Stereoselective Synthesis of the C1−C16 Fragment of the Purported Structure of Formosalide B

Srinivas Gajula, Aedula Vishnu V. Reddy, D. Prabhakar Reddy, Jhillu S. Yadav, and Debendra K. Mohapatra*

Cite This: ACS Omega 2020, 5, 10217−10224

ABSTRACT: The first stereoselective synthesis of the C1−C16 fragment possessing stereo-enriched fully substituted tetrahydropyran (THP) along with tetrahydrofuran (THF) rings of the proposed structure of formosalide B is described in 12 longest linear steps with 22% overall yield, starting from two cheap and commercially available1, 5-pentanediol and L-glutamic acid, following a convergent approach. The key steps involve in this synthesis are Horner−Wadsworth−Emmons reaction, Sharpless asymmetric dihydroxylation, and acid-mediated ketalization to assemble the substituted THP ring, one-pot Sharpless dihydroxylation−SN2-type cyclization, and Wittig homologation to construct the THF derivative.

INTRODUCTION

Marine dinoflagellates have been proven to be important sources for isolation of a diverse range of biologically active natural products, which intrigue chemists of their complexity in structures.1 Few representative bioactive molecules from dinoflagellates are okadaic acids, brevetoxins, and amphidinolides with unique structures. An okadaic acid, a polyether isolated from the black sponge Halichondria okadai, is a potent inhibitor for protein phosphatase PP1 and PP2A;2 brevetoxins, cyclic polyethers produced by Karenia brevis, are activators for voltage-sensitive sodium channels;3 amphidinolides are complex macrolides isolated from Amphidinium sp., which have exhibited strong cytotoxic activities against tumor cell lines.4

Recently, Lu’s research group isolated formosalides A (1) and B (2) from the cultured marine dinoflagellate Procorcentrum sp., which was extracted from the wash-off epiphytes of sea woods at South bay, southern Taiwan (Figure 1).5 Formosalides A (1) and B (2) are 17-membered ring macrolides consist of a substituted tetrahydropyran (THP) ring along with a tetrahydrofuran (THF) ring and a C-14 linear side chain attached to a ring at C16 having four cis-olefins. The gross structure and relative configuration of formosalides A and B were assigned based on the 1H NMR coupling constants and extensive 2D NMR studies (Figure 1). Only the relative configurations of the tetrahydrofuran, tetrahydropyran, and C16−C18 moieties have been determined by NMR analysis. However, the relative configuration between these moieties and the total absolute configuration have not been identified yet. Formosalides A and B also have been shown to exhibit good cytotoxicity activity against CCRF-CEM human T-cell acute lymphoblastic leukemia cells and/or DLD-1 human colon adenocarcinoma cells in vitro. (LD50 values of A: 0.54 and >40 μg/mL; those of B: 0.43 and 2.73 μg/mL, respectively).

In continuation of our research efforts toward the total syntheses of biologically active natural products that contain THF and THP rings,6 herein, we report a simple, efficient, and convergent synthetic strategy for the synthesis of the C1−C16 fragment of the proposed structure of formosalide B (2). It is worth mentioning here that even though the molecule was isolated in 2009, till now, no synthesis or synthetic approach is reported for formosalides A and B.

According to our retrosynthetic analysis, the THP−THF core 3 of formosalide B (C1−C16 fragment) could be synthesized by acid-catalyzed ketalization of diol, which could be derived via Sharpless asymmetric dihydroxylation of enone 4. The key intermediate 4 would be accessed from the
Horner–Wadsworth–Emmons (HWE) reaction of phosphonate 5 and the aldehyde 6. The THF ring of phosphonate 5 could be derived from the well-known lactone 7 via tandem Sharpless asymmetric dihydroxylation (SAD)–SN2 cyclization on \( \alpha,\beta \)-unsaturated ester in a complete stereospecific manner. The aldehyde 6 from commercially available 1,5-pentanediol (8) via Wittig olefination, reduction of \( \alpha,\beta \)-unsaturated ester, and Sharpless asymmetric epoxidation is shown in Scheme 1.

Scheme 1. Retrosynthetic Plan Featuring SAD/Ketalization and HWE Reaction

**RESULTS AND DISCUSSION**

The synthesis of phosphonate fragment 5 was started from the well-known TBDPS ether derivative 7’ of \((S)-5\)-hydroxymethyl-2,3-dihydrofuran-2(3H)-one, which was readily prepared from L-glutamic acid (Scheme 2). The lactone 7 was reduced with DIBAL-H at \(-78^\circ\text{C}\), and the resulting hemiacetal was immediately allowed to undergo Wittig olefination using (ethoxycarbonyl-methylene)triphenyl phosphonate to provide the corresponding \( \delta \)-hydroxy \( \alpha,\beta \)-unsaturated ester as a mixture of geometrical isomers (95% of \( E \)-isomer confirmed by \( 1^H \) NMR). The minor (\( Z \))-isomer was then easily separated from the major (\( E \))-isomer 9 by column chromatography.

The hydroxyl group of 9 was then converted into its mesylate ester 10 with MeSO\(_2\)Cl, Et\(_3\)N, and DMAP (catalytic) in CH\(_2\)Cl\(_2\). The mesylate ester (plays dual role) can be used as a protecting group and a leaving group at the next stage of the synthesis. The mesylate derivative 10 was subjected to Sharpless asymmetric dihydroxylation\(^9,10\) (Scheme 2) with ligand hydroquinidine-1,4-phthalazinediyldiether \( [(\text{DHQD})_2\text{PHAL}] \), K\(_2\)Fe(CN)\(_6\), K\(_2\)CO\(_3\), MeSO\(_2\)NH\(_2\), and OsO\(_4\) in \( \text{i-PrOH/H}_2\text{O} \) (1:1) for 24 h to afford the trans-tetrahydrofuran 11 in 88% yield. The reaction proceeded via asymmetric dihydroxylation followed by intramolecular \( S_N2 \) displacement in one pot to result in the trans-fused THF ring with excellent stereoselectivity (no traces of the other isomer was detectable by NMR), as shown in Scheme 2. The ester functionality of 11 was reduced with LiBH\(_4\) to obtain the diol 12 in 87% yield. Oxidative cleavage of diol with NaIO\(_4\)\(^11\) followed by Wittig olefination of the corresponding aldehyde 13 furnished \( \alpha,\beta \)-unsaturated ester 14 in 80% yield over two steps. Ester 14 was then subjected to hydrogenation with the Pd/C catalyst in ethyl acetate under a hydrogen atmosphere to furnish the saturated ester 15 in quantitative yield. Nucleophilic addition of the lithiated derivative of dimethyl methyl phosphonate on ester 15 furnished the required \( \beta \)-keto phosphonate 5 in 90% yield (Scheme 2).

The synthesis of aldehyde 6 commenced from the known epoxy alcohol 16,\(^12\) which was prepared from commercially available 1,5-pentane diol (8) in five steps with 60% overall yield. Regioselective epoxide opening proceeded smoothly after treatment of the epoxy alcohol 16 with lithium dimethylcuprate (Me\(_2\)CuLi) to afford 1,3-diol accompanied by the undesired 1,2-diol (6:1). The minor isomer 1,2-diol was readily removed by treating the mixture with sodium periodate to obtain pure 1,3-diol 17 in 75% yield possessing the anti-stereochemistry. Protection of the primary and secondary alcohols as bis-TBS ether 18 followed by selective deprotection of primary silyl ether with PPTS in methanol provided primary alcohol 19, which upon oxidation with Dess–Martin periodinane\(^13\) afforded the required aldehyde fragment 6 in 73% yield over three steps (Scheme 3).

After having the phosphonate 5 and aldehyde 6 in hand, we planned to conduct an experiment to couple both the fragments to achieve the THP ring. Accordingly, phosphonate 5 and aldehyde 6 were coupled under Horner–Wadsworth–Emmons conditions using LiCl and DIPEA in acetonitrile to furnish the enone 4 in 91% yield with \( E \)-geometry as the sole product. Dihydroxylation of the enone 4 using the Sharpless
ligand (DHQD)$_2$PHAL afforded the diol 20 in 80% yield with a diastereomeric ratio of 9:1. The low reactivity of the double bond in 20 required a longer reaction time at room temperature. The undesired minor isomer during the dihydroxylation reaction was separated by silica gel column chromatography. Finally, acid-mediated ketalization of diol 20 with PPTS in MeOH smoothly gave the fully functionalized THF–THP core structure 3 in 82% yield (Scheme 4).

2,6-syn-geometry in the THF ring was expected to have the minimum dipole–dipole interaction compared to the 2,6-trans-geometry. The 2,6-syn-geometry was further assigned by the help of the NOESY experiment (Figure 2).

The structure of C1–C16 fragment 3 was established by $^1$H, $^{13}$C, and 2D NMR data. The relative stereochemistry assignments of fragment 3 were made with the aid of TOCSY and NOESY experiments. The observation of NOE between H9 and H11, H10 and H12, H3 and H8, and H12 and H33 supported the relative stereochemistry of substituted THP and THF compound 3, which completes the synthesis of the C1–C16 fragment of the proposed structure of formosalide B (Figure 2).

CONCLUSIONS

In summary, we have developed an efficient and convergent stereoselective route for the synthesis of the C1–C16 fragment of the proposed formosalide B, a cytotoxic 17-membered ring macrolide, which consists of stereo-enriched substituted THP and THF rings. Our strategy is flexible and operationally simple, and we strongly believe that the synthetic strategy described in the manuscript is robust and will allow the completion of the total synthesis of formosalides A and B as well as other biologically significant similar THP and THF ring-containing natural products.

EXPERIMENTAL SECTION

General Information. Experiments that required an inert atmosphere were carried out under argon in flame-dried glassware. THF was freshly distilled over sodium/benzophenone and transferred via a syringe. Dichloromethane was freshly distilled from CaH$_2$. Tertiary amines were freshly distilled over KOH. Commercially available reagents were used as received. Unless detailed otherwise, “workup” means pouring the reaction mixture into brine followed by extraction with the solvent indicated in parentheses. If the reaction medium was acidic (basic), additional washing with saturated aqueous NaHCO$_3$ solution (saturated aqueous NH$_4$Cl solutions) was performed. Washing with brine, drying over anhydrous Na$_2$SO$_4$, and evaporating the solvent under reduced pressure followed by chromatography on a silica gel column (60–120 mesh) with the indicated eluent furnished the corresponding products. The solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings were incorporated to the main organic layer.

$^1$H and $^{13}$C NMR chemical shifts (δ) are reported in ppm, and coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra were run by the electron impact mode (ESIMS, 70 eV) or by the FAB mode (m-nitrobenzyl alcohol matrix) using an orbitrap mass analyzer. IR data were measured with oily films on NaCl plates (oils) or KBr pellets (solids). Specific optical rotations [α]$_D$ are given in 10$^{-1}$ deg cm$^2$ g$^{-1}$ and were measured at 25 °C or otherwise mentioned. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, and br = broad.

(S)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-dihydrofuran-2(3H)-one (7). To a stirred solution of (S)-5-(hydroxymethyl)dihydrofuran-2(3H)-one (2.0 g, 17.24 mmol) in CH$_2$Cl$_2$ (60 mL) under a nitrogen atmosphere was added imidazole (2.3 g, 34.48 mmol) followed by tert-butyldiphenylchlorosilane (5.6 g, 20.68 mmol) at 0 °C and allowed to stir for...
30 min. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (50 mL) and diluted with CH₂Cl₂ (100 mL), and the organic layer was separated. The organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to obtain the crude product that on purification by silica gel column chromatography (ethyl acetate/hexane = 1:19) furnished the desired lactone 7 (5.42 g, 89%), [α]D²⁵ + 28.7 (c 0.9, CHCl₃); lit.⁷⁴ [α]D + 28.95 (c 2.0, CHCl₃). [1H NMR (400 MHz, CDCl₃): δ 7.70–7.63 (m, 4 H), 7.47–7.65 (m, 6 H), 4.62–4.57 (m, 1 H), 3.88 (dd, J = 11.4, 3.4 Hz, 1 H), 3.69 (dd, J = 11.4, 3.4 Hz, 1 H), 2.71–2.63 (m, 1 H), 2.55–2.47 (m, 1 H), 2.33–2.18 (m, 2 H), 2.06 (s, 9 H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 177.4, 135.6, 135.5, 129.9, 127.8, 79.9, 65.5, 28.5, 26.7, 23.6, 19.2 ppm; HRMS (ESI): m/z calcd for C₂₁H₂₆O₃Si [M + Na]⁺, 377.1568.]

To a stirred solution of lactone 7 (4.5 g, 78 mmol) in CH₂Cl₂ (50 mL) at room temperature, after stirring for 4 h at 100 °C the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to give 9 (4.43 g, 82% over two steps). [α]D²⁵ + 6.07 (c 1.8, CHCl₃); IR (KBr): ν max 3427, 2978, 1716, 1445, 1151, 1039, 922 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.67–7.63 (m, 4 H), 7.45–7.36 (m, 6 H), 6.94 (dt, J = 13.8, 7.0 Hz, 1 H), 5.81 (dt, J = 17.2, 3.2 Hz, 1 H), 4.18 (q, J = 7.2 Hz, 2 H), 3.75–3.68 (m, 1 H), 3.65 (dd, J = 10.2, 3.6 Hz, 1 H), 3.49 (dd, J = 10.2, 7.2 Hz, 1 H), 2.49 (d, J = 3.7 Hz, 1 H), 2.40–2.19 (m, 2 H), 1.66–1.46 (m, 2 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.07 (s, 9 H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 166.6, 148.5, 135.5, 133.0, 130.0, 127.8, 121.6, 71.0, 67.8, 60.2, 31.1, 28.2, 26.8, 19.2, 14.2 ppm; HRMS (ESI): m/z calcd for C₁₉H₁₆O₅Si [M + Na]⁺, 423.1129; found, 423.1124.

(5)-(Ethyl-7-((tert-butylidiphenylsilyl)oxy)-6-hydroxy-hept-2-enoate (9). To a stirred solution of lactone 7 (4.5 g, 12.71 mmol) in CH₂Cl₂ (50 mL) at −78 °C under a nitrogen atmosphere, DIBAL-H (9.98 mL, 1.4 M in toluene, 13.98 mmol) was slowly added over a period of 15 min. After 30 min of stirring at the same temperature (TLC), the reaction was quenched by slow addition of saturated sodium potassium tartrate solution (50 mL), diluted with CH₂Cl₂ (50 mL), and allowed to stir at room temperature for another 2 h to get clear two separated layers. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (2 × 80 mL). The combined organic layer was dissolved in toluene (100 mL) and was added to ethoxy carbonylmethylenetriphenylphosphorane (8.84 g, 25.42 mmol) at room temperature. After stirring for 4 h at 100 °C, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to give 10 (3.8 g, 75.3 mmol, 1.0 equiv) in 1:1 t-BuOH/H₂O (100 mL) was stirred for 30 min at room temperature. This mixture was slowly poured into 4 °C solution of 10 (3.8 g, 75.3 mmol, 1.0 equiv) in t-BuOH/H₂O (500 mL). The reaction was stirred at 4 °C for 24 h. After completion of the reaction, solid Na₂SO₄ (10 g) was added and the mixture was stirred for 1 h while warming to room temperature (color change from orange to dark green). After phase separation, the aqueous layer was extracted with ethyl acetate (5 × 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give the crude product that was purified by silica gel column chromatography (ethyl acetate/hexane = 1:1) to give 11 (2.93 g, 88%), [α]D²⁵ + 8.3 (c 1.6, CHCl₃); IR (KBr): ν max 3477, 2931, 2858, 1739, 1110, 704 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.73–7.60 (m, 4 H), 7.46–7.34 (m, 6 H), 4.37 (dt, J = 13.9, 7.1 Hz, 1 H), 4.43–4.16 (m, 3 H), 4.07 (dd, J = 8.1, 2.0 Hz, 1 H), 3.63 (dq, J = 10.6, 4.6 Hz, 2 H), 2.94 (d, J = 8.2 Hz, 1 H), 2.13–2.20 (m, 3 H), 1.98–1.86 (m, 1 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.04 (s, 9 H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 173.0, 135.6, 135.5, 134.8, 133.6, 133.5, 129.6, 129.5, 127.6, 127.6, 80.8, 80.0, 72.5, 66.2, 61.6, 28.1, 27.8, 26.7, 19.2, 14.1 ppm; HRMS (ESI): m/z calcd for C₂₅H₃₄O₅Si [M + Na]⁺, 465.2086; found, 465.2085.

(R)-1-((2R,5R)-5-(((tert-butylidiphenylsilyl)oxy)-methyl)tetrahydrofuran-2-yl)-1,2-diol (12). To a solution of ester 11 (2.5 g, 5.65 mmol) in diethyl ether (50 mL), LiBH₄ (184 mg, 8.48 mmol) was added at 0 °C in a single portion. MeOH (5 mL) was added to the above reaction mixture at the same temperature. The above reaction mixture was stirred for additional 2 h at room temperature. After completion of reaction (TLC), it was quenched with aqueous NaHCO₃ solution (20 mL) and extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were dried over Na₂SO₄ and evaporated under reduced pressure to give the crude product that was purified by silica gel column chromatography (ethyl acetate/hexane = 1:1) to furnish diol 12 (1.96 g, 87%) as a colorless viscous liquid [α]D²⁵ + 4.0 (c 1.3, CHCl₃); IR (KBr): ν max 3421, 2921, 2858, 1427, 1110, 703 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.70–7.66 (m, 4 H), 7.45–7.35 (m, 6 H), 4.18–4.09 (m, 1 H), 4.03, 3.97 (m, 1 H), 3.72–3.60 (m, 4 H), 3.53 (q, J = 4.4 Hz, 1 H), 2.72 (br s, 1 H), 2.58 (br s, 1 H), 2.03–1.76 (m, 4 H), 1.05 (s, 9 H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 135.6, 133.6, 133.5, 129.6, 127.6, 80.7, 80.2, 72.8, 66.3, 64.9, 28.1, 27.9, 26.8, 19.2 ppm; HRMS (ESI): m/z calcd for C₂₃H₂₄O₅Si [M + Na]⁺, 423.162; found, 423.1620.
(2R,5R)-5-((tert-Butyldiphenylsilyl)oxy)methyl)-tetrahydrofuran-2-carbaldehyde (13). To the solution of 12 (1.4 g, 3.5 mmol) in CH₂Cl₂ (80 mL), NaO₂-silica (35 g) was added at 0 °C. The reaction was stirred for 30 min at room temperature. After completion of reaction (TLC), the reaction mixture was filtered and washed with CH₂Cl₂ (2 × 30 mL). The resulting solution was concentrated under reduced pressure to provide the crude product that upon silica gel column chromatography purification (ethyl acetate/hexane = 1:5), afforded 13 (0.828 g, 90%) as a colorless viscous liquid. [α]D25 + 3.41 (c 3.45, CHCl₃); IR (KBr): νmax 2933, 2859, 1711, 1187, 1110, 704 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 9.66 (d, J = 1.67 Hz, 1H), 7.70–7.76 (m, 4H), 7.44–7.53 (m, 6H), 4.36–4.32 (m, 1H), 4.29–4.22 (m, 1H), 3.71 (dq, J = 10.8, 4.4 Hz, 2H), 2.24–2.16 (m, 1H), 2.01–1.90 (m, 3H), 1.06 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 202.8, 135.5, 133.3, 133.2, 129.7, 127.6, 83.3, 81.0, 65.9, 27.3, 27.2, 26.8, 19.2 ppm; HRMS (ESI): m/z calcd for C₂₆H₃₉O₃Si [M + Na]+, 436.2146; found, 436.2155.

(E)-Ethyl-3-(2R,5R)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-tetrahydrofuran-2-yl)acetate (14). To a stirred suspension of ethyl 2-(triphenylphosphoranylidene)acetate (1.5 g, 4.34 mmol) in toluene (50 mL) was added a solution of methyl tetrahydrofuran-2-yl)acrylate (14). The mixture was cooled to room temperature, allowed to stir for another 12 h at the same temperature. The reaction mass was cooled to room temperature and poured into a small Celite pad and washed with ethyl acetate (2 × 20 mL). After completion of the reaction (TLC), the mixture was quenched with saturated NH₄Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic layers were washed with brine (50 mL) and dried over Na₂SO₄. The organic layer was concentrated under reduced pressure to obtain the crude product that was then purified by column chromatography over silica gel column chromatography (ethyl acetate/hexane = 1:1), afforded the desired 5 (428 mg, 90%) as a colorless liquid. [α]D25 + 4.0 (c 1.0, CHCl₃); IR (KBr): νmax 2933, 2859, 1716, 1109, 1034, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.70–7.65 (m, 4H), 7.44–7.35 (m, 6H), 6.12–5.05 (m, 1H), 3.76–3.65–3.58 (m, 2H), 3.16–3.04 (m, 2H), 2.80–2.61 (m, 2H), 2.05–1.95 (m, 2H), 1.85–1.70 (m, 3H), 1.55–1.46 (m, 1H), 1.05 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 201.7, 201.7, 135.6, 133.7, 129.5, 127.6, 78.9, 78.3, 66.5, 53.0, 52.9, 41.8, 40.9, 40.7, 31.7, 29.5, 28, 26.8, 19.2 ppm; HRMS (ESI): m/z calcd for C₉₃H₄₈O₃Si [M + Na]+, 536.2591; found, 536.2598.

Dimethyl-4-((2R,5R)-5-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)oxobutyl)benzene (17). To a stirred solution of dimethylmethylenephosphonate (570 mg, 4.60 mmol) in THF (30 mL), n-BuLi (1.7 mL, 4.29 mmol, 2.5 M in hexane) was slowly added at −78 °C under an argon atmosphere and allowed to slowly warm to 0 °C. After 1 h, the reaction mixture was again cooled to −78 °C, and the solution of ester 15 (450 mg, 1.02 mmol) in THF (30 mL) was slowly added and stirred at the same temperature for 1 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH₄Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic layers were washed with brine (50 mL) and dried over Na₂SO₄. The organic layer was concentrated under reduced pressure to obtain the crude mass that on purification by silica gel column chromatography (ethyl acetate/hexane = 1:1), afforded the desired 5 (428 mg, 90%) as a colorless liquid. [α]D25 + 4.0 (c 1.0, CHCl₃); IR (KBr): νmax 2933, 2859, 1716, 1109, 1034, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.70–7.65 (m, 4H), 7.44–7.35 (m, 6H), 6.12–5.05 (m, 1H), 3.76–3.65–3.58 (m, 2H), 3.16–3.04 (m, 2H), 2.80–2.61 (m, 2H), 2.05–1.95 (m, 2H), 1.85–1.70 (m, 3H), 1.55–1.46 (m, 1H), 1.05 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 201.7, 201.7, 135.6, 133.7, 129.5, 127.6, 78.9, 78.3, 66.5, 53.0, 52.9, 41.8, 40.9, 40.7, 31.7, 29.5, 28, 26.8, 19.2 ppm; HRMS (ESI): m/z calcd for C₉₃H₄₈O₃Si [M + Na]+, 536.2591; found, 536.2598.
extracted with CH₂Cl₂ (2 × 40 mL). The combined organic layer was washed with brine (70 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain the crude product that on purification by silica gel column chromatography (ethyl acetate/hexane = 1:19), furnished 18 (1.97 g, 91%). [α]D 25 + 6.9 (c 1.6, CHCl₃); IR (KBr): νmax 2934, 2857, 1515, 1209, 1094, 837, 772 cm⁻¹; 1H NMR (500 MHz, CDCl₃): δ 7.26 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.69 (q, J = 4.6 Hz, 1H), 3.55 (dd, J = 10.0, 6.5 Hz, 1H), 3.46-3.37 (m, 3H), 1.88-1.75 (m, 1H), 1.64-1.24 (m, 6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.83 (d, J = 7.0 Hz, 3H), 0.03 (s, 12H) ppm; 13C NMR (125 MHz, CDCl₃): δ 159.0, 130.8, 129.2, 113.7, 73.1, 72.5, 70.2, 65.2, 55.3, 40.9, 32.4, 30.0, 25.9, 21.8, 18.3, 18.1, 12.2, -4.4, -4.6, -5.4, -5.5 ppm; HRMS (ESI): m/z calcd for C₂₁H₂₃O₅Si [M + Na]+, 528.3898; found, 528.3902.

(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2-(ethylmethyl-1ol (19). To a stirred solution of 18 (1.6 g, 3.13 mmol) in CH₂Cl₂ (40 mL) and MeOH (40 mL), pyridinium p-toluenesulfonate (78 mg, 0.31 mmol) was added at 0 °C. The reaction was stirred for 6 h at the same temperature. Triethylamine (3 mL) was added to the reaction mixture and concentrated under reduced pressure to get the crude product that was purified by silica gel column chromatography (ethyl acetate/hexane = 1:9) to furnish 19 (1.1 g, 90%) as a colorless liquid. [α]D 25 + 5.3 (c 0.51 CHCl₃); IR (KBr): νmax 3447, 2932, 2857, 1513, 1249, 772 cm⁻¹; 1H NMR (500 MHz, CDCl₃): δ 7.25 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.34 (s, 2H), 3.80 (s, 3H), 3.67 (dd, J = 10.8, 3.8 Hz, 1H), 3.69 (dd, J = 11.13, 5.18 Hz, 1H), 3.52 (dd, J = 10.8, 5.2 Hz, 1H), 3.44 (dt, J = 6.4, 1.7 Hz, 2H), 1.76 (m, 1H), 1.63-1.50 (m, 4H), 1.37 (q, J = 7.9 Hz, 2H), 0.99 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; 13C NMR (75 MHz, CDCl₃): δ 151.9, 130.6, 129.2, 113.7, 77.2, 72.6, 69.9, 65.3, 55.2, 37.7, 34.6, 29.9, 25.8, 21.6, 18.0, 14.6, -4.3, -4.8 ppm; HRMS (ESI): m/z calcd for C₁₉H₂₇O₅Si [M + Na]+, 419.2594; found, 419.2581.

(2S,5R)-3-(tert-Butyldimethylsilyl)oxy)-7-(4-methoxybenzyl)oxy)-2-methylpentanal (6). To a solution of alcohol 19 (0.9 g, 2.27 mmol) in CH₂Cl₂ (25 mL), NaHCO₃ (0.381 g, 4.54 mL) and Dess–Martin periodinane (1.92 g, 4.54 mmol) were added at 0 °C under a nitrogen atmosphere and was stirred for 2 h at room temperature. After complete conversion of the starting material (monitored by TLC), the reaction was quenched with water (20 mL) and diluted with CH₂Cl₂ (25 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get the crude product that was passed through silica gel column chromatography (ethyl acetate/hexane = 1:19) to furnish 20 (0.157 g, 0.303 mmol) in MeCN (15 mL) was added DIPEA (39 mg, 0.303 mmol) at 0 °C under a nitrogen atmosphere. LiCl (13 mg, 0.303 mmol) followed by aldehyde 6 (120 mg, 0.303 mmol) was slowly added to the reaction mixture and stirred at the same temperature for 1 h. The reaction was allowed to warm to room temperature, and stirring was then continued for 8 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH₄Cl (15 mL) and diluted with ethyl acetate (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to provide the crude product that was purified by silica gel column chromatography (ethyl acetate/hexane = 1:8), furnished the desired ketone 4 (0.216 g, 91%) as a colorless liquid. [α]D 25 + 4.6 (c 1.0, CHCl₃); IR (KBr): νmax 2931, 2857, 1669, 1249, 1106, 701 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 7.71–7.65 (m, 4H), 7.44–7.33 (m, 6H), 7.25 (d, J = 8.55 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.82 (dd, J = 16.0, 7.8 Hz, 1H), 6.07 (dd, J = 16.0, 0.9 Hz, 1H), 4.41 (s, 2H), 4.15–4.08 (m, 1H), 3.99–3.91 (m, 1H), 3.79 (s, 3H), 3.68–3.57 (m, 3H), 3.45–3.37 (m, 2H), 2.78–2.68 (m, 1H), 2.64–2.54 (m, 1H), 2.49–2.40 (m, 1H), 2.06–1.96 (m, 2H), 1.88–1.70 (m, 3H), 1.60–1.48 (m, 3H), 1.48–1.24 (m, 4H), 1.05 (s, 9H), 1.04 (d, J = 0.9 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H) ppm; 13C NMR (125 MHz, CDCl₃): δ 200.3, 159.1, 149.1, 135.6, 133.7, 130.7, 130.2, 129.5, 129.2, 127.6, 113.7, 78.9, 78.7, 75.3, 72.5, 69.9, 66.5, 52.2, 41.9, 36.7, 34.1, 31.8, 29.9, 28.9, 26.8, 25.9, 22.1, 19.2, 18.1, 15.4, −4.3, −4.5 ppm; HRMS (ESI): m/z calcd for C₄₈H₆₄O₁₃Si [M + Na]+, 804.5049; found, 804.5066.
as a colorless liquid. Pyridinium triethylamine (0.5 mL) was added and concentrated under room temperature. After completion of the reaction (TLC), furnish the C1 silica gel chromatography (ethyl acetate/hexane = 3:7) to

\( (2R,3S,4R,5R,6S) - 2 - (22R,5R) - 5 - (1\text{ tert-Butyldiphenylsilylxylo)methyl})\text{tetrahydrofuran-2-yl-ethyl}) - 2\text{methoxy-6 - (4\text{-methoxybenzylxylo})propyl})\text{5-methyltetrahydro-2\text{-pyran-3,4-diol }} (3).\) To the solution of keto diol (20 (60 mg, 0.073 mmol) in MeOH (20 mL), pyridinium p-toluenesulfonate (1.8 mg, 0.0073 mmol) was added at 0 °C. The resulting solution was stirred for 12 h at room temperature. After completion of the reaction (TLC), triethylamine (0.5 mL) was added and concentrated under reduced pressure to give the crude residue that was purified by silica gel chromatography (ethyl acetate/hexane : 3:7) to furnish the C16 fragment of formosalide (500 MHz, CDCl3): max 3424, 2933, 2859, 1513, 1428, 1112, 705 cm⁻¹. δ 3.64 (dd, J = 4.8, 0.9 Hz, 2H), 3.46 (dd, J = 6.6 Hz, 3H) ppm; 13C NMR (125 MHz, CDCl3): 7.25 (d, J = 7.5 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.43 (s, 2H), 4.19–4.09 (m, 1H), 3.95–3.88 (m, 1H), 3.79 (s, 3H), 3.64 (dd, J = 4.9, 0.8 Hz, 2H), 2.40 (br s, 1H), 2.05–1.94 (m, 2H), 1.87–1.73 (m, 4H), 1.64–1.33 (m, 8H), 1.05 (s, 9H), 0.95 (d, J = 6.6 Hz, 3H) ppm; 13C NMR (125 MHz, CDCl3): δ 159.1, 135.6, 133.7, 129.5, 129.2, 127.6, 113.7, 100.5, 79.8, 79.1, 75.8, 74.8, 73.4, 72.5, 70.0, 66.5, 55.2, 47.4, 41.2, 32.1, 31.9, 29.9, 29.9, 29.7, 29.4, 28.0, 26.8, 21.9, 19.2, 12.9 ppm; HRMS (ESI): m/z calcd for C43H40O8Si [M + Na]⁺, 743.3955; found, 743.3945.

## ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01474.

Copies of ¹H and ¹³C NMR spectra for all new compounds (PDF)

## AUTHOR INFORMATION

### Corresponding Author
Debendra K. Mohapatra — Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh 201002, India; Email: mohapatra@iict.res.in

Authors
Srinivas Gajula — Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh 201002, India

Aedula Vishnu V. Reddy — Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India

D. Prabhakar Reddy — Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh 201002, India

### ACKNOWLEDGMENTS

The authors thank the Director, CSIR-ICT, for his constant support and providing research facilities. S.G., A.V.R., and D.P.R. thank CSIR and UGC, New Delhi, India, for financial assistance in the form of fellowships.

### REFERENCES

(1) (a) Kobayashi, J. Search for New Bioactive Marine Natural Products and Application to Drug Development. Chem. Pharm. Bull. 2016, 64, 1079. (b) Lorente, A.; Lama-Merketegi, J.; Alberio, F.; Alvarez, M. Tetrahydrofuran-Containing Macrolides: A Fascinating Gift from the Deep Sea. Chem. Rev. 2013, 113, 4567. (c) Kobayashi, J. Amphidinolides and Its Related Macrolides from Marine Dinoflagellates. J. Antibiot. 2008, 61, 271. (d) Kobayashi, J.; Kubota, T. Bioactive Macrolides and Polyketides from Marine Dinoflagellates of the Genus Amphidinium. J. Nat. Prod. 2007, 70, 451. (e) Satake, M. Marine polynuclear compounds. Top. Heterocycl. Chem. 2006, 5, 21. (f) Kobayashi, J.; Ishibashi, M. Amphidinolides: unique macrolides from marine dinoflagellates. Heterocycles 1997, 45, 543. (g) Kobayashi, J.; Ishibashi, M. Bioactive metabolites of symbiotic marine microorganisms. Chem. Rev. 1993, 93, 1753.

(2) (a) Holmes, C. F. B.; Luu, H. A.; Carrier, F.; Schmitz, F. J. Inhibition of protein phosphatases-1 and -2A with acanthifolicin: Comparison with diarrhetic shellfish toxins and identification of a region on okadaic acid important for phosphatase inhibition. FEBS Lett. 1990, 270, 216. (b) Murakami, Y.; Oshima, Y.; Yasumoto, T. Identification of okadaic acid as a toxic component of a marine dinoflagellate Protoceratium luma. Bull. Jpn. Soc. Sci. Fish. 1982, 48, 69. (3) Yasumoto, T.; Murata, M. Marine toxins. Chem. Rev. 1993, 93, 1897.

(4) Kobayashi, J.; Tsuda, M. Amphidinolides, bioactive macrolides from symbiotic marine dinoflagellates. Nat. Prod. Rep. 2004, 21, 77.

(5) (a) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsen, M. R. Marine natural products. Nat. Prod. Rep. 2011, 28, 196. (b) Lu, C.-K.; Chen, Y.-M.; Wang, S.-H.; Wu, Y.-Y.; Cheng, Y.-M. Formosalides A and B, cytotoxic 17-membered ring macrolides from a marine dinoflagellate Protoceratium sp. Tetrahedron Lett. 2009, 50, 1825.

(6) (a) Mallampudi, N. A.; Srinivas, A.; Reddy, J. G.; Mohapatra, D. K. Total Synthesis and Structural Revision of Monocillin VII. Org. Lett. 2019, 21, 5952. and references therein. (b) Srinivas, B.; Reddy, D. S.; Mallampudi, N. A.; Mohapatra, D. K. A General Diastereoselective Strategy for Both cis- and trans-2,6-Disubstituted Tetrahydropyrans: Formal Total Synthesis of (+)-Mucinin. Org. Lett. 2018, 20, 6910. (c) Mohapatra, D. K.; Das, P. P.; Pattanayak, M. R.; Yadav, J. S. Iodine-Catalyzed Highly Diastereoselective Synthesis of trans-2,6-Disubstituted -3,4-Dihydropyrans: Application to Concise Construction of C28–C37 Bicyclic Core of (+)-Sorangicin A. Chem. – Eur. J. 2010, 16, 2072.

(7) (a) Aitkin, L.; Chen, Z.; Robertson, A.; Surgess, D.; White, J. M.; Rizzacasa, M. A. Synthesis of Alkyl Citrates (– CJ-13,981, (–) CJ-13,982, and (–) L-731,120 via a Cyclobutene Diol. Org. Lett. 2018, 20, 4255. (b) Wilker, J. A.; Chen, J. J.; Wise, D. S.; Townsend, L. B. A Facile, Multigram Synthesis of Ribofuranous Glycals. J. Org. Chem. 1996, 61, 2219. (c) Beach, J. W.; Kim, H. O.; Jeong, L. S.; Nampalli,
S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K. A highly stereoselective synthesis of anti-HIV 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxynucleosides. J. Org. Chem. 1992, 57, 3887.

(d) Hanessian, S.; Murray, P. J. Stereochemical control of nature’s biosynthetic pathways: A general strategy for the synthesis of polyprenylate-derived structural units from a single chiral progenitor. Tetrahedron 1987, 43, 5055.

(e) Herdeis, C. Chiroselective Synthesis of (S)-(−)- and (R)-(−)-5-Amino-4-hydroxypentanoic Acid from L- and D-Glutamic Acid via (S)-(+) - and (R)-(−)-5-Hydroxy-2-oxopiperidine. Synthesis 1986, 232.

(f) Vigneron, J. P.; Méric, R.; Larchevêque, M.; Debal, A.; Lallemant, J. Y.; Junesch, G.; Tagatti, P.; Gallois, M. El’danolid, pheromone des glandes alaires de la pyrale de la canne à sucre, eldana saccharina (wilkr.): structure et synthèse de ses deux enantiomères. Tetrahedron 1984, 40, 3521.

(8) (a) Tomioka, K.; Cho, Y. S.; Sato, F.; Foga, K. Stereoselective Reactions. 14. Efficient Enantioselective Construction of Quaternary Carbon Centers by the Sequential Dialkylation of (S)-γ-[Trityloxy)methyl]-γ-butyrolactone. Synthesis of Optically Active β,β-Disubstituted γ-Butyrolactones. J. Org. Chem. 1988, 53, 4094.

(b) Nishida, Y.; Konno, M.; Fukushima, Y.; Ohru, H.; Meguro, H. 13C-NMR Studies on Marmelo Lactones and Related 2,4-di-Alkylated γ-Lactones. Agric. Biol. Chem. 2014, 50, 191.

(9) Marshal, J. A.; Sabatini, J. J. Synthesis of cis- and trans-2,5-Disubstituted Tetrahydrofurans by a Tandem Dihydroxylation-SN2 Cyclization Sequence. Org. Lett. 2005, 7, 4819.

(10) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. Chem. Rev. 1994, 94, 2483.

(b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. The osmium-catalyzed asymmetric dihydroxylation: a new ligand class and a process improvement. J. Org. Chem. 1992, 57, 2768.

(11) Zhong, Y.-L.; Shing, T. K. M. Efficient and Facile Glycol Cleavage Oxidation Using Improved Silica Gel-Supported Sodium Metaperiodate. J. Org. Chem. 1997, 62, 2622.

(12) Jung, M. E.; Berliner, J. A.; Angst, D.; Yue, D.; Koroniak, L.; Watson, A. D.; Li, R. Total Synthesis of the Epoxy Isoprostane Phospholipids PEIPC and PECPC. Org. Lett. 2005, 7, 3933.

(13) Dess, D. B.; Martin, J. C. Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. J. Org. Chem. 1983, 48, 4155.