (33.80 g, 402 mmol) followed by carefully adding a solution of Dess–Martin periodinane (DMP)[24] in CH_2Cl_2 (0.3 M, 160 mL, 48 mmol). The resultant mixture was stirred at room temperature for 0.5 h followed by treating with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 9% EtOAc in PE) to give the aldehyde **9**[20] (12.40 g, 99%) as a colorless oil. R_f=0.56 (9% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.67–7.64 (m, 4H), 7.50–7.30 (m, 6H), 3.70 (t, J=6.0 Hz, 2H), 2.56 (t, J=6.8 Hz, 2H), 1.90 (quintet, J=6.4 Hz, 2H), 1.05 (s, 9H).

4.2.4. Synthesis of 4-[(tert-butyldiphenylsilyl)oxy]-1-iodobutane (**10**)[19]

To a solution of the alcohol **8b** (2.01 g, 6.43 mmol) in dry CH_2Cl_2 (10 mL) cooled at 0 °C was added Et_3N (1.34 mL, 9.65 mmol) and $MeSO_2Cl$ (0.60 mL, 7.7 mmol) under a nitrogen atmosphere. The resultant mixture was allowed to warm to room temperature and was stirred at same temperature for 1 h. The reaction was quenched by adding EtOAc (50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude mesylate which, without purification, was dissolved in acetone (30 mL) followed by adding solid NaI (9.638 g, 64.3 mmol). The resultant suspension was stirred at reflux for 4 h. The reaction mixture was allowed to cool to room temperature and was then concentrated under reduced pressure. The residue was dissolved in EtOAc (30 mL) and washed with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc (2×30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with PE) to give the iodide **10**[19] (2.357 g, 84% over 2 steps from **8b**) as a colorless oil. R_f=0.52 (PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.45–7.38 (m, 6H), 3.70 (t, J=6.0 Hz, 2H), 3.21 (t, J=6.8 Hz, 2H), 2.01–1.92 (m, 2H), 1.71–1.63 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (4×), 133.8 (2×), 129.6 (2×), 127.6 (4×), 62.7, 33.3, 30.1, 26.9, 19.2, 7.01; MS ($^-$ESI) m/z (relative intensity) 423 (M−CH_3, 100).

4.2.5. Synthesis of (R)-(−)-1-[(3′-iodo-2′-methylpropoxy)methyl]-4-methoxybenzene (**12**)[26]

To a solution of (*S*)-(−)-3-(4′-methoxybenzyloxy)-2-methylpropan-1-ol[26] (6.80 g, 32.3 mmol) in dry PhMe (200 mL) at room temperature was added PPh_3 (21.20 g, 80.9 mmol), imidazole (5.50 g, 80.9 mmol), and I_2 (16.40 g, 64.7 mmol). The resultant mixture was stirred at room temperature for 3 h followed by treating with saturated aqueous $Na_2S_2O_3$. The reaction mixture was extracted with Et_2O (3×50 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 4% EtOAc in PE) to give the iodide (*R*)-(−)-**12**[26] (9.30 g, 90%) as a colorless oil. $[\alpha]_D^{20}$ −14.1 (*c* 1.23, acetone) and $[\alpha]_D^{20}$ −13.5 (*c* 2.9, CH_2Cl_2); lit.[26] $[\alpha]_D^{20}$ −13.5 (*c* 1.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J=8.4 Hz, 2H), 6.88 (d, J=8.4 Hz, 2H), 4.44 (s, 2H), 3.81 (s, 3H), 3.38–3.24 (m, 4H), 1.74–1.80 (m, 1H), 0.98 (d, J=6.8 Hz, 3H).

4.3. Synthesis of (2*S*,3*Z*)-7-[(*tert*-butyldiphenylsilyl)oxy]-1-(4′-methoxybenzyloxy)-2-methylhept-3-ene (11)

4.3.1. The Wittig olefination starting from the iodide **10** and the chiral aldehyde **7** (Method A)

To a solution of the iodide **10** (36.80 g, 84 mmol) in $MeNO_2$ (200 mL) was added PPh_3 (22.00 g, 84 mmol) followed by stirring at reflux in an oil bath for 21 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O (260 mL). The precipitate was collected by filtration and was washed with Et_2O. The solid was dried under reduced pressure to give the phosphonium salt **10a** (52.90 g, 92%) as a pale yellow solid.

To a solution of the phosphonium salt **10a** (687.0 mg, 1.0 mmol) in dry THF (4 mL) cooled at 0 °C was added KHMDS (0.7 M in toluene, 2.57 mL, 1.8 mmol) dropwise under a nitrogen atmosphere. After stirring at the same temperature for 30 min, a solution of the aldehyde **7** (104.0 mg, 0.5 mmol) in dry THF (2 mL) was added dropwise via a syringe. The resultant mixture was stirred at 0 °C for 1 h and the reaction was quenched by adding water. The reaction mixture was extracted with EtOAc (3×10 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 3% EtOAc in PE) to give **11** (216.0 mg, 86%) as a colorless oil. $[\alpha]_D^{22}$ +0.77 (*c* 3.80, acetone) and $[\alpha]_D^{20}$ +2.09 (*c* 3.0, $CHCl_3$).

Note. Racemization at the stereogenic carbon of the aldehyde **7** during the Wittig reaction was confirmed after transforming **11** into the target acid **18**.

4.3.2. The Wittig olefination starting from the chiral iodide **12** and the aldehyde **9** (Method B)

A 10 mL pressurized process vial was charged the iodide **12** (160.0 mg, 0.5 mmol) and PPh_3 (197.0 mg, 0.75 mmol) followed by adding $MeNO_2$ (2 mL). The vial was sealed with a cap containing a silicon septum. The loaded vial was placed into the microwave reactor cavity and, after being heated at 140 °C for 2 h, the iodide **12** was found to be mostly converted. The reaction mixture was concentrated under reduced pressure to give the crude phosphonium salt **12a** which, without purification, was used for the next step.

To a solution of the above phosphonium salt **12a** in dry THF (4 mL) cooled at 0 °C was added KHMDS (0.5 M in toluene, 1 mL, 0.5 mmol) dropwise under a nitrogen atmosphere. After stirring at the same temperature for 30 min, a solution of the aldehyde **9** (279.0 mg, 0.9 mmol) in dry THF (2 mL) was added dropwise via a syringe. The resultant mixture was stirred at 0 °C for 2 h and the reaction was quenched by adding water. The reaction mixture was extracted with EtOAc (3×10 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 4% EtOAc in PE) to give **11** (217.0 mg, 86% from **12**) as a colorless oil. $[\alpha]_D^{20}$ +29.8 (*c* 3.75, acetone); R_f=0.49 (4% EtOAc in PE); IR (film) 2931, 1612, 1513, 1247, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J=6.4 Hz, 4H), 7.44–7.36 (m, 6H), 7.25 (d, J=8.4 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 5.38 (dt, J=10.4, 7.2 Hz, 1H), 5.19 (dd, J=10.8, 9.6 Hz, 1H), 4.45 and 4.41 (ABq, J=12.0 Hz, 2H), 3.80 (s, 3H), 3.68 (t, J=6.8 Hz, 2H), 3.31–3.20 (m, 2H), 2.84–2.76 (m, 1H), 2.23–2.09 (m, 2H), 1.67–1.57 (m, 2H), 1.06 (s, 9H), 0.97 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 135.5 (4×), 134.0 (2×), 132.9, 130.8, 129.7, 129.5 (2×), 129.0 (2×), 127.6 (4×), 113.7 (2×), 75.0, 72.5, 63.4, 55.2, 32.8, 32.2, 26.8 (3×), 23.9, 19.2, 17.8; MS ($^+$ESI) m/z (relative intensity) 525 (M+Na^+, 100); HRMS ($^+$ESI) calcd for $C_{32}H_{42}O_3SiNa^+$ (M+Na^+) 525.2795, found 525.2782.

4.4. Synthesis of (*S*)-7-[(*tert*-butyldiphenylsilyl)oxy]-2-methylhept-1-yl 4′-methoxybenzyl ether

To a solution of the alkene **11** (239.0 mg, 0.48 mmol) in EtOH (2 mL) was added Pd/C (10% w/w, 50.5 mg, 4.7×10^{-2} mmol Pd). The loaded reaction flask was charged with a hydrogen gas balloon and was then gently evacuated and backfilled with hydrogen gas (repeated for three times). The mixture was vigorously stirred at room temperature for 1 h under a hydrogen atmosphere. The reaction mixture was filtered through a Celite plug with washing by EtOH (10 mL) and the combined filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 3% EtOAc in PE) to afford the saturated chiral silyl ether (237.0 mg, 99%) as a colorless oil. $[\alpha]_D^{20}$ −21.6 (*c* 0.66, CH_2Cl_2); R_f=0.49 (4% EtOAc in PE); IR (film) 2931, 1613, 1513, 1247, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J*=7.2 Hz, 4H), 7.39–7.34 (m, 6H), 7.25 (d, *J*=8.0 Hz, 2H), 6.86 (d, *J*=8.4 Hz, 2H), 4.43 and 4.40 (ABq, *J*=12.4 Hz, 2H), 3.76 (s, 3H), 3.66 (t, *J*=6.0 Hz, 2H), 3.28 (dd, *J*=9.2, 6.0 Hz, 1H), 3.19 (dd, *J*=9.2, 6.8 Hz, 1H), 1.77–1.66 (m, 1H), 1.61–1.51 (m, 2H), 1.43–1.18 (m, 6H), 1.06 (s, 9H), 0.90 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 135.5 (×4), 134.1 (2×), 130.9, 129.4 (2×), 129.0 (2×), 127.5 (4×), 113.6 (2×), 75.6, 72.5, 63.9, 55.1, 33.6, 33.4, 32.5, 26.8 (3×), 26.7, 26.1, 19.2, 17.1; MS ($^+$ESI) *m*/*z* (relative intensity) 522 (M+NH_4^+, 100), 527 (M+Na^+, 71); HRMS ($^+$ESI) calcd for $C_{32}H_{44}O_3SiNa^+$ (M+Na^+) 527.2953, found 527.2964.

4.5. Synthesis of (*S*)-7-(4′-methoxybenzyloxy)-6-methylheptan-1-ol

To a solution of the above chiral silyl ether (10.40 g, 20.6 mmol) in THF (200 mL) was added TBAF (1.0 M in THF, 30.9 mL, 30.9 mmol) followed by stirring at room temperature for 1 h. The reaction was then quenched by adding saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc (3×200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 25% EtOAc in PE) to give the chiral alcohol (5.20 g, 95%) as a colorless oil. $[\alpha]_D^{20}$ −7.2 (*c* 0.71, CH_2Cl_2); R_f=0.27 (25% EtOAc in PE); IR (film) 3404 (br), 2931, 1613, 1513, 1248, 1090, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J*=8.0 Hz, 2H), 6.87 (d, *J*=8.4 Hz, 2H), 4.44 and 4.41 (ABq, *J*=12.4 Hz, 2H), 3.79 (s, 3H), 3.60 (t, *J*=6.4 Hz, 2H), 3.28 (dd, *J*=8.8, 6.0 Hz, 1H), 3.20 (dd, *J*=8.8, 6.4 Hz, 1H), 1.90–1.67 (m, 2H), 1.60–1.50 (m, 2H), 1.47–1.20 (m, 5H), 1.15–1.05 (m, 1H), 0.91 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 130.8, 129.0 (2×), 113.6 (2×), 75.6, 72.5, 62.8, 55.2, 33.5, 33.3, 32.6, 26.6, 25.9, 17.1; MS ($^+$ESI) *m*/*z* (relative intensity) 289 (M+Na^+, 100); HRMS ($^+$ESI) calcd for $C_{16}H_{26}O_3Na^+$ (M+Na^+) 289.1774, found 289.1776.

4.6. Synthesis of (*S*)-7-(4′-methoxybenzyloxy)-6-methylheptanal (13)

To a solution of the above chiral alcohol (4.00 g, 15.0 mmol) in CH_2Cl_2 (300 mL) at room temperature was added solid $NaHCO_3$ (12.60 g, 150 mmol) followed by carefully adding a solution of Dess–Martin periodinane[1] in CH_2Cl_2 (0.3 M, 60 mL, 18 mmol). The resultant mixture was stirred at room temperature for 1 h followed by treating with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 25% EtOAc in PE) to give the aldehyde **13** (3.40 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ −6.7 (*c* 0.95, CH_2Cl_2); R_f=0.62 (25% EtOAc in PE); IR (film) 2933, 1724, 1612, 1513, 1247, 1092, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.25 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=9.2 Hz, 2H), 4.43 and 4.40 (ABq, *J*=12.4 Hz, 2H), 3.80 (s, 3H), 3.27 (dd, *J*=8.8, 6.4 Hz, 1H), 3.21 (dd, *J*=8.8, 6.8 Hz, 1H), 2.41 (td, *J*=7.2, 1.6 Hz, 2H), 1.78–1.68 (m, 1H), 1.66–1.56 (m, 2H), 1.50–1.22 (m, 3H), 1.17–1.07 (m, 1H), 0.90 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 159.0, 130.8, 129.1 (2×), 113.7 (2×), 75.4, 72.6, 55.2, 43.8, 33.3, 33.2, 26.4, 22.3, 17.0; MS ($^-$ESI) *m*/*z* (relative intensity) 263 (M−H, 100); HRMS ($^+$ESI) calcd for $C_{16}H_{24}O_3Na^+$ (M+Na^+) 287.1618, found 287.1628.

4.7. General procedure for SmI_2-mediated reductinve coupling reactions of aldehydes with the chiral crotonate 14

To a solution of the chiral crotonate **14**[14] (59.0 mg, 0.24 mmol), the aldehyde (0.20 mmol), and *t*-BuOH (0.24 mmol) in THF (1 mL) cooled at −20 °C under a nitrogen atmosphere was added a THF solution of SmI_2 (0.40 or 0.60 mmol). The resultant mixture was stirred at −20 to −15 °C for 3–6 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluting with 25% EtOAc in PE) to give the γ-butyrolactones **15a–c**. The yields of **15a–c** are found in Table 1 of the main text.

*4.7.1. (4S,5S)-5-Cyclohexyl-4-methyldihydrofuran-2(3H)-one (**15a**)*[14,15c]

A white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (dd, *J*=10.0, 4.8 Hz, 1H), 2.70 (dd, *J*=16.4, 6.8 Hz, 1H), 2.56–2.50 (m, 1H), 2.17 (d, *J*=16.8 Hz, 1H), 2.02 (br d, *J*=12.8 Hz, 1H), 1.80–1.55 (m, 4H), 1.30–0.80 (m, 6H), 0.97 (d, *J*=7.2 Hz, 3H).

*4.7.2. (4S,5S)-5-Heptyl-4-methyldihydrofuran-2(3H)-one (**15b**)*

A colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45–4.37 (m, 1H), 2.67 (dd, *J*=17.2, 8.0 Hz, 1H), 2.62–2.50 (m, 1H), 2.17 (dd, *J*=16.8, 3.2 Hz, 1H), 1.70–1.40 (m, 3H), 1.40–1.20 (m, 9H), 0.99 (d, *J*=6.8 Hz, 3H), 0.86 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 83.7, 37.5, 33.0, 31.7, 29.8, 29.4, 29.1, 25.8, 22.6, 14.0, 13.8.

*4.7.3. (4S,5S,5′S)-5-[6′-(4″-Methoxybenzyloxy)-5′-methylhexyl]-4-methyldihydrofuran-2(3H)-one (**15c**)*

A colorless oil. $[\alpha]_D^{17}$ −31.2 (*c* 2.7, CH_2Cl_2); R_f=0.46 (25% EtOAc in PE); IR (film) 2934, 1777, 1514, 1248, 1171, 1093, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J*=6.8 Hz, 2H), 6.88 (d, *J*=8.8 Hz, 2H), 4.42 (s, 2H), 4.45–4.39 (m, 1H), 3.80 (s, 3H), 3.27 and 3.22 (Abqd, *J*=8.8, 6.4 Hz, 2H), 2.68 (dd, *J*=17.2, 8.0 Hz, 1H), 2.61–2.53 (m, 1H), 2.19 (dd, *J*=17.2, 4.0 Hz, 1H), 1.78–1.60 (m, 2H), 1.54–1.25 (m, 6H), 1.16–1.07 (m, 1H), 1.00 (d, *J*=6.8 Hz, 3H), 0.91 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 159.1, 130.8, 129.1 (×2), 113.7 (×2), 83.6, 75.6, 72.6, 55.3, 37.5, 33.5, 33.4, 33.0, 29.8, 26.7, 26.2, 17.1, 13.8; MS ($^+$ESI) *m*/*z* (relative intensity) 357 (M+Na^+, 100); HRMS ($^+$ESI) calcd for $C_{20}H_{30}O_4Na^+$ (M+Na^+) 357.2036, found 357.2037.

4.8. A preparative scale synthesis of 15c

To a solution of SmI_2 in THF (0.1 M, 89.0 mL, 8.9 mmol) cooled at −20 to −15 °C, was added a solution of the chiral crotonate **14**[14] (885.0 mg, 3.58 mmol), the aldehyde **13** (789.0 mg, 2.98 mmol) and *t*-BuOH (0.34 mL, 3.62 mmol) in THF (5 mL) via a syringe under a nitrogen atmosphere. The resultant mixture was stirred at −20 to −15 °C for 3 h and the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc (3×50 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluting with 16% EtOAc in PE) to give the γ-butyrolactone **15c** (463.0 mg, 46%).

4.9. Synthesis of (2*S*,2′*S*,3′*S*,5′*R*)-6-(5′-allyl-3′-methyltetrahydrofuran-2′-yl)-2-methylhexanol (17)[7]

To a solution of **15c** (500.0 mg, 1.50 mmol) in dry CH_2Cl_2 (15 mL) cooled at −78 °C was added dropwise a solution of diisobutylaluminum hydride in hexane (1 M, 1.8 mL, 1.8 mmol) followed by stirring for 1 h at the same temperature. The reaction was quenched by carefully adding EtOAc (10 mL) and the mixture was allowed to warm to 0 °C. Saturated aqueous sodium potassium tartrate was added and the resultant mixture was diluted with Et_2O (50 mL) with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with Et_2O (2×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude lactol **16**.

To a solution of the above crude lactol **16** and allyltrimethylsilane (0.48 mL, 3.0 mmol) in dry CH_2Cl_2 (30 mL) cooled at −78 °C was added $BF_3\cdot OEt_2$ (0.57 mL, 4.5 mmol) via a syringe. The resultant mixture was stirred for 2 h at −78 °C and allowed to warm to room temperature slowly. The reaction was quenched by saturated $NaHCO_3$ and the reaction mixture was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography (eluting with 20% EtOAc in PE) to give the alcohol **17** (328.0 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ −10.9 (*c* 2.7, CH_2Cl_2); lit.[7] $[\alpha]_D^{25}$ −6.0 (*c* 1.0, $CHCl_3$); R_f=0.28 (25% EtOAc in PE); IR (film) 3391 (br), 2933, 1464, 1091, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83–5.73 (m, 1H), 5.06 (br d, *J*=18.0 Hz, 1H), 5.02 (br d, *J*=10.0 Hz, 1H), 4.09 (quintet, *J*=6.8 Hz, 1H), 3.86–3.80 (m, 1H), 3.48 and 3.39 (ABqd, *J*=10.8, 6.0 Hz, 2H), 2.35–2.28 (m, 1H), 2.23–2.14 (m, 2H), 1.94–1.80 (br s, 1H), 1.78–1.65 (m, 2H), 1.65–1.53 (m, 2H), 1.50–1.21 (m, 6H), 1.15–1.04 (m, 1H), 0.89 (d, *J*=6.8 Hz, 3H), 0.88 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 116.7, 81.3, 75.9, 68.2, 41.0, 39.2, 35.8, 35.7, 33.0, 30.3, 27.1, 26.8, 16.6, 13.9; MS ($^+$CI) *m*/*z* (relative intensity) 199 (M−$C_3H_5^+$, 100), 241 (M+H^+, 10); HRMS ($^+$ESI) calcd for $C_{15}H_{28}O_2Na^+$ (M+Na^+) 263.1982, found 263.1988.

4.10. Synthesis of (2*S*,2′*S*,3′*S*,5′*R*)-6-(5′-allyl-3′-methyltetrahydrofuran-2′-yl)-2-methylhexanoic acid (18)[5b]

To a solution of the alcohol **17** (335.0 mg, 1.4 mmol) in DMF (14 mL) was added 28 drops of water. Then, pyridinium dichromate (3.41 g, 9.0 mmol) was added and the resultant mixture was stirred overnight at room temperature.[24] The reaction mixture was directly transferred to a silica gel column followed by eluting with 25% EtOAc in PE to give the pure acid **18** (228.0 mg) and a mixed fraction with DMF and pyridine. The latter was dissolved in EtOAc and washed with 5% aqueous HCl for twice. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an additional 91.0 mg of the acid **18**. The acid **18** was obtained (319.0 mg, 90%) as a colorless oil. $[\alpha]_D^{20}$ +11.9 (*c* 4.3, CH_2Cl_2); lit.[5b] $[\alpha]_D^{23}$ +8.4 (*c* 4.5, CH_2Cl_2); R_f=0.25 (25% EtOAc in PE); IR (film) 3076, 2937, 1705, 1464, 1235, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84–5.74 (m, 1H), 5.07 (dd, *J*=17.6, 2.0 Hz, 1H), 5.03 (d, *J*=10.2 Hz, 1H), 4.11 (quintet, *J*=6.8 Hz, 1H), 3.87–3.82 (m, 1H), 2.49–2.40 (m, 1H), 2.37–2.29 (m, 1H), 2.27–2.14 (m, 2H), 1.80–1.63 (m, 3H), 1.53–1.22 (m, 7H), 1.16 (d, *J*=7.2 Hz, 3H), 0.89 (d, *J*=7.2 Hz, 3H) (The acidic proton is not seen.); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 135.0, 116.8, 81.3, 76.0, 40.9, 39.3, 39.2, 35.8, 33.5, 30.2, 27.3, 26.5, 16.8, 14.0; MS ($^-$ESI) *m*/*z* (relative intensity) 253 (M−H, 100), 254 (M, 11); HRMS ($^+$ESI) calcd for $C_{15}H_{26}O_3Na^+$ (M+Na^+) 277.1774, found 277.1776.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.070.

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