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Divergent Chiral-Pool Synthesis of the C1–C8 and C9–C13 Fragments of Pladienolide B from L-Malic Acid

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Abstract

Pladienolide B (**1**), a macrocyclic polyketide isolated from *Streptomyces platensis* Mer-11107, displays potent antiproliferative and antitumor activities through its interaction with the SF3b subunit of the spliceosome. Herein, we report a divergent, stereoselective synthetic route to access both the C1–C8 and C9–C13 fragments of the core moiety of Pladienolide B (**1**) starting from a common, inexpensive chiral-pool precursor, L-Malic acid. Key stereocenters and structural motifs were established using Sharpless asymmetric epoxidation, regioselective nucleophilic epoxide opening, Mannich reaction for exo-methylene introduction, and a tandem iodination–zinc elimination cascade. This unified precursor approach offers a streamlined tactical route toward the core macrolide framework.

Keywords: Pladienolide B; L-Malic acid; chiral-pool synthesis; divergent synthesis; stereoselective synthesis

1. Introduction

Pladienolides are a family of structurally complex 12-membered macrolides isolated from *Streptomyces platensis* Mer-11107. Among them, Pladienolide B (**1**) exhibits potent antiproliferative and antitumor activities and has attracted considerable attention owing to its unique mechanism of action involving the spliceosomal machinery [1–3]. Pladienolide B (**1**) selectively targets the SF3b complex containing SF3B1, thereby disrupting pre-mRNA splicing and inhibiting cancer cell proliferation. This distinctive mode of action has established Pladienolide B (**1**) as an important lead structure for developing novel anticancer agents and spliceosome-targeting therapeutics [4,5]. More recently, its therapeutic potential has been further demonstrated across different cancer models, including lung adenocarcinoma and hepatocellular carcinoma, where Pladienolide B (**1**) was shown to suppress tumor-cell proliferation and, in combination with cisplatin, enhance antitumor activity (Figure 1) [6–9].

The combination of potent biological activity, a highly functionalized macrolactone framework, multiple stereogenic centres, and an epoxide-containing side chain makes Pladienolide B (**1**) an attractive target for synthetic studies. Since the isolation and structural elucidation of the pladienolides, several synthetic approaches to Pladienolide B (**1**) and related analogues have been reported [10–12]. The first total synthesis of Pladienolide B (**1**) and D was reported by the Kotake group, representing a pioneering contribution to the synthesis of these potent antitumor macrolides [13]. Subsequent studies have established diverse strategies for constructing the stereochemically rich macrolide framework,

Check for updates

Academic Editor: Piotr Bałczewski

Received: 27 August 2026
Revised: 12 October 2026
Accepted: 29 October 2026
Published: 4 November 2026

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including asymmetric epoxidation, regioselective epoxide opening, olefination, ring-closing metathesis, and stereoselective C–C bond-forming reactions.

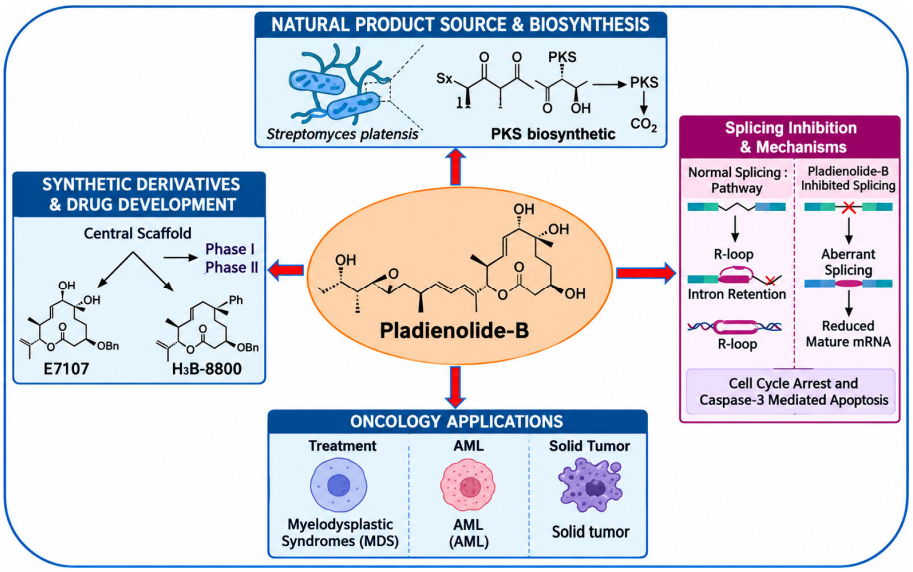


Figure 1. Pladienolide B: Mechanistic Insights and Clinical Applications.

These studies have established diverse strategies for constructing the stereochemically rich macrolide framework, including asymmetric epoxidation, regioselective epoxide opening, olefination, ring-closing metathesis, and stereoselective C–C bond-forming reactions. More recently, concise and convergent total syntheses of Pladienolide B (**1**) and related spliceosome modulators have been developed using catalytic asymmetric C–C bond formation and step-economical synthetic strategies [14–17].

The C1–C8 and C9–C13 segments constitute important stereochemically defined portions of the Pladienolide B (**1**). Chiral-pool synthesis provides an attractive strategy for accessing such complex fragments because the inherent stereochemical information of readily available chiral starting materials can be efficiently transferred to the target structures. L-Malic acid, an inexpensive and readily accessible chiral starting material, has been successfully utilized in the synthesis of stereochemically rich intermediates and natural products [18–20].

In the present work, we describe a divergent synthesis of the C1–C8 and C9–C13 fragments of Pladienolide B (**1**) using L-Malic acid as a common chiral-pool starting material. The C1–C8 fragment was constructed through epoxide opening, C–C bond formation, and Sharpless asymmetric epoxidation, followed by conventional functional-group transformations. The C9–C13 fragment was prepared from an L-malic-acid-derived triol through oxidative cleavage, olefination, reduction, and Sharpless asymmetric epoxidation. Thus, two stereochemically defined fragments of the Pladienolide B (**1**) core were accessed from a common chiral-pool precursor through complementary synthetic sequences.

2. Materials and Methods

All commercially available reagents and solvents, including L-Malic acid, were purchased from Sigma Aldrich (Hyderabad, India), TCI (Hyderabad, India), and Alfa Aesar (Hyderabad, India) and used without further purification unless otherwise noted. All reactions were carried out under an N_2 atmosphere in oven-dried glassware using anhydrous solvents (CH_2Cl_2, THF, CCl_4, benzene, or EtOAc), unless otherwise noted. Petroleum ether used had a boiling range of 60–80 °C. The progress of the reactions was monitored by thin-layer chromatography (TLC) using Merck 60 F254 silica gel plates (Hyderabad, India),

and visualization was accomplished under UV light 254 nm or by staining with phosphomolybdic acid or $KMnO_4$ solutions. Flash and column chromatography were performed using silica gel (60–120 mesh, Acme Chemical Co. Mumbai, Maharashtra). Reported yields correspond to materials that were homogeneous by chromatographic and spectroscopic (^{1}H NMR, ^{13}C NMR) analysis. Air- and moisture-sensitive reagents were transferred *via* oven-dried syringes or double-ended cannulas. Concentrating solutions under reduced pressure was performed using a Büchi rotary evaporator (Aditya Scientifics, Hyderabad, Inida). Optical rotations $[\alpha]_D$ were measured using a JASCO DIP-370 polarimeter (Aditya Scientifics, Hyderabad, India) at 25 °C. NMR spectra were recorded using Varian Unity 400 MHz or Varian Inova 500 MHz spectrometers (Agilent Technologies, Hyderabad, India). NMR chemical shifts (δ) are given in parts per million (ppm) relative to tetramethyl silane (TMS, δ = 0.00 ppm) as an internal standard using $CDCl_3$ as solvent. Low- and high-resolution mass spectrometric data were obtained using electron impact (70 eV) on an Agilent Technologies LC-MSD spectrometer (Agilent Technologies, Hyderabad, India). The ^{1}H NMR and ^{13}C NMR spectra of compounds **4**–**8**, **11**–**13**, **15**–**21**, **23**–**27** are provided in the Supplementary Materials.

(*R*)-1-((4-methoxybenzyl)oxy)hept-6-en-3-ol (11):

A well-stirred suspension of Mg turnings (5.2 g, 216.33 mmol) in diethyl ether (75 mL), allyl chloride (17.6 mL, 216.33 mmol) was added at 0 °C. The Grignard reagent thus generated was stirred until complete formation and then cooled to −40 °C. A solution of the epoxide **9** (15.0 g, 72.11 mmol) in diethyl ether (75 mL) was added slowly to the Grignard solution at −40 °C. The reaction mixture was stirred at −40 °C for 2 h. Upon completion, the reaction mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (2 × 100 mL). The pooled organic layers were washed with water (2 × 50 mL) and brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was purified by silica gel (60–120 mesh) column chromatography, using 4% EtOAc/pet ether as the eluent, to afford compound **11** as a product (12.6 g, 70% yield). $[\alpha]^{20}_D = -17.5$ (*c* 0.1, $CHCl_3$); IR ($CHCl_3$): ν 3489, 3487, 3323, 2978, 2922, 1714, 1640, 1609, 1512, 1373, 1246, 1173, 914, 821 C m^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (d, 2H, J = 8.49 Hz), 6.76 (d, 2H, J = 8.49 Hz), 5.72 (m, 1H), 4.94 (m, 2H), 4.36 (s, 2H), 3.72 (s, 3H), 3.51 (m, 3H), 2.7 (bs, 1H), 2.08 (m, 2H), 1.82 (m, 1H), 1.63 (q, 1H), 1.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 138.4, 131.4, 129.8, 129.1, 114.3, 113.6, 72.7, 70.4, 68.5, 55.0, 36.3, 29.7; HRMS: m/z calculated for $C_{15}H_{22}O_3Na$ 273.1388, found: 273.1394.

(*R*)-1-(((3-(Benzyloxy)hept-6-en-1-yl)oxy)methyl)-4-methoxybenzene (12):

A solution of the compound **11** (12.6 g, 48.0 mmol) in dry THF (10 mL) was added to a cooled suspension of NaH (3.45 g, 144 mmol; 60% *w*/*w* dispersion in paraffin oil) in dry THF (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, followed by the dropwise addition of benzyl bromide (6.27 mL, 52.8 mmol) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 4 h. After completion, the reaction mixture was cooled to 0 °C, and saturated aqueous NH_4Cl solution (10 mL) was added dropwise, followed by EtOAc (50 mL). The organic layer was separated, washed successively with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel (60–120 mesh) using 5% EtOAc in petroleum ether as the eluent to afford the compound **12** (12.0 g, 74%) as a light yellow color syrup; $[\alpha]^{20}_D = -37.7$ (*c* 0.1, $CHCl_3$); IR ($CHCl_3$): ν 3065, 3002, 2923, 2854, 1716, 1640, 1512, 1453, 1360, 1246, 1171, 911, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (m, 5H), 7.16 (d, 2H, J = 8.0 Hz), 6.78 (d, 2H, J = 8.0 Hz), 5.75 (m, 1H), 4.93 (m, 2H), 4.44 (q, 2H), 4.35 (q, 2H), 3.77 (s, 3H), 3.51 (m, 2H), 2.11 (m, 2H), 1.78 (m, 2H), 1.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 138.6, 130.5, 129.3, 128.2,

127.7, 127.4, 114.5, 113.7, 75.6, 72.6, 71.2, 66.5, 55.2, 34.3, 33.4, 29.4; HRMS: *m*/*z* calculated for $C_{22}H_{28}O_3Na$ 363.1931, found: 363.1944.

(*R*)-5-(Benzyloxy)-7-((4-methoxybenzyl)oxy)heptan-1-ol (13):

To a solution of cyclohexene (5.4 mL, 52.93 mmol) in THF (10 mL), BH_3·DMS (5.0 mL, 52.93 mmol) was added at 0 °C, and the resulting mixture was stirred for 30 min. A solution of the compound 12 (12.0 g, 35.29 mmol) in THF (20 mL) was then added, and the reaction mixture was stirred for an additional 4 h. After completion of the reaction, the reaction mixture was quenched with 2 N NaOH (20 mL), followed by the addition of H_2O_2 (10 mL). The mixture was extracted with EtOAc (100 mL), and the combined organic extracts were washed with water (2 × 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (60–120 mesh), using 8% EtOAc in petroleum ether as the eluent, to afford the compound **13** (8.84 g, 70%) as liquid; $[\alpha]^{20}_D = -37.4$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): *ν* 3393, 3360, 2925, 2855, 1712, 1610, 1585, 1456, 1363, 1247, 1173, 1034, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (m, 5H), 7.17 (d, 2H, *J* = 8.42 Hz), 6.8 (d, 2H, *J* = 8.42 Hz), 4.45 (q, 2H), 4.36 (t, 2H), 3.78 (s, 3H), 3.58–3.47 (m, 5H), 1.78 (m, 2H), 1.41 (m, 2H), 1.26 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 159.1, 138.8, 130.5, 129.3, 128.3, 127.7, 127.4, 113.7, 76.1, 72.6, 71.2, 66.5, 62.7, 55.2, 34.3, 33.8, 32.7, 21.3; HRMS: *m*/*z* calculated for $C_{22}H_{30}O_4Na$ 381.2036, found: 381.2048.

(*R*)-5-(Benzyloxy)-7-((4-methoxybenzyl)oxy)-2-methyleneheptan-1-ol (6):

*Preparation of aldehyde **13a***

Dry DMSO (5.26 mL, 74.07 mmol) was added dropwise to a solution of oxalyl chloride (3.17 mL, 37.03 mmol) in dry CH_2Cl_2 (15 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, followed by the addition of a solution of the alcohol **13** (8.84 g, 24.69 mmol) in CH_2Cl_2 (15 mL) over 10 min. The resulting mixture was stirred for 2 h, followed by the dropwise addition of Et_3N (20.6 mL, 148.14 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for an additional 30 min. The mixture was diluted with water (10 mL) and CH_2Cl_2 (50 mL), and the organic layer was separated, washed successively with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the aldehyde **13a** (5.0 g, 58% yield).

*Preparation of olefin **14***

Diethylamine (4.97 mL, 49.11 mmol) and CH_2Br_2 (16.7 mL, 210 mmol) were mixed and stirred at 55 °C for 1 h 30 min. After cooling the reaction mixture to room temperature, the aldehyde **13a** (5.0 g, 14.03 mmol) was introduced, and the mixture was maintained at room temperature for 1 h 30 min. Upon completion, the solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (60–120 mesh) using 2% EtOAc in petroleum ether as the eluent to furnish the olefin **14** (2.65 g, 45% yield).

*Preparation of compound **6***

$NaBH_4$ (0.18 g, 5.05 mmol) was added to a solution of the olefin **14** (2.65 g, 7.16 mmol) in CH_3OH (10 mL) at 0 °C, and the reaction mixture was stirred at 0 °C until completion. The reaction mixture was then subjected to the appropriate work-up, and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography over silica gel (60–120 mesh), using 4% EtOAc in petroleum ether as the eluent, to afford the compound **6** (1.15 g, 43%); $[\alpha]^{20}_D = -87.04$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): *ν* 3440, 3395, 3006, 2859, 2311, 1712, 1609, 1512, 1453, 1360, 1246, 1172, 1029, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.25 (m, 5H), 7.18 (d, 2H, *J* = 8.3 Hz), 6.81 (d, 2H, *J* = 8.3 Hz), 4.96 (s, 1H), 4.81 (s, 1H), 4.44 (t, 2H), 4.36 (s, 2H), 3.99 (bs, 1H), 3.78 (s, 3H), 3.54 (m, 3H), 2.12 (m, 2H), 1.8 (m, 2H), 1.68 (q, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 148.8, 138.6,

130.4, 129.3, 128.3, 127.8, 127.5, 113.7, 109.3, 75.8, 72.6, 71.2, 66.4, 65.8, 55.2, 34.1, 32.2, 28.4; HRMS: m/z, calculated for $C_{23}H_{30}O_4Na$ 393.2144, found 393.2148.

((*R*)-2-((*R*)-3-(Benzyloxy)-5-((4-methoxybenzyl)oxy)pentyl)oxiran-2-yl)methanol (15):

Activated 4 Å molecular sieves (0.30 g), $Ti(OiPr)_4$ (0.09 mL, 0.31 mmol), and cumene hydroperoxide (0.97 mL, 6.2 mmol) were added sequentially to a stirred solution of (+)-DIPT (0.13 mL, 0.62 mmol) in CH_2Cl_2 (15 mL) at −20 °C. The resulting mixture was stirred at −20 °C for 20 min. A solution of the compound **6** (1.15 g, 3.10 mmol) in CH_2Cl_2 (15 mL) was then added, and the reaction mixture was stirred at −20 °C for 5 h. The reaction was quenched by the addition of 10% KOH solution, prepared by dissolving KOH (3.0 g) in brine (30 mL), and the resulting mixture was stirred for 3 h. The mixture was then filtered through a pad of Celite and washed with EtOAc (20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was purified by silica gel column chromatography using 20% EtOAc in petroleum ether as the eluent, to afford the compound **15** (0.95 g, 80%) as a yellow syrup; $[\alpha]^{20}_D = -12.2$ (c 0.2, $CHCl_3$); IR ($CHCl_3$): ν 3420, 3019, 2985, 1726, 1679, 1514, 1215, 1033, 928 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.27 (m, 7H, ArH), 6.87 (d, 2H, J = 8.3 Hz, ArH), 4.47 (m, 2H, $ArCH_2$), 4.40 (s, 2H, $ArCH_2$), 3.80 (s, 3H, OMe), 3.53 (m, 5H, OCH), 2.84 (d, 2H, J = 4.53, epoxy), 2.62 (d, 1H, J = 4.15 Hz, epoxy), 1.69 (m, 6H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ 159.06, 148.76, 138.4, 130.3, 129.3, 128.3, 127.8, 127.6, 113.7, 76.3, 72.6, 71.3, 69.0, 66.4, 61.2, 61.1, 55.4, 55.2, 34.1, 33.9, 27.5, 26.2; HRMS: m/z calculated for $C_{23}H_{30}O_5Na$ 409.2169, found: 409.2160.

(2*R*,5*R*)-5-(Benzyloxy)-7-((4-methoxybenzyl)oxy)-2-methylheptane-1,2-diol (16):

To a cooled suspension of LAH (0.22 g, 6.15 mmol) in dry THF (2 mL) at 0 °C was added a solution of the compound 15 (0.95 g, 2.46 mmol) in dry THF (2 mL). The reaction mixture was stirred at 0 °C and then allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated Na_2SO_4 solution (2 mL) and stirred for 1 h. The resulting mixture was filtered and washed with EtOAc (2 × 15 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel, using 20% EtOAc in petroleum ether as the eluent, to furnish the compound **16** (0.66 g, 70%) as a yellow oil; $[\alpha]^{20}_D = -13.5$ (c 0.1, $CHCl_3$); IR ($CHCl_3$): ν 3409, 3063, 3031, 2857, 1701, 1611, 1512, 1456, 1363, 1302, 1248, 1175, 1035, 911 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 (m, 7H), 6.87 (d, 2H, J = 8.0 Hz), 4.5 (m, 2H), 4.40 (s, 2H), 3.80 (s, 3H), 3.58 (m, 3H), 3.39 (m, 2H), 1.86 (m, 6H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 148.7, 138.3, 130.3, 129.3, 128.3, 127.8, 127.5, 113.7, 76.5, 72.6, 71.2, 69.6, 66.3, 55.2, 34.2, 33.5, 33.4, 27.7, 23.2, 23.0; HRMS: m/z calculated for $C_{23}H_{32}O_5Na$ 411.2142, found 411.2145.

(4*R*,7*R*)-Ethyl 7-(benzyloxy)-4-hydroxy-9-((4-methoxybenzyl)oxy)-4-methylnon-2-enoate (17):

*Preparation of aldehyde **16a***

Dry DMSO (0.36 mL, 5.10 mmol) was added dropwise to a solution of oxalyl chloride (0.21 mL, 2.55 mmol) in dry CH_2Cl_2 (15 mL) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 30 min, followed by the addition of a solution of the alcohol 16 (0.66 g, 1.70 mmol) in CH_2Cl_2 (15 mL) over 10 min. The reaction mixture was stirred at −78 °C for 2 h, followed by the slow addition of Et_3N (1.41 mL, 10.2 mmol). The mixture was then allowed to warm to room temperature and stirred for an additional 30 min. The reaction mixture was diluted with water (10 mL) and CH_2Cl_2 (50 mL), and the organic layer was separated, washed successively with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude aldehyde 16a, which was used directly in the subsequent step without further purification.

Preparation of compound ***17***

A solution of the crude aldehyde 16a (0.66 g, 1.70 mmol) in benzene (30 mL) was treated with (ethoxycarbonylmethylene)triphenylphosphorane (0.90 g, 2.56 mmol). The reaction mixture was stirred at reflux for 2 h. Upon completion of the reaction, the solvent was removed under vacuum, and the resulting residue was purified by silica gel (60–120 mesh) column chromatography, using 5% EtOAc in petroleum ether as the eluent, to afford the compound **17**. (0.46 g, 60%); $[\alpha]^{20}_{D} = -22.5$, (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): ν 3452, 2924, 2854, 1715, 1655, 1610, 1513, 1457, 1368, 1251, 1176, 1094, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 7H), 6.88 (m, 3H), 6.02 (d, 1H, J = 15.48 Hz), 4.48 (s, 2H), 4.40 (s, 2H), 4.2 (q, 2H), 3.8 (s, 3H), 3.4 (m, 3H), 1.83–1.61 (m, 6H), 1.28 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 130.4, 129.3, 128.3, 127.8, 127.6, 118.5, 113.7, 75.9, 72.6, 72.5, 71.3, 66.4, 55.2, 51.5, 372, 36.8, 33.7, 28.1, 28.0, 27.8; HRMS: m/z calculated for $C_{27}H_{36}O_6Na$ 479.2409, found 479.2404.

(4*R*,7*R*)-7-(Benzyloxy)-9-((4-methoxybenzyl)oxy)-4-methylnon-2-ene-1,4-diol (18):

The compound **17** (0.46 g, 1.00 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C. DIBAL-H (1.8 mL, 2.52 mmol; 20% solution in toluene) was added slowly over 15 min, and the reaction mixture was subsequently allowed to reach room temperature and stirred for 4 h. Upon completion, the mixture was cooled to 0 °C and carefully quenched by sequential addition of methanol (1 mL) and sodium potassium tartrate solution (5 mL). The resulting suspension was filtered through a short pad of Celite and rinsed with EtOAc (2 × 50 mL). The combined filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (60–120 mesh) using 10% EtOAc in petroleum ether as the eluent to furnish the compound **18** (0.37 g, 90%) as a colorless oil; $[\alpha]^{20}_{D} = -31.5$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): ν 3420, 2926, 2856, 1713, 1609, 1513, 1455, 1364, 1251, 1220, 1172, 1030, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71–7.62 (m, 2H), 7.58–7.52 (m, 1H), 7.35–7.27 (m, 2H), 7.25–7.22 (m, 2H), 6.85–6.84 (m, 2H), 5.82–5.68 (m, 2H), 4.53–4.41 (m, 2H), 4.42– 4.38 (m, 2H), 4.13 (d, J = 4.88 Hz, 2H), 3.79 (s, 3H), 3.67–3.57 (m, 1H), 3.57–3.48 (m, 2H), 1.92–1.83 (m, 1H), 1.82–1.74 (m, 1H), 1.72–1.52 (m, 6H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 138.4, 138.2, 130.3, 129.3, 128.2, 127.8, 127.7, 127.5, 126.7, 113.6, 76.3, 76.1, 72.5, 72.2, 66.4, 62.9, 55.2, 37.6, 37.4, 34.0, 33.9, 28.0; HRMS: m/z calculated for $C_{25}H_{34}O_5Na$ 437.2298, found 437.2308.

(2*R*,5*R*)-5-(Benzyloxy)-2-((2*S*)-3-(hydroxymethyl)oxiran-2-yl)-7-((4-methoxybenzyl)oxy)- heptan-2-ol (19):

A mixture of (−)-DIPT (0.03 g, 0.18 mmol), $Ti(OiPr)_4$ (0.01 mL, 0.04 mmol), and cumene hydroperoxide (0.27 mL, 1.78 mmol) was added sequentially to a stirred suspension of activated 4 Å molecular sieves (0.30 g) in CH_2Cl_2 (15 mL) at −20 °C. The resulting mixture was maintained at −20 °C for 20 min. A solution of the compound **18** (0.37 g, 0.89 mmol) in CH_2Cl_2 (15 mL) was then introduced, and stirring was continued at −20 °C for 5 h. The reaction was quenched with 10% KOH solution, prepared by dissolving KOH (3.0 g) in brine (30 mL), and the mixture was stirred for a further 3 h. The reaction mixture was filtered, and the organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the resulting residue by column chromatography over silica gel (60–120 mesh), using 20% EtOAc in petroleum ether as the eluent, furnished the compound **19** (0.33 g, 88%) as a yellow syrup; $[\alpha]^{20}_{D} = -55.5$, (*c* 0.2, $CHCl_3$); (*c* 0.1, $CHCl_3$); IR ($CHCl_3$): ν 3424, 2924, 2854, 1713, 1608, 1513, 1460, 1374, 1253, 1219, 1092, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39–7.21 (m, 7H), 6.87 (d, J = 8.68 Hz, 2H), 4.5 (brs, 2H), 4.4 (m, 2H), 4.41 (bs, 2H), 3.78 (s, 3H), 3.69–3.48 (m, 5H), 3.24–3.16 (m, 1H), 3.00–2.84 (m, 1H), 2.00–1.75 (m, 2H), 1.72–1.55 (m, 4H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 138.4, 131.2, 130.8, 130.3, 129.3, 128.7, 128.2, 127.8, 127.5, 113.6, 76.3, 76.2, 72.6, 71.3, 69.0, 66.3, 61.1, 55.4, 34.1, 33.9, 27.4, 26.2; HRMS: m/z calculated for $C_{25}H_{34}O_6Na$ 453.2247, found 453.2259.

(3*S*,4*R*,7*R*)-7-(benzyloxy)-9-((4-methoxybenzyl)oxy)-4-methylnon-1-ene-3,4-diol (8):

*Preparation of iodo product **19a***

The compound **19** (0.33 g, 0.76 mmol) was dissolved in THF and cooled to 0 °C. PPh_3 (0.30 g, 1.15 mmol) and imidazole (0.078 g, 1.15 mmol) were then added, followed by the addition of iodine (I_2, 0.28 g, 1.15 mmol). The resultant reaction mass was stirred for 30 min at 0 °C and then quenched with aqueous $Na_2S_2O_3$ solution (2 mL). The mixture was extracted with EtOAc (50 mL), and the organic layer was washed successively with water (50 mL), brine (25 mL) and over anhydrous Na_2SO_4. The organic layer was concentrated under vacuum to afford the iodo product **19a** (0.41 g), which was used directly in the next step without further purification.

*Preparation of compound **8***

A solution of compound **19a** (0.41 g, 7.64 mmol) in CH_3OH (6 mL) was treated with Zn (1.99 g, 30.69 mmol) and NaI (1.10 g, 7.67 mmol) at room temperature. The reaction mixture was then heated under reflux for 6 h with stirring. Upon completion, the reaction mixture was filtered through a short pad of Celite and washed with EtOAc (20 mL). The filtrate was concentrated under vacuum, and the resulting residue was purified by column chromatography over silica gel (60–120 mesh), using 5% EtOAc in petroleum ether as the eluent, to afford compound **8** (0.19 g, 61%) as a yellow liquid; $[\alpha]^{20}_D = -23.5$, (*c* 0.2, $CHCl_3$); (*c* 0.1, $CHCl_3$); IR ($CHCl_3$): ν 3384, 3059, 2925, 2855, 1712, 1610, 1512, 1438, 1364, 1250, 1176, 1030, 925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 7.24 (d, J = 8.69 Hz, 2H), 6.87 (d, J = 8.69 Hz, 2H), 5.87 (m, 1H), 5.30 (m, 1H), 5.12 (m, 1H), 4.49 (bs, 2H), 4.4 (m, 2H), 3.85 (bs, 1H), 3.79 (s, 3H), 3.57 (m, 3H), 1.85 (m, 6H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 136.5, 132.0, 131.9, 129.3, 128.5, 128.4, 128.3, 127.8, 127.5, 117.2, 113.7, 77.5, 76.8, 73.9, 72.6, 71.7, 66.5, 55.2, 34.0, 31.6, 27.3, 23.2; HRMS: m/z calculated for $C_{25}H_{34}O_5Na$ 437.2298, found 437.2307.

(4*R*,5*S*)-4-((*R*)-3-(Benzyloxy)-5-((4-methoxybenzyl)oxy)pentyl)-4-methyl-2-phenyl-5-vinyl-1,3-dioxolane (20):

The compound **8** (0.19 g, 0.45 mmol) and *p*-toluenesulfonic acid (p-TSA; 0.078 g, 0.22 mmol) were dissolved in dry CH_2Cl_2 (25 mL) and cooled to 0 °C. Benzaldehyde dimethyl acetal (0.08 mL, 0.54 mmol) was then added, and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. Upon completion, the reaction mixture was neutralized with Et_3N (1 mL), and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography over silica gel (60–120 mesh), using 5% EtOAc in petroleum ether as the eluent, to afford the compound **20** (0.20 g, 88% yield) as a colourless product. NMR data were recorded for the major isomer; $[\alpha]^{20}_D = +8.2$, (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): ν 3440, 3395, 3006, 2859, 2311, 1712, 1609, 1512, 1453, 1360, 1246, 1172, 1029, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (m, 2H), 7.29 (m, 10H), 6.86 (m, 2H), 5.89 (m, 2H), 5.39 (m, 1H), 5.28 (m, 1H), 4.45 (m, 4H), 4.22 (m, 1H), 3.79 (s, 3H), 3.57 (m, 3H), 1.76 (m, 4H), 1.34 (s, 3H), 1.23 (m, 2H); HRMS: m/z calculated for $C_{32}H_{38}O_5Na$ 525.0715, found 525.0711.

(*R*)-3-(Benzyloxy)-5-((4*R*,5*S*)-4-methyl-2-phenyl-5-vinyl-1,3-dioxolan-4-yl)pentan-1-ol (21):

The compound **20** (0.20 g, 0.39 mmol) was dissolved in a mixture of CH_2Cl_2/H_2O (4 mL/1 mL), and DDQ (0.10 g, 0.43 mmol) was added at 25–30 °C The reaction mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under vacuum, and the resulting residue was purified by column chromatography over silica gel (60–120 mesh), using 17% EtOAc in petroleum ether as the eluent, to afford compound **21** (0.1 g, 72%) as a colorless oil; $[\alpha]^{20}_D = +8.26$, (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): ν 3422, 3032, 2924, 2854, 1719, 1454, 1378, 1273, 1219, 1176, 1093, 1027, 933, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.34 (m, 8H), 5.91 (m, 2H), 5.43 (m, 1H), 4.60 (m,

1H), 4.39 (m, 1H), 4.25 (m, 1H), 3.69 (m, 3H), 2.28 (brs, 1H), 1.79 (m, 6H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 138.2, 133.1, 129.5, 129.0, 128.9, 128.4, 128.2, 127.8, 126.7, 126.5, 126.2, 125.9, 118.9, 102.0, 87.7, 86.0, 83.5, 78.4, 78.2, 77.9, 70.8, 60.6, 35.8, 35.6, 28.0, 26.8, 26.2, 21.8; HRMS: *m*/*z* calculated for $C_{24}H_{34}O_4N$ 400.0015, found 400.0021.

(*R*)-3-(Benzyloxy)-5-((4*R*,5*S*)-4-methyl-2-phenyl-5-vinyl-1,3-dioxolan-4-yl)pentanoic acid (4):

The alcohol **21** (0.10 g, 0.26 mmol) was dissolved in a mixture of CH_2Cl_2/H_2O (20 mL/1 mL) and cooled to 0 °C. TEMPO (0.012 g, 0.07 mmol) was then added, followed by BAIB (0.25 g, 0.78 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Upon completion, the reaction mixture was quenched with aqueous sodium thiosulfate ($Na_2S_2O_3$) solution (50 mL). The organic layer was separated, washed successively with water (50 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel (60–120 mesh), using 70% EtOAc in petroleum ether as the eluent, to afford the compound 4. (0.06 g, 60%) as a light-yellow oil. $[\alpha]^{20}_D$ = +15.4 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): *ν* 2925, 2854, 1730, 1459, 1380, 1219, 1091, 1068, 7726 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (s, 1H), 7.48 (m, 2H), 7.34 (m, 8H), 5.91 (m, 2H), 5.43 (m, 2H), 4.60 (m, 1H), 4.39 (m, 1H), 4.25 (m, 1H), 3.69 (m, 1H), 2.28 (m, 2H), 1.79 (m, 4H), 1.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.2, 130.0, 129.6, 128.6, 123.5, 113.6, 71.7, 68.5, 65.8, 55.1; HRMS: *m*/*z* calculated for $C_{24}H_{27}O_5$ 395.0019 found 395.0011.

(*R*)-Ethyl 5-hydroxy-2,4-dimethylpent-2-enoate (23):

*Preparation of the aldehyde **22a***

Compound **22** (5.0 g, 41.66 mmol) was dissolved in a 5:1 mixture of acetone/H_2O (30 mL) and cooled to 0 °C. $NaIO_4$ (10.7 g, 50.0 mmol) was then added, and the reaction mixture was allowed to warm to room temperature and stirred for 1 h. Upon completion, the solvent was removed under reduced pressure, and the residue was extracted with $CHCl_3$ (2 × 25 mL). The combined organic extracts were concentrated under reduced pressure to afford the aldehyde **22a** (3.66 g), which was carried forward to the next step without further purification.

*Preparation of the compound **23***

The Wittig ylide (20.17 g, 57.88 mmol) was dissolved in toluene (10 mL), and a solution of the aldehyde **22a** (3.96 g, 48.24 mmol) in toluene (10 mL) was added. The resulting mixture was heated under reflux for 2 h with stirring. Upon completion, the solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (60–120 mesh), using 15% EtOAc in petroleum ether as the eluent, to afford the compound **23** (5.07 g, 71%) as a colorless oil; $[\alpha]^{20}_D$ = −13.6 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): *ν* 3456, 3017, 2978, 2933, 2874, 1708, 1648, 1451, 1390, 1263, 1214, 1131, 1091, 930, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (d, 1H, *J* = 11.33), 4.18 (q, 2H), 3.51 (m, 2H, OCH), 2.74 (m, 1H), 1.88 (s, 3H), 1.62 (bs, 1H), 1.31 (t, 3H), 1.03 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 168.1, 143.8, 129.1, 67.0, 60.6, 36.1, 16.0, 14.2, 12.7; HRMS: *m*/*z* calculated for $C_9H_{16}O_3Na$ 199.0992, found 199.0995.

(*R*)-Ethyl 5-((*tert*-butyldiphenylsilyl)oxy)-2,4-dimethylpent-2-enoate (24):

To a solution of ester **23** (5.07 g, 29.47 mmol) in CH_2Cl_2 (25 mL) at 0 °C, imidazole (6.01 g, 88.43 mmol) and TBDPSCl (9.68 g, 35.36 mmol) were added sequentially and the reaction mixture was stirred at 0 °C for 1 h. Upon completion of the reaction, the solvent was removed under vacuum, and the resulting residue was purified by silica gel (60–120 mesh) column chromatography, using 3% EtOAc in petroleum ether as the eluent, to afford compound **24** (8.45 g, 70%); $[\alpha]^{20}_D$ = −66.2 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$): *ν* 3070, 3050, 2959, 2931, 2896, 2858, 1711, 1651, 1588, 1469, 1427, 1365, 1266, 1234, 1109, 1083, 803 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (m, 4H), 7.35 (m, 6H), 6.53 (d, 1H, *J* = 10.00 Hz),

4.17 (q, 2H), 3.52 (d, 2H), 2.71 (m, 1H), 1.78 (d, 3H), 1.29 (t, 3H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ 168.2, 144.4, 135.6, 133.6, 129.6, 127.9, 127.6, 67.7, 60.3, 36.1, 26.8, 19.2, 16.3, 14.3, 12.6, HRMS: *m*/*z* calculated for $C_{25}H_{34}O_3SiNa$ 433.1029 found 433.1024.

(*R*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylpent-2-en-1-ol (7):

Compound **24** (8.45 g, 20.6 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C. DIBAL-H (21.3 mL, 30.91 mmol; 20% solution in toluene) was added dropwise over 15 min, and the reaction mixture was subsequently allowed to warm to room temperature and stirred for 4 h. The mixture was then cooled to 0 °C and carefully quenched by sequential addition of methanol (1 mL) and sodium potassium tartrate solution (5 mL). The resulting mixture was filtered through a short pad of Celite and washed with EtOAc (2 × 50 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography over silica gel (60–120 mesh), using 10% EtOAc in petroleum ether as the eluent, to afford the compound **7** (6.0 g, 72%) as a colorless oil; $[\alpha]^{20}_D = -57.2$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): ν 3440, 3395, 3019, 2958, 2930, 2858, 1468, 1427, 1214, 1110, 1082, 1007, 931, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (m, 4H), 7.36 (m, 6H), 5.2 (m, 1H), 3.9 (m, 2H), 3.46 (m, 2H), 2.6 (m, 1H), 1.6 (d, 2H), 1.32 (bs, 1H), 1.05 (s, 9H), 0.99 (d); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.9, 129.5, 128.9, 127.5, 68.8, 68.4, 35.0, 26.8, 19.2, 17.2, 13.8; HRMS: *m*/*z* calculated for $C_{23}H_{32}O_2SiNa$ 391.0105 found 391.0109.

((2*S*,3*S*)-3-((*S*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)-2-methyloxiran-2-yl)methanol (25):

A stirred solution of (+)-DIPT (0.78 g, 3.35 mmol) in CH_2Cl_2 (15 mL) containing activated 4 Å molecular sieves (0.30 g) was cooled to −20 °C. $Ti(OiPr)_4$ (0.47 g, 1.67 mmol) and cumene hydroperoxide (5.14 g, 33.5 mmol) were then added sequentially, and the resulting mixture was stirred at −20 °C for 20 min. A solution of the compound 7 (6.0 g, 16.75 mmol) in CH_2Cl_2 (15 mL) was subsequently added, and the reaction mixture was maintained at −20 °C for 5 h. The reaction was quenched with 10% KOH solution, prepared by dissolving KOH (3.0 g) in brine (30 mL), and the mixture was stirred for an additional 3 h. The resulting mixture was filtered, and the organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (60–120 mesh), using 20% EtOAc in petroleum ether as the eluent, to afford the compound 25 (4.0 g, 62%) as a yellow oil; $[\alpha]^{20}_D = -87.04$ (*c* 0.1, $CHCl_3$); IR ($CHCl_3$): ν 3439, 3397, 3070, 2958, 2930, 2857 1726, 1589, 1469, 1427, 1388, 1216, 1187 1107, 1029, 889, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (m, 5H), 7.29 (m, 5H), 3.66 (m, 2H), 3.50 m, 2H), 2.79 (m, 1H), 1.5 (m, 1H), 1.18 (bs, 3H), 1.04 (s, 9H), 0.97 (d, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 129.5, 127.6, 66.3, 65.4, 61.3, 35.4, 26.8, 14.1, 13.4; HRMS: *m*/*z* calculated for $C_{23}H_{32}O_3NaSi$ 407.2013, found 407.2017.

(3*S*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylpent-1-en-3-ol (26):

*Preparation of the iodo compound **25a***

Compound **25** (4.0 g, 10.41 mmol) was dissolved in THF, followed by the sequential addition of PPh_3 (4.0 g, 15.62 mmol), imidazole (2.12 g, 31.23 mmol), and iodine (I_2, 3.93 g, 15.61 mmol). The reaction mixture was stirred at room temperature for 30 min and then quenched with saturated aqueous NaOH solution (5 mL). The mixture was extracted with EtOAc (100 mL), and the organic layer was washed successively with aqueous sodium thiosulfate (hypo) solution (50 mL), water (50 mL), and brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the compound 25a (5.15 g), which was carried forward to the next step without further purification.

*Preparation of the compound **26***

A solution of compound **25a** (5.15 g, 10.42 mmol) in CH_3OH (25 mL) was treated with Zn (2.0 g, 31.27 mmol) and NaI (2.32 g, 15.63 mmol). The reaction mixture was heated

under reflux and stirred for 6 h. Upon completion, the mixture was filtered through a short pad of Celite and washed with EtOAc (20 mL). The filtrate was concentrated under vacuum, and the resulting residue was purified by column chromatography over silica gel (60–120 mesh), using 5% EtOAc in petroleum ether as the eluent, to afford compound **26** (2.37 g, 62%) as a yellow oil; $[\alpha]^{20}_{D} = -37.4$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): ν 3439, 3397, 3070, 2958, 2930, 2857 1726, 1632, 1620, 1589, 1490, 1469, 1427, 1388, 1216, 1187 1107, 1029, 889, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 5H), 7.38 (m, 5H), 4.93 (m, 2H), 4.27 (bs, 1H), 3.95 (d, 1H, J = 8.12 Hz), 3.72 (m, 2H), 1.85 (m, 1H), 1.68 (s, 3H), 1.27 (s, 3H), 1.07 (s, 9H), 0.8 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 138.3, 130.3, 129.3, 128.3, 127.8, 127.5, 113.7, 76.5, 72.6, 72.4, 71.2, 69.6, 66.3, 55.2, 33.9, 33.5, 27.7, 23.2, 23.0; HRMS: m/z calculated for $C_{23}H_{32}O_2NaSi$ 391.0015, found 391.0019.

(3*S*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylpent-1-en-3-yl benzoate (27):

The compound **26** (2.37 g, 6.44 mmol) was dissolved in CH_2Cl_2 and cooled to 0 °C. Et_3N (1.8 mL, 12.88 mmol) and benzoyl chloride (BzCl, 0.9 mL, 6.44 mmol) were then added sequentially, followed by a catalytic amount of DMAP. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. Upon completion, the solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography over silica gel (60–120 mesh), using 15% EtOAc in petroleum ether as the eluent, to afford the compound **27** (1.97 g, 65%) as syrup; $[\alpha]^{20}_{D} = +22.5$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): ν 2958, 2930, 2857 1726, 1632, 1620, 1589, 1490, 1469, 1427, 1388, 1216, 1187 1107, 1029, 889, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, 2H, J = 7.17 Hz), 7.72 (d, 3H, J = 7.17 Hz), 7.74 (m, 10H), 5.01 (m, 2H), 4.41 (dd, 1H), 4.21 (m, 1H), 2.33 (m, 1H), 2.07 (t, 3H), 1.78 (d, 3H), 1.05 (s, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 141.5, 135.5, 133.5, 132.6, 130.5, 129.5, 129.4, 128.2, 127.5, 127.4, 114.9, 79.2, 65.3, 64.6, 53.3, 37.4, 29.6, 26.7, 19.2, 17.8, 13.9; HRMS: m/z calculated for $C_{30}H_{36}O_3NaSi$ 495.0011, found 495.0015.

(3*S*,4*S*)-5-hydroxy-2,4-dimethylpent-1-en-3-yl benzoate (5):

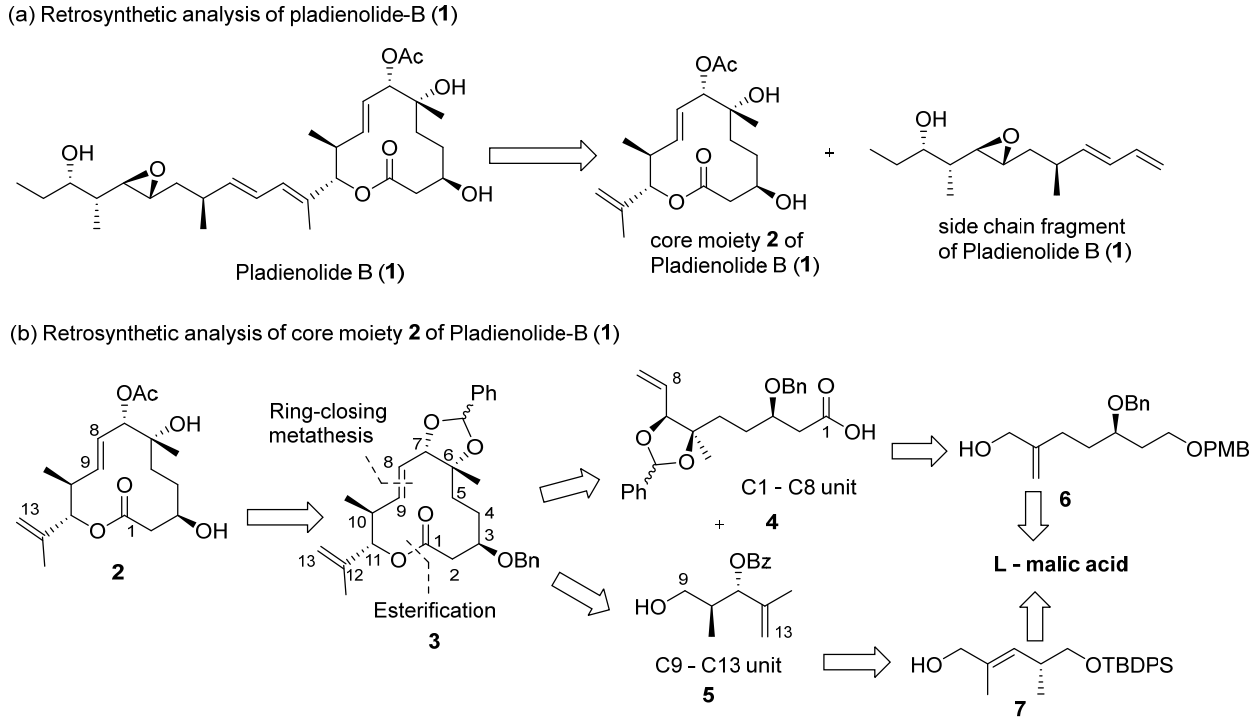
The compound **27** (1.97 g, 4.17 mmol) was dissolved in anhydrous THF (10 mL) and cooled to 0 °C. TBAF (4.2 mL, 4.17 mmol; 1.0 M solution in THF) was then added, and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. Upon completion, the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed successively with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel (60–120 mesh), using 20% EtOAc in petroleum ether as the eluent, to afford the compound **5** (0.58 g, 60%) as a colorless oil; $[\alpha]_D^{25}$ +12.5 (*c* 0.2, $CHCl_3$); IR (neat): 3416, 2935, 1711, 1608, 1514, 1441, 1252, 1101, 1034, 916, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, 2H, J = 6.29 Hz), 7.58 (t, 1H, J = 7.32 Hz), 7.46 (t, 2H), 5.37 (d, J = 9.0 Hz, 1H), 5.07 (s, 1H), 5.01 (s, 1H), 3.65 (m, 2H), 2.09 (m, 2H), 1.8 (s, 3H) 1.01 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 141.6, 134.7, 133.1, 130.0, 129.6, 128.4, 127.6, 115.1, 79.9, 63.9, 37.2, 26.5, 17.8, 13.8; HRMS: m/z calculated for $C_{14}H_{18}O_3Na$ 257.1148, found 257.1151.

3. Results

3.1. Retrosynthesis

The synthesis of Pladienolide B (**1**) was envisaged from its core moiety **2** and the corresponding side-chain fragment, as shown in Scheme 1a. The macrolide core was designed to be assembled through esterification of the C1–C8 acid fragment **4** with the C9–C13 alcohol fragment **5**, followed by ring-closing olefin metathesis (RCM). Retrosynthetic analysis of **2** identified a convergent disconnection into two polyketide subunits, which were traced back to intermediates **6** and **7**, respectively (Scheme 1b) [13]. To minimize the use of multiple non-overlapping chiral starting materials and improve the overall efficiency and

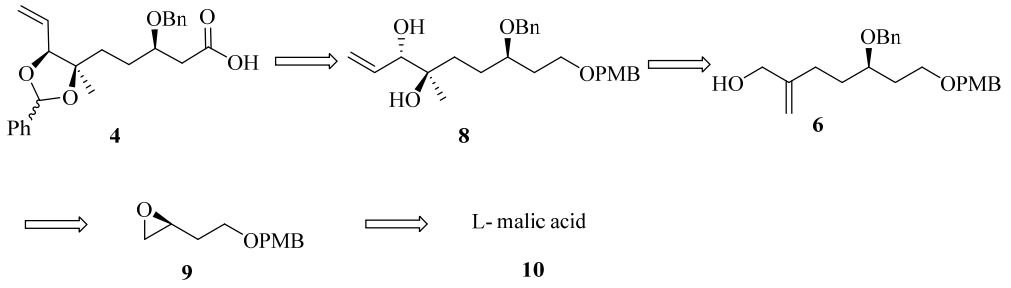
cost-effectiveness of the synthesis, both intermediates were derived from the common chiral-pool precursor L-Malic acid **10**.



Scheme 1. Retrosynthetic analysis of Pladienolide B (**1**).

3.2. Synthesis of C1–C8 Fragment 4 of Pladienolide B (1)

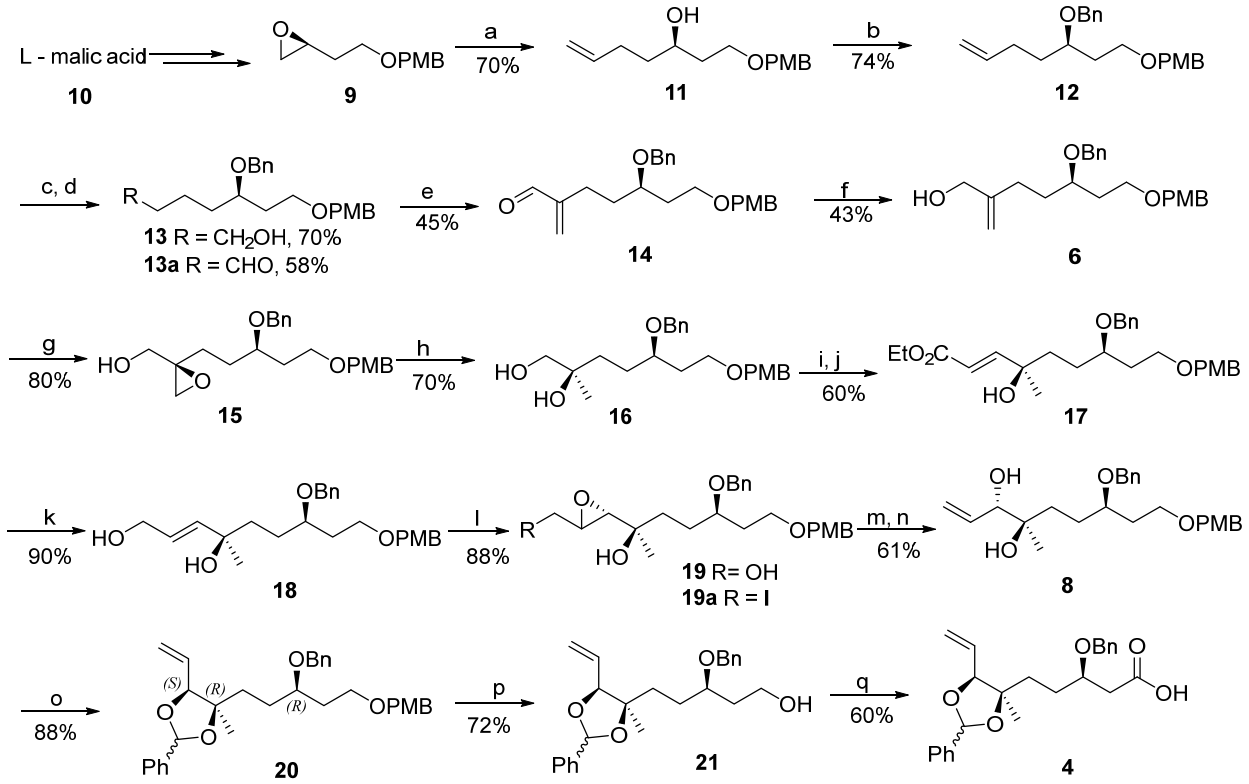
The retrosynthetic plan for the C1–C8 acid fragment **4** is depicted in Scheme 2. Target fragment **4** was envisioned to be accessible from the 1,2-diol **8**, which in turn could be constructed from the allylic alcohol **6** via a sequence involving Sharpless asymmetric epoxidation, regioselective epoxide opening, and functional group transformations. The allylic alcohol **6** could be derived through short, sequential manipulations of known epoxide **9** [21], prepared from L-Malic acid **10**.



Scheme 2. Retrosynthetic analysis of acid fragment **4**.

The forward synthesis commenced with the regioselective ring opening of the epoxide **9** by Grignard reaction with allyl magnesium chloride in ether at −20 °C for 3 h, delivering secondary alcohol **11** in 80% yield (Scheme 3). *O*-Benzylation of the alcohol **11** using benzyl bromide and sodium hydride in anhydrous THF at 0 °C for 5 h afforded the corresponding benzyl ether **12**. Selective hydroboration–oxidation of the terminal alkene in **12** with BH_3.DMS and cyclohexene in THF at 0 °C for 4 h furnished the primary alcohol **13**. Subsequent Swern oxidation of **13a** yielded aldehyde **13b**, which was then subjected

to a Mannich methylene insertion reaction using a preheated mixture of diethylaminem diethylamine and dibromo methane at r.t. for 3 h to afford the α,β-unsaturated aldehyde **14** (enal). Chemo-selective reduction of enal **14** using sodium borohydride in methanol at 0 °C for 0.5 h smoothly afforded the allylic alcohol **6**. Sharpless asymmetric epoxidation of the allylic alcohol **6** using L-(+)-diethyl tartrate, $Ti(iOPr)_4$, and *tert*-butyl hydroperoxide in dichloromethane at −20 °C successfully proceeded the required epoxy stereocenters in the compound **15**. Regioselective reduction of epoxy alcohol **15** with lithium aluminum hydride ($LiAlH_4$) in THF at 0 °C for 1 h afforded the 1,2-diol **16**. Subsequent Swern oxidation of **16**, followed by Wittig homologation using methyl (triphenylphosphoranylidene)-acetate, afforded the corresponding α,β-unsaturated ester **17**.



Reagents and conditions: (a) allyl chloride, Mg, Et_2O,–20 °C, 3 h; (b) BnBr, NaH, THF, 0 °C – rt, 5 h; (c) BH_3.DMS, cyclohexene, THF, 0°C – rt, 4 h; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 2h; (e) Et_2NH, CH_2Br_2, 55 °C – rt, 1 h; (f) $NaBH_4$, CH_3OH, 0 °C – rt, 0.5 h; (g) (–) DIPT, $Ti(iOPr)_4$, CHP, CH_2Cl_2, –20 °C; (h) $LiAlH_4$, THF, 0 °C – rt, 1 h; (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 2h; (j) $Ph_3P{=}CHCO_2Et$, toulene, reflux, 0.5 h; (k) DIBAL–H, CH_2Cl_2, 0 °C – rt, 1 h; (l) (–) DIPT, $Ti(iOPr)_4$, CHP, CH_2Cl_2, –20 °C; (m) Ph_3P, I_2, Imidazole, THF, 0 °C – rt, 0.5 h;(n) Zn, NaI, MeOH, reflux, 4 h; (o) $PhCH(OCH_3)_2$, PTSA, CH_2Cl_2, 0 °C – rt, 3 h; (p) DDQ, CH_2Cl_2: H_2O (19:1), 0 °C – rt, 2 h; (q) TEMPO, BIAB, CH_2Cl_2 : H_2O (1:1), 0 °C – rt, 1 h.

Scheme 3. Synthesis of C1–C8 fragment **4** of Pladienolide B (**1**).

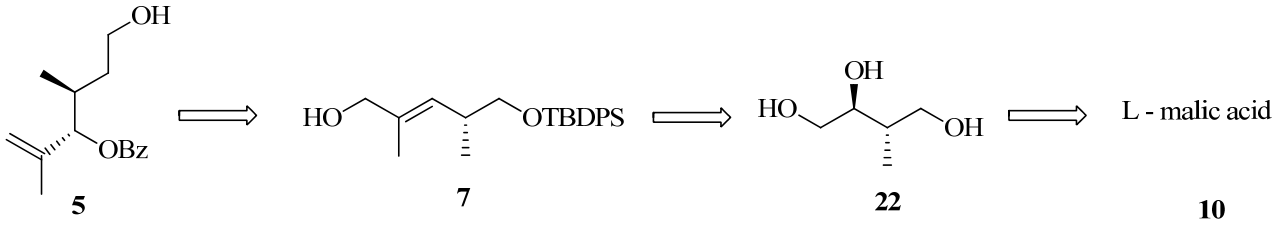
Reduction of the ester **17** using DIBAL-H in dichloromethane at 0 °C for 1 h afforded the corresponding allylic alcohol **18**. A second Sharpless asymmetric epoxidation of the allylic alcohol **18** under identical kinetic resolution conditions delivered the epoxy alcohol **19**. Treatment of the **19** under Appel-type iodination conditions led to the iodomethyl intermediate **19a**. Tandem zinc-promoted reductive elimination of the compound **19a** using zinc powder and sodium iodide in refluxing methanol for 4 h cleanly installed the exo-methylene motif, yielding the diol **8**.

Protection of the diol **8** with benzaldehyde dimethyl acetal using catalytic *p*-toluene sulfonic acid (pTSA) in dichloromethane at 0 °C for 3 h afforded the benzylidene acetal **20**. Oxidative deprotection of the secondary benzyl ether in the compound **20** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in DCM/H_2O mixture (19:1) provided the

primary alcohol **21**. Finally, TEMPO/BAIB-mediated oxidation of the primary alcohol **21** in DCM/H_2O mixture (19:1) at room temperature for 1 h successfully furnished the target C1–C8 acid fragment **4**.

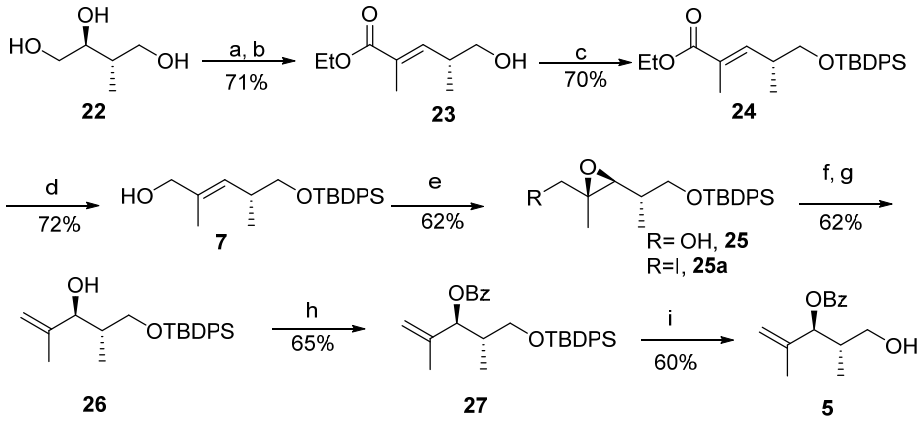
*3.3. Synthesis of the C9–C13 Alcohol Fragment 5 of Pladienolide B (**1**)*

The retrosynthetic strategy for the C9–C13 alcohol fragment **5** is depicted in Scheme 4. The target subunit **5** was envisaged to be derived from allylic alcohol **7**, which could, in turn, be prepared from the known triol **22** through a short sequence of transformations starting from L-malic acid (**10**).



Scheme 4. Retrosynthetic analysis of the C9–C13 fragment 5 of Pladienolide B (**1**).

The forward synthesis commenced with the oxidative cleavage of the triol **22** [21] using sodium periodate ($NaIO_4$) in an acetone/water mixture (5:1) to generate the corresponding aldehyde, as shown in Scheme 5. Subsequent Wittig olefination of this intermediate with ethyl 2-(triphenylphosphoranylidene)propanoate yielded the α,β-unsaturated ester **23** in 71% overall yield over two steps. Protection of the secondary hydroxyl group in the compound **23** as a *tert*-butyldiphenylsilyl (TBDPS) ether using TBDPSCl and imidazole in dichloromethane at 0 °C for 1 h provided the silyl ether **24**. Chemoselective reduction of the ester **24** using DIBAL-H in dichloromethane delivered the alcohol **7** in 72% yield. Sharpless asymmetric epoxidation of the allylic alcohol **7** using L-(+)-diethyl tartrate, $Ti(OiPr)_4$, and *tert*-butyl hydroperoxide (TBHP) in dichloromethane at −20 °C afforded epoxy alcohol **25** with the desired stereochemistry at the epoxide centers. Treatment of the epoxy alcohol **25** under Appel-type conditions afforded the corresponding iodomethyl intermediate **25a**. Subsequent zinc-promoted reductive elimination of **25a** using zinc powder and NaI in refluxing methanol for 4 h furnished the desired 1,1-disubstituted allylic alcohol **26**.



Reagents and conditions: (a) $NaIO_4$, acetone:H_2O (5:1), 0 °C, 0.5 h; (b) $Ph_3P{=}C(CH_3)CO_2Et$, toulene, reflux, 0.5 h; (c) TBDPSCl, imidazole, CH_2Cl_2, 0 °C – rt, 1 h; (d) DIBAL–H, CH_2Cl_2, 0 °C – rt, 1 h; (e) (+)DIPT, $Ti(iOPr)_4$, CHP, CH_2Cl_2, –20 °C, 5 h; (f) Ph_3P, I_2, Imidazole, THF, 0 °C – rt, 0.5 h; (g) Zn, NaI, CH_3OH, reflux, 4 h; (h) BzCl, Et_3N, CH_2Cl_2, 0 °C – rt, 2 h; (i) TBAF, THF, 0 °C – rt, 2 h.

Scheme 5. Synthesis of C9–C13 fragment **5** of Pladienolide B.

Benzoylation of the allylic alcohol **26** with benzoyl chloride in the presence of triethylamine in dichloromethane at 0 °C for 2 h furnished benzoate ester **27**. Finally, fluoride-mediated desilylation of **27** using tetra-*n*-butylammonium fluoride in THF for 2 h smoothly unmasked the primary hydroxyl group, affording the target C9–C13 alcohol fragment **5**.

4. Conclusions

In conclusion, a divergent and stereoselective synthetic strategy was developed for the preparation of the C1–C8 acid fragment **4** and the C9–C13 alcohol fragment **5** of the core moiety **2**. Both fragments were accessed from L-Malic acid (**10**) as a common, inexpensive chiral-pool precursor. The synthesis utilized key asymmetric and stereoselective transformations, including Sharpless asymmetric epoxidation, regioselective epoxide opening, and stereoselective functional-group transformations, to establish the required stereochemical features. This common chiral-pool approach provides a unified route to two stereochemically defined building blocks of Pladienolide B (**1**) and demonstrates the utility of L-Malic acid (**10**) for the synthesis of structurally complex natural product fragments.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/org7040049/s1, Copies of ^{1}H NMR and ^{13} C NMR Spectra of compounds **4**–**8**, **11**–**13**, **15**–**21**, **23**–**27**.

Author Contributions: Conceptualization, M.H.; Methodology, S.K.C., N.A. and M.H.; Formal analysis, S.K.C. and N.A.; Investigation, S.K.C., N.A. and M.H.; Resources, N.A.; Writing—original draft, M.H.; Writing—review & editing, R.R.P.; Supervision, R.R.P.; Project administration, R.R.P.; Funding acquisition, S.K.C. and R.R.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Acknowledgments: The authors gratefully acknowledge the University Grants Commission (UGC) and the Council of Scientific and Industrial Research (CSIR), New Delhi, for their financial support. The authors also acknowledge Gachon University for its financial support.

Conflicts of Interest: The authors declare no conflicts of interest.

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