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A Carbohydrate-Based Synthesis of the C13–C22 Fragment of Amphidinolide X

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A facile carbohydrate-based route was developed for the synthesis of the tetrahydrofuran (C13–C22) fragment of amphidinolide X. Starting from L-sorbose, the key reactions followed include the stereoselective synthesis of a quaternary center at C1, Barton–McCombie deoxygenation at C2, Mitsunobu inversion at C3, and chain elongation by a Wittig reaction at C5.

Introduction

Amphidinolides are a unique class of biologically interesting secondary metabolites isolated from marine dinoflagellates of the genus *Amphidinium* sp.[1] To date, more than 30 amphidinolides have been isolated from this species which are symbionts of the Okinawan marine acoel flatworms, *Amphiscolops* sp.[2] These macrolides have a variety of backbone skeletons and different sizes of macrocyclic lactone rings (12 to 29 membered) that are endowed with *exo*-methylene groups, vicinal one-carbon branches, and 1,3-diene units. All of the amphidinolides exhibit potent cytotoxic properties against various cancer cell lines and thus have attracted great interest as challenging targets for total synthesis and for further biological studies.[3]

Amphidinolide X (**1**), a 16-membered cytotoxic macrodiolide (Figure 1), was isolated by Kobayashi and co-workers in 2003 from the laboratory-cultured dinoflagellates *Amphidinium* sp.[4] The detailed structure of **1**, including the disposition of the chiral centers, was elucidated on the basis of 1D and 2D spectroscopic data. Amphidinolide X is known to possess good cytotoxicity against murine lymphoma L1210 (IC_{50} = 0.6 μg mL^{-1}) and human epidermoid carcinoma KB cells (IC_{50} = 7.5 μg mL^{-1}) in vitro. Structurally, it has neither the characteristic *exo*-methylene group nor the 1,3-diene unit found in virtually all other members of this series. Moreover, it is the only naturally occurring macrodiolide known to date that consists of a diacid and a diol unit rather than of two hydroxy acid entities. Its promising toxicity, scarcity, and unique structural features have prompted many groups to view amphidinolide X as a synthesis target.

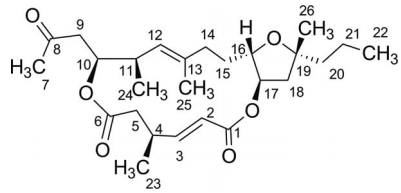

Figure 1. Amphidinolide X (**1**).

Fürstner et al. reported the first total synthesis of amphidinolide X.[5] Here, the main tetrahydrofuran fragment was constructed from a chiral allene by iron-catalyzed opening of propargyl epoxide and further assembly by silver nitrate catalyzed cyclization as a mixture of diastereomers in a ratio of 8:1. The target molecule was achieved by assembling the fragments by Suzuki cross-coupling and macrolactonization by using Yamaguchi conditions. Dai et al. also achieved the synthesis of the tetrahydrofuran fragment by an acid-catalyzed 5-*endo* ring-opening cyclization of the epoxide possessing a vinyl moiety and the total synthesis of amphidinolide X by formation of the C12–C13 trisubstituted double bond by ring-closing metathesis.[6] In parallel with our studies, Urpi and Vilarrasa reported the total synthesis of amphidinolide X by a silicon-tethered metathesis reaction.[7] It was envisaged that construction of the tetrahydrofuran fragment of **1** in a stereocontrolled manner remains central to the total synthesis of amphidinolide X. Synthetic studies toward the total synthesis of amphidinolides C, E, and W were previously reported by our group by using a carbohydrate-based approach.[8] As part of our ongoing research directed towards the synthesis of highly substituted tetrahydrofuran ring systems bearing natural products from carbohydrates,[9] we report here the synthesis of the tetrahydrofuran (C13–C22) fragment of amphidinolide X starting from L-sorbose.

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As amphidinolide X has two ester linkages along with two olefin functionalities forming the macrodiolide ring, the obvious sites of disconnection were at the C12–C13 and C1–O bonds, resulting in two building blocks: main tetrahydrofuran fragment **2** and left dicarbonyl entity fragment **3** (Figure 2). The critical carbon–carbon bond formation between fragment **2** and **3** (C12–C13 bond) was planned to proceed through a modified Julia olefination procedure.[10] The final cyclization to form the C1–O ester bond could be accomplished by using Yamaguchi lactonization.[11] To construct the 16-membered multifunctionalized macrolactone as the first target towards the total synthesis of amphidinolide X, fragment **2** (Figure 2) was chosen to permit the incorporation of the side chain at a later stage by using Wittig olefination. Key intermediate **4** was planned from **5** by reduction, deoxygenation, and inversion of the hydroxy center by using a Mitsunobu[12] inversion protocol, and **5** in turn by stereoselective installation of an allyl group by simultaneous stereocontrolled removal of the 1,2-isopropylidine protection from the deoxygenated derivative of sorbose diacetonide **6** (Figure 2).

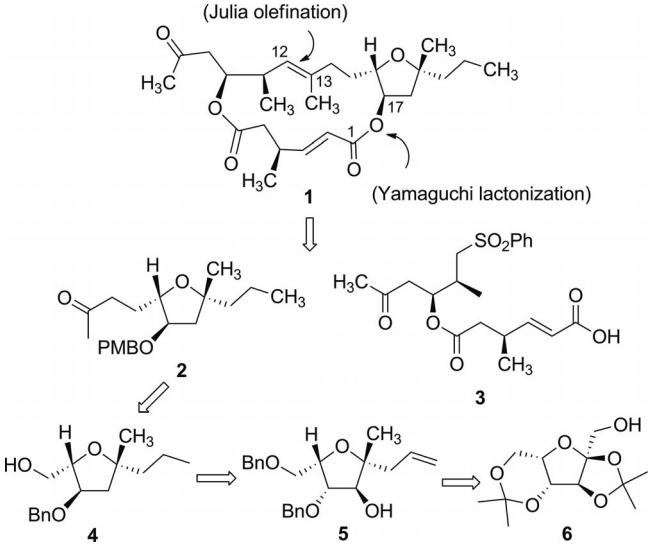
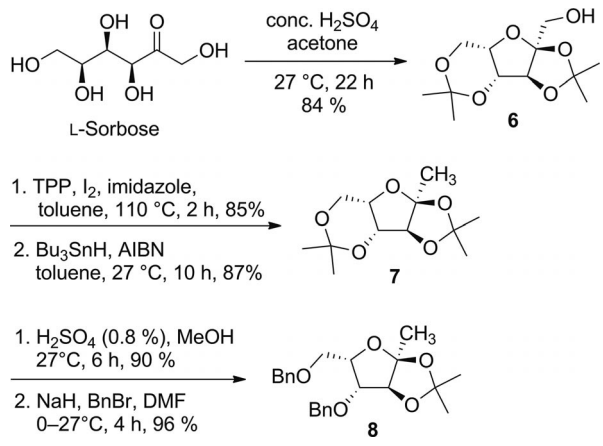


Figure 2. Retrosynthetic strategy for amphidinolide X.

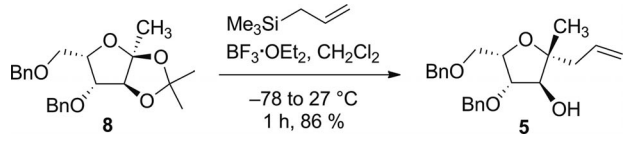
Results and Discussion

The synthesis of the tetrahydrofuran fragment began with the preparation of 2,3:4,6-di-*O*-isopropylidene-L-sorbose (**6**) by employing a literature procedure[13] (Scheme 1). Deoxygenation of **6** at C1 was carried out through a two-step halogenation and dehalogenation protocol. Sorbose diacetonide **6** was subjected to iodine, a stoichiometric amount of triphenylphosphane, and imidazole to afford the iodide in 85% yield, which was subsequently heated at reflux with tributyltin hydride in the presence of a catalytic amount of AIBN in toluene to furnish 1-deoxysorbose diacetonide **7** in 87% yield. Selective removal of the 4,6-isopropylidene protecting group, retaining the 2,3-isopropylidene functionality was achieved by using 0.8% H_2SO_4 in MeOH at room temperature.[14,15] The resulting free hydroxy groups were protected as their benzyl ethers by treatment with sodium hydride followed by benzyl bromide in DMF at ambient temperature to furnish dibenzyl derivative **8** in 96% yield.



Scheme 1. Synthesis of intermediate **8**.

Compound **8** was treated with allyl trimethylsilane and $BF_3{\cdot}OEt_2$ in dichloromethane at –78 °C and allowed gradually to reach room temperature to afford **5** with high stereoselectivity (≥98% *de*, Scheme 2). The structure of **5** is supported by spectroscopic data.



Scheme 2. Stereoselective construction of the quaternary center.

The stereochemistry of the newly generated stereocenter was confirmed by NOESY experiments. NOESY analysis of **5** showed a strong NOE between C1-Me and C4-H as well as between C1-Me and C3-H indicating their *cis* relationship, whereas C2-H showed an NOE with the C5 methylenic proton confirmed the *cis* relationship between C2-H and the C5 methylenic protons. There was no NOE between C1-Me and C2-H. All these observations confirmed the stereochemical assignment of **5** (Figure 3).

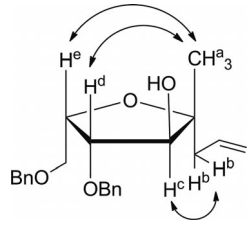


Figure 3. Key nuclear Overhauser effects of **5**.

The pronounced selectivity of the allylation reaction can be explained on the basis of the plausible mechanism depicted in Figure 4. The isopropylidine oxygen at C1 complexes with the Lewis acid and cleavage of the C1–O bond is assisted by the ring oxygen. It is known[16] that for stereo-

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selective C-glycosylation reactions of ribose derivatives, the C3 alkoxy group exerts the largest influence on selectivity leading to the 1,3-*cis* product. With the C3 alkoxy group having a strong tendency to be pseudoaxial and the C2 alkoxy group having a strong tendency to be pseudoequatorial, conformer A is strongly favored. The C4 alkyl group exerts no discernible influence on the conformational preference. Thus, the C1 methyl group and the C2 hydroxy group direct a *syn* conformation leading to the desired stereochemistry at the C1 quaternary center.

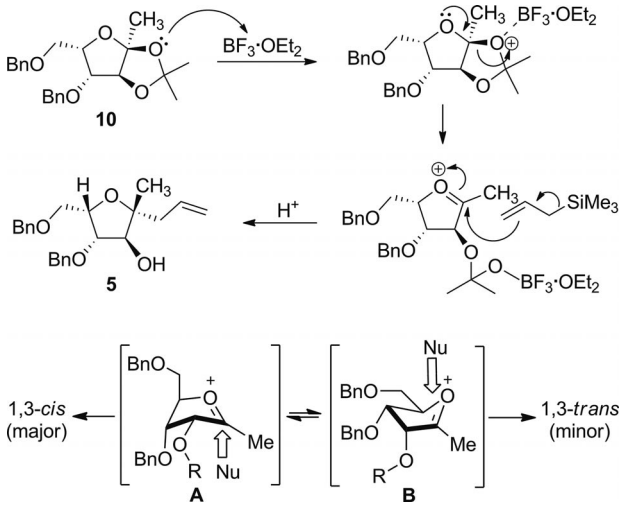


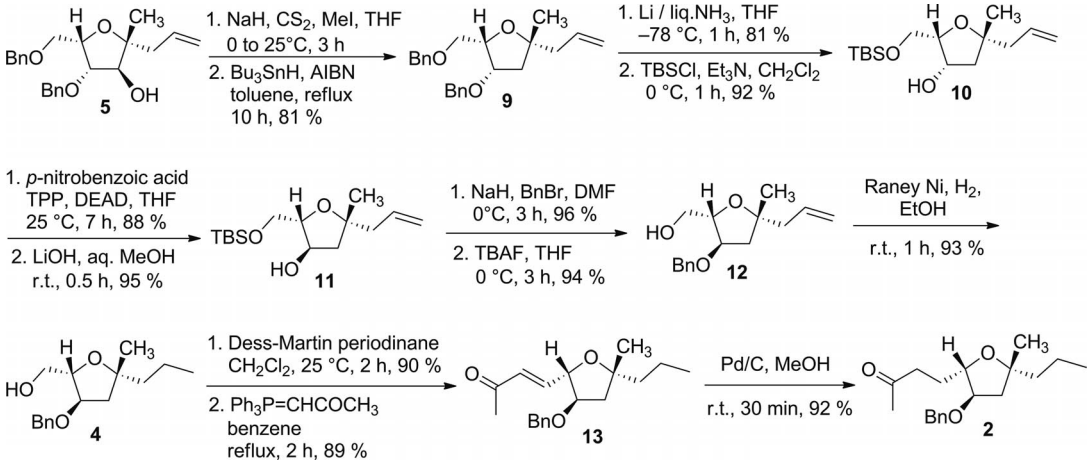
Figure 4. Plausible mechanism for establishment of the quaternary center.

With the quaternary center installed in a highly stereoselective manner, we then proceeded to the construction of the tetrahydrofuran fragment. The free hydroxy at C2 of **5** was deoxygenated under Barton–McCombie conditions.[17] Compound **5** was treated with NaH, carbon disulfide, and methyl iodide to obtain the xanthate derivative, which upon heating at reflux with nBu$_3$SnH and a catalytic amount of AIBN in toluene afforded deoxy derivative **9** in 81% yield over two steps. The next critical transformation was the inversion of the stereochemistry at C3 by a Mitsunobu protocol. For this purpose, the benzyl protecting group was removed by using lithium metal in liquid ammonia to obtain the diol, and selective protection of the primary hydroxy group as its silyl ether then afforded **10**. The requisite stereochemistry at C3 was achieved by applying Mitsunobu inversion conditions. Thus, compound **10** was treated with 4-nitrobenzoic acid in the presence of triphenylphosphane (TPP) and diethyl azodicarboxylate (DEAD) to afford the benzoate ester. Hydrolysis of the benzoate ester was achieved upon treatment with lithium hydroxide monohydrate in aqueous methanol to yield alcohol **11** in 84% yield over two steps.

The C3 hydroxy group was protected as its benzyl ether by using sodium hydride and benzyl bromide in DMF at 0 °C followed by removal of the silyl protecting group of the primary hydroxy with TBAF at 0 °C to afford alcohol **12** in 90% yield over two steps (Scheme 3). The terminal double bond was reduced with Raney Ni to obtain alcohol **4** in 93% yield, which was oxidized by using Dess–Martin periodinane.[18] Upon treatment with (acetylmethylene)triphenylphosphorane, the resulting aldehyde afforded unsaturated ketone **13** in 80% yield over two steps. Finally, hydrogenation of **13** with Pd/C furnished ketone **2** at room temperature in 92% yield. The structure of **2** was confirmed by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and mass spectrometry.

Conclusions

In summary, we have successfully accomplished the syntheses of the C13–C22 fragment with suitable protections for the projected total synthesis of amphidinolide X. Starting from L-sorbose, the tetrahydrofuran (C13–C22) fragment of amphidinolide X was synthesized in a highly stereoselective manner in 17 steps in 14.5% overall yield. The allylation and simultaneous installation of the quaternary center with correct stereochemistry of the tetrahydrofuran fragment was achieved with excellent diastereocontrol.



Scheme 3. Synthesis of the tetrahydrofuran fragment **2**.

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Experimental Section

General Remarks: Solvents were distilled following standard procedures before use. TLC was performed on precoated silica gel aluminum plates 60 F254. IR spectra were recorded with an FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a 200 MHz spectrometer with TMS as an internal standard. Mass spectra were obtained with a TSQ 70 mass spectrometer. Optical rotations were determined with a JASCO 370 digital polarimeter with a sodium light source. Elemental analyses were carried out with a CHNS-O analyzer.

1-Deoxy-2,3:4,6-di-*O*-isopropylidene-L-sorbofuranose (7): 2,3:4,6-Di-*O*-isopropylidene-L-sorbofura-nose (**6**; 20.0 g, 0.077 mol), triphenylphosphane (40.3 g, 153.8 mmol), I_2 (39.0 g, 0.154 mol), and imidazole (15.7 g, 0.231 mol) in toluene (300 mL) were heated at reflux for 2 h. Toluene was removed, and the residue was partitioned between water (100 mL) and ethyl acetate (150 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic phase was washed with aqueous $NaHCO_3$ (2 × 150 mL), aqueous $Na_2S_2O_3$ (2 × 150 mL), and brine (200 mL), dried with Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:3) to afford the iodide (24.0 g, 85%) as a light yellow syrup. This iodide (24.0 g, 0.065 mol) was dissolved in toluene (200 mL), and the solution was degassed with argon. AIBN (100 mg) and tri-*n*-butyltin hydride (26.0 mL, 0.098 mol) were added successively to the reaction mixture. The contents were heated under reflux for 10 h and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:9) to afford **7** (13.7 g, 87%) as a colorless liquid. $[\alpha]_D^{25}$ = –15.1 (*c* = 1.25, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.39 (s, 3 H), 1.44 (s, 3 H), 1.48 (s, 3 H), 1.72 (s, 3 H), 4.05 (m, 3 H), 4.22 (s, 1 H), 4.28 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5, 24.5, 26.2, 27.1, 28.9, 60.2, 71.9, 73.6, 87.2, 97.2, 110.8, 113.5 ppm. MS (ESI): *m*/*z* = 267 [M + Na]$^+$. $C_{12}H_{20}O_5$ (244.29): calcd. C 59.00, H 8.25; found C 58.79, H 8.67.

1-Deoxy-4-benzyloxy-5-(benzyloxymethyl)-2,3-*O*-isopropylidene-L-sorbofuranose (8): A solution of compound **7** (15.0 g, 61.4 mmol) and 0.8% aqueous H_2SO_4 (1 mL) in MeOH (150 mL) was stirred at room temperature for 6 h. The reaction mixture was neutralized with aqueous $NaHCO_3$ (100 mL), and methanol was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layer was dried with Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:1) to obtain the diol compound (11.3 g, 90%) as a colorless liquid. To a solution of the diol (10.0 g, 0.049 mol) in DMF (100 mL) was added NaH (60% w/w dispersion in paraffin oil, 4.9 g, 0.123 mol) portionwise over a period of 30 min at 0 °C. BnBr (14.5 mL, 0.123 mol) was then introduced into the reaction mixture dropwise. After stirring for 4 h, the reaction mixture was quenched with ice-cold water (110 mL) and extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with water (150 mL), brine (150 mL), dried (Na_2SO_4), and concentrated. The crude residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:9) to afford **8** (17.93 g, 96%) as a colorless liquid. $[\alpha]_D^{25}$ = +41.1 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.47 (s, 3 H), 1.65 (s, 3 H), 3.74 (dd, *J* = 3.7, 6.5 Hz, 2 H), 3.95 (d, *J* = 3.0 Hz, 1 H), 4.30 (s, 1 H), 4.42 (dd, *J* = 3.0, 6.2 Hz, 1 H), 4.50 (ABq, *J* = 2.4, 12.3 Hz, 2 H), 4.64 (ABq, *J* = 10.1, 12.0 Hz, 2 H), 7.28–7.33 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.7, 26.3, 27.2, 67.5, 71.8, 73.4, 79.5, 82.1, 84.9, 110.8, 113.2, 127.3 (2 C), 127.5, 127.6, 127.7 (2 C), 128.2 (2 C), 128.3 (2 C), 137.7, 138.0 ppm. MS (ESI): *m*/*z* = 407 [M + Na]$^+$. $C_{23}H_{28}O_5$ (384.47): calcd. C 71.85, H 7.34; found C 71.57, H 7.39.

(2*R*,3*S*,4*S*,5*S*)-2-Allyl-4-(benzyloxy)-5-(benzyloxymethyl)-2-methyltetrahydrofuran-3-ol (5): A solution of **8** (5.0 g, 13.0 mmol) and allyltrimethylsilane (12.4 mL, 78 mmol) in CH_2Cl_2 (40 mL) was cooled to –78 °C. Freshly distilled $BF_3{\cdot}OEt_2$ (2.5 mL, 20 mmol) was added dropwise, and the solution was allowed to attain ambient temperature. After completion of the reaction (monitored by TLC), the mixture was quenched with saturated $NaHCO_3$ solution (25 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether (2:9) to afford **5** (4.17 g, 86%) as a colorless liquid. $[\alpha]_D^{25}$ = –4.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.18 (s, 3 H), 1.70 (br. s, 1 H), 2.38 (d, *J* = 7.3 Hz, 2 H), 3.57 (dd, *J* = 6.5, 10.1 Hz, 1 H), 3.71 (dd, *J* = 4.7, 10.1 Hz, 1 H), 4.05 (d, *J* = 4.4 Hz, 1 H), 4.06 (s, 1 H), 4.31–4.34 (m, 1 H), 4.58 (ABq, *J* = 12.3, 17.2 Hz, 2 H), 4.61 (ABq, *J* = 11.7, 15.9 Hz, 2 H), 5.02–5.10 (m, 2 H), 5.73–5.94 (m, 1 H), 7.30–7.32 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.9, 44.8, 69.5, 72.4, 73.3, 75.9, 79.4, 82.4, 85.3, 118.0, 127.4 (2 C), 127.5, 127.6, 127.7 (2 C), 128.2 (2 C), 128.4 (2 C), 134.2, 138.0, 138.2 ppm. MS (ESI): *m*/*z* = 391 [M + Na]$^+$. $C_{23}H_{28}O_4$ (368.47): calcd. C 74.97, H 7.66; found C 74.56, H 8.26.

(2*R*,4*S*,5*S*)-2-Allyl-4-(benzyloxy)-5-(benzyloxymethyl)-2-methyltetrahydrofuran (9): To a solution of **5** (5.0 g, 13.5 mmol) in dry THF (50 mL) at 0 °C was added NaH (60% w/w dispersion in mineral oil, 0.8 g, 20.4 mmol) followed by carbon disulfide (1.6 mL, 20.4 mmol). After 20 min, methyl iodide (1.3 mL, 20.4 mmol) was added at the same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (30 mL). The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude xanthate derivative (5.2 g, 11.4 mmol) was dissolved in toluene (60 mL), and the solution was degassed with argon. AIBN (50 mg) and tri-*n*-butyltin hydride (4.6 mL, 17.1 mmol) were added to the reaction mixture. The reaction mixture was heated under reflux for 10 h and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:9) to afford **9** (3.45 g, 81%) as a colorless liquid. $[\alpha]_D^{25}$ = +41.9 (*c* = 1.20, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (s, 3 H), 1.75 (dd, *J* = 5.8, 13.2 Hz, 1 H), 2.11 (dd, *J* = 2.2, 13.2 Hz, 1 H), 2.40 (d, *J* = 6.6, Hz, 2 H), 3.66 (dd, *J* = 5.1, 9.5 Hz, 1 H), 3.78 (dd, *J* = 5.1, 9.5 Hz, 1 H), 4.11–4.21 (m, 2 H), 4.35–4.64 (m, 4 H), 5.00–5.08 (m, 2 H), 5.78–5.87 (m, 1 H), 7.27–7.32 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.5, 41.3, 46.6, 69.1, 70.8, 73.1, 79.7, 79.9, 81.8, 117.2, 127.0 (2 C), 127.2 (2 C), 127.5 (2 C), 128.0 (2 C), 128.1 (2 C), 134.9, 138.1, 138.2 ppm. MS (ESI): *m*/*z* = 375 [M + Na]$^+$. $C_{23}H_{28}O_3$ (352.47): calcd. C 78.38, H 8.01; found C 78.58, H 8.49.

(2*S*,3*S*,5*R*)-5-Allyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-5-methyltetrahydrofuran-3-ol (10): A solution of **9** (4.5 g, 12.8 mmol) in anhydrous THF (20 mL) was added to a solution of lithium (0.76 g, 128.0 mmol) in liquid NH_3 (50 mL) maintained at –78 °C. The reaction mixture was stirred for 1 h and quenched with solid NH_4Cl. The excess ammonia gas was allowed to evaporate, and then the resulting residue was taken up in ethyl acetate (75 mL), washed with water (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column

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chromatography (ethyl acetate/light petroleum ether, 4:1) to obtain the diol (1.8 g, 81%), which was used for the next step without further purification. TBDMSCl (1.7 g, 11.5 mmol) was added to a solution of the diol (1.8 g, 10.5 mmol) and triethylamine (2.2 mL, 15.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C and stirred for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:4) to afford **10** (2.8 g, 92%) as colorless liquid. $[\alpha]_D^{25}$ = +17.1 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.10 (2s, 6 H), 0.91 (s, 9 H), 0.92 (s, 1 H), 1.18 (s, 3 H), 1.93–2.05 (m, 2 H), 2.41 (d, *J* = 7.3 Hz, 2 H), 3.40 (d, *J* = 5.6 Hz, 1 H), 3.92–3.95 (m, 2 H), 4.48–4.58 (m, 1 H), 5.06–5.12 (m, 2 H), 5.73–5.94 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.5 (2 C), 18.3, 25.9 (3 C), 27.2, 44.2, 47.0, 64.6, 75.0, 82.5, 83.5, 117.8, 134.5 ppm. MS (ESI): *m*/*z* = 309 [M + Na]$^+$. $C_{15}H_{30}O_3Si$ (286.49): calcd. C 62.89, H 10.55; found C 62.19, H 11.34.

(2*S*,3*R*,5*R*)-5-Allyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-5-methyltetrahydrofuran-3-ol (11): To a solution of **10** (2.0 g, 7.0 mmol), TPP (3.7 g, 14.0 mmol), and *p*-nitrobenzoic acid (2.4 g, 14.0 mmol) in THF (23 mL) at 0 °C was added DEAD (2.5 mL, 17.5 mmol) dropwise. Stirring was continued at 0 °C for 1 h and then at room temperature for the next 6 h. The solvent was removed under reduced pressure, and the crude residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:9) to afford the ester (2.7 g, 88%). To a solution of the ester (2.7 g, 6.2 mmol) in moist methanol (27 mL) was added $LiOH·H_2O$ (945 mg, 24.8 mmol), and the reaction mixture was stirred at room temperature for 0.5 h and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:5) to furnish **11** (1.70 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$ = –6.5 (*c* = 1.35, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.08 (2 s, 6 H), 0.90 (s, 9 H), 1.34 (s, 3 H), 1.65 (s, 1 H), 1.72 (dd, *J* = 6.3, 12.9 Hz, 1 H), 2.14–2.25 (m, 3 H), 3.58 (dd, *J* = 2.7, 8.7 Hz, 1 H), 3.77–3.89 (m, 2 H), 4.21–4.31 (m, 1 H), 5.02–5.10 (m, 2 H), 5.70–5.91 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.4 (2 C), 18.0, 25.9 (3 C), 27.2, 44.3, 47.0, 64.6, 74.9, 82.4, 83.7, 117.7, 134.5 ppm. MS (ESI): *m*/*z* = 309 [M + Na]$^+$. $C_{15}H_{30}O_3Si$ (286.49): calcd. C 62.89, H 10.55; found C 62.82, H 11.18.

[(2*S*,3*R*,5*R*)-3-(Benzyloxy)-5-methyl-5-propyltetrahydrofuran-2-yl]-methanol (4): To an ice-cooled solution of **11** (1.4 g, 4.9 mmol) in anhydrous DMF (12 mL) was added NaH (60% w/w dispersion in mineral oil, 295 mg, 7.4 mmol) portionwise. Stirring was continued at the same temperature for 1 h. To the above stirred reaction mixture was added BnBr (0.7 mL, 5.9 mmol) dropwise at 0 °C. The reaction mixture was stirred at the same temperature for an additional 3 h. The reaction mixture was quenched by the addition of ice, diluted with water (25 mL), and extracted with ethyl acetate (3 × 40 mL). The combined organic layer was washed with brine (75 mL), dried (Na_2SO_4), and concentrated to afford the benzyl-protected compound. This benzyl derivative (1.8 g, 4.8 mmol) was taken up in THF (15 mL) and treated with TBAF (1 M in THF, 7.2 mL, 7.2 mmol). The reaction mixture was stirred for 3 h at 0 °C and then concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:3) to afford alcohol **12** (1.14 g, 90% over two steps). To a suspension of catalytic Raney nickel in EtOH (10 mL) was added a solution of **12** (0.9 g, 3.4 mmol) in EtOH (10 mL), and the mixture was stirred for 1 h under a hydrogen atmosphere. The reaction mixture was filtered through a plug of Celite and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:3) to afford **4** (0.84 g, 93%) as a colorless liquid. $[\alpha]_D^{25}$ = –34.4 (*c* = 0.95, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.3 Hz, 3 H), 1.29–1.37 (m, 2 H) 1.33 (s, 3 H), 1.46–1.52 (m, 2 H), 1.85 (dd, *J* = 3.8, 13.2 Hz, 1 H), 1.95 (dd, *J* = 7.3, 13.2 Hz, 1 H), 2.30 (s, 1 H), 3.55 (dd, *J* = 4.5, 11.5 Hz, 1 H), 3.71 (dd, *J* = 3.3, 11.5 Hz, 1 H), 3.98–4.02 (m, 1 H), 4.04–4.07 (m, 1 H), 4.48 (ABq, *J* = 11.5, 17.4 Hz, 2 H), 7.32–7.34 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.5, 17.8, 25.6, 42.8, 44.7, 63.1, 71.5, 80.6, 83.1, 83.6, 126.7, 127.3 (2 C), 128.2 (2 C), 138.1 ppm. MS (ESI): *m*/*z* = 287 [M + Na]$^+$. $C_{16}H_{24}O_3$ (264.36): calcd. C 72.69, H 9.15; found C 71.98, H 9.21.

4-[(2*S*,3*R*,5*R*)-3-(Benzyloxy)-5-methyl-5-propyltetrahydrofuran-2-yl]butan-2-one (2): To a stirred solution of **4** (1.0 g, 3.8 mmol) in anhydrous CH_2Cl_2 (20 mL) was added Dess–Martin periodinane (3.2 g, 7.6 mmol), and the mixture was stirred for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure at room temperature to obtain the aldehyde (0.89 g, 90%). A mixture of the aldehyde (0.89 g, 3.4 mmol) and (acetylmethylene)triphenylphosphorane (2.2 g, 6.8 mmol) was heated at reflux in benzene for 2 h. The solvent was evaporated to leave a residue, which was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:9) to afford **13** (0.91 g, 89%) as a colorless liquid. To a solution of **13** (0.91 g, 3.16 mmol) in MeOH (5 mL) was added 10% Pd/C (10 mg), and the mixture was stirred under a H_2 atmosphere at room temperature for 30 min. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:9) to give **2** (0.85 g, 92%) as a colorless liquid. $[\alpha]_D^{25}$ = –42.9 (*c* = 0.80, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2983, 1741, 1373, 1242, 1047 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.0 Hz, 3 H), 1.25–1.36 (m, 2 H), 1.28 (s, 3 H), 1.40–1.49 (m, 2 H), 1.64–1.82 (m, 2 H), 1.87–2.02 (m, 2 H), 2.12 (s, 3 H), 2.52 (dd, *J* = 6.2, 17.8 Hz, 1 H), 2.53 (d, *J* = 6.2 Hz, 1 H), 3.66–3.79 (m, 1 H), 3.90 (dt, *J* = 4.6, 8.5 Hz, 1 H), 4.50 (ABq, *J* = 11.8, 17.2 Hz, 2 H), 7.29–7.32 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.6, 17.8, 26.3, 28.4, 29.9, 40.1, 42.4, 45.2, 71.6, 81.4, 82.9, 84.0, 127.6 (3 C), 128.4 (2 C), 138.2, 208.7 ppm. MS (ESI): *m*/*z* = 304 [M + Na]$^+$. $C_{19}H_{28}O_3$ (304.43): calcd. C 74.96, H 9.27; found C 75.23, H 8.87.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra of all synthesized compounds and the NOESY spectrum of compound **5**.

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