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Synthesis of the $C_{21}-C_{34}$-segment of the aplyronines using the dimer of methylketene

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Abstract—This report describes a convergent synthesis of the $C_{21}-C_{34}$-segment of aplyronine. The starting point for both halves of this segment was the dimer of methylketene, readily available in either enantiomeric form by asymmetric catalysis. Diastereoselective reduction and functional group manipulation afforded the partners for a Wittig coupling reaction. The appropriate choice of oxygen protecting groups allowed the Wittig reaction to proceed, and hydrogenation of the resulting olefin afforded the $C_{21}-C_{34}$-synthon. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The aplyronines are a stereochemically complex family of polyketide natural products. The three members of this family share a common carbon skeleton, including a 24-membered macrolactone, but differ in the position of various aminoester substitutents.[1] The aplyronines exhibit strong cytoxicity toward a variety of cancer lines.[1] This activity most likely stems from the ability of these molecules to bind and depolymerize actin filaments (Fig. 1).[2]

The challenging structures and interesting biological activity of these molecules have caused several groups to pursue their synthesis. One total synthesis of a member of the aplyronine family has appeared,[3] along with several subunit syntheses.[4] These syntheses generally rely on chiral pool synthons or chiral auxiliaries to control the absolute stereochemistry of the numerous chiral centers of the target. We were interested in discovering a route to these molecules that would instead take advantage of the efficiency of asymmetric catalysis. We report here a synthesis of the $C_{21}-C_{34}$ segment of aplyronine starting with the dimer of methylketene, **1**, readily available in high enantiomeric excess using cinchona alkaloid catalysis (Scheme 1).[5]

We based our route to the $C_{21}-C_{34}$ segment on the easy availability of the *syn*,*syn*-polypropionate diastereomer from **1** (Scheme 2).[6] This diastereomer results from the aldol reaction of the enolate produced by the opening of **1** with the lithium amide derived from *N*,*O*-dimethylhydroxylamine.

We envisioned that the *syn*,*syn*-aldol reactions of the enolates derived from **1** and its enantiomer could produce the stereoarrays present in both halves of the target segment.

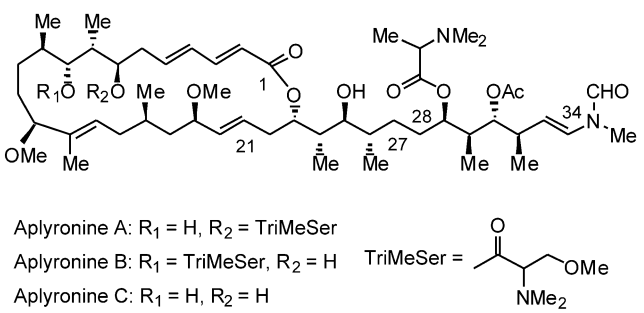
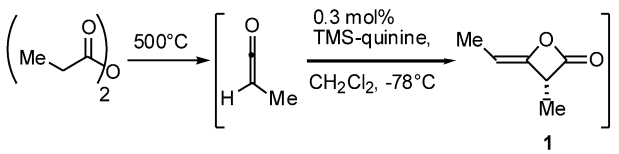
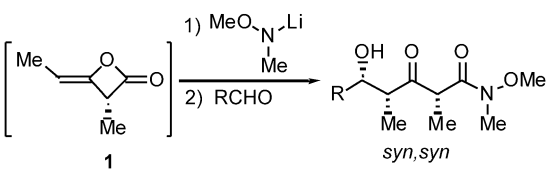


Figure 1. The aplyronines.



Scheme 1.



Scheme 2.

Keywords: methylketene dimer; aplyronine; Wittig reaction.

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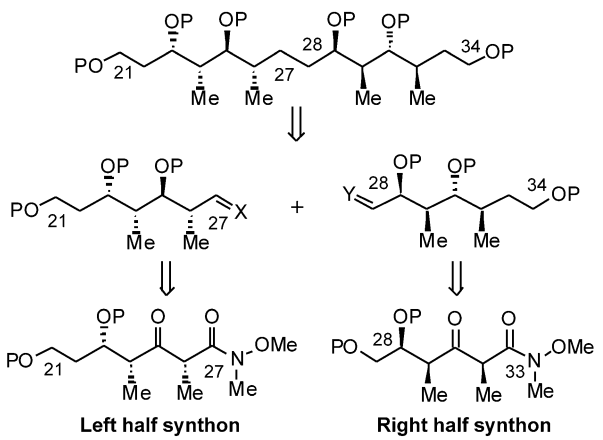


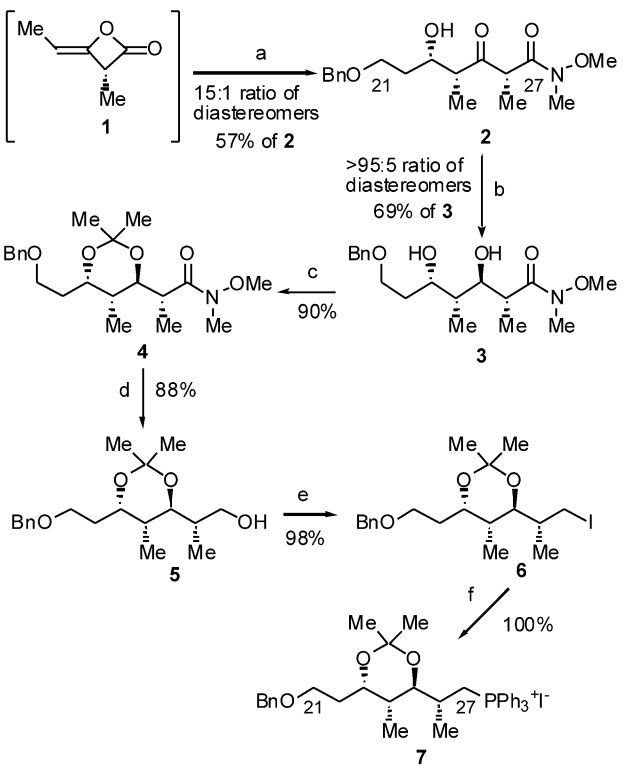
Scheme 3.

anti-Selective reductions, followed by protection and refunctionalization, could produce both halves in an appropriate form for coupling (Scheme 3).

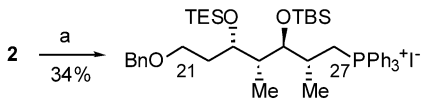
2. Results and discussion

2.1. Synthesis of the left half synthon

As we were unsure as to the optimal protecting group scheme for this portion of the molecule, we synthesized left hand synthons with two different sets of protecting groups. Synthesis of both versions of the left half began with aldol adduct **2**, available from **1** and β-benzyloxypropionaldehyde (Scheme 4). *anti*-Reduction of **2** to **3**,[7] followed by acetonide formation, yielded **4**.[8] Reduction of **4** to the aldehyde, followed by immediate further reduction, afforded primary alcohol **5**. We converted this alcohol to the corresponding iodide **6** using a slight modification of the conditions reported by Corey.[9] We employed CH_2Cl_2 as a solvent for this reaction rather than the Et_2O/CH_3CN mixture initially reported, as reaction in the latter solvent mixture led to significant decomposition. Finally, phosphonium salt formation yielded **7**.[10]



Scheme 4. (a) (i) LiN(OMe)Me; (ii) β-benyloxypropionaldehyde, THF, −78°C. (b) $NaBH(OAc)_3$, HOAc. (c) $Me_2C(OMe)_2$, TsOH, Me_2CO. (d) (i) DIBAL-H, THF, −78°C; (ii) $NaBH_4$, EtOH, 0°C. (e) I_2, PPh_3, imidazole, CH_2Cl_2, 0°C. (f) PPh_3, *i*-Pr_2NEt, MeCN, 84°C.



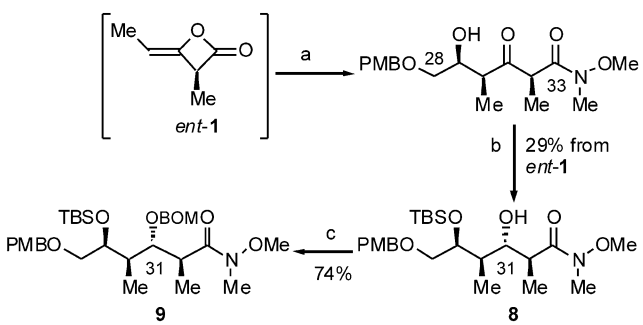
Scheme 5. (a) (i) TESCl, imidazole, DMF; (ii) $KBEt_3H$, Et_2O, −78°C; (iii) TBSCl, Et_3N, DMF; (iv) DIBAL-H, THF, −78°C; (v) $NaBH_4$, EtOH, 0°C; (vi) I_2, PPh_3, imidazole, CH_2Cl_2, 0°C; (vii) PPh_3, *i*-Pr_2NEt, MeCN, 84°C.

We also prepared an alternative left half synthon with the C_{23} and C_{25}-hydroxyls protected with different silyl groups (Scheme 5, Eq. (1)). We prepared this compound from **2** by silylation, Cram–Felkin–Nguyen selective reduction,[11] and silylation, followed by a similar sequence to that used to prepare **7**.

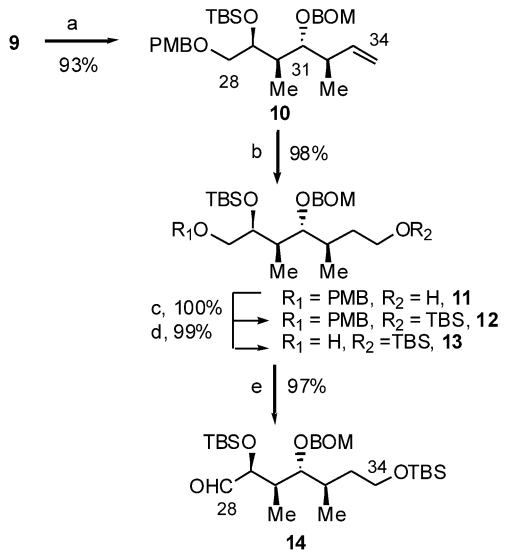
2.2. Synthesis of the right half synthon

The route to this synthon began with the aldol adduct prepared by the reaction of the enolate derived from the enantiomer of **1** with α-(*p*-methoxybenzyloxy) acetaldehyde (Scheme 6). Although this reaction proceeds in good overall yield, it afforded the product as an inseparable mixture of diastereomers in a 6:1 ratio. After silylation of the mixture, we were still unable to separate the diastereomers. Treatment of this mixture of diastereomers with $KBEt_3H$ reduced the major diastereomer in high diastereoselectivity without effecting the minor compound, allowing us to isolate **8** as a diastereomerically pure compound. We next chose to protect the C_{31}-hydroxyl as a benzyloxymethyl (BOM) ether to afford **9**.[12]

We next homologated **9** to the fully elaborated right hand synthon (Scheme 7). Reduction to the aldehyde, followed by Wittig reaction,[13] yielded monosubstituted olefin **10**. Hydroboration gave primary alcohol **11**,[14] which was silylated to produce **12**. Removal of the PMB group to



Scheme 6. (a) (i) LiN(OMe)Me; (ii) α-(*p*-methoxybenzyloxy) acetaldehyde THF, −78°C. (b) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C; (ii) $KBEt_3H$, Et_2O, −78°C. (c) BOMCl, *i*-Pr_2NEt, CH_2Cl_2.



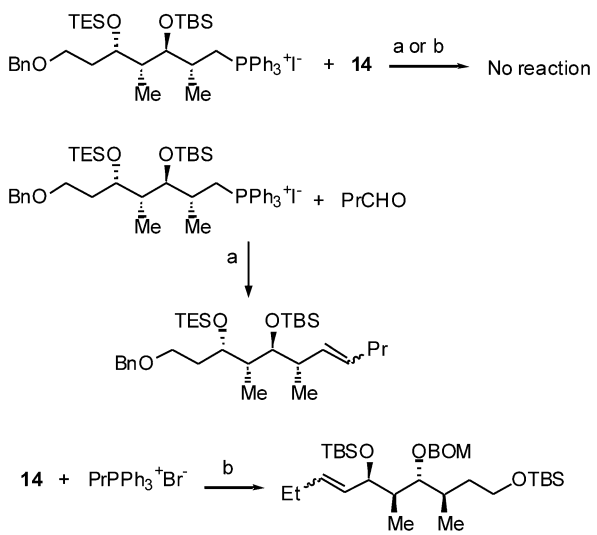
Scheme 7. (a) (i) DIBAL-H, THF, −78°C; (ii) (Ph_3PCH_3)·Br, NaHMDS, Et_2O, 0°C. (b) (i) 9-BBN, THF, 0°C; (ii) H_2O_2, NaOH, THF, 0°C. (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°. (d) DDQ, CH_2Cl_2, H_2O. (e) Dess–Martin periodinane, pyridine, CH_2Cl_2.

give **13**,[15] followed by Dess–Martin oxidation,[16] yielded aldehyde **14**.

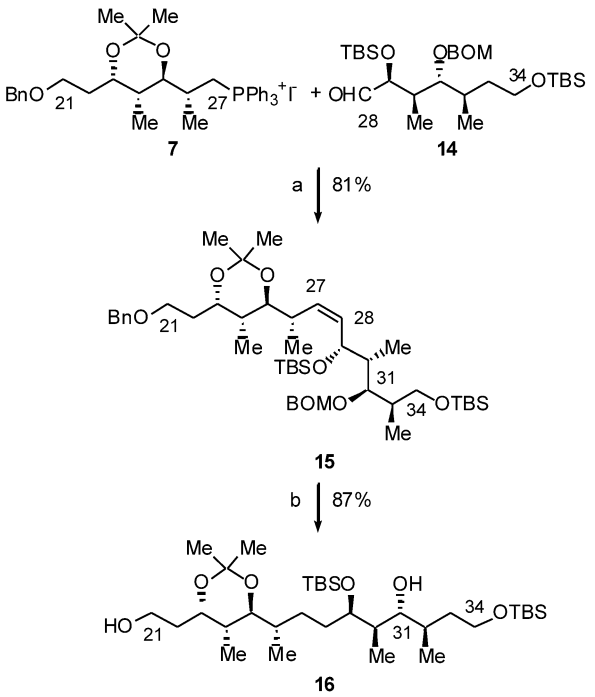
2.3. Coupling of left and right half synthons

We initially attempted to couple the bis-silyl ether version of the left hand synthon with aldehyde **14** (Scheme 8). This reaction did not yield coupled product under conditions reported for similar Wittig reactions.[10,17] Preliminary experiments revealed that both the bis-silyl ether and **14** would undergo Wittig reaction with unhindered substrates. Apparently, the combination of the steric bulk of the silyl protecting groups on both partners prevented the Wittig reaction from proceeding.

We next pursued the coupling of **14** with the less hindered ylide precursor **7** (Scheme 9). The reaction with the ylide generated in the presence of a lithium counterion proceeded



Scheme 8. (a) LiHMDS, THF, 0°C. (b) NaHMDS, THF, 0°C.



Scheme 9. (a) LiHMDS, THF. (b) (i) 1 atm H_2, 20% $Pd(OH)_2$/C, EtOH; (ii) 55 psi H_2, 5% Rh–Al_2O_3, EtOAc.

readily to form disubstituted olefin **15**. Surprisingly, this reaction afforded the *Z*-isomer in high selectivity. Completion of the side chain synthesis next required hydrogenation of the disubstituted double bond. Hydrogenation at atmospheric conditions with a variety of catalysts resulted in the loss of the C_{21} and C_{31}-hydroxyl protecting groups without reduction of the double bond. As we needed to refunctionalize the C_{21} and C_{31}-hydroxyl groups prior to coupling, the loss of these protecting groups was not unwelcome. However, the resulting diol was somewhat unstable toward desilylation, so we immediately submitted the unpurified compound to hydrogenation at 55 psi in the presence of rhodium on alumina to afford saturated diol **16**. The two step hydrogenation sequence was necessary, as direct hydrogenation of **15** in the presence of Rh/Al_2O_3 led to saturation of the aromatic ring of the BOM group.

We are currently exploring the refunctionalization of **16** into a compound suitable for coupling to the remainder of the target. We anticipate that selective transformation of the primary hydroxyl at C_{21} into the nucleophilic component for an olefination reaction, followed by formation of the C_{31}-acetate, will afford a coupling partner for the completion of the aplyronine skeleton.

3. Conclusions

We have developed an efficient synthesis of the C_{21}–C_{34}-segment of the aplyronines. This synthesis serves to further demonstrate the utility of the methylketene dimer in asymmetric polypropionate synthesis, and also illustrates the effect of oxygen protecting groups on complex Wittig reactions. Work on refunctionalization of **16** continues, as does work on the remaining portions of the target.

4. Experimental

4.1. General methods and materials

For general experimental details, see previously cited work.[18]

4.1.1. (2*R*,4*R*,5*S*)-7-Benzyloxy-5-hydroxy-2,4-dimethyl-3-oxo-heptanoic acid methoxy-methyl-amide (2). To a solution of 0.382 mL (0.317 g, 5.20 mmol) of *N*,*O*-dimethylhydoxylamine in THF (10 mL) at −78°C was added 2.08 mL (5.20 mmol) of 2.5 M *n*-BuLi in hexane. After stirring at −78°C for 20 min, the mixture was rapidly cannulated into a solution of 0.582 g (5.20 mmol) of **1** in THF (50 mL) at −78°C. Immediately after the cannulation was completed, a solution of 0.656 g (4.00 mmol) of β-benzyloxypropionaldehyde in THF (6.0 mL) was added. The reaction mixture was stirred at −78°C for 40 min. Then a mixture of 110 mL of CH_2Cl_2 and 20 mL of aqueous 1.0 M HCl was added at −78°C and the mixture was allowed to warm to rt over 30 min. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. ^{1}H NMR analysis of the unpurified reaction mixture showed a 15:1 ratio of the major aldol diastereomer to the minor one. Purification by flash column chromatography afforded 0.767 mg (57%) of **3** as a pale yellow oil: $[\alpha]_D^{23}=+8.3°$ (*c* 0.99, $CHCl_3$); IR (neat) 3472, 2939, 1711, 1660, 1454, 1383, 1101, 990, 752, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.45 (s, 2H), 4.10 (dt, 1H, *J*=9.4, 3.5 Hz), 3.98 (q, H, *J*=7.2 Hz), 3.69–3.59 (m, 2H), 3.63 (s, 3H), 3.17 (s, 3H), 2.76 (qd, 1H, *J*=7.1, 4.2 Hz), 1.81–1.64 (m, 2H), 1.31 (d, 3H, *J*=7.1 Hz), 1.13 (d, 3H, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 171.6, 137.9, 128.3, 127.6, 127.5, 73.2, 70.5, 68.7, 61.2, 53.3, 49.2, 49.0, 33.4, 12.9, 11.2. Anal. calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.80; H, 8.01; N, 4.08.

4.1.2. (2*R*,3*R*,4*R*,5*S*)-7-Benzyloxy-3,5-dihydroxy-2,4-dimethyl-heptanoic acid methoxy-methyl-amide (3). To 1.88 g (8.85 mmol) of $NaBH(OAc)_3$ in a dry round bottom flask at rt was added 45 mL of HOAc and the mixture was stirred at rt for 2.5 h. This clear solution was then cannulated into 0.595 g (1.77 mmol) of **2** in a dry flask at rt. The mixture was stirred at rt for 45 min, 25 mL of aqueous 1.0 M K^+,Na^+-tartrate was added and the mixture was allowed to stir for another 30 min at rt. Then, 45 mL of CH_2Cl_2 was added while the reaction mixture was still being stirred and the pH value of the aqueous layer was adjusted to approximately 7 with saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2 (2×30 mL). The organic layers were combined and washed again with saturated aqueous $NaHCO_3$. This aqueous $NaHCO_3$ layer was washed with CH_2Cl_2 (2×20 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give pale yellow oil. This oil was azeotroped with MeOH (3×15 mL) and HOAc (3×2 drops). ^{1}H NMR analysis of the unpurified reaction mixture showed a single reduction product. Purification by column chromatography afforded 0.412 g (69%) of **3** as a colorless oil: $[\alpha]_D^{23}=-17.5°$ (*c* 1.47, $CHCl_3$); IR (neat) 3417, 2969, 2938, 1659, 1634, 1495, 1462, 1455, 1391, 1101, 991, 739, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 4.50 (s, 2H), 4.18–4.12 (m, 2H), 3.70 (s, 3H), 3.70–3.60 (m, 2H), 3.24–3.15 (br, 1H), 3.18 (s, 3H), 1.92–1.83 (m, 1H), 1.65–1.55 (m, 2H), 1.21 (d, 3H, *J*=7.1 Hz), 0.93 (d, 3H, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 138.1, 128.3, 127.6, 127.5, 77.7, 73.1, 70.3, 68.8, 61.5, 53.3, 40.3, 36.7, 34.0, 31.7, 15.3, 11.3. Anal. calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.66; H, 8.82; N, 3.94.

4.1.3. [2*R*(4*R*,5*R*,6*S*)]-2-[6-(2-Benzyloxy-ethyl)-2,2,5-trimethyl-[1,3]dioxan-4-yl]-*N*-methoxy-*N*-methyl-propionamide (4). To a solution of 0.385 g (1.13 mmol) of **3** in acetone (18 mL) at rt was added 18 mL of 2,2-dimethoxy propane and 0.024 g (0.14 mmol) of *p*-toluenesulfonic acid. After the mixture was stirred for 30 min at rt, saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (60 mL) were added and the mixture was stirred for another 30 min. The aqueous layer was then separated and washed CH_2Cl_2 (2×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give crude product. Purification by column chromatography afforded 0.366 g (86%) of **4** as a colorless oil: $[\alpha]_D^{23}=-1.4°$ (*c* 1.19, $CHCl_3$); IR (neat) 2982, 2937, 1661, 1455, 1418, 1381, 1227, 1177, 1135, 1099, 1044, 1028, 991, 964, 880, 821, 739, 699, 603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5H), 4.48 (s, 2H), 4.02 (dt, 1H, *J*=10.0, 3.9 Hz), 3.69 (s, 3H), 3.58–3.51 (m, 2H), 3.18 (s, 3H), 3.12–3.05 (br, 1H), 1.73–1.60 (m, 3H), 1.28 (s, 3H), 1.21 (s, 3H), 1.07 (d, 3H, *J*=7.0 Hz), 0.89 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 138.3, 128.2, 127.7, 127.5, 100.3, 75.7, 73.1, 66.9, 65.5, 61.2, 40.4, 37.3, 31.9, 30.8, 25.3, 23.3, 13.0, 12.5. Anal. calcd for $C_{21}H_{33}NO_5$: C, 66.46; H, 8.76; N, 3.69. Found: C, 66.22; H, 8.72; N, 3.74.

4.1.4. [2*S*(4*S*,5*R*,6*S*)]-2-[6-(2-Benzyloxy-ethyl)-2,2,5-trimethyl-[1,3]dioxan-4-yl]-propan-1-ol (5). To a solution of 0.623 g (1.65 mmol) of **4** in THF (45 mL) at −78°C was added 5.0 mL (5.0 mmol) of a 1.0 M solution of DIBAL-H in hexane. After stirring for 20 h at −78°C, acetone (7.5 mL) was added and the mixture was stirred for another 30 min at −78°C. The mixture was then poured into 450 mL of 1:1 mixture of aqueous 0.5 M tartaric acid and hexane at rt and stirred vigorously for 50 min. The aqueous layer was separated from the clear organic layer and washed with hexanes (2×100 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated in vacuo to give 0.514 g of product as a colorless oil, which was used in the following step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, 1H, *J*=2.6 Hz), 7.39–7.29 (m, 5H), 4.52 (s, 2H), 4.09 (dt, 1H, *J*=9.1, 4.5 Hz), 3.58–3.55 (m, 2H), 3.51–3.46 (m, 1H), 2.48 (qdd, 1H, *J*=7.0, 5.5, 2.5 Hz), 1.93–1.88 (m, 1H), 1.73–1.67 (m, 2H), 1.34 (s, 3H), 1.30 (s, 3H), 1.16 (d, 3H, *J*=7.1 Hz), 0.91 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 138.2, 128.3, 127.7, 127.5, 100.7, 76.3, 73.1, 66.8, 65.6, 49.7, 37.5, 30.8, 24.7, 23.3, 12.2, 11.0.

To the unpurified aldehyde from the previous step in EtOH (45 mL) at 0°C was added 0.610 mg (1.61 mmol) of $NaBH_4$. The reaction mixture was stirred for 40 min at 0°C, and then it was poured into a mixture of aqueous 1.0 M NH_4Cl (20 mL) and CH_2Cl_2 (40 mL) at rt and stirred for another

15 min. The aqueous layer was separated and washed (2×40 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography afforded 0.468 g (88% from **4**) of **5** as a colorless oil: $[\alpha]_D^{23}=+0.3°$ (*c* 0.89, $CHCl_3$); IR (neat) 3467, 2965, 2933, 2877, 1496, 1455, 1380, 1221, 1176, 1102, 1018, 992, 883, 750, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 4.48 (s, 2H), 4.05 (dt, 1H, *J*=9.4, 4.3 Hz), 3.76–3.71 (m, 1H), 3.57–3.51 (m, 3H), 3.25 (dd, 1H, *J*=7.3, 6.0 Hz), 1.79–1.62 (m, 4H), 1.32 (s, 3H), 1.28 (s, 3H), 0.98 (d, 3H, *J*=7.4 Hz), 0.84 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.7, 127.7, 127.5, 100.6, 80.7, 73.1, 66.8, 66.7, 65.8, 38.8, 38.1, 30.8, 25.2, 23.4, 13.9, 12.5. Anal. calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.55; H, 9.39.

4.1.5. [4*S*,5*R*,6*R*(1*R*)]-4-(2-Benzyloxy-ethyl)-6-(2-iodo-1-methyl-ethyl)-2,2,5-trimethyl-[1,3]dioxane (6). To a solution of 0.184 g (0.572 mmol) of **5** in CH_2Cl_2 (6 mL) at 0°C was added 0.117 g (1.72 mmol) of imidazole and 0.300 mg (1.14 mmol) of triphenylphosphine. After these two compounds had completely dissolved, 0.291 g (1.14 mmol) of iodine was added and the reaction mixture was stirred for 30 min at 0°C. The mixture was then warmed to rt and stirred for 4 h. Aqueous 0.1 M $Na_2S_2O_3$ (10 mL) and CH_2Cl_2 (6 mL) were added and the mixture was stirred for another 10 min at rt. The organic layer was separated, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography afforded 0.241 g (98%) of **6** as a pale yellow oil: $[\alpha]_D^{23}=-15.1°$ (*c* 0.91, $CHCl_3$); IR (neat) 3029, 2982, 2933, 2876, 2360, 2341, 1496, 1455, 1380, 1298, 1226, 1176, 1132, 1097, 1050, 1016, 991, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 4.47 (s, 2H), 3.99 (dt, 1H, *J*=9.8, 3.9 Hz), 3.53–3.51 (m, 2H), 3.38–3.29 (m, 2H), 3.05 (t, 1H, *J*=7.2 Hz), 1.73–1.58 (m, 3H), 1.50–1.42 (m, 1H), 1.32 (s, 3H), 1.25 (s, 3H), 0.99 (d, 3H, *J*=6.7 Hz), 0.86 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.3, 127.7, 127.5, 100.4, 77.4, 73.1, 66.9, 65.6, 39.3, 37.5, 30.8, 25.2, 23.7, 16.8, 15.0, 12.8. Anal. calcd for $C_{19}H_{29}IO_3$: C, 52.78; H, 6.76. Found: C, 53.07; H, 6.76.

4.1.6. {[2*R*(4*R*,5*R*,6*S*)]-2-[6-(2-Benzyloxy-ethyl)-2,2,5-trimethyl-[1,3]dioxan-4-yl]-propyl}-triphenyl-phosphonium iodide (7). To a solution of 0.223 g (0.515 mmol) of **6** in MeCN (15 mL) at rt was added 0.27 mL (0.20 mg, 1.6 mmol) of *i*-Pr_2NEt and 2.04 g (7.79 mmol) of triphenylphosphine. The mixture was heated to 84°C and allowed to reflux for 24 h. After cooling to rt, the solvents were removed in vacuo. The residue was purified by flash chromatography to give 0.358 g (100%) of **7** as a pale yellow foam: $[\alpha]_D^{23}=+33.0°$ (*c* 0.34, $CHCl_3$); IR (neat) 2919, 1587, 1485, 1455, 1438, 1382, 1231, 1176, 1112, 997, 750, 722, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92–7.65 (m, 15H), 7.32–7.29 (m, 5H), 4.48 (d, 1H, *J*=11.8 Hz), 4.45 (d, 1H, *J*=11.8 Hz), 3.98 (dt, 1H, *J*=10.2, 3.4 Hz), 3.77–3.50 (m, 4H), 3.33 (dd, 1H, *J*=8.9, 6.4 Hz), 2.08–1.94 (m, 1H), 1.69–1.48 (m, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 0.85 (d, 3H, *J*=6.8 Hz), 0.73 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 135.0, 134.9, 133.9, 133.8, 132.0, 131.9, 131.8, 131.8, 130.4, 130.2, 128.4, 128.3, 128.2, 127.7, 127.5, 118.9, 118.0, 100.8, 78.5, 78.4, 73.1, 66.6, 65.3, 38.5, 34.5, 34.5, 30.7, 25.5, 25.4, 24.9, 24.0, 16.7, 13.0. Anal. calcd for $C_{37}H_{44}IO_3P$: C, 63.98; H, 6.38. Found: C, 63.81; H, 6.41.

4.1.7. (2*S*,3*S*,4*R*,5*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-3-hydroxy-6-(4-methoxy-benzyloxy)-2,4-dimethyl-hexanoic acid methoxy-methyl-amide (8). To a solution of 0.257 mL (0.214 g, 3.50 mmol) of *N*,*O*-dimethylhydroxylamine in hexane (11 mL) at −78°C was added 1.40 mL (3.50 mmol) of 2.5 M *n*-BuLi in hexane. After stirring at −78°C for 20 min, the resulting slurry was rapidly cannulated into a solution of 0.392 g (3.50 mmol) of *ent*-**1** in CH_2Cl_2 (35 mL) at −78°C. Immediately after the cannulation was completed, a solution of 0.360 mg (2.00 mmol) of α-(*p*-methoxybenzyloxy)acetaldehyde in CH_2Cl_2 (3 mL) at −78°C was cannulated into the solution from above and the mixture was stirred at −78°C for 40 min. Then pH 7 buffer solution (20 mL of a 1:1 mixture of concentrated pH 7 buffer and H_2O) was added at −78°C and the mixture was allowed to warm to rt over 30 min. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography afforded 0.538 g (76%) of an inseparable mixture of the two *syn*-aldol diastereomers. Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 2H, *J*=8.6 Hz), 6.86 (d, 2H, *J*=8.6 Hz), 4.46 (d, 1H, *J*=11.4 Hz), 4.41 (d, 1H, *J*=11.4 Hz), 4.09 (dt, 1H, *J*=6.4, 5.0 Hz), 3.96 (q, 1H, *J*=7.2 Hz), 3.79 (s, 3H), 3.65 (s, 3H), 3.46–3.36 (m, 2H), 3.17 (s, 3H), 2.89 (qd, 1H, *J*=7.2, 5.0 Hz), 1.31 (d, 3H, *J*=7.1 Hz), 1.13 (d, 3H, *J*=7.2 Hz).

To a solution of 0.538 g (1.52 mmol) of the mixture of the aldol diastereomers from the previous reaction in CH_2Cl_2 (15 mL) at −78°C was added 0.36 mL (0.33 g, 3.1 mmol) of 2,6-lutidine and 0.52 mL (0.60 g, 2.3 mmol) of TBSOTf. The mixture was stirred for 30 min and then was quenched at −78°C by the addition of pH 7 buffer solution (10 mL of a 1:1 mixture of concentrated pH 7 buffer and H_2O). The mixture was allowed to warm to rt over 30 min and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2×9 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography afforded 0.483 g (68%) of the silylated aldol products as an inseparable, 6:1 mixture of diastereomers. Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, 2H, *J*=8.6 Hz), 6.84 (d, 2H, *J*=8.6 Hz), 4.41 (d, 1H, *J*=11.8 Hz), 4.36 (d, 1H, *J*=11.8 Hz), 4.11 (q, 1H, *J*=5.6 Hz), 4.02–3.95 (m, 1H), 3.78 (s, 3H), 3.60 (s, 3H), 3.37–3.28 (m, 2H), 3.14 (s, 3H), 3.01–2.93 (m, 1H), 1.32 (d, 3H, *J*=7.1 Hz), 1.11 (d, 3H, *J*=7.2 Hz), 0.84 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

To a solution of 2.1 mL (2.1 mmol) of 1.0 M $KBEt_3H$ in Et_2O (9 mL) at −78°C was added a solution of 0.483 g (1.03 mmol) of the mixture of silylated aldol products from above in Et_2O (4 mL) via a syringe pump over 20 min. After 30 min, pH 7 buffer solution (10 mL) was added at −78°C. Then the mixture was warmed to rt over 30 min and the organic layer was separated. The aqueous layer was washed twice with Et_2O (2×8 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. ^1H NMR analysis of the unpurified reaction mixture indicated the

presence of only a single reduction product and unreacted minor silylated aldol adduct. Purification by flash column chromatography afforded 0.271 g (29% total from *ent*-**1**) of **8** as a single diastereomer (colorless oil): $[\alpha]_D^{23}=-19.9°$ (*c* 0.51, $CHCl_3$); IR (neat) 3393, 2929, 2856, 1614, 1586, 1513, 1462, 1417, 1387, 1302, 1251, 1175, 1147, 1079, 1041, 993, 952, 838, 778, 739, 705, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, 2H, *J*=8.6 Hz), 6.85 (d, 2H, *J*=8.6 Hz), 4.45 (d, 1H, *J*=11.6 Hz), 4.42 (td, 1H, *J*=6.4, 1.5 Hz), 4.35 (d, 1H, *J*=11.6 Hz), 3.78 (s, 3H), 3.70 (s, 3H), 3.38–3.32 (m, 3H), 3.16 (s, 3H), 3.20–3.13 (br, 1H), 1.70–1.62 (m, 1H), 1.31 (d, 3H, *J*=7.1 Hz), 0.84 (s, 9H), 0.77 (d, 3H, *J*=6.9 Hz), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 130.4, 129.1, 113.5, 75.7, 72.9, 72.5, 69.6, 61.4, 55.1, 40.2, 35.6, 31.6, 25.8, 18.1, 16.0, 9.8, −4.3, −5.2. Anal. calcd for $C_{24}H_{43}NO_6Si$: C, 61.37; H, 9.23; N, 2.98. Found: C, 61.55; H, 9.41; N, 2.87.

4.1.8. (2*S*,3*S*,4*R*,5*S*)-3-Benzyloxymethoxy-5-(*tert*-butyl-dimethyl-silanyloxy)-6-(4-methoxy-benzyloxy)-2,4-dimethyl-hexanoic acid methoxy-methyl-amide (9). To a solution of 0.166 g (0.354 mmol) of **8** in CH_2Cl_2 (3.5 mL) at rt was added 0.68 mL (0.50 g, 3.9 mmol) of *i*-Pr_2NEt and 0.53 mL (0.55 g, 3.5 mmol) of BOMCl. The mixture was stirred for eight days, and then quenched by the addition of aqueous 1.0 M HCl (5 mL), H_2O (2 mL) and CH_2Cl_2 (4 mL) at rt. The mixture was stirred for 10 min and the organic layer was separated. The aqueous layer was washed twice with CH_2Cl_2 (2×10 mL) and the combined organic layers were washed with H_2O, dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography afforded 0.153 g (74%) of **9** as a colorless oil: $[\alpha]_D^{23}=+15.7°$ (*c* 0.62, $CHCl_3$); IR (neat) 2930, 1660, 1613, 1514, 1463, 1386, 1302, 1249, 1036, 836, 776, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.29 (m, 5H), 7.23 (d, 2H, *J*=8.6 Hz), 6.83 (d, 2H, *J*=8.6 Hz), 4.77 (d, 1H, *J*=6.6 Hz), 4.72 (d, 1H, *J*=6.6 Hz), 4.54 (s, 2H), 4.44 (d, 1H, *J*=11.6 Hz), 4.38 (d, 1H, *J*=11.6 Hz), 4.00 (dt, 1H, *J*=5.4, 4.7 Hz), 3.83 (dd, 1H, *J*=7.9, 4.4 Hz), 3.79 (s, 3H), 3.63 (s, 3H), 3.50–3.42 (m, 3H), 3.14 (s, 3H), 2.07–1.99 (m, 1H), 1.10 (d, 3H, *J*=6.9 Hz), 0.93 (d, 3H, *J*=7.1 Hz), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 158.9, 138.0, 130.4, 129.1, 128.2, 127.6, 127.3, 113.5, 96.4, 83.4, 73.2, 72.7, 72.3, 69.9, 61.1, 55.1, 38.8, 38.1, 32.0, 25.8, 18.1, 13.5, 12.4, −4.1, −4.8. Anal. calcd for $C_{32}H_{51}NO_7Si$: C, 65.16; H, 8.71; N, 2.37. Found: C, 65.33; H, 8.87; N, 2.14.

4.1.9. [(1*S*,2*R*,3*R*,4*R*)-3-Benzyloxymethoxy-1-(4-methoxy-benzyloxymethyl)-2,4-dimethyl-hex-5-enyloxy]-*tert*-butyl-dimethyl-silane (10). To a solution of 0.127 g (0.215 mmol) of **9** in THF (2.2 mL) at −78°C was added 0.75 mL (0.75 mmol) of 1.0 M solution of DIBAL-H in hexane. The mixture was stirred for 30 min at −78°C and then quenched by addition of acetone (1.8 mL). The mixture was stirred at −78°C for another 30 min and then poured into 60 mL of a 1:1 mixture of aqueous 0.5 M tartaric acid and hexane at rt. This mixture was stirred vigorously for 45 min and the organic layer was separated. The aqueous layer was washed with hexane (2×15 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The unpurified reaction mixture was used directly in the next step.

To a suspension of 0.230 g (0.645 mmol) of CH_3PPh_3Br in Et_2O (6.5 mL) at 0°C was added 0.56 mL (0.56 mmol) of a 1.0 M solution of NaHMDS in THF. The resulting yellow suspension was stirred for 4 h at 0°C, and then a solution of the unpurified aldehyde from the previous reaction in Et_2O (2.2 mL) was added dropwise and the mixture was stirred for another 25 min at 0°C. Then H_2O (10 mL) was added and the mixture was warmed to rt for 10 min. The organic layer was separated and the aqueous layer was washed with Et_2O (2×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography afforded 0.106 g (93% from **9**) of **10** as a colorless oil: $[\alpha]_D^{23}=+3.35°$ (*c* 0.51, $CHCl_3$); IR (neat) 3068, 2929, 2856, 1613, 1586, 1514, 1462, 1360, 1302, 1249, 1172, 1147, 1039, 913, 836, 777, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 5H), 7.22 (d, 2H, *J*=8.6 Hz), 6.84 (d, 2H, *J*=8.7 Hz), 5.93–5.84 (m, 1H), 5.02 (br, 1H), 4.99 (br, 1H), 4.82 (d, 1H, *J*=6.7 Hz), 4.80 (d, 1H, *J*=6.7 Hz), 4.69 (d, 1H, *J*=11.9 Hz), 4.58 (d, 1H, *J*=11.9 Hz), 4.44 (d, 1H, *J*=11.6 Hz), 4.35 (d, 1H, *J*=11.6 Hz), 4.16 (td, 1H, *J*=5.8, 2.0 Hz), 3.78 (s, 3H), 3.40–3.30 (m, 3H), 2.53–2.45 (m, 1H), 1.80–1.73 (m, 1H), 1.10 (d, 3H, *J*=7.2 Hz), 0.84 (s, 9H), 0.77 (d, 3H, *J*=7.2 Hz), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 140.2, 138.0, 130.3, 129.1, 128.2, 127.6, 127.4, 114.3, 113.5, 96.7, 85.7, 73.6, 72.5, 70.7, 69.8, 55.1, 39.8, 39.6, 25.9, 18.3, 17.9, 10.0, −3.8, −5.0. Anal. calcd for $C_{31}H_{48}O_5Si$: C, 70.41; H, 9.15. Found: C, 70.55; H, 9.27.

4.1.10. (3*R*,4*R*,5*R*,6*S*)-4-Benzyloxymethoxy-6-(*tert*-butyl-dimethyl-silanyloxy)-7-(4-methoxy-benzyloxy)-3,5-dimethyl-heptan-1-ol (11). To a solution of 119 mg (0.225 mmol) of **10** in THF (4.5 mL) at rt was added 1.2 mL (0.58 mmol) of 0.5 M solution of 9-BBN in THF. After stirring for 7 h, the mixture was cooled to 0°C and 0.58 mL (0.58 mmol) of aqueous 1.0 M NaOH was added, followed by 0.197 g (1.74 mmol) of a 30% aqueous solution of H_2O_2. The mixture was then stirred for 1 h at 0°C and Et_2O (120 mL) was added. The mixture was washed with H_2O, then brine and dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography afforded 0.121 g (98%) of **11** as a colorless oil: $[\alpha]_D^{23}=+10.0°$ (*c* 0.51, $CHCl_3$); IR (neat) 3426, 2929, 1628, 1586, 1514, 1462, 1360, 1302, 1249, 1173, 1039, 836, 777, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.31 (m, 5H), 7.22 (d, 2H, *J*=8.7 Hz), 6.84 (d, 2H, *J*=8.6 Hz), 4.82 (br, 2H), 4.67 (d, 1H, *J*=11.9 Hz), 4.59 (d, 1H, *J*=11.9 Hz), 4.44 (d, 1H, *J*=11.6 Hz), 4.35 (d, 1H, *J*=11.5 Hz), 4.17 (td, 1H, *J*=5.8, 1.5 Hz), 3.78 (s, 3H), 3.75–3.69 (m, 1H), 3.60–3.54 (m, 1H), 3.40–3.31 (m, 3H), 1.97–1.84 (m, 2H), 1.68–1.53 (m, 2H), 1.03 (d, 3H, *J*=7.2 Hz), 0.83 (s, 9H), 0.77 (d, 3H, *J*=6.8 Hz), 0.00 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 137.7, 130.3, 129.1, 128.2, 127.7, 127.4, 113.5, 96.9, 86.7, 73.6, 72.6, 70.5, 70.0, 60.1, 55.1, 39.1, 33.1, 31.5, 25.9, 18.2, 17.3, 10.0, −3.8, −5.0. Anal. calcd for $C_{31}H_{50}O_6Si$: C, 68.09; H, 9.22. Found: C, 68.37; H, 9.28.

4.1.11. 1-[(2*S*,3*R*,4*R*,5*R*)-4-Benzyloxymethoxy-2,7-bis-(*tert*-butyl-dimethyl-silanyloxy)-3,5-dimethyl-heptyloxymethyl]-4-methoxy-benzene (12). To a solution of 0.110 g (0.201 mmol) of **11** in CH_2Cl_2 (5 mL) at −78°C was added

0.05 mL (0.04 g, 0.4 mmol) of 2,6-lutidine and 0.07 mL (0.08 g, 0.3 mmol) of TBSOTf. The mixture was stirred for 1 h at −78°C and then brine (10 mL) was added. The mixture was warmed to rt over 30 min and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2×10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography afforded 0.133 g (100%) of **12** as a colorless oil: $[\alpha]_D^{23}=+5.90°$ (*c* 0.58, $CHCl_3$); IR (neat) 2955, 2856, 1613, 1514, 1463, 1387, 1360, 1302, 1250, 1099, 1041, 835, 776, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 5H), 7.22 (d, 2H, *J*=8.6 Hz), 6.84 (d, 2H, *J*=8.6 Hz), 4.81 (d, 1H, *J*=6.6 Hz), 4.78 (d, 1H, *J*=6.5 Hz), 4.65 (d, 1H, *J*=11.9 Hz), 4.58 (d, 1H, *J*=11.9 Hz), 4.45 (d, 1H, *J*=11.6 Hz), 4.35 (d, 1H, *J*=11.6 Hz), 4.18 (td, 1H, *J*=5.9, 1.7 Hz), 3.78 (s, 3H), 3.71–3.66 (m, 1H), 3.60–3.54 (m, 1H), 3.39–3.31 (m, 3H), 1.88–1.67 (m, 3H), 1.34–1.23 (m, 1H), 0.99 (d, 3H, *J*=6.8 Hz), 0.87 (s, 9H), 0.83 (s, 9H), 0.77 (d, 3H, *J*=7.2 Hz), 0.02 (s, 6H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 138.0, 130.4, 129.1, 128.2, 127.6, 127.3, 113.5, 96.9, 87.1, 73.6, 72.5, 70.6, 69.7, 61.2, 55.1, 39.0, 33.1, 30.8, 25.9, 25.8, 18.2, 18.1, 17.5, 9.8, −3.9, −5.0, −5.4, −5.5. Anal. calcd for $C_{37}H_{64}O_6Si_2$: C, 67.22; H, 9.76. Found: C, 67.39; H, 9.77.

4.1.12. (2*S*,3*R*,4*R*,5*R*)-4-Benzyloxymethoxy-2,7-bis-(*tert*-butyl-dimethyl-silanyloxy)-3,5-dimethyl-heptan-1-ol (13). To a solution of 0.122 g (0.185 mmol) of **12** in CH_2Cl_2 (5 mL) and H_2O (0.3 mL) at rt was added 0.0557 g (0.245 mmol) of DDQ. After the mixture was stirred for 2 h at rt, saturated aqueous $NaHCO_3$ (12 mL) and CH_2Cl_2 (3 mL) were added and the mixture was stirred for another 10 min. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography afforded 0.0989 g (99%) of **13** as a colorless oil: $[\alpha]_D^{23}=-5.0°$ (*c* 0.76, $CHCl_3$); IR (neat) 3457, 2955, 2857, 1472, 1387, 1361, 1255, 1098, 1042, 939, 906, 835, 776, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 4.80 (d, 1H, *J*=6.8 Hz), 4.78 (d, 1H, *J*=6.8 Hz), 4.64 (d, 1H, *J*=12.0 Hz), 4.60 (d, 1H, *J*=11.9 Hz), 3.98 (td, 1H, *J*=5.3, 3.3 Hz), 3.7–3.66 (m, 1H), 3.61–3.50 (m, 3H), 3.32 (dd, 1H, *J*=7.9, 3.0 Hz), 1.94–1.83 (m, 2H), 1.80–1.72 (m, 1H), 1.32–1.24 (m, 1H), 0.97 (d, 3H, *J*=6.9 Hz), 0.87 (s, 18H), 0.86 (d, 3H, *J*=7.3 Hz), 0.05 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 128.2, 127.7, 127.5, 96.5, 87.3, 72.9, 69.9, 66.0, 61.1, 38.5, 33.5, 31.2, 25.8, 18.1, 17.4, 11.4, −4.2, −4.6, −5.4, −5.5. Anal. calcd for $C_{29}H_{56}O_5Si_2$: C, 64.39; H, 10.43. Found: C, 64.57; H, 10.45.

4.1.13. (2*S*,3*R*,4*R*,5*R*)-4-Benzyloxymethoxy-2,7-bis-(*tert*-butyl-dimethyl-silanyloxy)-3,5-dimethyl-heptanal (14). To a solution of 0.100 g (0.185 mmol) of **13** in CH_2Cl_2 (4 mL) at rt were added 0.15 mL (0.15 g, 1.9 mmol) of pyridine and 0.0978 g (0.230 mmol) of the Dess–Martin periodinane. The mixture was stirred at rt for 45 min and Et_2O (40 mL) was then added. The mixture was poured into a 1:1 mixture of aqueous 0.1 M $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (40 mL) and was stirred for another 20 min. The organic layer was separated and the aqueous layer was washed with Et_2O (2×35 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were removed in vacuo. Purification by flash column chromatography afforded 0.0963 g (97%) of **14** as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (d, 1H, *J*=1.1 Hz), 7.50–7.24 (m, 5H), 4.76 (d, 1H, *J*=6.8 Hz), 7.73 (d, 1H, *J*=6.7 Hz), 4.62 (d, 1H, *J*=11.8 Hz), 4.58 (d, 1H, *J*=11.8 Hz), 4.31 (dd, 1H, *J*=2.7, 1.2 Hz), 3.71–3.66 (m, 1H), 3.60–3.54 (m, 1H), 3.31 (dd, 1H, *J*=8.6, 2.6 Hz), 2.24–2.16 (m, 1H), 2.00–1.91 (m, 1H), 1.77–1.68 (m, 1H), 1.34–1.26 (m, 1H), 1.00 (d, 3H, *J*=6.8 Hz), 0.89 (s, 9H), 0.86 (s, 9H), 0.83 (d, 3H, *J*=6.8 Hz), 0.02 (s, 6H), 0.00 (s, 3H), −0.01 (s, 3H). This aldehyde was then azeotroped three times with toluene, dried in vacuo for 3 h and used immediately in the coupling reaction.

4.1.14. [4*S*,5*R*,6*S*(1*S*,2*Z*,4*R*,5*R*,6*R*,7*R*)]-4-(2-Benzyloxy-ethyl)-6-[6-benzyloxymethoxy-4,9-bis-(*tert*-butyl-dimethyl-silanyloxy)-1,5,7-trimethyl-non-2-enyl]-2,2,5-trimethyl-[1,3]dioxane (15). To a solution of 0.53 mL (0.41 g, 2.5 mmol) of hexamethyldisilazane in THF (1.5 mL) at 0°C was added 1.0 mL (2.5 mmol) of a 2.5 M solution of *n*-BuLi in hexane. This LiHMDS solution was stirred at 0°C for 15 min and used directly in the next reaction. Directly prior to reaction, 0.225 g (0.324 mmol) of **7** was azeotroped with toluene (3×5 mL). To this compound in THF (5.5 mL) at 0°C was added 0.41 mL (0.35 mmol) of the LiHMDS solution prepared above. The dark orange mixture was warmed to rt and stirred 40 min. At this time, a solution of 0.0963 g (0.179 mmol) of **14** in THF (1.0 mL) was added. The mixture was stirred for 2 h at rt. And then aqueous 1.0 M NH_4Cl (8 mL) was added and the mixture was extracted with Et_2O (40 mL). The separated aqueous layer was washed with Et_2O (2×10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography afforded 0.120 g (81%) of **15** as a pale yellow oil: $[\alpha]_D^{23}=+40.6°$ (*c* 0.55, $CHCl_3$); IR (neat) 2956, 1462, 1380, 1251, 1098, 1044, 835, 775, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 10H), 5.56 (dd, 1H, *J*=11.6, 8.8 Hz), 5.34 (t, 1H, *J*=11.0 Hz), 4.83–4.77 (m, 3H), 4.68 (d, 1H, *J*=12.0 Hz), 4.57 (d, 1H, *J*=12.0 Hz), 4.47 (s, 2H), 3.94–3.90 (m, 1H), 3.67–3.62 (m, 1H), 3.57–3.50 (m, 3H), 3.33 (brd, 1H, *J*=8.9 Hz), 3.13 (dd, 1H, *J*=8.1, 3.4 Hz), 2.69–2.62 (m, 1H), 1.91–1.84 (m, 1H), 1.68–1.47 (m, 5H), 1.33–1.22 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 0.99 (d, 3H, *J*=6.9 Hz), 0.98 (d, 3H, *J*=6.9 Hz), 0.86 (s, 9H), 0.85 (s, 9H), 0.81 (d, 3H, *J*=6.9 Hz), 0.80 (d, 3H, *J*=6.9 Hz), 0.01 (s, 6H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.1, 134.0, 130.0, 128.2, 128.1, 127.7, 127.5, 127.4, 127.3, 100.3, 97.2, 87.2, 78.0, 73.1, 69.7, 67.5, 67.1, 65.8, 61.1, 43.9, 36.9, 34.3, 32.7, 30.8, 30.6, 25.8, 24.7, 23.3, 18.1, 17.3, 17.2, 11.9, 9.2, −3.4, −4.9, −5.4, −5.5. Anal. calcd for $C_{48}H_{82}O_7Si_2$: C, 69.68; H, 9.99. Found: C, 69.89; H, 10.12.

4.1.15. [4*S*,5*R*,6*S*(1*S*,4*R*,5*R*,6*R*,7*R*)]-4-(2-Benzyloxy-ethyl)-6-[6-benzyloxymethoxy-4,9-bis-(*tert*-butyl-dimethyl-silanyloxy)-1,5,7-trimethyl-nonyl]-2,2,5-trimethyl-[1,3]dioxane (16). To a solution of 0.0341 g (0.0413 mmol) **15** in EtOH (12 mL) at rt was added 0.0095 g of 20% $Pd(OH)_2/C$. The reaction flask was then connected to a H_2 balloon and the mixture was stirred for

10 h at rt. The mixture was then filtered through celite with EtOAc and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (10 mL) and transferred into a large test tube into which 0.0536 g of 5% Rh/Al_2O_3 and then several glass beads were added. The tube was then placed inside a high pressure vial packed with glass wool. The vial was then connected to a Parr hydrogenation apparatus and pressurized with 55 psi of H_2. After the mixture was shaken for 48 h, the mixture was filtered through a column of celite with EtOAc and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography to give 0.0221 g (87%) of **16** as a colorless oil: $[\alpha]_D^{23}=21.2°$ (*c* 1.07, $CHCl_3$); IR (neat) 3419, 2931, 1463, 1380, 1255, 1094, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.13 (br, 1H), 4.03 (ddd, 1H, J=11.0, 4.0, 2.5 Hz), 3.82–3.73 (m, 4H), 3.66–3.60 (m, 1H), 3.56 (dd, 1H, J=9.5, 1.5 Hz), 3.12 (dd, 1H, J=7.0, 5.2 Hz), 2.51 (br, 1H), 1.94–1.38 (m, 12H), 1.36 (s, 3H), 1.33 (s, 3H), 1.03 (d, 3H, J=6.9 Hz), 0.97 (d, 3H, J=6.8 Hz), 0.92 (s, 9H), 0.91 (s, 9H), 0.90 (d, 3H, J=5.0 Hz), 0.79 (d, 3H, J=7.0 Hz), 0.14 (s, 3H), 0.11 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.3, 78.6, 77.9, 70.1, 62.6, 61.2, 39.8, 37.4, 37.3, 32.7, 31.6, 31.4, 29.1, 29.0, 25.9, 25.8, 25.6, 23.4, 18.3, 17.9, 17.0, 16.1, 13.2, 13.0, −4.3, −4.7, −5.3, −5.4. Anal. calcd for $C_{33}H_{70}O_6Si_2$: C, 64.02; H, 11.40. Found: C, 64.33; H, 11.38.

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