Stereoselective Synthesis of the C1–C11 Tetrahydropyran Core Unit of (+)-Zincophorin

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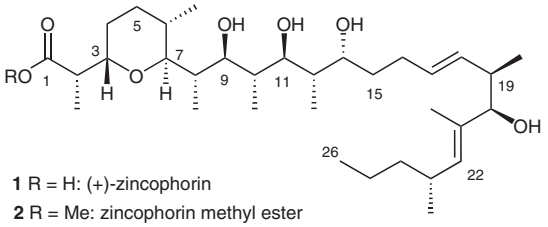
Abstract: Synthesis of the C1–C11 tetrahydropyran core unit of (+)-zincophorin using a desymmetrization strategy is reported. Horner–Wadsworth–Emmons (HWE) and Mitsunobu cyclization reactions are the key transformations.

Key words: tetrahydropyran, zincophorin, desymmetrization, Mitsunobu cyclization, HWE reaction

(+)-Zincophorin (**1**; Figure 1) is a polyoxygenated ionophoric antibiotic that was isolated independently by two groups from *Streptomyces griseus* in 1984.[2,3] Its strong ability to bind with divalent cations, especially zinc, was the origin of its trivial name zincophorin. This compound exhibits broad in vitro antibiotic activity against Gram-positive bacteria as well as *Clostridium welchii*. In addition, the ammonium and sodium salts of zincophorin shows significant anticoccidal activity against *Eimeria tenella* in chicken embryos.[2,3] Its methyl ester has also been reported to possess antiviral activity, with reduced host cell toxicity compared to the free acid.[4] The structure of zincophorin was first established by extensive NMR experiments, and its three-dimensional structure, including its absolute configuration, was ascertained by X-ray diffraction of its zinc-magnesium salt.[3] The challenging structure of the molecule, coupled with its biological activity, prompted us to undertake its total synthesis. Until now, three total syntheses and several elaborated fragment syntheses have been reported.[5] In a continuation of our efforts towards the synthesis of natural products using desymmetrization strategies,[6] we herein report the stereoselective synthesis of the C1–C11 tetrahydropyran core unit **3** of (+)-zincophorin using a desymmetrization strategy involving Horner–Wadsworth–Emmons (HWE) and Mitsunobu cyclization reactions as key steps.



1 R = H: (+)-zincophorin
2 R = Me: zincophorin methyl ester

Figure 1

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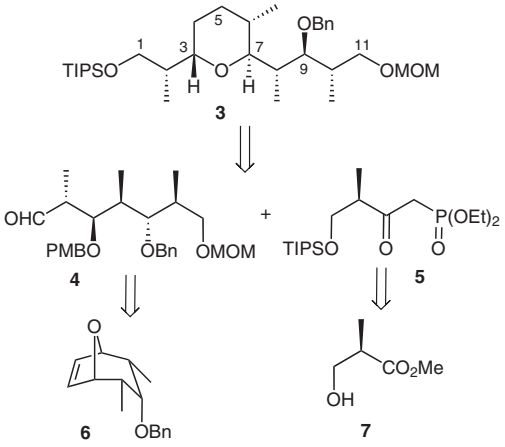
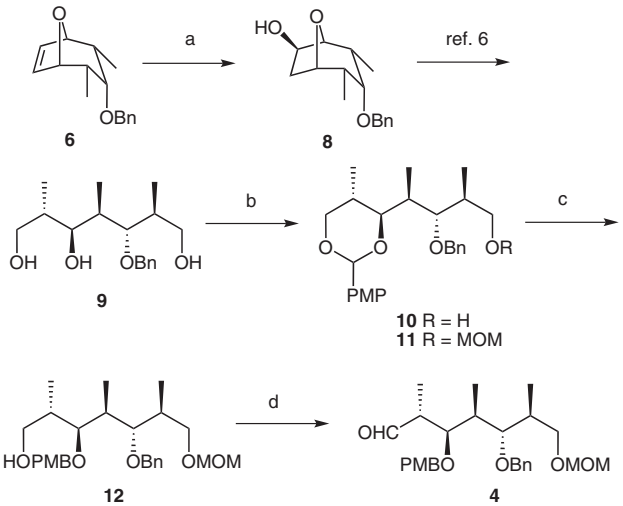
The retrosynthetic analysis of zincophorin (**1**) is outlined in Scheme 1. It was envisaged that the trisubstituted tetrahydropyran ring could be constructed by Mitsunobu cyclization. The two fragments – the C1–C4 unit **5** and the C5–C11 unit **4** – could be combined by a HWE reaction. Fragment **4**, in turn, could be made from the bicyclic olefin **6** by a desymmetrization strategy. Fragment **5** could be prepared from the (*R*)-Roche ester.

As shown in Scheme 2, the synthesis of the C1–C11 segment commenced with a known triol **9**,[6] which was pre-



Scheme 1 Retrosynthetic analysis

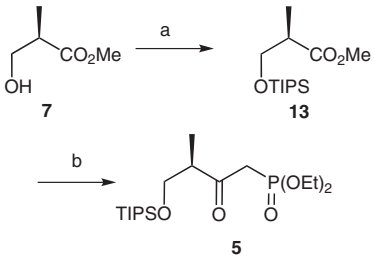


Scheme 2 *Reagents and conditions*: (a) (+)-IPC$_2$BOMe, THF, –20 °C, 5 d, 92%; (b) (i) 1-(MeO)$_2$CH-4-MeOC$_6$H$_3$, anhyd CH$_2$Cl$_2$, CSA, 0 °C to r.t., 2 h, 85%; (ii) MOM-Cl, DIPEA, anhyd CH$_2$Cl$_2$, 0 °C, 3 h, 75%; (c) DIBAL-H, anhyd CH$_2$Cl$_2$, 0 °C, 1 h, 80%; (d) IBX, anhyd DMSO, anhyd CH$_2$Cl$_2$, 0 °C, 2 h, 90%.

pared by desymmetrization of bicyclic olefin **6** using Brown's chiral hydroboration.

Triol **9** was converted into acetal **10** in 85% yield using *p*-methoxybenzaldehyde (PMB) dimethyl acetal and a catalytic amount of 10-camphorsulfonic acid (CSA) in dichloromethane, followed by protection of the primary hydroxyl group as its methoxymethyl (MOM) ether **11** using chloromethyl methyl ether (MOMCl) and *N*,*N*-diisopropylethylamine (DIPEA). Further elaboration to the aldehyde **4** was then effected by regioselective reductive ring opening of the PMP acetal **11** with diisobutylaluminum hydride (DIBAL-H) and oxidation of the resulting alcohol **12** using 2-(iodoxy)benzoic acid (IBX), which completed the synthesis of fragment **4**.

The synthesis of the segment **5** (Scheme 3), began with the (*R*)-Roche ester **7**. The hydroxyl group was protected as its silyl ether **13** using triisopropylsilyl chloride (TIPS-Cl) and imidazole, and the ester group in **13** was converted into β-ketophosphonate **5** by treatment with diethyl methylphosphonate in the presence of *n*-butyllithium.[7]

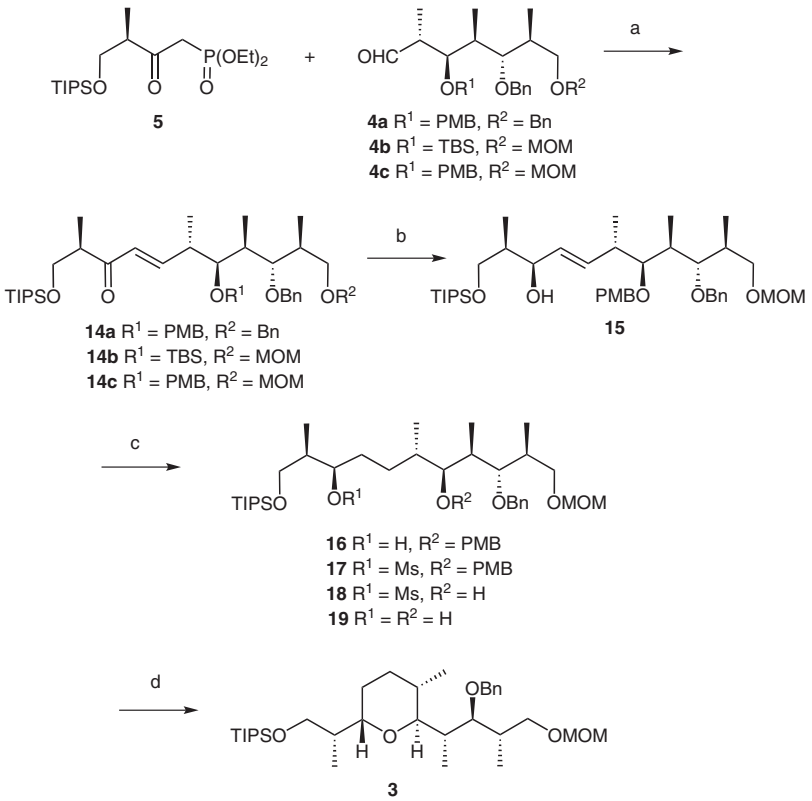


Scheme 3 *Reagents and conditions*: (a) TIPS-Cl, imidazole, anhyd CH_2Cl_2, 0 °C, 4 h, 90%; (b) $MeP(O)(OC_2H_5Et)_2$, *n*-BuLi, anhyd THF, –78 °C, 1 h, 55%.

The coupling reaction between two pairs (i.e., **4a/5** and **4b/5**) failed to give the required products **14a** and **14b**, respectively (Scheme 4). However, by protecting group manipulation, the reaction between β-ketophosphonate **5** and the unpurified aldehyde **4c** in the presence of $Ba(OH)_2{\cdot}8H_2O$[8] in wet tetrahydrofuran (THF–H_2O, 40:1) was successful and gave the desired enone **14c** *E*-selectively in good yield (83%). Thus, the selection of protecting groups in fragments **4** and **5** played a crucial role in further transformation; repetition of protecting groups in both the fragments failed to give HWE products **14a** and **14b**. The silyl protecting group in compound **5** was also found to be a superior group for the HWE reaction.

A reagent-controlled reduction of enone **14c** was then required. The (*R*)-Me-CBS reagent[9] was found to give excellent selectivity in setting the desired configuration at C3, leading to the allylic alcohol **15** (66%, dr 19:1). Reduction of the double bond was achieved by using PtO_2 in ethyl acetate at room temperature, to afford the saturated compound **16**.

To achieve the tetrahydropyran ring formation, the free hydroxyl group was converted into the corresponding mesyl group, generating compound **17**; oxidative deprotection of the PMB group gave compound **18**, which failed to give the THP ring by S_N2 reaction. Therefore, the PMB group of compound **16** was removed and the result-



Scheme 4 *Reagents and conditions*: (a) $Ba(OH)_2$, THF–H_2O (9:1), 1 h, 83%; (b) (*R*)-CBS, $BH_3{\cdot}SMe_2$, anhyd toluene, 0 °C, 1 h, 66%; (c) (i) PtO_2, EtOAc, 3 h, r.t., 90%; (ii) DDQ, CH_2Cl_2–H_2O (9:1), 1 h, 0 °C to r.t., 50%; (d) DEAD, Ph_3P, toluene, 0 °C to r.t., 12 h, 37%.

ing diol **19** was subjected to Mitsunobu cyclization[10] to give the desired C1–C11 tetrahydropyran core unit **3** in 37% yield. This cyclization is known to occur in zincophorin on the side of the chain with less chiral centers. In the present study, a similar cyclization was applied to the fragment with more chiral centers. The bulky phosphonium group was attached to the less hindered C-3 alcohol function and the more hindered C-7 hydroxyl group acted as the nucleophile; this assumption was based on an earlier report.[11]

In summary, we have described the synthesis of the C1–C11 tetrahydropyran core unit of (+)-zincophorin. Further efforts towards the completion of the total synthesis of the zincophorin are ongoing.

Reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualizing under UV light). Petroleum ether (PE; bp 60–80 °C) was used. Yields refer to chromaographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by either syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Büchi rotary evaporator. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded with Varian FT-200 MHz (Gemini) or Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0 ppm) as an internal standard. Mass spectra were recorded under EI conditions at 70 eV with an LC-MSD (Agilent technologies) spectrometer. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with a JASCO DIP-370 polarimeter.

(2*S*,3*S*,4*S*)-3-(Benzyloxy)-4-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-2-methylpentan-1-ol (10)

A solution of triol **9** (5.0 g, 16.8 mmol) in anhydrous CH_2Cl_2 (50 mL) was cooled to 0 °C, and a catalytic amount of CSA was added, followed by PMB acetal (3.1 mL, 18.5 mmol) over a period of 10 min. Upon completion, the reaction was quenched with $NaHCO_3$ (2 M, 5 mL) and the product was extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was washed with brine (20 mL) and dried over Na_2SO_4. Solvent was removed under vacuum and the residue was purified by column chromatography (EtOAc–hexane, 25%) to give the required alcohol **10**.

Yield: 6.0 g (85%); colorless liquid; TLC: R_f 0.7 (EtOAc–hexane, 30%); $[\alpha]_D^{25}$ +56 (c = 0.05, $CHCl_3$).

IR (neat): 3449, 2961, 2926, 1614, 1516, 1458, 1387, 1248, 1075, 1030, 828, 737, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 7 H), 6.87 (d, J = 8.5 Hz, 2 H), 5.30 (s, 1 H), 4.66 (d, J = 11.1 Hz, 1 H), 4.54 (d, J = 11.1 Hz, 1 H), 4.13–4.06 (m, 1 H), 3.91–3.87 (m, 1 H), 3.81 (s, 3 H), 3.80–3.76 (m, 1 H), 3.62–3.52 (m, 2 H), 3.43 (t, J = 11.1 Hz, 1 H), 2.14–2.01 (m, 2 H), 1.98–1.87 (m, 1 H), 1.22 (d, J = 7.2 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.75 (d, J = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 138.3, 131.4, 128.5, 127.7, 27.4, 127.3, 113.5, 100.9, 85.7, 81.5, 76.0, 73.3, 64.1, 55.2, 37.2, 35.8, 30.3, 16.3, 12.0, 10.3.

ESIMS: m/z = 415 $[M]^+$, 437 $[M + Na]^+$.

(4*S*,5*S*)-4-[(1*S*,2*S*,3*S*)-2-(Benzyloxy)-4-(methoxymethoxy)-1,3-dimethylbutyl]-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (11)

To a stirred solution of compound **10** (6.0 g, 14.4 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C under an N_2 atmosphere, DIPEA (5.0 mL, 28.9 mmol) was added, followed by dropwise addition of MOMCl (1.7 mL, 21.7 mmol). After stirring for 4 h at r.t., the reaction mixture was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were washed with brine (25 mL) and dried over anhydrous Na_2SO_4. The filtrate was concentrated under vacuum and purified by silica gel column chromatography (EtOAc–hexane, 20%) to afford the pure compound **11**.

Yield: 4.9 g (75%); colorless liquid; TLC: R_f 0.6 (EtOAc–hexane, 20%); $[\alpha]_D^{25}$ +58 (c = 0.05, $CHCl_3$).

IR (neat): 2929, 2878, 2839, 1693, 1516, 1459, 1387, 1249, 1105, 1039, 829, 738, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 7 H), 6.86 (d, J = 8.7 Hz, 2 H), 5.26 (s, 1 H), 4.63 (d, J = 4.7 Hz, 1 H), 4.60 (d, J = 6.4 Hz, 1 H), 4.57 (d, J = 6.4 Hz, 1 H), 4.52 (d, J = 11.7 Hz, 1 H), 4.06 (dd, J = 4.5, 11.1 Hz, 1 H), 3.80 (s, 3 H), 3.77–3.71 (m, 2 H), 3.49–3.43 (m, 1 H), 3.41–3.35 (m, 2 H), 3.33 (s, 3 H), 2.14–1.98 (m, 3 H), 1.11 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.72 (d, J = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 139.1, 131.5, 128.2, 127.3, 127.2, 113.5, 100.8, 96.5, 83.2, 81.6, 75.3, 73.3, 69.0, 55.2, 55.1, 36.7, 35.8, 30.3, 16.6, 12.0, 10.0.

ESIMS: m/z = 459 $[M]^+$, 481 $[M + Na]^+$.

(2*S*,3*S*,4*S*,5*S*,6*S*)-5-(Benzyloxy)-3-[(4-methoxybenzyl)oxy]-7-(methoxymethoxy)-2,4,6-trimethylheptan-1-ol (12)

A cooled (–20 °C) solution of PMB acetal **11** (4.9 g, 10.7 mmol) in anhydrous CH_2Cl_2 (75 mL) was treated with DIBAL-H (26.8 mL, 26.82 mmol), and the reaction mixture was allowed to warm to 0 °C over 1 h. After completion of reaction, excess hydride was quenched by the dropwise addition of saturated sodium potassium tartarate (CAUTION: vigorous evolution of H_2 may result) and the mixture was allowed to warm to r.t. After vigorous stirring for 1 h, the two layers were separated, the aqueous layer was extracted with Et_2O (25 mL) and the combined organic phases were washed with brine (25 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under vacuum and the residue was purified by column chromatography (EtOAc–hexane, 25%) to afford alcohol **7**.

Yield: 3.9 g (80%); colorless liquid; TLC: R_f 0.3 (EtOAc–hexane, 20%); $[\alpha]_D^{25}$ +24 (c = 0.05, $CHCl_3$).

IR (neat): 3450, 2931, 2880, 1612, 1513, 1459, 1247, 1040, 958, 821 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 5 H), 7.14 (d, J = 8.7 Hz, 2 H), 6.81 (d, J = 8.7 Hz, 2 H), 4.66 (d, J = 11.3 Hz, 1 H), 4.61 (d, J = 6.6 Hz, 1 H), 4.59 (d, J = 6.6 Hz, 1 H), 4.51 (d, J = 10.7 Hz, 1 H), 4.46 (d, J = 11.3 Hz, 1 H), 4.39 (d, J = 10.7 Hz, 1 H), 3.81–3.79 (m, 1 H), 3.78 (s, 3 H), 3.71–3.62 (m, 2 H), 3.59–3.52 (m, 2 H), 3.49 (dd, J = 7.4, 9.3 Hz, 1 H), 3.35 (s, 3 H), 2.73–2.65 (m, 1 H), 1.99–1.84 (m, 2 H), 1.10 (d, J = 7.0 Hz, 3 H), 1.04 (d, J = 7.0 Hz, 3 H), 0.89 (d, J = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 138.6, 130.7, 129.2, 128.3, 127.5, 127.4, 113.7, 96.6, 84.8, 83.0, 74.3, 73.8, 69.7, 66.5, 55.2, 39.0, 38.6, 36.2, 15.7, 14.7, 12.0.

ESIMS: m/z = 461 $[M]^+$, 483 $[M + Na]^+$.

Methyl (2*R*)-2-Methyl-3-[(1,1,1-triisopropylsilyl)oxy]propanoate (13)

To a solution of alcohol **7** (3.0 g, 25.3 mmol) in anhydrous CH_2Cl_2 (30 mL) was added imidazole (2.0 g, 30.4 mmol), followed by dropwise addition of TIPS-Cl (5.3 mL, 25.3 mmol) at 0 °C and the reaction was stirred for 2 h at the same temperature. Upon completion, the reaction was quenched by addition of sat. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic phase was

washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc–hexane, 5%) to afford **13**.

Yield: 6.2 g (90%); colorless liquid; TLC: R_f 0.8 (EtOAc–hexane, 10%); $[\alpha]_D^{25}$ –23 (c = 0.05, $CHCl_3$).

IR (neat): 2944, 2866, 1742, 1463, 1106, 882, 680 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.85 (dd, J = 6.6, 9.3 Hz, 1 H), 3.74 (dd, J = 6.0, 9.3 Hz, 1 H), 3.66 (s, 3 H), 2.68–2.57 (m, 1 H), 1.15 (d, J = 7.0 Hz, 3 H), 1.08–1.02 (m, 21 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5, 65.6, 51.4, 42.6, 17.8, 13.4, 11.9.

ESIMS: m/z = 297 $[M + Na]^+$.

Diethyl (3*R*)-3-Methyl-2-oxo-4-[(1,1,1-triisopropylsilyl)oxy]butylphosphonate (5)

Diethyl methylphosphonate (3.9 g, 26.2 mmol) was dissolved in anhydrous THF (30 mL) under an N_2 atmosphere, and *n*-BuLi (1.6 M in *n*-hexane, 15 mL, 24.06 mmol) was added dropwise at –78 °C over 10 min and the reaction was stirred at the same temperature for 1 h. Compound **13** in THF (10 mL) was introduced into the reaction mixture slowly over a period of 10 min under an N_2 atmosphere. The resulting mixture was stirred for 1 h at the same temperature and then warmed to ambient temperature before quenching with sat. aq NH_4Cl (15 mL) at 0 °C. The product was extracted with EtOAc (2 × 50 mL), washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, the solvent was removed under vacuum and the residue was purified by column chromatography (EtOAc–hexane, 50%) to afford **5**.

Yield: 4.7 g (55%); yellow liquid; TLC: R_f 0.4 (EtOAc–hexane, 50%); $[\alpha]_D^{25}$ –73 (c = 0.05, $CHCl_3$).

IR (neat): 2941, 2867, 1714, 1463, 1390, 1256, 1099, 1025, 965, 882, 790, 683 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.21–4.07 (m, 4 H), 3.80 (d, J = 9.6 Hz, 1 H), 3.74 (d, J = 9.6 Hz, 1 H), 3.33 (dd, J = 13.6, 22.9 Hz, 1 H), 3.12–2.97 (m, 2 H), 1.34 (t, J = 7.0 Hz, 6 H), 1.10–1.00 (m, 24 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205, 62.3, 49, 43.4, 41.7, 17.8, 16.15, 12.6, 11.7.

ESIMS: m/z = 395 $[M]^+$, 417 $[M + Na]^+$.

(2*R*,4*E*,6*S*,7*S*,8*S*,9*S*,10*S*)-9-(Benzyloxy)-7-[(4-methoxybenzyl)oxy]-11-(methoxymethoxy)-2,6,8,10-tetramethyl-1-[(1,1,1-triisopropylsilyl)oxy]-4-undecen-3-one (14c)

To an ice-cold solution of 2-(iodoxy)benzoic acid (IBX; 3.5 g, 12.7 mmol) in anhydrous DMSO (3.6 mL, 50.8 mmol) was added a solution of alcohol **12** (3.9 g, 8.4 mmol) in anhydrous CH_2Cl_2 (20 mL). The mixture was stirred at r.t. for 2 h and then filtered through a Celite pad. The filtrate was concentrated under reduced pressure, extracted with Et_2O (20 mL) and H_2O (20 mL), and the organic layer was concentrated under vacuum to give crude aldehyde **4** (3.4 g, 90%), which was used directly for the next reaction.

To a solution of β-ketophosphonate **5** (3.2 g, 8.1 mmol, 1.1 equiv) in THF (50 mL) was added $Ba(OH)_2{\cdot}8H_2O$ (2.3 g, 7.4 mmol, 1.0 equiv), which was preactivated by heating at 110 °C for 1 h and then dried under vacuum. The reaction mixture was stirred for 30 min, then crude aldehyde **8** (3.4 g, 7.4 mmol) in THF–H_2O (9:1; 20 mL) was added. Upon completion, the reaction mixture was diluted with sat. aq NH_4Cl (25 mL) and EtOAc (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (2 × 15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc–hexane, 8%) to furnish keto compound **14c**.

Yield: 4.4 g (83%); colorless liquid; TLC: R_f 0.7 (EtOAc–hexane, 10%); $[\alpha]_D^{25}$ –10 (c = 0.025, $CHCl_3$).

IR (neat): 2937, 2867, 1669, 1619, 1619, 1513, 1460, 1247, 1103, 1044, 686 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.22 (m, 5 H), 7.10 (d, J = 8.3 Hz, 2 H), 6.91 (dd, J = 8.3, 15.8 Hz, 1 H), 6.76 (d, J = 8.3 Hz, 2 H), 6.18 (d, J = 15.8 Hz, 1 H), 4.63–4.53 (m, 3 H), 4.46–4.32 (m, 3 H), 3.85 (dd, J = 6.8, 9.1 Hz, 1 H), 3.77 (s, 3 H), 3.70–3.59 (m, 2 H), 3.56 (dd, J = 1.5, 6.8 Hz, 1 H), 3.45 (dd, J = 7.6, 9.1 Hz, 1 H), 3.32 (s, 3 H), 3.31–3.27 (m, 1 H), 2.96–2.85 (m, 1 H), 2.64–2.52 (m, 1 H), 2.29 (t, J = 7.6 Hz, 1 H), 1.98–1.90 (m, 1 H), 1.10–1.94 (m, 33 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.7, 158.9, 149.7, 138.8, 131.0, 129.2, 128.8, 128.2, 127.3, 113.5, 96.6, 84.4, 81.8, 74.2, 73.3, 69.6, 65.8, 55.1, 46.6, 41.3, 38.7, 36.1, 17.9, 16.6, 15.9, 13.5, 11.8, 11.7.

ESIMS: m/z = 699 $[M]^+$, 722 $[M + Na]^+$.

(2*R*,3*R*,4*E*,6*S*,7*S*,8*S*,9*S*,10*S*)-9-(Benzyloxy)-7-[(4-methoxybenzyl)oxy]-11-(methoxymethoxy)-2,6,8,10-tetramethyl-1-[(1,1,1-triisopropylsilyl)oxy]-4-undecen-3-ol (15)

A flame-dried 100 mL round-bottomed flask was charged with ketone **14c** (2.5 g, 6.0 mmol) and toluene (25 mL). The vessel was cooled to –20 °C and (*R*)-methyl-CBS-oxazaborolidine (1.00 M in toluene, 1.2 mL, 1.2 mmol) was added. Borane–methyl sulfide complex (2 M, 4.5 mL, 9.01 mmol) was slowly added over 10 min and the reaction was stirred for 50 min at this temperature before being slowly quenched with MeOH (10 mL) over a period of about 15 min. The reaction was warmed to r.t. and, after the majority of gas evolution had subsided, the solvent was removed under vacuum. The crude oil was purified by column chromatography (EtOAc–hexane, 10%) to afford alcohol **15**.

Yield: 2.77 g (66%); colorless liquid; dr = 19:1; TLC: R_f 0.5 (EtOAc–hexane, 10%); $[\alpha]_D^{25}$ +12 (c = 0.025, $CHCl_3$).

IR (neat): 3477, 2938, 2867, 1512, 1459, 1247, 1100, 1043, 686 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.21 (m, 5 H), 7.15 (d, J = 8.7 Hz, 2 H), 6.77 (d, J = 8.7 Hz, 2 H), 5.71 (dd, J = 8.3, 15.7 Hz, 1 H), 5.50 (dd, J = 6.6, 15.7 Hz, 1 H), 4.60–4.52 (m, 3 H), 4.49 (d, J = 11.0 Hz, 1 H), 4.44 (d, J = 11.5 Hz, 1 H), 4.36 (d, J = 11.0 Hz, 1 H), 4.22–4.14 (m, 1 H), 3.77 (s, 3 H), 3.73–3.68 (m, 2 H), 3.67–3.61 (m, 1 H), 3.51–3.41 (m, 2 H), 3.32 (s, 3 H), 3.31–3.26 (m, 1 H), 2.79–2.74 (m, 1 H), 2.52–2.43 (m, 1 H), 2.01–1.92 (m, 1 H), 1.87–1.75 (m, 1 H), 1.14–0.96 (m, 30 H), 0.84 (d, J = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.0, 134.6, 131.5, 130.4, 128.7, 128.6, 128.2, 127.2, 113.7, 96.6, 84.5, 82.1, 75.8, 74.1, 73.0, 69.8, 67.6, 55.2, 40.8, 40.1, 38.5, 36.1, 17.9, 16.0, 12.0, 11.7, 11.3.

ESIMS: m/z = 723 $[M + Na]^+$.

(2*R*,3*R*,6*S*,7*S*,8*S*,9*S*,10*S*)-9-(Benzyloxy)-7-[(4-methoxybenzyl)oxy]-11-(methoxymethoxy)-2,6,8,10-tetramethyl-1-[(1,1,1-triisopropylsilyl)oxy]undecan-3-ol (16)

To a stirred solution of **15** (2.5 g, 3.5 mmol), PtO_2 (0.08 g, 0.35 mmol) in EtOAc (50 mL) was added, and the reaction was stirred under an H_2 atmosphere for 4 h. The contents were then filtered over Celite and the crude reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc–hexane, 10%) to give pure **16**.

Yield: 2.25 g (90%); colorless liquid; R_f 0.5 (EtOAc–hexane, 10%); $[\alpha]_D^{25}$ –16 (c = 0.05, $CHCl_3$).

IR (neat): 3507, 2936, 2867, 1612, 1513, 1461, 1247, 1101, 1045, 688 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.22 (m, 5 H), 7.14 (d, *J* = 8.6 Hz, 2 H), 6.77 (d, *J* = 8.6 Hz, 2 H), 4.60–4.53 (m, 3 H), 4.48–4.33 (m, 3 H), 3.81–3.62 (m, 4 H), 3.77 (s, 3 H), 3.49–3.41 (m, 2 H), 3.22 (s, 3 H), 3.30–3.24 (m, 1 H), 2.13–1.90 (m, 2 H), 1.83–1.56 (m, 2 H), 1.14–0.96 (m, 27 H), 0.92 (d, *J* = 7.0 Hz, 3 H), 0.88 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 139.4, 131.7, 128.7, 128.2, 127.2, 113.5, 96.6, 84.9, 82.2, 75.0, 74.1, 72.8, 69.8, 68.9, 55.2, 55.1, 38.5, 37.8, 36.7, 36.0, 31.9, 29.0, 17.9, 16.4, 16.0, 12.1, 11.8, 1.0.

ESIMS: *m*/*z* = 703 $[M]^+$, 725 $[M + Na]^+$.

(2*R*,3*R*,6*S*,7*S*,8*R*,9*S*,10*S*)-9-(Benzyloxy)-11-(methoxymethoxy)-2,6,8,10-tetramethyl-1-[(1,1,1-triisopropylsilyl)oxy]undecane-3,7-diol (19)

To a solution of **16** (2.1 g, 2.9 mmol) in CH_2Cl_2–H_2O (10:1, 20 mL) was added dichlorodicynoquinone (DDQ; 1.0 g, 4.4 mmol) at 0 °C and the reaction was stirred for 1 h. When the reaction was complete, the solution was filtered through a pad of Celite and washed with CH_2Cl_2 (2 × 25 mL). The combined filtrate was concentrated and purified by column chromatography (EtOAc–hexane, 12%) to provide diol **19**.

Yield: 0.87 (50%); yellow liquid; R_f 0.3 (EtOAc–hexane, 10%); $[\alpha]_D^{25}$ –22 (*c* = 0.025, $CHCl_3$).

IR (neat): 3450, 2934, 2867, 1460, 1101, 1047, 683 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.24 (m, 5 H), 4.66–4.55 (m, 4 H), 3.82–3.72 (m, 2 H), 3.69–3.61 (m, 1 H), 3.61–3.44 (m, 4 H), 3.33 (s, 3 H), 1.97–1.64 (m, 2 H), 1.62–1.38 (m, 2 H), 1.11–1.02 (m, 24 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 7.0 Hz, 3 H), 0.79 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 128.5, 127.8, 127.6, 96.7, 87.2, 76.0, 75.2, 74.0, 69.9, 69.1, 55.3, 38.2, 36.6, 35.8, 34.5, 30.6, 29.1, 17.9, 15.4, 14.8, 11.8, 11.4, 9.8.

ESIMS: *m*/*z* = 583 $[M]^+$.

({(2*R*)-2-(2*S*,5*S*,6*R*)-6-[(1*S*,2*S*,3*S*)-2-(benzyloxy)-4-(methoxymethoxy)-1,3-dimethylbutyl]-5-methyltetrahydro-2*H*-2-pyranylpropyl}oxy)(triisopropyl)silane (3)

To a solution of diol **19** (0.8 g, 1.3 mmol) in anhydrous toluene (10 mL) was added Ph_3P (1.8 g, 6.8 mmol), followed by dropwise addition of diethyl azodicarboxylate (DEAD; 1.0 mL, 6.8 mmol) at 0 °C and the reaction was stirred at r.t. for 12 h. After completion of the reaction, H_2O (20 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine (2 × 5 mL), dried over Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography (EtOAc–hexane, 8%) to furnish the cyclized product **3**.

Yield: 0.271 g (37%); colorless liquid; TLC: R_f 0.6 (EtOAc–hexane, 10%); $[\alpha]_D^{25}$ –20 (*c* = 0.025, $CHCl_3$).

IR (neat): 2925, 2858, 1742, 1460, 1379, 1047, 968, 761 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 5 H), 4.64–4.53 (m, 4 H), 3.77–3.39 (m, 7 H), 3.34 (s, 3 H), 2.50–2.04 (m, 2 H), 2.01–1.65 (m, 3 H), 1.63–1.45 (m, 2 H), 1.44–1.34 (m, 1 H), 1.11–0.92 (m, 30 H), 0.79 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 128.5, 127.8, 127.7, 96.8, 87.3, 76.1, 74.3, 73.9, 70.0, 68.7, 55.3, 36.7, 31.9, 31.6, 31.4, 30.2, 29.4, 18.0, 14.9, 14.1, 12.1, 12.0, 11.4.

ESIMS: *m*/*z* = 565 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{61}O_5Si$: 565.4283; found: 565.4284.

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