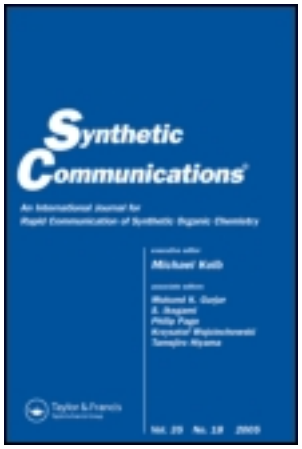

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SYNTHESIS OF (±)-BIMATOPROST

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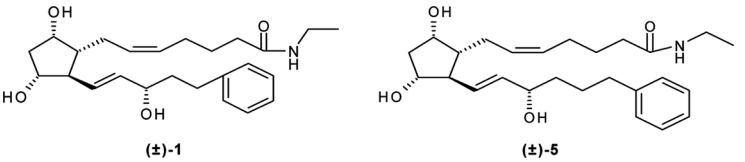
GRAPHICAL ABSTRACT



Abstract *A general synthetic approach has been developed for the synthesis of a key intermediate (**6**) that can be elaborated into several ophthalmic prostaglandins and their derivatives. Using these strategy, we have obtained (±)-bimatoprost (**1**) and its analog, (±)-homobimatoprost (**5**).*

Keywords (±)-Bimatoprost; (±)-homobimatoprost; ophthalmic; prostaglandins

INTRODUCTION

Glaucoma, a potentially blinding eye disorder, is characterized by increased intraocular pressure (IOP), excavation of optic nerve head, and gradual loss of visual field.[1] Initial treatment usually involves topical application of muscarinic agonists, particularly pilocarpine, or adrenergic agonists or antagonists (e.g., epinephrine and timolol, respectively).[2] If treatment with such topically applied drugs is not effective, systemic administration of carbonic anhydrase inhibitors or surgical intervention may be employed.[3] In recent years, attention has been focused on prostaglandins (PGs), primarily prostaglandin $F_{2\alpha}$ esters, as IOP-lowering substances. They have the advantages of mechanism of action and their local and systemic pharmacokinetic profiles.[4] There are currently four prostaglandin analogs [latanoprost (**2**), bimatoprost (**1**), travoprost (**3**), and uniprostone (**4**)[5] (Fig. 1) approved for glaucoma treatment by the U.S. Food and Drug Administration.

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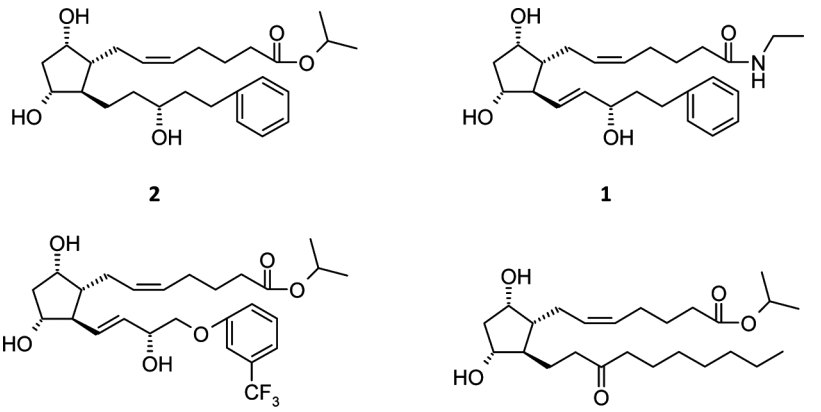


Figure 1. Ophthalmic prostaglandins.

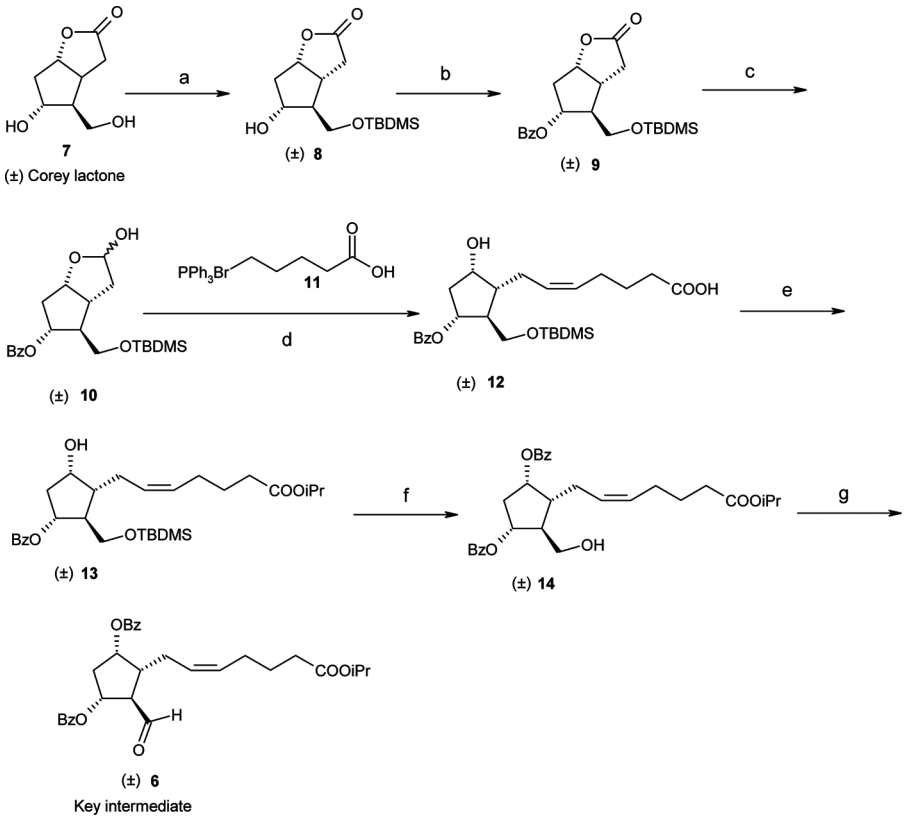
Several studies have established that PGs of the $F_{2\alpha}$ type reduce IOP by increasing uveoscleral outflow of aqueous humor.[6]

The PG ocular hypotensives are PGF_2 derivatives in which the α -side chain has been converted to either ester or amide functionality. These esters are more lipophilic than the corresponding acid and penetrate ocular tissues more readily. In these the ω-side chain is modified with aromatic units. In this article, we report the development of a versatile key intermediate (**6**) from racemic Corey lactone (purchased from Hygeia Laboratories, India), which can be elaborated into a variety of ophthalmic prostaglandins and their derivatives. As a demonstration of this general approach, we have converted key intermediate (**6**) into (±)-bimatoprost (**1**) and (±)-homobimatoprost (**5**), and the details are reported.

RESULTS AND DISCUSSION

Synthesis of Key Intermediate 6 (Scheme 1)

Protection of primary alcohol of Corey lactone (**7**) with TBDMSCl in the presence of imidazole and a catalytic quantity of dimethylaminopyridine in dimethylformamide (DMF) solvent at room temperature gave 8, quantitatively. The secondary hydroxyl group of **8** was benzoylated with benzoyl chloride using triethylamine base in dichloromethane (DCM) solvent at reflux for 2 h followed by the usual workup to obtain **9** in 55% yield after flash column purification. Formation of the desired lactol (**10**) was achieved by reducing **9** with diisobutylaluminumhydride (DIBAL) in tetrahydrofuran (THF) at −78 °C in 77% yield.[7] Wittig reaction of **10** with phosponate reagent **11** in the presence of $KOBu^t$ solution in THF (1 M) at −40 °C gave **12** with 82% yield.[7,8] It was observed that during the preparation of **12**, temperature (−40 °C) and content of KOH (<1.0%) in $KOBu^t$ solution were very critical to avoid debenzoylations. Esterification of **12** with isopropyl iodide using 1,8-diazabicyclo

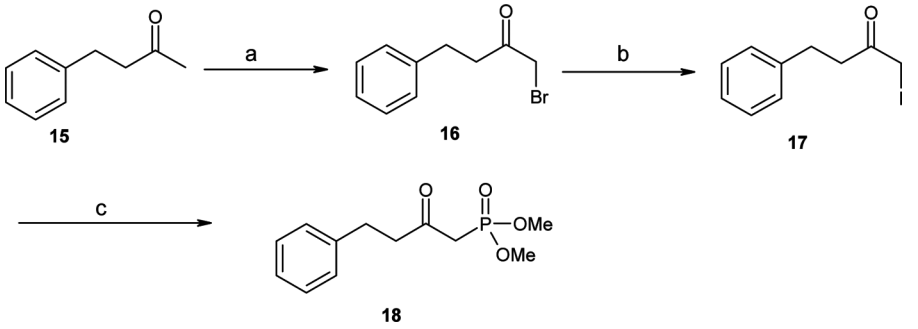


Scheme 1. Reagents: (a) TBDMSCl, imidazole, DMAP, DMF, 4 h, 100%; (b) benzoyl chloride, TEA, DMAP, DCM, 2 h, 55%; (c) DIBAL, THF, 1.5 h, −70 °C, 77%; (d) $KOBu^t$ (1 M soln. in THF), THF, 2 h, −40 °C, 82%; (e) DBU, isopropyl iodide, acetone, 12 h, rt, 92%; (f) benzoyl chloride, TEA, DMAP, DCM, 2 h reflux, 60%; (g) Dess–Martin periodinane, DCM, 1.5 h, 10 °C, 100%.

[5.4.0]undec-7-ene (DBU) in acetone solvent in 12 h at room temperature gave **13** with 92% yield. Free secondary hydroxyl group of **13** was benzoylated with benzoyl chloride using triethylamine followed by deprotection of the *tert*-butyldimethylsilyl (TBDMS) group using tetrabutylammonium fluoride in THF for 2 h at room temperature to give **14** with 60% yield. Oxidation of **14** with Dess–Martin periodinane in DCM gave **6** in quantitative yield.[8,9]

Synthesis of 18[8] (Scheme 2)

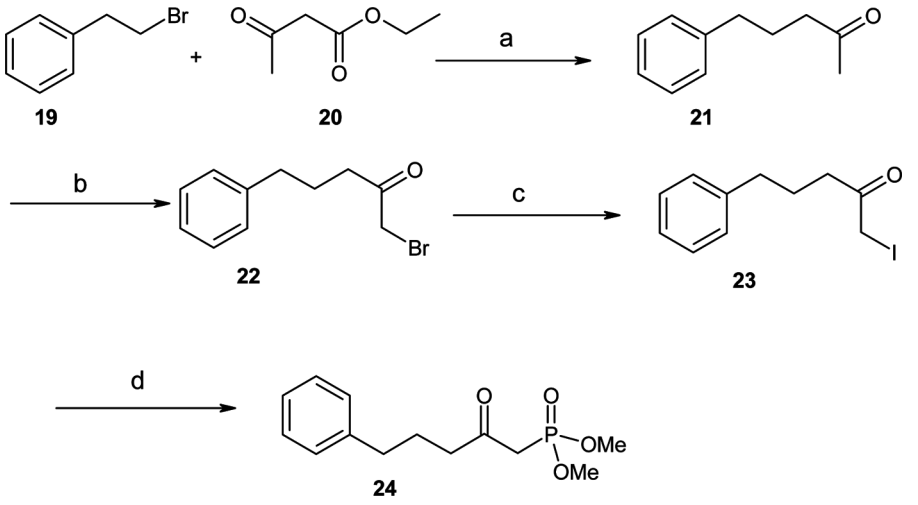
Bromination of benzylacetone (**15**) with bromine in methanol solvent at 10–15 °C for 2 h followed by selective recrystallization (dibromo compound remains in the mother liquor) using hexane gave **16** in 50% yield. Iodination of **16** with sodium iodide in acetone at room temperature for 6 h gave **17** in 80% yield. Reaction of **17** with trimethylphosphite in acetonitrile at reflux temperature for 2 h followed by column purification afforded **18** with 60% yield.



Scheme 2. Reagents: (a) Br, methanol, 2 h, 15–20 °C, 50%; (b) NaI, acetone, 6 h, rt, 83%; (c) trimethylphosphite, acetonitrile, 2 h reflux, 60%.

Synthesis of 24[8,10] (Scheme 3)

Reaction of phenylethyl bromide (**19**) with ethyl acetoacetate (**20**) in the presence of sodium metal in ethanol at reflux temperature followed by usual workup and 50% sulfuric acid treatment at 90 °C for 5 h gave **21** in 40% yield. Bromination of **21** with bromine in methanol at 10–15 °C for 2 h followed by workup and column chromatography gave **22** with 50% yield. Iodination of **22** with sodium iodide in acetone at room temperature for 6 h yielded **23** in 70% and the reaction of **23** with trimethylphosphite in acetonitrile at reflux temperature for 3 h followed by flash column chromatography gave **24** with 50% yield.



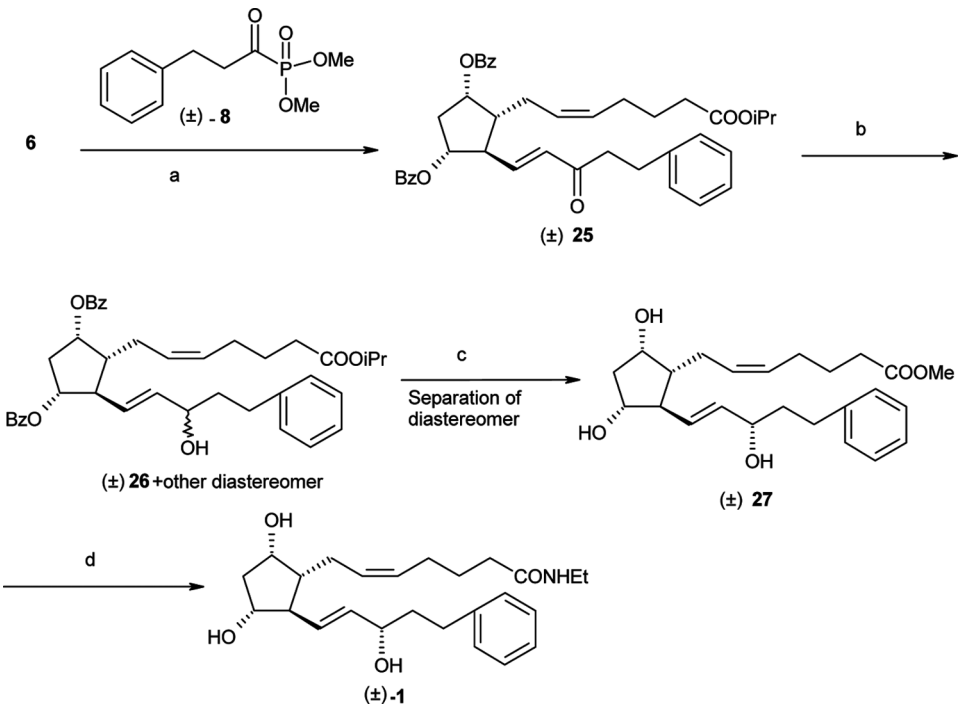
Scheme 3. Reagents: (a) Na, ethanol, 21 h, reflux, 5% NaOH, 5 h, reflux, 50% H_2SO_4, 5 h, 90 °C, 40%; (b) Br, methanol, 2 h, 10–15 °C, 50%; (c) NaI, acetone, 6 h, rt, 70%; (d) trimethylphosphite, acetonitrile, 2 h reflux, 50%.

Synthesis of (±)-Bimatoprost (1) (Scheme 4)

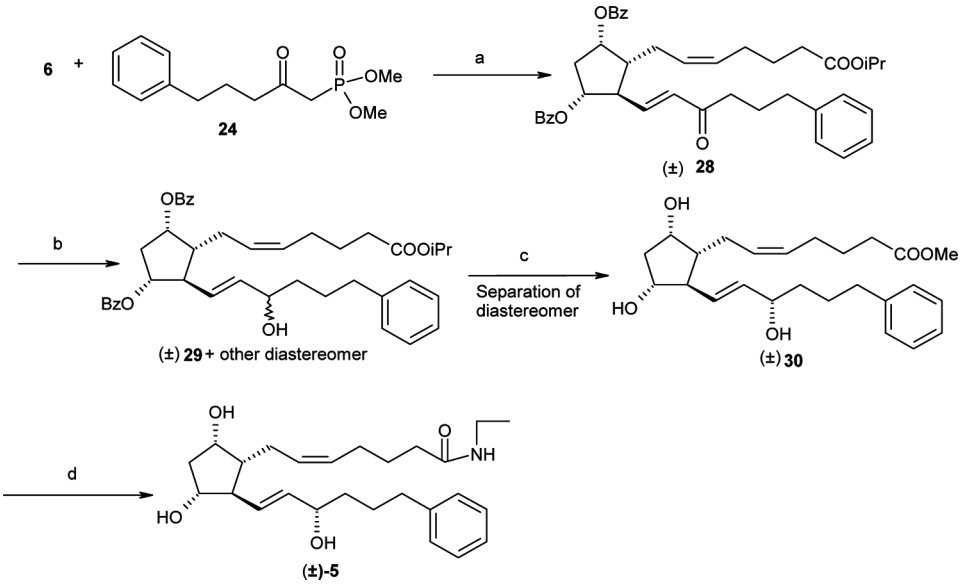
Wittig reaction of **6** with phosphonate reagent **18** in the presence of sodium hydride in dimethoxyethane (DME) solvent for 2 h at 0–5 °C followed by flash chromatography afforded **25**.[7,9] We have studied the synthesis of compound **25** in different solvents such as THF, 2-methyl THF, and DME and found that the best results were obtained using DME as a solvent. Reduction of the keto group on **25** with sodium borohydride in methanol at 25 °C for 30 min yielded compound **26** in 90% yield. Deprotection of both benzoyl groups of **26** with K_2CO_3 in methanol for 6 h at room temperature gave **27** in 30% yield and its diastereo isomer was separated by column chromatography. Trans-esterification was observed from isopropyl ester to methyl ester during deprotection of **26** to **27** in methanol/K_2CO_3. Reaction of **27** with 70% ethylamine solution in water for 12 h at room temperature followed by flash column purification gave **1** with 70% yield. Spectral data for **(±)-1** compare well with those reported for bimatoprost.[11]

Synthesis of (±)-Homobimatoprost (5) (Scheme 5)

The Wittig reaction of **6** with phosphonate reagent **24**[10] in the presence of sodium hydride in DME solvent for 30 min at −30 °C followed by flash chromatography gave **28**[7,9] in 45% yield, and we have observed more impurities when we



Scheme 4. Reagents: (a) NaH, DME, 3 h, rt, 65%; (b) $NaBH_4$, methanol, 0.5 h, rt, 90%; (c) K_2CO_3, methanol, 5 h, rt, diastereo isomer separation, 30%; (d) 40% ethylamine, 12 h, rt, 70%.



Scheme 5. Reagents: (a) NaH, DME, 3 h, rt, 58%; (b) $NaBH_4$, methanol, 0.5 h, rt, 80%; (c) K_2CO_3, methanol, 5 h, rt, diastereo isomer separation, 25%; (d) 40% ethyl amine, 12 h, rt, 70%.

carried out the reaction at 0–5 °C. Reduction of the keto group on **28** with sodium borohydride in methanol at 25 °C for 30 min gave **29** with 80% yield followed by removal of benzoyl groups of **29** with K_2CO_3 in methanol for 6 h at room temperature, which yielded a mixture of diastereomers. The desired diastereo isomer, **30**, was separated by column chromatography. Reaction of 30 with 70% ethylamine solution in water for 12 h at room temperature followed by flash column purification gave **5** with 60% yield.

CONCLUSION

A versatile intermediate **6** was obtained from (±)-Corey lactone, which can be elaborated into all clinical ophthalmic prostaglandins. (±)-Bimatoprost was synthesized using **6**. Using the same strategy, the optically pure ophthalmic prostaglandins can be obtained by starting from chiral pure Corey lactone.

EXPERIMENTAL

All reactions were performed either under an argon or nitrogen atmosphere, unless otherwise mentioned. The progress of the reactions was monitored by thin-layer chromatography (TLC) over silica gel 60 F (E. Merck, 0.25 mm). The chromatograms were visualized by irradiation with ultraviolet light or by heat staining with polyphosphoric acid and p-anisaldehyde in ethanol/sulfuric acid. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh), and flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) using the

indicated solvent. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300-MHz Bruker Avance-II NMR Spectrometer using $CDCl_3$ as solvent. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR 1605 spectrometer. Mass spectra were measured on Waters Quatro Micro mass spectrometer.

4-((*tert*-Butyldimethylsilyloxy)methyl)-5-hydroxyhexahydro-2H-cyclopenta[b]furan-2-one (8)

A solution of **7** (50 g, 290.69 mmol) in DMF (180 mL) was added to a mixture of dimethylaminopyridine (DMAP) (0.035 g, 0.29 mmol) and imidazole (29.68 g, 436.03 mmol) at 25 °C. The reaction mixture was cooled to 0 °C and stirred for 10 min at 0 °C. TBDMSCl (52.5 g, 348.3 mmol) in DMF (70 mL) was added slowly to the reaction mass at 0 °C and stirred for 10 min at 0 °C. The reaction mass temperature was allowed to raise to 25 °C and stirred for 4 h at 25 °C, at which point TLC indicated complete conversion of **7** to **8**. The resulting reaction mixture was added to water (2 L) and EtOAc (1 L) at 25 °C and stirred for 45 min. Both layers were separated, and the aqueous layer was extracted with EtOAc (2×100 mL). The organic layer was washed with water (500 mL) followed by brine solution (500 mL), dried over Na_2SO_4, and concentrated at 40 °C under vacuum to get 83.19 g of **8 (**100%) as a viscous syrup.

IR (KBr cells): 3379, 2896, 2926, 1758, 1468, 1359, 1208, 1108, 1089 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H, $Si(CH_3)_2$), 0.88 [s, 9H, $(CH_3)_3$], 1.93–2.02 (m, 3H, CH_2, CH), 2.46–2.49 (m, 2H, CH_2), 2.78 (dd, $J = 17.7$, 9.9 Hz, 1H, CH), 3.58 (dd, $J = 9.9$, 6.6 Hz, 1Ha), 3.71 (dd, $J = 10.2$, 5.1 Hz, 1Hb), 4.12 (q, $J = 6.3$ Hz, 1H, CH), 4.90 (td, $J = 6.9$, 2.7, 1H, CH); MS (ES): m/z 287 $(M + H)^+$.

4-((*tert*-Butyldimethylsilyloxy)methyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl Benzoate (9)

A solution of **8** (83.19 g, 290.67 mmol) in DCM (832 mL), TEA (117.43 g, 1162.34 mmol), and DMAP (0.0354 g, 0.29 mmol) were added and stirred at 25 °C under a nitrogen atmosphere. The reaction mass was cooled to 0 °C, and benzoyl chloride (81.67 g, 581.34 mmol) was added slowly into the reaction mass at 0 °C. The reaction mixture temperature was raised to reflux and stirred for 2 h, at which point TLC indicated complete conversion. The reaction mass temperature was cooled to 25 °C, MeOH (100 mL) was added, and the mixture was heated to reflux for 20 min. The resulting reaction mixture was cooled to 25 °C and concentrated under vacuum at 40 °C to get the residue. The residue was dissolved in water (500 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×200 mL). The organic layer was washed with brine (500 mL), dried over Na_2SO_4, and concentrated at 40 °C under vacuum to get crude **9**. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) with an ethyl acetate–hexane (1:1) as eluent to give 62.72 g of **9** (160.73 mmol, 55.3%) as a colorless viscous liquid.

IR (KBr cells): 2930, 2857, 1717, 1584, 1452, 1277, 1109, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 [s, 6H, $Si(CH_3)_2$], 0.88 [s, 9H, $(CH_3)_3$], 2.28–2.34 (m, 1H, CH), 2.41–2.59 (m, 3H, CH_2, CH), 2.87–2.95 (m, 2H, CH_2), 3.69 (qd, $J = 9.9$, 5.1 Hz, 2H, CH_2), 5.08 (t, $J = 5.7$ Hz, 1H, O-CH), 5.34 (m, 1H, O-CH), 7.43 (t, $J = 7.5$ Hz,

2H, H_{Ar}), 7.55 (m, 1H, H_{Ar}), 7.99 (d, $J = 7.5$ Hz, 2H, H_{Ar}); MS (ES): m/z 391 $(M+H)^+$.

4-((*tert*-Butyldimethylsilyloxy)methyl)-2-hydroxyhexahydro-2H-cyclopenta[b]furan-5-yl Benzoate (10)

A solution of **9** (60 g, 153.76 mmol) in THF (1.2 L) was cooled to −70 °C, and 1 M DIBAL solution in THF (600 mL) was added slowly to the reaction mixture at −70 °C and stirred for 1.5 h at −70 °C. Sodium bisulfate (15%,500 mL) was slowly added to reaction mass at −70 °C, and the reaction mass temperature was raised to −30 °C. The mixture was stirred for 20 min at −30 °C. The resulting mixture temperature further raised to 25–30 °C, both layers were separated, and the aqueous layer was extracted with EtOAc (2 × 250 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum at 40 °C to give 54.2 g of **10** (138.45 mmol, 90%) as a pale yellow viscous liquid. IR (KBr cells): 3093, 2955, 2928, 1776, 1719, 1450, 1272, 1100, 1070, 838, 714 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 0.04 [s, 6H, $Si(CH_3)_2$], 0.89 [s, 9H, $(CH_3)_3$], 1.98–2.27 (m, 4H, CH_2), 2.43–2.49 (m, 1H, CH), 2.68–2.74 (m, 1H, CH), 3.64–3.73 (m, 2H, CH_2), 4.79 (td, $J = 6.6$, 2.1 Hz, 1H, CH), 5.22–5.27 (m, 1H, CH), 5.67–5.71(m, 1H, CH), 7.43 (t, $J = 7.2$ Hz, 2H, H_{Ar}), 7.53–7.57 (m, 1H, H_{Ar}), 8.00 (d, $J = 7.2$ Hz, 2H, H_{Ar}); MS (ES): m/z 415 $(M + Na)^+$.

(*Z*)-7-(3-(Benzoyloxy)-2-((*tert*-butyldimethylsilyloxy)methyl)-5-hydroxycyclopentyl)hept-enoic Acid (12)

A solution of **11** (208.3 g, 469.14 mmol) in THF (230 mL) was cooled to −40 °C under a nitrogen atmosphere. Potassium *tert*-butoxide 1 M solution (937.5 mL, 938.2 mmol) in THF was added at −40 °C and stirred for 30 min at −40 °C. Compound **10** (46 g, 117.28 mmol) in THF (230 mL) was added slowly to the reaction mass at −40 °C. The reaction mass temperature was maintained at −40 °C for 2 h, at which point TLC indicated complete conversion. Reaction mass temperature was raised to −20 °C, and pH was adjusted to 6–7 with 10% citric acid solution. The resulting mass was concentrated to remove THF, and further pH of constants was adjusted to 4 using 10% citric acid solution. The aqueous layer was extracted with EtOAc (3 × 200 mL), and combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated at 40 °C under vacuum to get the crude material. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) with an ethyl acetate–hexane (4:6) as eluent to give 46.0 g of **12** (96.49 mmol, 82.3%) as a yellow viscous liquid.

IR (KBr cells): 3006, 2952, 2929, 1714, 1596, 1451, 1316, 1277, 1100, 837, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.06 [s, 6H, $Si(CH_3)_2$], 0.86 [s, 9H, $(CH_3)_3$], 1.71 (t, $J = 7.5$ Hz, 2H, CH_2), 1.74–1.89 (m, 3H, CH_2, CH), 1.99–2.45 (m, 7H, $3CH_2$, CH), 3.66–3.69 (m, 1Ha), 3.89–3.94 (m, 1Hb), 4.22–4.27 (m, 1H, CH), 5.30–5.43 (m, 3H, CH), 7.42–7.48 (m, 2H, H_{Ar}), 7.56–7.60 (m, 1H, H_{Ar}), 8.02–8.06 (m, 2H, H_{Ar}); MS (ES): m/z 499 $(M + Na)^+$.

(*Z*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4-hydroxy-3-(7-isopropoxy-7-oxohept-2-enyl)cyclopentyl Benzoate (13)

A solution of **12** (46.0 g, 96.49 mmol) in acetone (1.0 L) was cooled to −5 °C, and DBU (88.12 g, 578.98 mmol) was added slowly to reaction mass at −5 °C. The reaction mass temperature raised to 25 °C and stirred for 30 min at 25 °C. Isopropyl iodide (81.97 g, 482.48 mmol) was slowly added to the reaction mass at 25 °C and stirred for 12 h at 25 °C, at which point TLC indicated complete conversion of **12** to **13**. The reaction mass was concentrated under vacuum at 40 °C to get the residue. The residue was dissolved in EtOAc (1000 mL), 10% citric acid (500 mL) solution was added and stirred for 10 min at 25 °C (clear solution was observed). The organic layer was separated and washed with 10% citric acid (500 mL), 5% sodium bicarbonate solution (500 mL), and brine solution (500 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum at 40 °C to get 46 g of **13** (88.68 mmol, 92%) as a yellow viscous liquid.

IR (KBr cells): 3413, 2952, 2929, 1719, 1451, 1361, 1277, 1108, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 [s, 6H, $Si(CH_3)_2$], 0.87 [s, 9H, $(CH_3)_3$], 1.21 (d, $J = 6.3$ Hz, 6H, $3CH_2$), 1.69 (t, $J = 7.5$ Hz, 2H, CH_2), 1.73–1.95 (m, 3H, CH_2, CH), 2.03–2.52 (m, 7H, $3CH_2$, CH), 3.67 (dd, $J = 10.2$, 3.6 Hz, 1Ha,), 3.93 (dd, $J = 10.2$, 3.6 Hz, 1Hb), 4.22–4.26 (m, 1H, CH), 4.95–5.01 (m, 1H, CH), 5.32–5.47 (m, 3H, 3CH), 7.40–7.45 (m, 2H, H_{Ar}), 7.54–7.57 (m, 1H, H_{Ar}), 8.00–8.03 (m, 2H, H_{Ar}); MS (ES): m/z 519 $(M + H)^+$.

(*Z*)-4-(Hydroxymethyl)-5-(7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl Dibenzoate (14)

A solution of **13** (46.0 g, 88.68 mmol) in CH_2Cl_2 (460 mL) was cooled to 10 °C, and TEA (71.75 g, 710.39 mmol) and DMAP (0.014 g, 0.116 mmol) were added at 25 °C under a nitrogen atmosphere. The reaction mass was cooled to 0 °C, and benzoyl chloride (49.72 g, 355.14 mmol) was added slowly into the reaction mass at 0 °C. The reaction mixture was refluxed for 2 h, at which point TLC indicated complete conversion. The reaction mass temperature was cooled to 25 °C, and MeOH (50 mL) was added and heated to reflux for 20 min. The resulting reaction mixture was cooled to 25 °C and evaporated under vacuum at 40 °C to get the residue. The residue was dissolved in CH_2Cl_2 (600 mL) and washed with water (2 × 200 mL). The organic layer was washed with brine (200 mL), dried over Na_2SO_4, and concentrated at 40 °C under vacuum to get the crude material. The crude in THF (400 mL) was cooled to 0–5 °C; TBAF (102.9 mL, 103.0 mmol) was added at 0–5 °C and stirred for 60 min at room temperature, at which point TLC indicated complete conversion. Water (300 mL) was added to the reaction mass at room temperature and extracted with ethyl acetate (200 mL). The ethyl acetate layer was washed with 5% sodium bicarbonate solution (100 mL) and the organic layer was dried over anhydrous Na_2SO_4. The organic layer was concentrated to get the crude, which was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate–hexane (2:8) as eluent to give 27.0 g of **14** (53.28 mmol, 60%) as a pale yellow viscous liquid.

IR (KBr cells): 3490, 3063, 2979, 2933, 1717, 1585, 1451, 1374, 1272, 1111, 1071, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 [d, $J = 6.3$ Hz, 6H, $(CH_3)_2$], 1.51–1.57 (m, 2H, CH_2), 1.91–1.97 (m, 3H, CH_2, CH), 2.08 (t, $J = 7.5$ Hz, 2H, CH_2), 2.32–2.37 (m, 5H, $2CH_2$, CH), 3.73 (dd, $J = 11.1$, 6.9 Hz, 1Ha), 3.91 (dd, $J = 11.1$, 3.6 Hz, 1Hb), 4.92–4.96 (m, 1H, CH), 5.37–5.48 (m, 4H, 4CH), 7.23 (t, $J = 7.5$ Hz, 2H, H_{Ar}), 7.40 (t, $J = 7.5$ Hz, 2H, H_{Ar}), 7.43–7.47 (m, 1H, H_{Ar}), 7.55–7.58 (m, 1H, H_{Ar}), 7.84 (dd, $J = 8.1$, 1.2 Hz, 2H, H_{Ar}), 8.08 (dd, $J = 8.1$, 1.2 Hz, 2H, H_{Ar}); MS (ES): m/z 509 $(M + H)^+$.

(*Z*)-4-Formyl-5-(7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl Dibenzoate (6)

A suspension of Dess–Martin periodinane (44.8 g, 106.7 mmol) in CH_2Cl_2 (675 mL) was cooled to 0 °C under a nitrogen atmosphere and stirred for 10 min. Compound **14** (45 g, 88.9 mmol) in CH_2Cl_2 (125 mL) was added slowly to the reaction mass at 0 °C. The reaction mass temperature was raised to 10 °C and stirred for 1.5 h at 15 °C, at which point TLC indicated complete conversion. The reaction mixture was added to a mixture of sodium thiosulfate (900 mL) and aqueous sodium bicarbonate solution (180 mL) at 15 °C and stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×200 mL). Combined organic layers were washed with saturated sodium bicarbonate solution (3×200 mL) followed by brine (2×100 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum at 40 °C to get **6** with quantitative yield as a colorless viscous liquid.

IR (KBr cells): 2948, 2939, 2843, 1728, 1712, 1472, 1357, 1268, 1109, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 [d, $J = 6.3$ Hz, 6H, $(CH_3)_2$], 1.56–1.60 (m, 2H, CH_2), 1.93–1.97 (m, 2H, CH_2), 2.09 (t, $J = 7.5$ Hz, 2H, CH_2), 2.17–2.62 (m, 5H, $2CH_2$, CH), 3.10–3.16 (m, 1H, CH), 4.89–4.96 (m, 1H, CH), 5.36–5.41 (m, 2H, 2CH), 5.48–5.54 (m, 2H, 2CH), 7.29 (t, $J = 8.1$ Hz, 2H, H_{Ar}), 7.41 (t, $J = 8.1$ Hz, 2H, H_{Ar}), 7.48–7.52 (m, 1H, H_{Ar}), 7.55–7.58 (m, 1H, H_{Ar}), 7.89 (dd, $J = 8.1$, 1.2 Hz, 2H, H_{Ar}), 8.06 (dd, $J = 8.1$, 1.2 Hz, 2H, H_{Ar}), 10.07 (d, $J = 2.1$ Hz, aldehyde -CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.70 $(CH_3)_2$, 24.60 (CH_2), 26.29 (CH_2), 26.52 (CH_2), 33.82 (CH_2), 38.67 (CH_2), 45.62 (CH), 63.17 (CH), 67.27 (CH), 75.78 (CH), 126.99, 128.22, 128.37, 129.43, 129.52 (H<u>C</u>=CH), 129.53, 130.09 (HC=<u>C</u>H), 131.05, 133.09, 133.12, 165.62 (Bz C=O), 166.18 (Bz C=O), 172.80 [C<u>O</u>OCH$(CH_3)_2$], 200.54 (aldehyde C=O); MS (ES): m/z 529 $(M + Na)^+$; HRMS (ESI): calcd. for $C_{30}H_{34}O_7$ $NH_4[M + NH_4]^+$ 524.2643; found 524.2629.

1-Bromo-4-phenylbutan-2-one (16)

A solution of **15** (100.0 g, 675 mmol) in methanol (400 mL) was cooled to −5 to 0 °C, and bromine (40.3 mL, 783 mmol) dissolved in precooled methanol (200 mL) was added at −5 to 0 °C over a period of 50 min. Reaction mass temperature was raised to 15–20 °C and stirred for 2 h, at which point TLC indicated, complete conversion of the product. The reaction mass was added to water at 5–10 °C and stirred for 10 min, and both layers were separated. The organic layer was added to hexane (200 mL) and stirred for 0–5 °C for 30 min. The resulting mass was filtered, and the

product obtained was washed with 2×100 mL hexane to get 76.0 g of **16**[8b] (337 mmol, 50%) as a white crystalline solid. Mp 39–40 °C; IR (KBr): 3085, 3029, 2933, 2866, 1719, 1497, 1388, 756, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.92–3.05 (m, 4H, $2CH_2$), 3.84 (s, 2H), 7.18–7.24 (m, 5H, H_{Ar}).

1-Iodo-4-phenylbutan-2-one (17)

Compound **16** (50 g, 220 mmol) in acetone (200 mL) was added to a suspension of sodium iodide (33.3 g, 220 mmol) in acetone (300 mL) at room temperature, and the reaction mass was stirred for 6 h at room temperature, at which point TLC indicated, complete conversion of **17**. The resulting mass was filtered, and the cake was washed with acetone (100 mL). The filtrate was concentrated to get the residue. The residue was dissolved in DCM (300 mL) and washed with water (100 mL) followed by 10% sodium thiosulfate solution (100 mL). The organic layer was evaporated under vacuum at 40 °C to get 50 g of **17**[8] (182 mmol, 83%) as a yellow crystalline solid.

Mp 44–45 °C; IR (KBr): 3084, 3027, 2988, 2928, 1711, 1601, 1495, 1378, 753, 551 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.92–3.06 (m, 4H, $2CH_2$), 3.76 (s, 2H, CH_2), 7.18–7.29 (m, 5H, H_{Ar}); MS (ES): m/z 297 $(M + Na)^+$.

Dimethyl 2-Oxo-4-phenylbutylphosphonate (18)

Trimethyl phosphite (57.0 g 460 mmol) was added to a solution of **17** (70.0 g, 255 mmol) in acetonitrile (300 mL) at room temperature over a period of 30 min. The reaction mass temperature was raised to reflux, and the mixture was stirred for 2 h at reflux temperature, at which point TLC indicated complete conversion of **18**. The reaction mass was cooled to 0–5 °C, and 5% sodium hydroxide solution (300 mL) was added at below 15 °C. The resulting mass was extracted with DCM (3×250 mL) and concentrated to get the residue, which was purified by column chromatography to get 39.2 g of **18**[8c] (153 mmol, 60%) as a pale green liquid.

IR (KBr cells): 3062, 3028, 2958, 2927, 1716, 1604, 1497, 1455, 1258, 1185, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.88–2.93 (m, 4H, $2CH_2$), 3.05 (d, $J = 24.0$ Hz, 2H, P-C$\underline{H_2}$), 3.72 [d, $J = 11.2$ Hz, 6H, P-$OCH_3)_2$], 7.15–7.25 (m, 5H, H_{Ar}); MS (ES): m/z 257 $(M + H)^+$.

5-Phenylpentan-2-one (21)

Sodium metal (2.33 g, 101.6 mmol) was added to a solution of ethanol (60 mL), at room temperature under a nitrogen atmosphere and stirred until the sodium dissolved at room temperature. Compound **20** (13.16 g, 102.7 mmol) was added to the reaction mass at room temperature, and stirred for 1 h at reflux. The reaction mass was cooled to room temperature, and **19** (20 g, 108.1 mmol) was added at rt, heated to reflux, and maintained at reflux for 21 h. TLC indicated complete conversion of product, and the resulting mixture was cooled to rt and filtered. The filtrate was concentrated under reduced pressure to get the residue. To the residue, 5% NaOH solution (106 mL) was added at rt and heated at 90 °C for 5 h. The reaction mass was cooled to rt, and 50% sulfuric acid (46 mL) was added at rt. The reaction mass was heated to 90 °C and stirred for 5 h at 90 °C. The resulting mass was cooled to room

temperature, extracted with diethyl ether (2 × 100 mL), dried over Na_2SO_4, and concentrated under vacuum to get the crude product. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate–hexane (9:1) as eluent to give 7 g of **21**[10a] (43.2 mmol, 40%) as a colorless liquid.

IR (KBr cells): 3058, 3025, 2983, 2953, 1718, 1652, 1495, 1427, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.90 (p, $J = 7.5$ Hz, 2H, $CH_2C\underline{H_2}CH_2$), 2.11 (s, 3H, O=C-C$\underline{H_3}$), 2.43 (t, $J = 7.5$ Hz, 2H, CH_2), 2.62 (t, $J = 7.5$ Hz, 2H, CH_2), 7.18–7.28 (m, 5H, H_{Ar}).

1-Bromo-5-phenylpentan-2-one (22)

A solution of **21** (10 g, 61.65 mmol) in methanol (60 mL) was cooled to −5 to 0 °C. Precooled bromine (3.6 mL, 71.51 mmol) in methanol (40 mL) was added slowly to the reaction mass at −5 to 0 °C. After completion of the addition, the reaction mass was maintained at 10–15 °C for 2 h, at which point TLC indicated complete conversion of the product. Water (100 mL) was added to the reaction mass at room temperature and stirred for 1 h. The aqueous layer was extracted with EtOAc (2 × 100 mL), dried over Na_2SO_4, and concentrated under vacuum to get the residue. The residue obtained was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate–hexane (9:1) as eluent to give 7.4 g of **22**[10c] (30.7 mmol, 50%) as a pale brown liquid.

IR (KBr cells): 3062, 3026, 2926, 1715, 1603, 1496, 1393, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.93–1.98 (p, $J = 7.2$ Hz, 2H, $CH_2C\underline{H_2}CH_2$), 2.62–2.68 (m, 4H, $2CH_2$), 3.85 (s, 2H, O=C$\underline{H_2}$-Br), 7.17–7.29 (m, 5H, H_{Ar}); MS (ES): m/z 241 $(M + H)^+$ and 263 $(M + Na)^+$ (bromine isotopic abundance was observed).

1-Iodo-5-phenylpentan-2-one (23)

A suspension of NaI (3.1 g, 21.07 mmol) in acetone (30 mL) was stirred at room temperature. Compound **22** (5 g, 20.73 mmol) in acetone (20 mL) was slowly added to the reaction mass and stirred for 4 h at room temperature, at which point TLC indicated complete conversion of the starting material. The reaction mass was filtered, and the cake was washed with acetone (10 mL). The filtrate was concentrated under vacuum at 40 °C to get the residue and was dissolved in DCM (100 mL) and water (50 mL). Both layers were separated, and the organic layer was washed with water (50 mL) followed by 10% sodium thiosulfate (50 mL), dried over Na_2SO_4, and distilled under vacuum at 40 °C to obtain 4.2 g of **23** (14.53 mmol, 70%) as a pale brown liquid.

IR (KBr cells): 3083, 3026, 2934, 2858, 1706, 1602, 1496, 1367, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.92–1.98 (p, $J = 7.2$ Hz, 2H, $CH_2C\underline{H_2}CH_2$), 2.64 (t, $J = 7.2$ Hz, 2H, CH_2), 2.72 (t, $J = 7.2$ Hz, 2H, CH_2), 3.77 (s, 2H, O=C$\underline{H_2}$-I), 7.18–7.29 (m, 5H, H_{Ar}); MS (ES): m/z 289 $(M + H)^+$; HRMS (ESI): calcd. for $C_{11}H_{13}IO\ NH_4[M + NH_4]^+$ 306.0349; found 306.0336.

Dimethyl 2-Oxo-5-phenylpentylphosphonate (24)

A solution of **23** (4.5 g, 15.6 mmol) in acetonitrile (45 mL) was cooled to 20 °C. Trimethyl phosphite (3.3 mL, 28.1 mmol) was added to the reaction mass at room

temperature. The resulting mass was stirred at reflux for 2 h, at which point TLC indicated complete conversion of the starting material. The reaction mass was cooled to −5 to 0 °C, and 5% NaOH solution (225 mL) was added and stirred for 15 min. Both layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL), dried over Na_2SO_4, and distilled under vacuum at 40 °C to get the crude product. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate–hexane (9:1) as eluent to give 2.1 g of **24**[10d] (7.8 mmol, 50%) as a light green liquid.

IR (KBr cells): 3062, 3026, 2956, 2856, 1714, 1648, 1497, 1371, 1254, 1184, 1031, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.89–1.94 (p, $J = 7.2$ Hz, 2H, $CH_2C\underline{H}_2CH_2$), 2.62 (t, $J = 7.2$ Hz, 4H, $2CH_2$), 3.05 (d, $J = 22.8$, 2H, P-$C\underline{H}_2$), 3.76 [d, $J = 11.2$ Hz, 6H, P-$(OCH_3)_2$], 7.15–7.27 (m, 5H, H_{Ar}); MS (ES): m/z 271 $(M + H)^+$ and 293 $(M + Na)^+$.

(±)-(1*R*,3*S*,4*R*,5*R*)-4-((*Z*)-6-(Isobutyryloxy)hex-2-enyl)-5-((*E*)-3-oxo-5-phenylpent-1-nyl)cyclopentane-1,3-diyl Dibenzoate (25)

A suspension of 55% sodium hydride (6.9 g, 158.1 mmol) in DME (200 mL) was cooled to −5 °C under a nitrogen atmosphere. Compound **18** (37.9 g, 148.22 mmol) was dissolved in DME (100 mL), added slowly to the reaction mass at −5 to 0 °C, and stirred for 15 min at 0 °C. The reaction mass temperature was raised to 25 °C and stirred for 1 h at 25 °C, then cooled to −5 °C. Compound **6** (25 g, 49.34 mmol) dissolved in DME (100 mL) was added slowly to the reaction mass for 30 min at −5 °C. The temperature of the reaction mass was raised to 25 °C and stirred for 1.5 h, at which TLC indicated completion of the reaction. The reaction mixture was cooled to 10 °C, and saturated ammonium chloride solution (250 mL) was added. Then the reaction mass temperature was raised to 25 °C, stirred for 10 min, and concentrated under vacuum at 40 °C. The residue was dissolved in EtOAc (100 mL) and both layers were separated. The aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum at 40 °C. The obtained crude was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate–hexane (1:9) as eluent to give 20.4 g of **25** (32.11 mmol, 65%) as a colorless viscous liquid.

^1H NMR (300 MHz, $CDCl_3$): δ 1.17 [d, $J = 6.3$ Hz, 6H, HC-$(C\underline{H}_3)_2$], 1.35–1.76 (m, 4H, $2CH_2$), 1.78–2.45 (m, 6H, $3CH_2$), 2.55–3.15 (m, 6H, $2CH_2$, 2CH), 4.91–4.97 [m, 1H, $C\underline{H}(CH_3)_2$], 5.30 (m, 1H, OBz-C$\underline{H}$), 5.35 (m, 1H, OBz-C$\underline{H}$), 5.44–5.48 [m, 2H, $\underline{H}C{=}C\underline{H}$(*cis*)], 6.25 [d, $J = 15.9$ Hz, 1H, O=C-C$\underline{H}$ (*trans*)], 6.84 [dd, $J = 15.9$, 8.7 Hz, 1H, HC-C$\underline{H}$ (*trans*)], 7.10–7.38 (m, 7H, H_{Ar}), 7.44 (d, $J = 7.2$ Hz, 2H, H_{Ar}), 7.50 (t, $J = 7.5$ Hz, 1H, H_{Ar}), 7.59 (t, $J = 7.5$ Hz, 1H, H_{Ar}), 7.88–7.91 (m, 2H, H_{Ar}), 8.05–8.08 (m, 2H, H_{Ar}); MS (ES): m/z 659 $(M + Na)^+$; HRMS (ESI): calcd. for $C_{40}H_{44}O_7[M + H]^+$ 637.316; found 637.3178.

(±)-(1*S*, 3*R*, 4*R*, 5*R*)-4-((*E*)-3-Hydroxy-5-phenylpent-1-enyl)-5-((*Z*)-6-(isobutyryloxy)hex-2-enyl)cyclopentane-1,3-diyl Dibenzoate (26)

A solution of **25** (10.0 g, 15.70 mmol) in methanol (100.0 mL) was cooled to 0 °C, and sodium borohydride (1.16 g, 31.40 mmol) was added at 0 °C and stirred

for 10 min. The reaction mass temperature was raised to 25 °C and stirred for 30 min, at which point TLC indicated complete conversion of the reaction. The solvent was distilled out under vacuum at 40 °C. Ammonium chloride solution (100 mL) was added to the residue at 25 °C and stirred for 10 min. Both the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum at 40 °C to obtain the crude. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) with an ethyl acetate–hexane (2:8) as eluent. The pure fractions were combined, and the solvent was removed in vacuo at 40 °C to give 9.0 g of **26** (14.15 mmol, 90%) as a colorless viscous liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, $J = 6.3$ Hz, 6H, HC-($C\underline{H}_3$)$_2$), 1.63–1.67 (m, 2H, CH_2), 1.70–2.35 (m, 12H), 2.66–2.71 (m, 2H, CH_2), 4.07–4.11 [m, 2H, OH-C$\underline{H}$, $\underline{H}$C-(CH_3)$_2$], 4.95–4.99 (m, 1H, OBz-C$\underline{H}$), 5.31–5.34 (m, 1H, OBz-C$\underline{H}$), 5.45–5.49 [m, 2H, $\underline{H}$C=C$\underline{H}$(*cis*)], 5.56–5.61 [m, 2H, $\underline{H}$C-C$\underline{H}$ (*trans*)], 7.08–7.68 (m, 11H, H_{Ar}), 8.00–8.04 (m, 2H, H_{Ar}), 8.04–8.07 (m, 2H, H_{Ar}); MS (ES): m/z 661 $(M + Na)^+$; HRMS (ESI): calcd. for $C_{40}H_{46}O_7$ $NH_4[M + NH_4]^+$ 656.3582; found 656.3589.

(±)-(*Z*)-Methyl7-((1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-((*E*)-3-hydroxy-5-phenylpent-1-nyl)cyclopentyl)hept-5-enoate (27)

Potassium carbonate (8.65 g, 62.61 mmol) was added to a mixture of **26** (10.0 g, 15.65 mmol) in MeOH (100 mL) at 25 °C and stirred for 5 h, at which point TLC indicated complete conversion of the reaction. Demineralized (DM) water (100 mL) was added to the reaction mixture at 25 °C and stirred for 10 min. The pH of the reaction mixture was adjusted to 2 with 10% citric acid (100 mL), and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layers were dried over Na_2SO_4 and concentrated under vacuum at 40 °C to obtain the crude product. The crude product contained two diastereo isomers, and the desired isomer was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate–hexane (6:4) as eluent. The pure fractions were combined, and the solvent was removed in vacuum at 40 °C to give 1.88 g of **27** (4.70 mmol, 30%) as a colorless viscous liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44–1.49 (m, 1H, CH), 1.62–1.67 (m, 2H, CH_2-C$\underline{H}_2$-CH_2), 1.74–2.28 (m, 10H, 5CH_2), 2.31–2.35, [m, 1H, HC-CH (*trans*)-C$\underline{H}$], 2.66–2.73 (m, 2H, Ph-C$\underline{H}_2$), 3.67 (s, 3H, O-CH_3), 3.91–3.96 (m, 1H, HO-C$\underline{H}$), 4.05–4.10 (m, 1H, HO-C$\underline{H}$), 4.10–4.13 (m, 1H, HO-C$\underline{H}$), 5.35–5.40 (m, 2H, $\underline{H}$C=C$\underline{H}$(*cis*)), 5.50–5.61 (m, 2H, $\underline{H}$C=C$\underline{H}$(*trans*)), 7.16–7.21 (m, 3H, H_{Ar}), 7.23–7.27 (m, 2H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.66, 25.29, 26.49, 31.72, 33.30, 38.59, 42.69, 50.40, 51.47, 55.33, 71.44, 72.30, 77.79, 125.68, 128.25, 128.30, 129.46, 131.92, 133.22, 135.13, 141.82, 174.32; MS (ES): m/z 410 $(M + Na)^+$; HRMS (ESI): calcd. for $C_{24}H_{34}O_5$ Na $[M + Na]^+$ 425.2298; found 425.2318.

(±)N-((*Z*)-6-((1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-((*E*)-3-hydroxy-5-phenylpent-1-enyl)cyclopentyl)hex-4-enyl)propionamide (1)

A solution of **27** (500.0 mg, 1.2 mmol) in ethylamine (70%) in water solution (15.0 mL) was stirred for 12 h at 25 °C, at which point TLC indicated complete

conversion of the reaction. The reaction mass was concentrated under vacuum to distill off ethylamine from the reaction mass. Water (10 mL) was added to the reaction mixture at 25 °C and stirred for 10 min, and then the aqueous layer was extracted with EtOAc (3×20 mL). The organic layers were dried over Na_2SO_4 and concentrated under vacuum at 40 °C to give the crude product. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate–hexane (9:1) followed by EtOAc–methanol (9.5:0.05) as eluent to give 360 mg of **1**[11] (0.87 mmol, 70%) as a pale yellow viscous liquid.

IR (KBr cells): 3323, 3025, 2931, 2862, 1758, 1645, 1634, 1558, 1454, 1295, 1031, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, 3H, $J = 7.2$ Hz, N-CH_2-$C\underline{H}_3$), 1.46–1.52 (m, 1H, CH), 1.66–2.26 (m, 12H, $6CH_2$), 2.33–2.37 (m, 1H, CH), 2.70–2.75 (m, 2H, $\underline{H}$C-Ph), 3.23–3.28 (m, 2H, N-$C\underline{H}_2$-CH_3), 3.93–3.98 (m, 1H, $\underline{H}$C-OH), 4.08–4.13 (m, 1H, $\underline{H}$C-OH), 4.15–4.20 (m, 1H, $\underline{H}$C-OH), 5.38–5.43 [m, 2H, $\underline{H}$C=C$\underline{H}$(*cis*)], 5.55 (br, NH), 5.52–5.61 (m, 2H, $\underline{H}$C-C$\underline{H}$(*trans*)), 7.16–7.21 (m, 3H, H_{Ar}), 7.23–7.27 (m, 2H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.72, 25.45, 26.51, 27.22, 34.31, 35.66, 35.73, 36.70, 42.85, 50.55, 51.00, 55.63, 72.36, 72.93, 78.05, 125.60, 128.18, 128.30, 129.59, 132.55, 134.72, 142.28, 173.08; MS (ES): m/z 438 $(M + Na)^+$.

(±)-(1*R*,3*S*,4*R*,5*R*)-4-((*Z*)-6-(Isobutyryloxy)hex-2-enyl)-5-((*E*)-3-oxo-6-phenylhex-1-enyl)cyclopentane-1,3-diyl Dibenzoate (28)

A suspension of 55% sodium hydride (0.68 g, 15.8 mmol) in DME (12.5 mL) was cooled to −5 °C under a nitrogen atmosphere.Compound **24** (4.2 g, 14.8 mmol) was dissolved in DME (12.5 mL), added slowly to the reaction mass at −5 to 0 °C and stirred for 15 min at 0 °C. The reaction mass was raised to 25 °C and stirred for 1 h at 25 °C, then cooled to −5 °C. Compound **6** (2.5 g, 4.9 mmol) dissolved in DME (12.5 mL) was added slowly to the reaction mass for 30 min at −5 °C. The temperature of the reaction mass was raised to 25 °C and stirred for 1.5 h, at which point TLC indicated completion of the reaction. The reaction mixture was cooled to 10 °C, and saturated ammonium chloride solution (25 mL) was added. The reaction mass was raised to 25 °C, stirred for 10 min, and concentrated under vacuum at 40 °C to get the residue. The residue was dissolved in EtOAc (50 mL), and the aqueous layer was separated and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine solution, dried over Na_2SO_4, and concentrated under vacuum at 40 °C to get the crude product. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate–hexane (3:7) as eluent to give 1.86 g **28** (2.86 mmol, 58%) as a colorless viscous liquid.

^1H NMR (300 MHz, $CDCl_3$): δ 1.18 [d, $J = 6.3$ Hz, 6H, HC-($C\underline{H}_3$)$_2$], 1.47–1.52 (m, 2H), 1.73–2.49 (m, 12H), 2.57–2.65 (m, 5H, $2CH_2$, CH), 2.97–2.99 (m, 1H, CH), 4.89–4.98 [m, 1H, C$\underline{H}$(CH_3)$_2$], 5.33–5.47 [m, 4H, $\underline{H}$C=C$\underline{H}$(*cis*), benzoyl $(CH)_2$], 6.24 [dd, $J = 15.9$, 0.6 Hz, 1H, O=C-C$\underline{H}$ (*trans*)], 6.80 [dd, $J = 15.9$, 9.0 Hz, 1H, HC-C$\underline{H}$ (*trans*)], 7.16–7.20 (m, 3H, H_{Ar}), 7.24–7.35 (m, 4H, H_{Ar}), 7.42–7.65 (m, 4H, H_{Ar}), 7.88–7.91 (m, 2H, H_{Ar}), 8.05–8.08 (m, 2H, H_{Ar}); MS (ES): m/z 651 $(M + H)^+$ and 673 $(M + Na)^+$; HRMS (ESI): calcd. for $C_{41}H_{46}O_7$ $NH_4[M + NH_4]^+$ 668.3582; found 668.3589.

(±)-(1*S*,3*R*,4*R*,5*R*)-4-((*E*)-3-Hydroxy-6-phenylhex-1-enyl)-5-((*Z*)-6-(Isobutyryloxy)hex-2-enyl)cyclopentane-1,3-diyl Dibenzoate (29)

A solution of **28** (2.0 g, 3.0 mmol) in methanol (20.0 mL) was cooled to 0 °C and sodium borohydride (0.22 g, 5.94 mmol) was added at 0 °C, and stirred for 10 min. The reaction mass temperature was raised to 25 °C and stirred for 30 min, at which point TLC indicated complete conversion of the reaction. Methanol was distilled out under vacuum at 40 °C to get the residue. Ammonium chloride solution (20 mL) was added to the residue at 25 °C and stirred for 10 min. Both layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum at 40 °C to obtain the crude. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate–hexane (2:8) as eluent to give 1.6 g of **29** (2.45 mmol, 80%) as a colorless viscous liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 [d, $J = 6.3$ Hz, 6H, HC-($C\underline{H}_3$)$_2$], 1.48–1.82 (m, 11H), 2.04–2.29 (m, 5H, $2CH_2$, CH), 2.63 (t, $J = 7.5$ Hz, 2H, CH_2), 3.91–3.96 (m, 1H, HO-C$\underline{H}$), 4.08–4.12 (m, 1H, BzO-C$\underline{H}$), 4.20 (t, $J = 3.6$ Hz, 1H, BzO-C$\underline{H}$), 4.98–5.03 [m, 1H, $\underline{H}C(CH_3)_2$], 5.37–5.42 [m, 2H, $\underline{H}C{=}C\underline{H}$(*cis*)], 5.48–5.58 [m, 2H, $\underline{H}C$-C$\underline{H}$ (*trans*)], 7.13–7.30 (m, 5H, H_{Ar}), 7.40–7.62 (m, 6H, H_{Ar}), 7.98–8.10 (m, 4H, H_{Ar}); MS (ES): m/z 675 $(M + Na)^+$.

(±)-(*Z*)-Methyl-7-((1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-((*E*)-3-hydroxy-6-phenylhex-1-enyl)cyclopentyl)hept-5-enoate (30)

Potassium carbonate (1.27 g, 9.2 mmol) was added at 25 °C to a mixture of **29** (1.5 g, 2.3 mmol) in MeOH (15 mL), and stirred for 5 h, at which point TLC indicated complete conversion of the reaction. DM water (15 mL) was added to the reaction mixture at 25 °C and stirred for 10 min. The pH of the reaction mixture was adjusted to 2 with 10% citric acid (15 mL), and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum at 40 °C to get the crude product. The crude product contained two diastereo isomers, and the desired stereo isomer was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate–hexane (1:1) as eluent to give 0.23 g of **30** (0.57 mmol, 25%) as a colorless viscous liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40–1.88 (m, 4H), 2.00–2.48 (m, 11H, $5CH_2$, CH), 2.52–2.68 (m, 3H, CH_2, CH), 3.66 (s, 3H, COOC$\underline{H}_3$), 3.90–3.96 (m, 1H, HO-C-$\underline{H}$), 4.07–4.15 (m, 2H, (HO-C$\underline{H}$)$_2$), 5.35–5.41 [m, 2H, $\underline{H}C{=}C\underline{H}$(*cis*)], 5.50–5.58 [m, 2H, $\underline{H}$C-C$\underline{H}$ (*trans*)], 7.14–7.18 (m, 3H, H_{Ar}), 7.23–7.29 (m, 2H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 25.44, 26.43, 27.19, 33.23, 35.67, 36.65, 42.81, 50.55, 51.53, 55.43, 72.11, 72.79, 77.95, 125.60, 128.18, 128.29, 129.14, 129.39, 131.83, 134.63, 142.25, 174.40; MS (ES): m/z 439 $(M + Na)^+$; HRMS (ESI): calcd. for $C_{25}H_{36}O_5$ Na $[M + Na]^+$ 439.2455; found 439.2475.

(±)-(*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-((*E*)-3-hydroxy-6-phenylhex-1-enyl)cyclopentyl)-*N*-ethylhept-5-enamide (5)

A solution of **30** (0.2 g, 0.48 mmol) in ethylamine (70% in water) solution (6.0 mL) was stirred for 12 h at 25 °C, at which point TLC indicated complete

conversion of the reaction. The reaction mass was concentrated under vacuum at less than 50 °C to get the residue. Water (6 mL) was added to the residue at 25 °C and stirred for 10 min, and the aqueous layer was extracted with EtOAc (3×10 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum at 40 °C to get the crude. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) with ethyl acetate as eluent to give 0.14 g of **5** (0.336 mmol, 70%) as a pale yellow viscous liquid.

IR (KBr cells): 3306, 3089, 2934, 1645, 1634, 1557, 1454, 1375, 1078, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, $J = 7.2$ Hz, 3H, C<u>H</u>$_3$), 1.52–1.83 (m, 10H), 2.05–2.36 (m, 6H, 2C<u>H</u>$_2$, 2C<u>H</u>), 2.63 (t, $J = 7.5$ Hz, 2H), 3.22–3.31 (m, 2H, N-C-<u>H</u>$_2$CH$_3$), 3.94–3.96 (m, 1H, HO-C<u>H</u>), 4.10 (t, 1H, $J = 7.2$ Hz, HO-C<u>H</u>), 4.15–4.19 (m, 1H, HO-C<u>H</u>), 5.36–5.41 [m, 2H, <u>H</u>C=C<u>H</u>(*cis*)], 5.51–5.54 [m, 2H, <u>H</u>C-C<u>H</u> (*trans*)], 5.56–5.61 (m, NH), 7.14–7.30 (m, 5H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.68, 25.52, 26.58, 27.28, 34.29, 34.39, 35.65, 35.76, 36.63, 42.81, 50.09, 55.35, 72.29, 72.70, 77.61, 125.59, 128.17, 128.28, 129.13, 129.55, 132.84, 135.06, 142.29, 173.31; MS (ES): m/z 452 $(M + Na)^+$; HRMS (ESI): calcd. for $C_{26}H_{39}NO_4Na$ $[M + Na]^+$ 452.2771; found 452.2767.

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