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Synthesis of 2-Normisoprostol, Methyl 6-(3-Hydroxy-2-((*E*)-4-hydroxy-4-methyloct-1-enyl)-5-oxocyclopentyl)hexanoate

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Abstract: Synthesis of 2-normisoprostol, methyl 6-(3-hydroxy-2-((*E*)-4-hydroxy-4-methyloct-1-enyl)-5-oxocyclopentyl)hexanoate (**3**), employing two-component coupling strategy based on 1,4-addition followed by DDQ-mediated triethyl silyl deprotection is reported. Desired key intermediates, methyl 6-(3-triethyl silyloxy-5-oxocyclopent-1-enyl)hexanoate (**4**) and (*E*)-1-(tributylstannyl)-4-methyloct-1-en-4-yloxy)triethylsilane (**5**), were prepared from commercially available cycloheptanone and propargyl bromide, and the intermediates were coupled to obtain **3** in a convergent approach.

Keywords: 1,4-Addition, normisoprostol, prostaglandins, two-component coupling

INTRODUCTION

Prostaglandins are a group of unsaturated carboxylic acids consisting of a 20-carbon skeleton with a cyclopentane unit and two side chains. These are biosynthetically derived from arachidonic acid,[1] are present in virtually every cell of the body, and exhibit a wide variety of biological functions. Prostaglandins are like hormones in that they act as chemical messengers but do not move to other sites; they work right within the

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cells where they are synthesized. The bioactivity profile of prostaglandins include activation of the inflammatory response, production of pain and fever, induction of labor and other reproductive processes, inhibition of acid synthesis in the gastrointestinal tract, and stimulation of constriction and clotting of platelets.

The general synthetic route to the natural prostaglandins was developed by Corey and his coworkers and involves the key intermediate, "Corey lactone." The approach continues to be the general strategy for industrial synthesis of prostaglandins.[2] However, several alternate methods have been reported to construct the core structure of prostaglandins.[3]

The two-component coupling strategy, first reported by Syntex group,[4] has been used mainly for the synthesis of racemic prostaglandins, such as misoprostol. The most elegant synthesis, consisting of the three-component coupling, was developed by Noyori et al.[5]

Retrosynthetic analysis revealed that two key units, 4 and 5, could be readily obtained from commercially available raw materials.

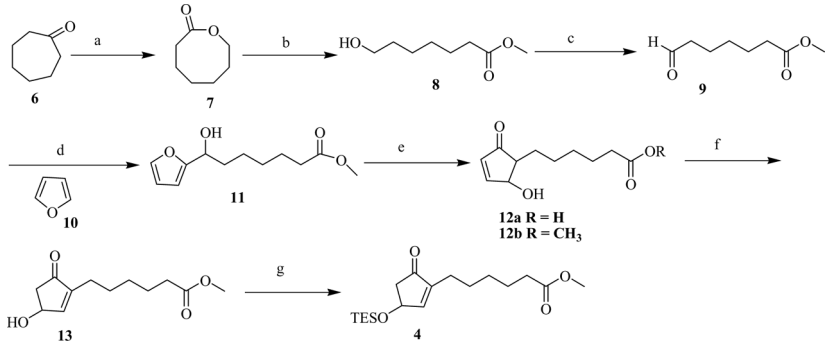
RESULTS AND DISCUSSION

Synthesis of 4 (Scheme 1)

Bayer–Villiger oxidation of cycloheptanone with m-3-chloroperbenzoic acid (CPBA) gave the corresponding lactone[6] (**7**) in good yield. Hydrolysis of lactone **7** was accomplished by BF_3 etherate in methanol to produce the hydroxy ester, **8**. Oxidation of primary alcohol in **8** carried out with conventional methods using pyridinium chlorochromate (PCC) or 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)[7] gave the aldehyde ester **9** in good yield. Lithiation of furan in the presence of $MgCl_2$ using n-BuLi followed by addition of aldehyde ester **9** at -10 to $30^{\circ}C$ gave the desired alkylated product **11**[8] in good yield. Intramolecular cyclization of **11** by reaction with $ZnCl_2$ provided 3-hydroxy-substituted cyclopentenone derivative, **12a**, which was converted to the corresponding methyl ester using methyl iodide to obtain **12b**. Isomerization of cyclopentenone derivative **12b** with chloral in triethylamine gave 4-hydroxy cyclopentenone derivative **13**. The secondary hydroxyl group in **13** was protected as triethyl silyl derivative[9] using chlorotriethylsilane (TESCl) in the presence of triethylamine to obtain the key unit **4** in good yield.

Synthesis of 5 (Scheme 2)

Reaction of propargyl bromide in presence of Zn,[10] followed by the addition of 2-hexanone, gave **15** in reasonable yield. However,

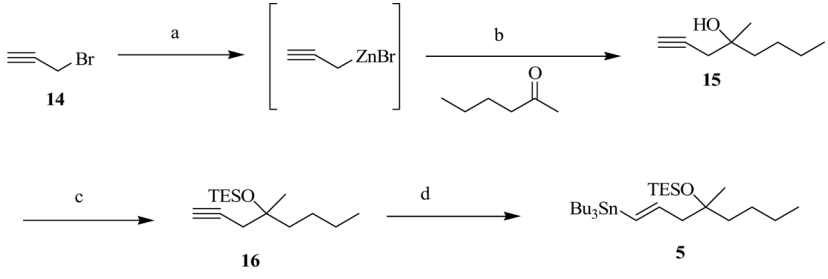


Scheme 1. Reagents: (a) mCPBA, DCM, 20 h, 55%; (b) BF_3 etherate, methanol, 16 h, 94%; (c) TEMPO, NaOCl, DCM, rt, 75%; (d) $MgCl_2$, THF, n-BuLi, −10°C; (e) $ZnCl_2$, dioxane, MeI, acetone, reflux, 16 h; (f) chloral, toluene, TEA, reflux, 6 h, 31% for three-step conversion from **11** to **13**; and (g) TESCl, TEA, THF, rt, 3 h, 66%.

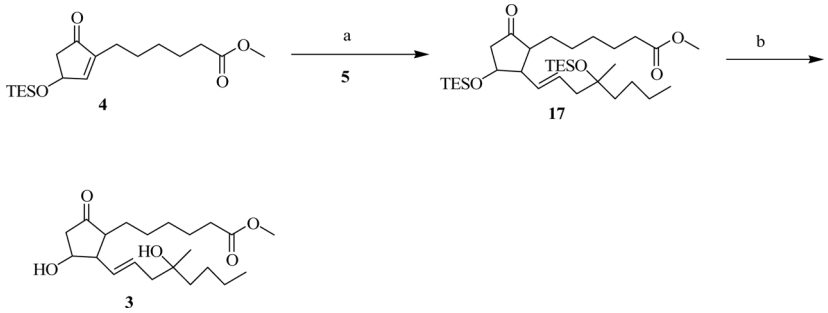
Mg-mediated Grignard reaction did not give the desired product. Protection of hydroxyl group in **15** by triethylsilane (TES) ether followed by reaction of terminal alkyne with tributyl tin hydride in the presence of 2,2′-azobis(2-methylpropionitrile (AIBN) gave the stannane derivative **5**, which was used for 1,4-addition without further purification.

2-Normisoprostol (3)

Condensation of **4** with stannane derivative **5** under Lipshutz conditions[9] through the generation of mixed cuprate gave the 1,4-addition product, which was subjected to purification by column chromatography to give product **17** in good yield (Scheme 3).



Scheme 2. Reagents: (a, b) Zn, DMF, 2-hexanone, rt, 5 h, 57%; (c) TESCl, imidazole, DMF, rt, 6 h, 75%; (d) Bu_3SnH, AIBN, 100°C, 85%.



Scheme 3. Reagents: (a) THF, MeLi, CuCN, −70°C to −75°C, 55%; and (b) DDQ, AcCN, H_2O, 60%.

Deprotection of triethyl silyl groups in **17** was achieved under neutral conditions by employing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in acetonitrile to obtain the desired 2-normisoprostol (**3**) in good yield. The spectral data of **3** corroborated well with the structure proposed.

CONCLUSION

We have obtained 2-normisoprostol, **3**, a rearranged prostaglandin, in 2.6% overall yield starting from commercially available cycloheptanone and propargyl bromide utilizing an efficient two-component coupling strategy. The synthesis can be scaled up to produce **3** for the bioactivity studies.

EXPERIMENTAL

Materials and Methods

All the reactions that were moisture- and air-sensitive were carried out using dried glassware under an argon or nitrogen atmosphere. The progress of the reactions was monitored by thin-layer chromatography (TLC) over silica gel 60F (E. Merck) in a thin layer (0.25 mm). The chromatograms were visualized by irradiation with ultraviolet (UV) light or by heat staining with poly-phosphoric acid and p-anisaldehyde in ethanol/sulfuric acid. Silica gel (230–400 mesh), (Spectrochem) was used for flash chromatography, and solvents used were lab reagent (LR) grades from spectrochem and RanKem without further purification. NMR spectra were recorded on a Bruker DPX 200 instrument with tetramethylsilane (TMS) as internal standard. The chemical shifts are reported in δ values (ppm).

Oxocan-2-one (7)

Cycloheptanone (40 g, 35.71 mmol) and m-chloroperbenzoic acid (70%, 50 mmol) were dissolved in dichloromethane (400 mL) and stirred for 20 h at room temperature. The resulting cloudy mixture was washed with saturated sodium carbonate solution (3×250 mL) and brine solution (250 mL). The organic layer was dried (Na_2SO_4) and concentrated at 35–40°C in vacuo to get crude (**7**), which was purified by column chromatography on silica gel (60–120 mesh) with an EtOAc/hexane step gradient as eluent. The selected fractions were combined, and the solvent was removed in vacuo at 40–45°C to give 25 g of **7** (19.53 mmol, 55%) as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.25 (2 H, t, *J* 5.5 Hz, C8-H_2), 2.45 (2 H, t, *J* 6.0 Hz, C3-H_2), 1.38–1.82 (8H, br, C4-C7-$(H_2)_4$) $2CH_2$.

Methyl 7-Hydroxyheptanoate (8)

Compound **7** (24.5 g, 19.14 mmol) was dissolved in methanol (250 mL) under a nitrogen atmosphere, and boron trifluoride etherate (0.1 eq) was added to the reaction mass at room temperature. The resulting mixture was stirred for 16 h at room temperature, and methanol was then removed at 40–45°C in vacuo to get the residue, which was dissolved in 250 mL of water. The aqueous layer was extracted with ethyl acetate (3×200 mL). The organic layer was washed with 2% sodium bicarbonate solution (150 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated at 40–45°C in vacuo to get crude **8**. The crude product was purified by column chromatography on silica gel (60–120 mesh) with an EtOAc/hexane step gradient as eluent. The pure fractions were combined, and the solvent was removed in vacuo at 40–45°C to give 28.75 g of **8** (17.99 mmol, 94%) as colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.67 (3H, s, OCH_3), 3.41 (2H, t, *J* 8.0 Hz, CH_2OH), 2.14 (2H, t, *J* 7.0 Hz, CH_2CO), 1.29–1.54 (4H, m, $OCH_2\underline{CH_2}C_2H_4C\underline{H_2}$), 1.08–1.29 (4H, m, $HOC_2H_4C_2\underline{H_4}$).

Methyl 6-Formylhexanoate (9)

A mixture of compound **8** (28 g, 17.5 mmol), dichloromethane (DCM; 420 mL), water (200 mL), and sodium bromide (18.23 g 17.7 mmol) was taken in a round-bottom flask (2.0 L) and cooled to 0°C. TEMPO (0.179 g, 0.115 mmol) was added in one lot, followed by addition of sodium hypochlorite (4–6%) (16.48 g, 22.15 mmol) in 6% sodium

bicarbonate solution (250 mL) at 0–5°C. The resulting mixture was stirred for 15 min, at which TLC indicated complete conversion of **8** to **9**. The reaction mass was quenched by water (300 mL) at 0–5°C, and the DCM layer was separated. The aqueous layer was extracted twice with DCM (400 mL, total), and combined extracts were washed with 10% $KHSO_4$ solution (250 mL), 2.5% sodium thiosulphate solution (200 mL), and brine solution (100 mL); dried (Na_2SO_4); and filtered. Filtrate was concentrated at 40–45°C in vacuo to give 26 g of crude **9**, which was purified by high vacuum distillation at 75–85°C under 0.5 to 1 mm of Hg vacuum to give 21 g of **9** (13.2 mmol, 75.9%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.76 (s, 1 H, –CHO), 3.67 (s, 3 H, CH_3O), 2.48–2.28 (m, 4H, *J* 7.2 Hz $2CH_2$), 1.73–1.36 (m, 6H, *J* 7.2 Hz $3CH_2$); mass: 157 (M−1).

Methyl 7-(Furan-2-yl)-7-hydroxyheptanoate (11)

A solution of furan (15.8 g, 133 mmol) in THF (200 mL) was cooled to −10°C, and a solution of 1.6 M n-butyl lithium in hexane (95.7 mL, 146.3 mmol) was added dropwise while the reaction temperature was maintained at less than 0°C. The solution was stirred at 0°C for 30 min, and anhydrous $MgCl_2$ (13.93 g, 146.3 mmol) was added in one portion. The mixture was warmed to room temperature for 1.5 h and then cooled to −25°C. A solution of aldehyde ester **9** (20 g, 133 mmol) in THF (40 mL) was added, and the mixture was stirred at −25°C for 30 min. The progress of the reaction was monitored by gas chromatography (GC). After completion of the reaction as shown by GC analysis, the reaction mixture was quenched by dropwise addition of saturated aqueous NH_4Cl solution (100 mL) and diluted with EtOAc (100 mL). The layers were separated, and the aqueous layer was extracted three times with EtOAc (3 × 100 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give 27.2 g of crude hydroxy ester **11**, which was used without further purification.

An analytical sample of **11** was prepared via chromatography over silica gel with an EtOAc/hexane step gradient as eluent. The pure fractions (R_f 0.15; 20/80 EtOAc/hexane) were combined, and the solvent was removed in vacuo to give a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36 (d, 1H), 6.32 (d, 1H, *J* 1.8 Hz), 6.22 (d, 1H, *J* 3.4 Hz), 4.66 (t, 1H), 3.65 (s, 3H, OCH_3), 2.33–2.26 (t, 2H, *J* 7.2 Hz), 1.95–1.56 (m, 5H, *J* 6.8 Hz), 1.49–1.25 (m, 4H); mass: 227 (M + 1).

Methyl 6-(2-Hydroxy-5-oxocyclopent-3-enyl)hexanoate (12)

A solution of **11** (26 g, 115 mmol) and $ZnCl_2$ (78.2 g, 575 mmol) in 1,4-dioxane (312 mL) and water (210 ml) was refluxed for 16 h (TLC analysis indicated the complete disappearance of starting material). The mixture was cooled to room temperature, acidified to pH 2 with 6 N HCl, and extracted with EtOAc (300 mL). The extract was dried with over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give 28 g of a product mixture that contained **12a** as the major component. The crude mixture was dissolved in acetone (416 mL) and treated with K_2CO_3 (79.38 g, 575 mmol) and methyl iodide (81.68 g, 575 mmol). The mixture was refluxed for 12 h (TLC indicated complete conversion of **12a** to **12b**). The mixture was filtered, and the filtrate was concentrated in vacuo to give 27 g of crude cyclopentenone **12b,** which was used without further purification.

An analytical sample of **12b** was prepared by chromatography over silica gel (60–120 mesh) with EtOAc/hexane step gradient as eluent. Selected fractions (R_f 0.16; 50/50 EtOAc/hexane) were combined, and the solvent was removed in vacuo to give pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50 (dd, 1H, *J* 3.8 Hz), 6.20 (d, 1H, *J* 5.8 Hz), 4.67 (m, 1H), 3.66 (s, 3H), 2.87–2.74 (dd, 1H, *J* 6.2 Hz), 2.35–2.16 (m, 4H, *J* 7.4 Hz), 1.88–1.32 (m, 7H, *J* 7.4 Hz); mass: 227 (M + 1).

Methyl 6-(3-Hydroxy-5-oxocyclopent-1-enyl)hexanoate (13)

A solution of **12b** (26 g, 115 mmol), Et_3N (17.46 g, 172 mmol), anhydrous chloral (8.47 g, 57.5 mmol), and toluene (340 mL) was heated to 70–75°C for 6 h (TLC analysis indicated complete conversion of **12b** to **13**). The mixture was added to a slurry of anhydrous LiBr (260 g) in heptane (312 mL) and toluene (200 mL). The resulting mixture was stirred for 2 h at 30°C. The LiBr complex was collected by filtration under nitrogen atmosphere and washed with a mixture of toluene (200 mL) and heptane (100 mL). The isolated LiBr complex was added portion wise to a mixture of water (800 mL) and toluene (400 mL) at 0°C and stirred for 30 min. The layers were separated, and the aqueous layer was extracted one time with toluene (200 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give 18 g of crude **13**, which was purified by column chromatography over silica gel (60–120 mesh) with EtOAc/hexane step gradient as eluent. Selected fractions (R_f, 0.15; 50/50 EtOAc/hexane) were combined, and the solvent was removed in vacuo at 40–45°C to give 8.0 g of compound **13** (35 mmol, 31% yield) as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.16 (d, 1H), 4.93 (br, 1H), 3.66 (s, 3H), 2.87–2.75 (dd, 2H, *J* 6.2, 18.3 Hz), 2.34–2.16 (m, 4H, *J* 7.4 Hz), 1.71–1.34 (m, 7H, *J* 7.2 Hz); mass: 227 (M + 1). ^{13}C NMR (200 MHz, $CDCl_3$): 206.6 (C=O), 174.19 ($COOCH_3$), 156.56 (CH), 147.17, 67.91 (CH-OH), 51.25 (OCH_3), 44.57, 33.7, 28.59, 26.92, 24.47, 24.03.

Methyl 6-(3-Triethyl silyloxy-5-oxocyclopent-1-enyl)hexanoate (4)

A solution of **13** (5 g, 22 mmol) and Et_3N (33 g, 330 mmol) in dimethylformamide (DMF, 50 mL) was cooled to 10°C, and chlorotriethylsilane (4.31 g, 28 mmol) was slowly added dropwise over a period of 10 min. The mixture was allowed to warm to room temperature and stirred for 6 h (TLC indicated complete conversion of **13** to **4**). Reaction mass was quenched by the addition of ice-cold water (25 mL) and extracted five times with heptane (250 mL, total), and the combined extracts were washed twice with saturated aqueous NaCl solution (200 mL total), dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo to give 7 g of crude **4**, which was purified by chromatography over silica gel (60–120 mesh) with EtOAc/hexane step gradient as eluent. The pure fractions (*Rf,* 0.52; 30/70 EtOAc/hexane) were combined, and the solvent was removed in vacuo to give 5 g (14 mmol, 66%) of silyl ether **4** as pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.04 (m, 1H), 4.88 (m, 1H), 3.66 (s, 3H), 2.80–2.68 (dd, 1H, *J* 6.2, 18.4 Hz), 2.28 (dd, 1H, *J* 5.6, 18.4 Hz), 2.35–2.16 (m, 4H, *J* 4.6 Hz), 1.88–1.32 (m, 6H, *J* 6.8 Hz), 1.02–0.94 (q, 9H, *J* 7.6 Hz), 0.70–0.62 (t, 6H, *J* 7.6 Hz); mass: 341 (M + 1). ^{13}C NMR (200 MHz, $CDCl_3$): 205.4 (C=O), 173.5 ($COOCH_3$), 156 (CH), 146.6, 68 (CH-OSi), 50.85 (OCH_3), 45.08, 33.51, 28.58, 26.84, 24.38, 23.97, 6.27, 4.38.

4-Methyloct-1-yn-4-ol (15)

Zn (13.1 g, 20 mmol) and DMF (100 mL) were added to a mixture of 2-hexanone (10 g, 10 mmol) at room temperature under an N_2 atmosphere; **14** (23.6 g, 20 mmol) was added dropwise over a period of 25 min (reaction is exothermic and external cooling is required to maintain temperature at 30°C). The mixture was stirred for 5 h, at which time GC analysis indicated complete conversion of 2-hexanone to **15**. The reaction mass was quenched by the addition of saturated NH_4Cl (100 mL) at 10–20°C, stirred for 10 min, and filtered. The filtrate was extracted with three times with DCM (300 mL, total), and combined extracts were washed twice with water (200 mL, total), dried (Na_2SO_4),

and filtered. The filtrate was concentrated in vacuo to give 13 g of crude **15**, which was purified by high vacuum distillation at 48–54°C under 3–4 mm of Hg vacuum to get 8 g of **15** (5.7 mmol, 57%) as an oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.48 (br, OH), 2.41–2.30 (dq, 2H, *J* 2.8, 16.4 Hz, $C\underline{H}_2CCH$), 1.96 (t, 1H, *J* 2.8 Hz, CH), 1.65–1.5 (m, 2H, CH_2), 1.38–1.28 [m, 7H, $C\underline{H}_3(C\underline{H}_2)_2$]; mass: 141 (M + 1). ^{13}C NMR (200 MHz, $CDCl_3$): 82.04 ($C\underline{C}H$), 75.05, 69.79 (CH), 41.63, 32.61, 27.48 (CCH_3), 26.05, 23.13, 14.07 (CH_2CH_3).

4-Methyloct-1-yn-4-yloxy)triethylsilane (16)

A mixture of compound **15** (7 g, 5 mmol) and imidazole (6.8 g, 10 mmol) in DMF (50 mL) was cooled to 10°C, and chlorotriethylsilane (11.3 g, 7.5 mmol) was added dropwise over a period of 10 min. The mixture was allowed to warm to room temperature and stirred for 6 h (TLC indicated complete conversion of **15** to **16**). The reaction mass was quenched by the addition of water (100 mL) and extracted two times with DCM (200 mL, total), and the combined extracts were washed twice with water (200 mL, total), dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo to give 12 g of crude **16**, which was purified by chromatography over silica gel (60–120 mesh) with EtOAc/hexane step gradient as eluent. Selected fractions were combined, and the solvent was removed in vacuo at 35°C to give 9.5 g (3.74 mmol, 75%) of silyl ether **16** as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.41–2.30 (dq, 2H, *J* 2.8, 16.4 Hz, $C\underline{H}_2CCH$), 1.96 (t, 1H, *J* 2.8 Hz, CH), 1.65–1.5 (m, 2H, CH2), 1.38–1.28 [m, 7H, $CH_3(CH_2)_2$], 1.05–0.82 (m, 9H), 0.65–0.58 (q, 6H, *J* 7.6 Hz); mass: 255 (M + 1). ^{13}C NMR (200 MHz, $CDCl_3$): 81.96 (CCH), 74.86, 69.79 (CH), 41.63, 32.61, 27.48 (CCH_3), 26.05, 23.13, 14.07 (CH_2CH_3), 7.03, 6.79.

(*E*)-1-(Tributylstannyl)-4-methyloct-1-en-4-yloxy)triethylsilane (5)

A mixture of **16** (8.5 g, 3.3 mmol), AIBN (0.38 g, 0.23 mmol), and tributyltinhydride (9.73 g, 3.3 mmol) was heated to 110°C and stirred for 2 h, at which time TLC indicated complete conversion of **16** to **5** (100% hexane). Reaction mass was cooled to 30°C, and 50 mL of n-hexane were added. Filtrate was concentrated at 40°C in vacuo to give 15.5 g of **5** (2.83 mmol, 85%) as a pale yellow liquid, which was used in the next step without purification.

Methyl 6-(3-Triethylsilyloxy-2-((*E*)-4-triethylsilyloxy-4-methyloct-1-enyl)-5-oxocyclopentyl)hexanoate (17)

A solution of CuCN (2.31 g, 25 mmol) in THF (60 mL) in a flame-dried flask was degassed with a vacuum and placed under Ar by releasing the vacuum with Ar. The solution was cooled to −5 to 0°C, and a solution of 1.6 M methyl lithium in diethyl ether (40 mL, 51 mmol) was added through the cannula at −5 to 0°C. The resulting solution was stirred for 15 min and a solution of **5** (14.1 g, 25 mmol) in THF (20 mL) was added slowly to the reaction mass at −5 to 0°C. The resulting mixture was stirred for 1.5 h at 25–30°C, cooled to −75°C, and stirred for 5 min. Solution of **4** (4 g, 11 mmol) in THF (20 mL) was added to the reaction mass at −75°C and and stirred for 1 h (TLC indicated complete conversion of **3** to **16**). The reaction mixture was poured into a mixture of saturated aqueous NH_4C1/NH_4OH solution (9:1, 100 mL). The mixture was vigorously stirred for 30 min, and the layers were separated. The aqueous phase was extracted twice with EtOAc (2 × 50 mL), and the combined organic phases were washed twice with a mixture of **9**/**1** saturated aqueous NH_4Cl/NH_4OH solution (100 mL total). The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo to give 5.26 g of crude **17**, which was purified by column chromatography over silica gel (230–400 mesh) with EtOAc/hexane step gradient as eluent. Selected fractions were combined, and the solvent was removed in vacuo to give 3.8 g of **17** (6.4 mmol, 55%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.77–5.73 (m, 1H), 5.46–542 (m, 1H), 4.06 (q, 1H), 3.66 (s, 3H), 2.80–2.67 (dd, 1H, *J* 18.0, 7.2 Hz), 2.39–2.14 (m, 6H, *J* 7.6 Hz), 2.04–1.93 (m, 1H, *J* 6.2), 1.67–1.17 (m, 17H), 1.05–0.82 (m, 21H), 0.65–0.58 (t, 12H); ES-MS: 369 (M + 1). ^{13}C NMR (200 MHz, $CDCl_3$): 216.1 (C=O), 174 ($C\overline{O}OCH_3$), 132, 129.9 (CH), 73.1, 72.9 (CH), 54.5 (CH), 53.9 (CH), 51.4, 47.6, 45.7, 42.2, 34, 29.3, 27.7, 27.6, 26.4, 26.1, 24.7, 23.2, 14.1, 7.1, 6.9, 6.6, 5.7, 5.3, 4.7.

Methyl 6-(3-Hydroxy-2-(*E*)-4-hydroxy-4-methyloct-1-enyl)-5-oxocyclopentyl)hexanoate (3)

The compound **17** (3.0 g, 0.5 mmol) was dissolved in acetonitrile (42 mL) and water (21 mL) at room temperature. The solution was treated with DDQ (0.114 g, 0.05 mmol) and stirred for 4 h at 25–30°C, at which time TLC indicated complete conversion of **17** to **3**. Most of the acetonitrile was removed in vacuo at 30–35°C, and methyl-tert-butyl ether (MTBE) (50 mL) was added at room temperature. The organic layer was separated, and the aqueous layer was extracted twice with MTBE (100 mL,

total). Combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo at 25°C to give crude **2** (2.8 g). The crude sample was purified by column chromatography over silica gel (230–400 mesh) with an MTBE/*n*-hexane step gradient as eluent. Selected fractions (R_f, 0.40, 100% MTBE) were combined, and the solvent was removed in vacuo at 25°C to give 1.1 g of compound **3** (0.29 mmol, 60%), characterized by NMR, mass, and ^{13}C NMR.

^1H NMR (200 MHz, $CDCl_3$): δ 5.77–5.73 (m, 1H), 5.46–542 (m, 1H), 4.06 (q, 1H), 3.66 (s, 3H), 2.80–2.67 (dd, H, *J* 18.0, 7.2 Hz), 2.39–2.14 (m, 6H, *J* 7.6 Hz), 2.04–1.93 (m, 1H, *J* 6.2), 1.67–1.17 (m, 19H), 0.95–0.88 (t, 3H, *J* 7.2 Hz); ES-MS: 369 (M + 1). ^{13}C NMR (200 MHz, $CDCl_3$): 216.1 (C=O), 174 ($\underline{C}OOCH_3$), 132, 129.9 (CH), 73.1, 72.9 (CH), 54.5 (CH), 53.9 (CH), 51.4, 47.6, 45.7, 42.2, 34, 29.3, 27.7, 27.6, 26.4, 26.1, 24.7, 23.2, 14.1.

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