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# Stereoselective synthesis of fully functionalized acyclic core of Tianchimycin A

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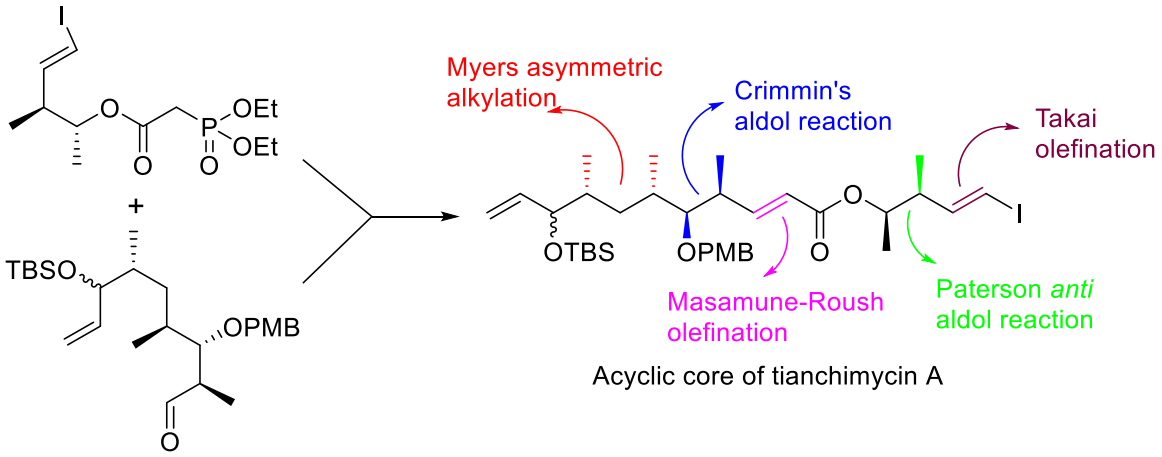
## Abstract

A highly convergent synthetic approach towards the macrolactone polyketide tianchimycin A is described. Notable features of our synthetic approach include highly stereoselective Myers alkylation, substrate controlled *anti* aldol reaction, and Masamune-Roush olefination.




**Keywords:** Tianchimycin, Crimmins's protocol, Paterson's aldol reaction, Takai olefination, Masamune-Roush olefination, intramolecular Heck-cyclization

## Introduction

Actinobacteria are important sources of bioactive secondary metabolites.[1] In 2013, Deng and co-workers isolated two new 16-membered macrolactone type polyketides from the rare actinomycete *Saccharothrix xinjiangensis* B-24321 and named them as tianchimycin A and tianchimycin B (Figure 1).[2] Structures of tianchimycins A-B were determined based on detailed NMR and MS spectroscopy. Architecturally tianchimycin A is quite interesting. It is a macrocyclic lactone adorned with six stereogenic centers and three olefinic moieties. Out of three double bonds, two are part of 1,4–butadiene system and the third one is a part of *α,β*-unsaturated lactone moiety. Initial biological studies revealed that they do not have antibacterial activity. However modification of the structure might provide good antibacterial lead. Thus with this intention we initiated a program for the total synthesis of tianchimycin A and its analogs to unveil the full biological potential. In 2015 Sabitha et al. reported the synthetic study of tianchimycin A. They synthesized the entire acyclic C1-C16 framework of the molecule. However the macrolactonization under different conditions was unsuccessful.[3] Thus we thought an alternate approach to construct **1** could be intramolecular Heck-cyclization for the formation of macrocyclic ring.[4] Recently the employment of intramolecular Heck reaction for macrocyclization has flourished in natural product synthesis.[4,16,17,18,19] It is interesting to note that this reaction is applicable to variation depending upon the macrocyclic ring size (16-24 size macrocycles), which requires optimization of variety of reaction parameters.

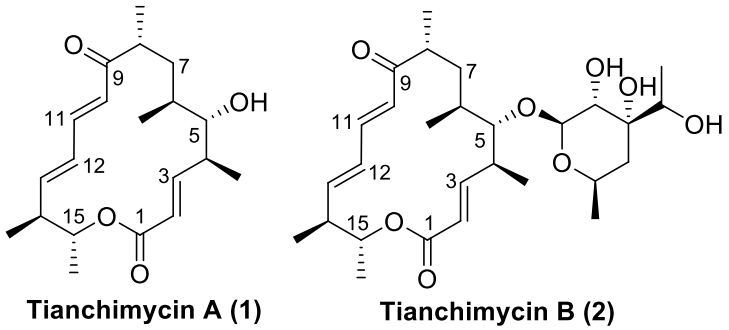
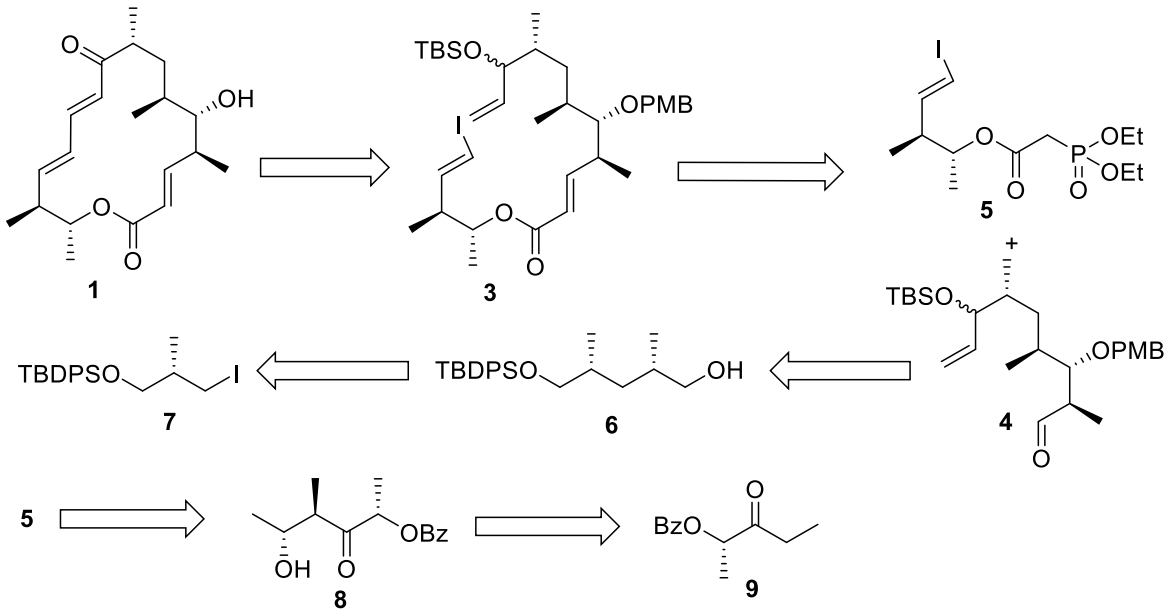



**Figure 1.** Structures of Tianchimycins.

## Results and Discussion

Retrosynthetically, we dissected **3** into building blocks **4** and **5** (Scheme 1). Heck coupling of substrate **3** was envisaged as a key step to close the macrocycle, while connection of the cyclization precursor **3** was planned to arise from Masamune-Roush olefination of aldehyde **4** and ketophosphonate **5**.[5,6] The aldehyde **4** would be acquired from the known compound **7**[7] using Myers asymmetric alkylation and the ketophosphonate **5** might be synthesized from known compound **9**[8] using Paterson's *anti* aldol reaction.

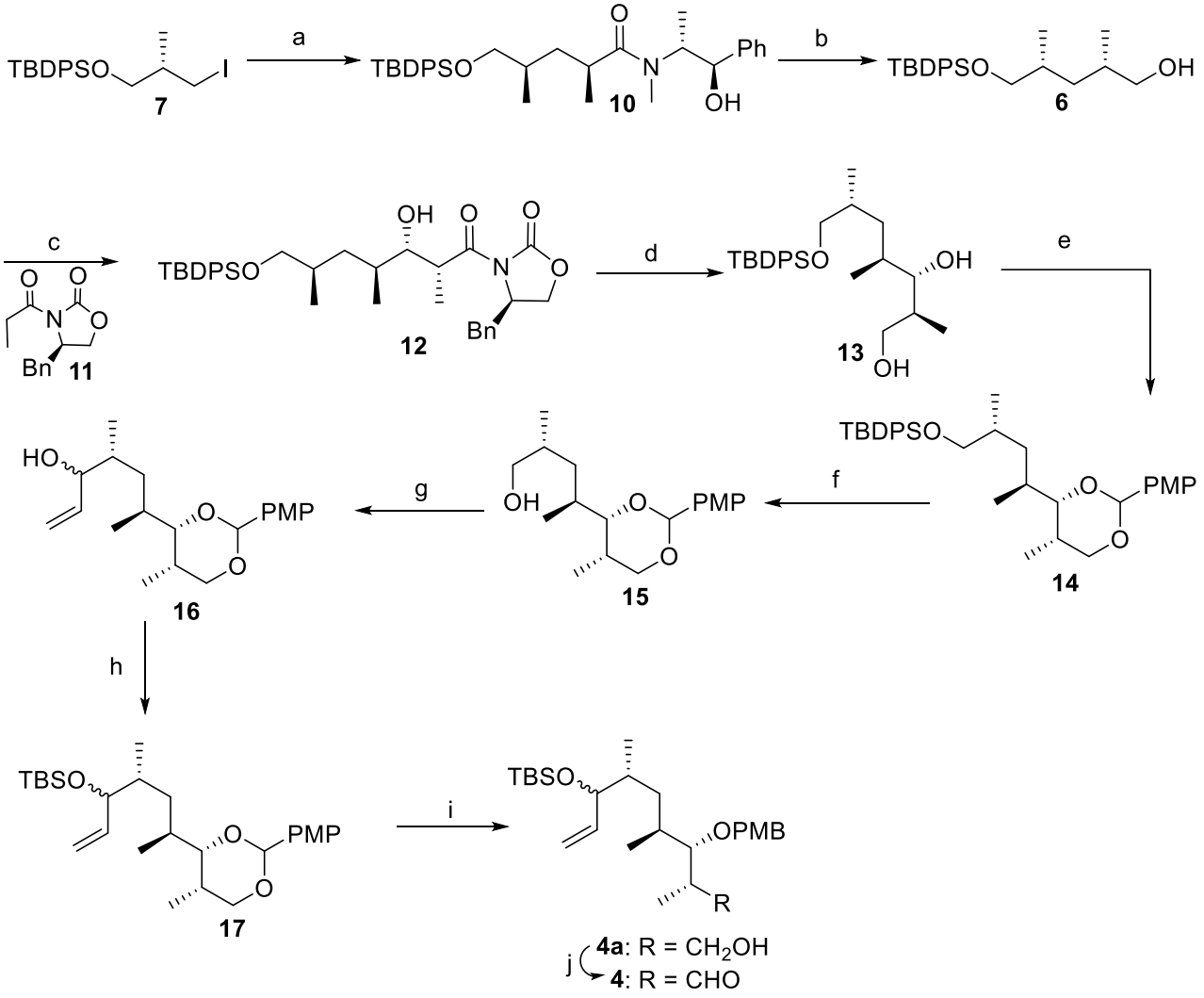
 




**Scheme 1**. Retrosynthetic analysis of tianchimycin A.

From the synthetic perspective, synthesis of **4** (Scheme 2) began with the diastereoselective alkylation of the known iodide **7**[7] with Myers pseudoephedrine derived auxiliary[9,10] to yield amide **10** as a single diastereomer in 95% yield. Reduction of **10** with $BH_3.NH_3$ gave primary alcohol **6** in 90% yield. Compound **6** on oxidation under Dess-Martin Periodinane conditions provided an aldehyde, to which addition of (*Z*)-enolate, generated from **11**, using Crimmins's protocol[11] afforded **12** with excellent diastereoselectivity (98:2 dr), which are separated by standard silica gel column chromatography to obtain the required single isomer **12** in 96% yield. Reductive removal of the chiral auxiliary with $LiBH_4$ in ether furnished the 1,3-diol compound **13**, which on protection as PMP-acetal followed by TBDPS deprotection with TBAF gave a primary alcohol **15**. Oxidation of **15** with DMP gave an aldehyde which on reaction with vinylmganesium bromide yielded diastereomerically mixture of alcohols **16**, which on TBS protection with TBSOTf in presence of 2,6-lutidine gave globally protected compound **17**. At this stage the *p*-methoxybenzylidine acetal of **17** was opened regioselectively with DIBAL-H to give a primary alcohol **4a**, which was oxidized with DMP to give required aldehyde **4** in 90% yield.

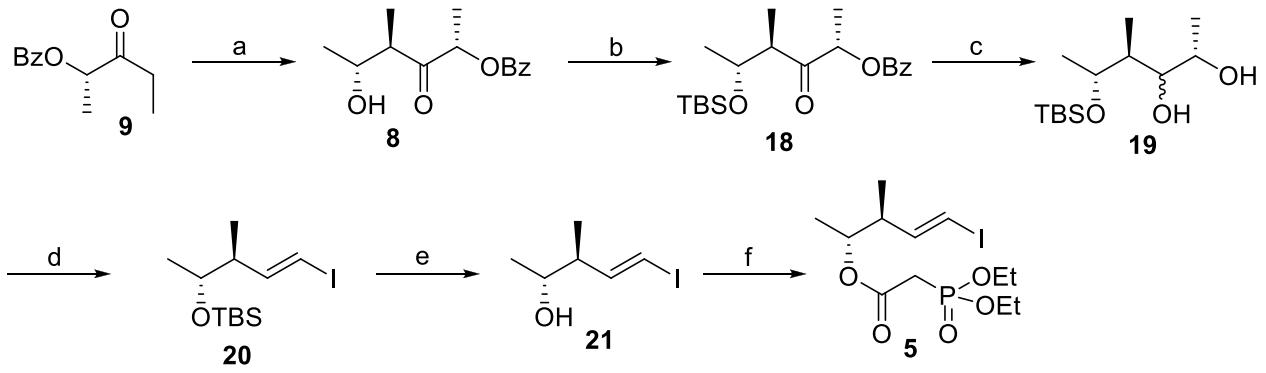
 




**Scheme 2.** Reagents and conditions: (a) *n*-BuLi, LiCl, DIPA, (1*R*, 2*R*)-(-)-Pseudoephedrine propionamide, THF, -78 °C- -20 °C, 14 h, 95%; (b) *n*-BuLi, LiCl, $BH_3.NH_3$, THF, 0 °C-rt, 4 h, 90%; (c) i. DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C-rt, 2 h; ii. $TiCl_4$, (-)-sparteine, 0 °C, $CH_2Cl_2$, 20 min then 11, 0 °C, 10 min, 96% (over two steps); (d) $LiBH_4$, 0 °C, $Et_2O$, 10 min, 96%; (e) PMP-acetal, CSA (cat), $CH_2Cl_2$, 0 °C-rt, 12 h, 94%; (f) TBAF, THF, 0 °C, 12 h, 91%; (g) i. DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C-rt, 2 h; ii. vinylmagnesium bromide, THF, 0 °C, 1 h, 84% (over two steps); (h) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C-rt, 2 h, 93%; (i) DIBAL-H, $CH_2Cl_2$, -40 °C-0 °C, 2 h, 90%; (j) DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C-rt, 2 h.

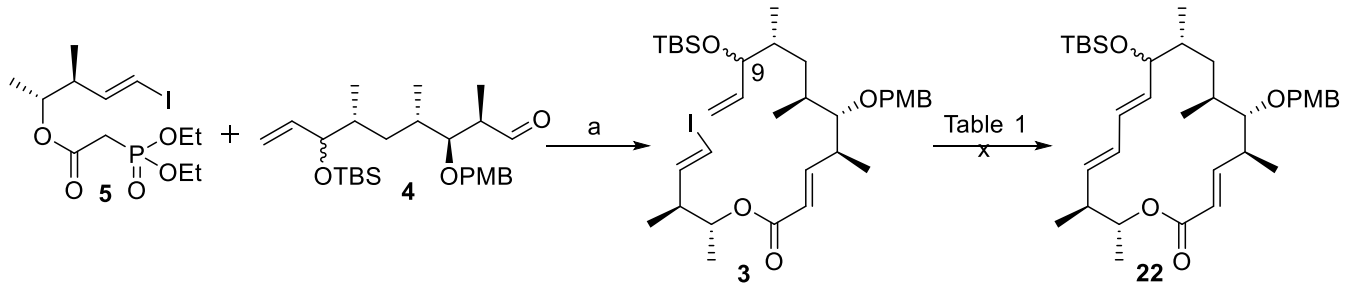
Synthesis of phosphonate fragment **5** commenced from known keto compound **9**[8] (Scheme 3), which on reaction with acetaldehyde under Paterson's *anti*-aldol conditions[12,13] using dicyclohexylborane chloride afforded *β*-keto alcohol **8**, in 96% yield with excellent diastereoselectivity which was protected as its TBS ether to give compound **18** in 92% yield. Reduction of the keto as well as benzoate group in **18** with $LiBH_4$ afforded diastereomerically mixture of diols **19** in 92% yield.[7] Oxidative cleavage of the diol with $NaIO_4$ furnished an aldehyde, which on Takai olefination gave vinyl iodide **20** (*E*:*Z* ratio 19:1) in 80% yield over two steps.[14,15] TBS deprotection from compound **20** furnished a secondary alcohol, which on acylation with diethyl phosphonoacetic acid under EDCI/DMAP conditions afforded the phosphonate **5** in 85% yield.




**Scheme 3.** Reagents and conditions: (a) *c*-$Hex_2BCl$, $Me_2NEt$, acetaldehyde, $Et_2O$, -78 °C- -20 °C, 14 h, 96%; (b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C-rt, 2 h, 92%; (c) $LiBH_4$, THF, -78 °C-0 °C, 21 h, 92%; (d) i. $NaIO_4$, MeOH:$H_2O$ (2:1), rt, 30 min; ii. $CHI_3$, $CrCl_2$, THF, rt, 1 h, 80% (over two steps); (e) TBAF, THF, 0 °C, 12 h, 91%; (f) Diethyl phosphonoacetic acid, EDCI, DMAP, $CH_2Cl_2$, 0 °C-rt, 4 h, 85%.

Having both the fragments in our hand, the Horner-Wadsworth-Emmons reaction[5] under Masamune-Roush conditions was carried out between aldehyde **4** and the phosphonate **5** in presence of DBU and LiCl in acetonitrile to give key acyclic precursor **3** (Scheme 4) for intramolecular Heck-cyclization. At this stage the crucial intramolecular Heck-cyclization under assorted conditions (Table 1) was not successful leaving the total synthesis still elusive.[4,16,17,18,19]




**Scheme 4**. Reagents and conditions: (a) LiCl, DBU, $CH_3CN$, 0 °C-rt, 12 h, 77%.

**Table 1**. Attempts to Intramolecular Heck cross Coupling for Macrocyclization.

| Sl. No | Catalyst | Conditions | Yield (%) |
|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $Cs_2CO_3$, $Et_3N$, DMF, rt, 48 h | Decomposition |
| 2 | $PdCl_2(MeCN)_2$ | $Et_3N$, HCOOH, MeCN, rt, 1 h | Decomposition |
| 3 | $Pd(OAc)_2$ | $K_2CO_3$, DMF, 80 °C, 24h | Decomposition |
| 4 | $Pd(OAc)_2$ | $K_2CO_3$, $Bu_4NCl$, DMF, 60 °C, 1 h | Decomposition |

## Conclusions

The synthesis of acyclic precursor of macrocyclic tianchimycin A was achieved by employing Myers asymmetric alkylation, Crimmins's aldol reaction, Paterson's aldol reaction, Takai olefination and Masamune-Roush olefination as key steps. Currently we are working to develop a diverse strategy to circumvent the problem of

macrocyclization, which might help us to achieve the total synthesis of tianchimycin A and its potential analogs and for biological screening, which will be reported in due course.

## Experimental Section

**General.** All the reactions were performed in oven-dried glass apparatus under nitrogen or argon atmosphere under magnetic stirring. Standard methods were used to make anhydrous solvents. Unless otherwise noted, commercially available reagents were used without further purification. Glass columns packed with silica gel (60-120 or 100-200 mesh) were used for column chromatography. $^{1}$H and $^{13}$C NMR were recorded on 400 MHz, 500 MHz and 100MHz, 125 MHz spectrometer, respectively, in $CDCl_3$ solvent using TMS as an internal standard. Chemical shifts are measured as ppm values relative to internal $CHCl_3$ δ 7.26 or TMS δ 0.0 for $^{1}$H NMR and $CHCl_3$ δ 77 for $^{13}$C NMR. In $^{1}$H NMR multiplicity defined as: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublet; ddd = doublet of doublet of doublet; dt = doublet of triplet; m = multiplet; brs = broad singlet. Horiba sepa 300 polarimeter was used to record optical rotation using a 2 mL cell with a 10 mm path length. Alpha (Bruker) infrared spectrophotometer was used to record FTIR spectra. Either a TOF or a double focusing spectrometer was used to obtain high resolution mass spectra (HRMS) $[ESI]^+$.

**(2*S*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2,4-trimethylpentan-amide (10).** *n*-BuLi was added drop wise (29.18 mL of 2.5 M solution in hexanes, 72.96 mmol) to a stirred solution of flame dried LiCl (3.73 g, 91.2 mmol) and diisopropylamine (11.69 mL, 82.08 mmol) in THF (10 mL) at 0 °C, over 1 h. This mixture was stirred at 0 °C for an additional 15 min before being cooled to -78 °C. A solution of (1*R*, 2*R*)-(-)-pseudoephedrine propionamide (6.32 g, 38.30 mmol) in THF (20 mL) was then added to the reaction mixture very slowly using syringe pump. After being stirred at -78 °C for 30 min the reaction mixture was warmed to -20 °C and treated with a solution of the iodide **7** (2.0 g, 9.12 mmol) in THF (10 mL). The reaction mixture was stirred at -20 °C for 24 h and quenched with saturated aqueous solution of $NH_4Cl$ (5 mL). The reaction mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated under vacuo. The residue was purified by column chromatography ($SiO_2$, 25% EtOAc/hexane) to afford **10** (2.40 g, 95%) as a colorless liquid. $R_f$ 0.5 (50% EtOAc in hexanes); $[\alpha]_D^{25}$ –42.1 (c 0.96, $CHCl_3$). IR (neat): $\nu_{max}$ 3742, 3393, 3065, 2931, 1696, 1620, 1464, 1105, 819, 744, 700 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): *δ* 7.67-7.64 (m, 4H), 7.44-7.28 (m, 11H), 4.60 (d, *J* 7.4 Hz, 1H), 4.34 (brs, 1H), 3.51 (dd, *J* 9.9, 5.1 Hz, 1H), 3.42 (dd, *J* 9.9, 5.8 Hz, 1H), 2.78 (s, 3H), 2.68 (m, 1H), 1.76-1.60 (m, 2H), 1.18 (m, 1H), 1.12 (d, *J* 6.5 Hz, 3H), 1.06 (d, *J* 6.7 Hz, 3H), 1.05 (m, 1H), 1.05 (s, 9H), 0.87 (d, *J* 6.5, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): *δ* 179.08, 142.62, 135.60, 135.58, 133.88, 133.84, 129.54, 128.28, 127.58, 126.20, 77.20, 76.50, 68.75, 37.59, 34.09, 33.24, 26.89, 19.31, 17.69, 17.31, 14.37; HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{33}H_{45}NO_3SiNa$ 554.3039, found 554.3060.

**(2*S*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylpentan-1-ol (6).** To a stirred solution of diisopropylamine (4.81 mL, 33.76 mmol) in THF (20 mL) at 0 °C was added *n*-BuLi (12.54 mL of 2.5 M solution in hexanes, 31.36 mmol) drop wise and the solution was stirred at 0 °C for an additional 15 min. Then Borane-ammonia complex (90%, 0.96 g, 31.36 mmol) was added to the solution. After stirring for 30 min at 0 °C, the solution was warmed to rt and stirred for additional 30 min. Then the reaction mixture was cooled to 0 °C and it was treated with a solution of amide **10** (2.1 g, 3.94 mmol) in 10 mL of THF. After stirring for 4 h at room temperature, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ (5 mL) solution and extracted with EtOAc (2x50 mL). The combined organic extracts were washed with brine (20 mL) and dried over $Na_2SO_4$.

Evaporation of the solvent under reduced pressure gave crude mass which on purification via silica gel column chromatography ($SiO_2$, 17% EtOAc/hexanes) afforded **6** (980 mg, 90% yield) as a colourless viscous liquid. $R_f$ 0.6 (25% EtOAc in hexanes); $[\alpha]_D^{25}$ –2.04 (c 1.23, $CHCl_3$). IR (neat): $\nu_{max}$ 2956, 2860, 1515, 1466, 1107, 821, 740, 613 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.69-7.66 (m, 4H), 7.45-7.36 (m, 6H), 3.53 (dd, *J* 9.8, 5.3 Hz, 1H), 3.48 (dd, *J* 10.6, 5.1 Hz, 1H), 3.44(dd, *J* 9.8, 6.2 Hz, 1H), 3.35 (dd, *J* 10.5, 6.6 Hz, 1H), 1.75 (m, 1H), 1.64 (m, 1H), 1.46 (m, 1H), 1.34 (m, 1H), 1.07 (s, 9H), 0.97 (d, *J* 6.6, 3H), 0.90 (d, *J* 6.7 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 135.61, 133.95, 129.51, 127.56, 68.70, 68.26, 37.13, 33.14, 26.87, 19.27, 17.88, 17.39; HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{23}H_{34}O_2SiNa$ 393.2226, found 393.2221.

**(*R*)-4-Benzyl-3-((2*R*,3*S*,4*S*,6*R*)-7-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-2,4,6-trimethylheptanoyl)oxazolidin-2-one (12).** To a stirred solution of **6** (800 mg, 2.08 mmol) in $CH_2Cl_2$ (10 mL), $NaHCO_3$ (0.34 g, 4.16 mmol) was added at 0 °C, followed by Dess-Martin periodinane (1.32 g, 3.12 mmol) under nitrogen atmosphere and stirred for 2 h at room temperature. Saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (7 mL) were added to the reaction mixture and extracted with EtOAc (2x10 mL). The organic phase was washed with water (10 mL), brine (10 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The aldehyde, thus obtained, was used directly, for the next reaction without any further characterization.

$TiCl_4$ (2.4 mL, 2.32 mmol) was added to the compound **11** (0.53 g, 2.24 mmol) in dry $CH_2Cl_2$ (10 mL) at 0 °C and after 5 min, (-)-sparteine (1.23 mL, 5.3 mmol) was added. After stirring at the same temperature for 20 min, a solution of crude aldehyde in $CH_2Cl_2$ (5mL) was added under nitrogen atmosphere. After 10 min the reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (5 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with 0.5 N HCl (5 mL), water (5 mL), brine (5 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, 18% EtOAc/hexanes) to afford **12** (1.24 g, 96% yield over two steps) as a colourless viscous liquid. $R_f$ 0.2 (20% EtOAc in hexane); $[\alpha]_D^{25}$ +15.88 (c 0.86, $CHCl_3$). IR (neat): $\nu_{max}$ 2927, 1781, 1694, 1515, 1462, 1384, 1206, 1108, 823, 740, 703 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.69-7.65 (m, 4H), 7.44-7.27 (m, 9H), 7.22-7.18 (m, 2H), 4.65 (m, 1H), 4.21-4.14 (m, 2H), 3.97 (m, 1H), 3.68 (t, *J* 5.5 Hz, 1H), 3.54 (dd, *J* 9.8, 5.0 Hz, 1H), 3.44 (dd, *J* 9.8, 6.4 Hz, 1H), 3.24 (dd, *J* 13.4, 3.4 Hz, 1H), 2.77 (dd, *J* 13.4, 9.5 Hz, 1H), 2.34 (brs, 1H), 1.78 (m, 1H), 1.69-1.56 (m, 2H), 1.49 (m, 1H), 1.24 (d, *J* 7.0 Hz, 3H), 1.06 (s, 9H), 0.96, (d, *J* 6.7 Hz, 3H), 0.90 (d, *J* 6.6 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 177.13, 152.84, 135.68, 135.65, 135.10, 133.97, 129.54, 129.46, 128.98, 127.62, 127.43, 74.93, 68.46, 66.06, 55.16, 40.22, 37.76, 37.11, 33.25, 32.86, 26.93, 19.31, 18.24, 15.23, 12.12; HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{36}H_{47}NO_5SiNa$ 624.3109, found 624.3106.

**(2*S*,3*S*,4*S*,6*R*)-7-(*tert*-Butyldiphenylsilyloxy)-2,4,6-trimethylheptane-1,3-diol (13).** To a stirred solution of compound **12** (1.1 g, 1.76 mmol) in dry ether (25 mL) at 0 °C were added one drop of distilled water followed by $LiBH_4$ (77 mg, 3.53 mmol) in portion wise. The reaction mixture was stirred at the same temperature for 10 min before being quenched with the careful addition of distilled water and extracted with EtOAc (2 x 20 mL), the combined organic layers were washed with water (10 mL), brine (10 mL), dried over $Na_2SO_4$ and concentrated in vacuo. Purification of the residue by column chromatography ($SiO_2$, 25% EtOAc/hexanes) afforded **13** (680 mg, 96% yield) as a colourless viscous liquid. $R_f$ 0.3 (30% EtOAc in hexane); $[\alpha]_D^{25}$ –3.6 (c 1.01 , $CHCl_3$). IR (neat): $\nu_{max}$ 3856, 3618, 3393, 2957, 2859, 1515, 1427, 1386, 1107, 1081, 972, 821, 740, 701 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.68-7.64 (m, 4H), 7.43-7.34 (m, 6H), 3.65 (d, *J* 4.8 Hz, 2H), 3.52 (dd, *J* 9.8, 4.9 Hz, 1H), 3.47-3.40 (m, 2H), 2.0 (brs, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.60 (m, 1H), 1.46 (m, 1H), 1.05 (s, 9H), 0.95 (d, *J* 6.8 Hz, 3H), 0.92 (d, *J* 6.9 Hz, 3H), 0.91 (d, *J* 6.6 Hz, 3H), 0.85 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 135.64, 135.58, 133.92, 133.87, 129.54, 127.58, 78.11, 68.18, 67.50, 37.18, 36.60, 33.64, 33.14, 26.89, 19.28, 18.43, 15.69, 10.29; HRMS (ESI) *m/z* $[M + H]^+$ calcd. for $C_{26}H_{41}O_3Si$ 429.2821, found 429.2825.

***tert*-Butyl((2*R*,4*S*)-4-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-ethyl-1,3-dioxan-4-yl)-2-methylpentyloxy)diphenyl-silane (14).** Freshly prepared PMP acetal (0.36 mL, 2.09 mmol), followed by CSA (30 mg, 0.14 mmol) were added to the compound **13** (0.6 g, 1.40 mmol) in anhydrous $CH_2Cl_2$ (25 mL) at 0 °C. The resulting reaction mixture was stirred for 12 h at ambient temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with EtOAc (2 x 15 mL). Combined organic layers were washed with water (10 mL), brine (10 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, 12% EtOAc/hexanes) to afford **14** (0.72 g, 94% yield) as a colourless liquid. $R_f$ 0.7 (30% EtOAc in hexanes); $[\alpha]_D^{25}$ –8.90 (c 1.94 , $CHCl_3$). IR (neat): $\nu_{max}$ 2956, 2853, 1616, 1515, 1387, 1246, 1108, 1004, 822, 740, 701, 613 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.70-7.66 (m, 4H), 7.46-7.36 (m, 8H), 6.90 (d, *J* 8.6 Hz, 2H), 5.43 (s, 1H), 4.01 (s, 2H), 3.81 (s, 3H), 3.60 (dd, *J* 10.0, 4.6 Hz, 1H), 3.46 (dd, *J* 9.8, 6.3 Hz, 1H), 3.39 (dd, *J* 9.6, 1.9 Hz, 1H), 1.82 (m, 1H), 1.75-1.66 (m, 2H), 1.48 (m, 1H), 1.10 (d, *J* 7.0 Hz, 3H), 1.08 (s, 9H), 1.0 (d, *J* 6.6 Hz, 3H), 0.95 (d, *J* 6.4 Hz, 3H), 0.79 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 159.73, 135.65, 135.58, 133.91, 133.84, 131.72, 129.54, 129.51, 127.56, 127.21, 113.52, 101.65, 85.06, 67.53, 55.26, 35.13, 32.69, 32.23, 29.99, 19.29, 19.09, 16.24, 11.19; HRMS (ESI) *m/z* $[M + H]^+$ calcd. for $C_{34}H_{47}O_4Si$ 547.3233, found 547.3238.

**(2*R*,4*S*)-4-((4*S*,5*S*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-2-methylpentan-1-ol (15).** TBAF (1M solution in THF 1.3 mL, 1.3 mmol) was added to a stirred solution of compound **14** (0.65 g, 1.18 mmol) in dry THF (15 mL), at 0 °C. Reaction mixture was warmed to room temperature and stirred for 12 h. It was quenched with saturated aqueous $NH_4Cl$ solution (5 mL), extracted with EtOAc (2 x 15 mL), washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, 16% EtOAc/hexanes) to afford **15** (333 mg, 91% yield) as a colourless viscous liquid. $R_f$ 0.4 (20% EtOAc in hexanes); $[\alpha]_D^{25}$ –2.81 (c 0.76 , $CHCl_3$). IR (neat): $\nu_{max}$ 2969, 2854, 1615, 1516, 1248, 1110, 1034, 826, 739, 703 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.42-7.37 (m, 2H), 6.91-6.86 (m, 2H), 5.42 (s, 1H), 4.02 (s, 2H), 3.79 (s, 3H), 3.51-3.38 (m, 3H), 1.81-1.63 (m, 5H), 1.15 (d, *J* 6.8 Hz, 3H), 0.92 (d, *J* 6.4 Hz, 3H), 0.86 (d, *J* 6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 159.86, 131.28, 127.23, 113.61, 101.88, 85.06, 73.93, 67.16, 55.22, 37.42, 33.67, 32.38, 30.08, 18.62, 15.63, 10.83; HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{18}H_{28}O_4SiNa$ 331.1871, found 331.1874.

**(4*R*,6*S*)-6-((4*S*,5*S*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methylhept-1-en-3-ol (16).** To a stirred solution of **15** (0.30 g, 1.94 mmol) in $CH_2Cl_2$ (10 mL), $NaHCO_3$ (0.16 g, 1.94 mmol) was added at 0 °C, followed by Dess-Martin periodinane (0.82 g, 1.94 mmol) under nitrogen atmosphere. The reaction mixture was allowed to come to room temperature and stirred for 2 h before being quenched with saturated $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (3 mL) and extracted with EtOAc (2x10 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over anhydrous $Na_2SO_4$. Evaporation of the solvent furnished crude aldehyde, which was passed through a short pad of silica gel and used as such for the next reaction.

To a stirred solution of crude aldehyde in dry THF (10 mL), vinyl magnesium bromide (1M solution in THF 1.94 mL, 1.94 mmol) was added at 0 °C. Reaction mixture was warmed to room temperature and stirred for 1 h. It was quenched with saturated aqueous $NH_4Cl$ solution (5 mL), extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, 14% EtOAc/hexanes) to afford **16** (0.27 g, 84% yield) as a colourless viscous liquid. $R_f$ 0.6 (20% EtOAc in hexanes); $[\alpha]_D^{25}$ –2.85 (c 0.7 , $CHCl_3$). IR (neat): $\nu_{max}$ 2856, 1514, 1465, 1248, 1035, 621 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.44-7.41 (m, 2H), 6.90-6.86 (m, 2H), 5.89 (ddd, *J* 16.0, 10.7, 5.4 Hz, 1H) 5.44 (s, 1H), 5.23 (dt, *J* 17.3, 1.6 Hz, 1H), 5.15 (dt, *J* 10.5, 1.6 Hz, 1H), 4.16 (m, 1H), 4.03-4.01 (m, 2H), 3.79 (s, 3H), 3.44 (dd, *J* 9.6, 2.2 Hz, 1H), 1.87-1.72 (m, 3H), 1.66 (ddd, *J* 13.3, 9.5, 3.2 Hz, 1H), 1.18 (d, *J* 7.0 Hz, 3H), 1.01 (d, *J* 6.4 Hz, 3H) 0.89 (d, *J* 6.8 Hz, 3H), 0.77 (ddd, *J* 15.3, 10.9, 4.4 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 159.75, 140.43, 131.73, 127.23, 114.58, 113.54, 101.69, 84.96, 73.98, 73.50, 55.27, 34.96, 34.54, 32.25, 30.11, 16.27, 15.09, 11.15; HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{20}H_{30}O_4Na$ 357.2047, found 357.2051.

***tert*-Butyl((4*R*,6*S*)-6-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-ethyl-1,3-dioxan-4-yl)-4-methylhept-1-en-3-yloxy) dimethylsilane (17).** 2,6-Lutidine (0.26 mL, 2.26 mmol) and TBSOTf (0.14 mL, 0.83 mmol) were added sequentially to a stirred solution of compound **16** (0.25 g, 0.75 mmol) in $CH_2Cl_2$ (7 mL) at 0 °C. After 2 h, reaction was quenched with saturated $NH_4Cl$ solution (5 mL), the reaction mixture was extracted with EtOAc (2 x 10 mL). The organic layer was washed with saturated aqueous $CuSO_4$ solution (5 mL), brine (5 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, 3% EtOAc/hexanes) to afford **17** (0.32 g, 93% yield) as a colourless viscous liquid. $R_f$ 0.8 (10% EtOAc in hexanes); $[\alpha]_D^{25}$ +5.2 (c 0.52, $CHCl_3$). IR (neat): $\nu_{max}$ 2915, 2858, 1515, 1427, 1386, 972, 822, 740, 624 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.42-7.38 (m, 2H), 6.88-6.84 (m, 2H), 5.82 (ddd, *J* 17.0, 10.4, 6.5 Hz, 1H) 5.43 (s, 1H), 5.16-5.06 (m, 2H), 4.20-4.01 (m, 2H), 3.80 (s, 3H), 3.39 (dd, *J* 9.6, 2.2 Hz, 1H), 1.83-1.60 (m, 5H), 1.16 (d, *J* 6.9 Hz, 3H), 1.01 (d, *J* 6.4 Hz, 3H), 0.91 (d, *J* 6.7 Hz, 3H), 0.89 (s, 9H), 0.63 (m, 1H) 0.04 (s, 3H), 0.01 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 159.74, 139.68, 131.82, 127.24, 115.05, 113.53, 101.73, 85.30, 77.64, 74.02, 55.28, 37.68, 34.30, 33.36, 30.23, 25.9, 17.18, 16.92, 11.53, -4.05, -4.86; HRMS (ESI) *m/z* $[M + H]^+$ calcd. for $C_{26}H_{45}O_4Si$ 449.3089, found 449.3087.

**(3*R*,4*S*,6*R*)-7-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-4,6-dimethylnon-8-enal (4).** To a stirred solution of compound **17** (0.270 g, 0.60 mmol) in dry $CH_2Cl_2$ (8 mL) at -40 °C, DIBAL-H (1.5 M solution in toluene, 1.6 mL, 2.4 mmol) was added drop wise under nitrogen atmosphere. After stirring for 0.5 h at the same temperature, the reaction mixture was slowly brought to 0 °C and stirred for 2 h. Dry MeOH (3 mL) was added drop wise at -78 °C to quench the reaction mixture, and stirred for 0.5 h at the same temperature, then added potassium sodium tartrate, stirred at room temperature for 1 h and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, 25% EtOAc/hexanes) to afford primary alcohol **4a** (220 mg, 90% yield) as a colourless viscous liquid. $R_f$ 0.2 (30% EtOAc in hexane); $[\alpha]_D^{25}$ +4.90 (c 1.03, $CHCl_3$). IR (neat): $\nu_{max}$ 2925, 2855, 1699, 1515, 1463, 1248, 1036, 835, 775 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.28-7.25 (m, 2H), 6.88-6.84 (m, 2H), 5.77 (ddd, *J* 16.4, 10.4, 6.5 Hz, 1H), 5.11 (dt, *J* 17.1, 3.1, Hz, 1H), 5.06 (dt, *J* 10.3, 3.0 Hz, 1H), 4.51 (ABq, *J* 10.9 Hz, 2H), 3.89 (m, 1H), 3.79 (s, 3H), 3.62 (dd, *J* 10.6, 7.0 Hz, 1H), 3.53 (dd, *J* 10.6, 5.8 Hz, 1H), 3.30 (t, *J* 4.5, 1H), 2.01 (m, 1H), 1.90-1.81 (m, 2H), 1.66-1.58 (m, 2H), 1.00 (d, *J* 6.8 Hz, 3H), 0.95 (d, *J* 6.9 Hz, 3H), 0.88 (s, 9H), 0.87 (d, *J* 6.8 Hz, 3H), 0.02 (s, 3H), 0.00 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 159.08, 139.99, 131.07, 114.81, 113.72, 83.90, 77.88, 73.93, 66.46, 55.24, 37.96, 37.50, 32.97, 25.90, 18.25, 16.41, 15.90, -4.18, -4.86; HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{26}H_{46}O_4SiNa$ 459.2911, found 459.2914.

To a stirred solution of primary alcohol (0.1 g, 0.22 mmol) in $CH_2Cl_2$ (3 mL), $NaHCO_3$ (0.37 mg, 0.44 mmol) was added at 0 °C, followed by Dess-Martin periodinane (0.18 mg, 0.44 mmol) under nitrogen atmosphere. The reaction mixture was allowed to attain room temperature and stirred for 2 h. Saturated $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (2 mL) were added to quench the reaction mixture. After stirring 15 min the reaction mixture was extracted with EtOAc (2 x 20mL). The organic phase was washed with water (20 mL), brine (20 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The aldehyde **4** thus obtained was directly used, after passing through a short pad of silica, for the next reaction without any further characterization.

**(2*S*, 4*R*, 5*R*)-5-Hydroxy-4-methyl-3-oxohexan-2-yl benzoate (8).** To a stirred solution of *c*-$Hex_2BCl$ (14.54 mL, 14.54 mmol) in $Et_2O$ (20 mL) at –78 °C was added $Me_2NEt$ (1.68 mL, 19.4 mmol), followed by ketone **9** (2 g, 9.7 mmol) in $Et_2O$ (10 mL). The reaction mixture was warmed to -10 °C for first 30 min and then to 0 °C for next 1 h before being cooled to –78 °C. The commercially available acetaldehyde (2.70 mL, 48.48 mmol) was added and stirred for further 2 h at the same temperature. Then the reaction mixture temperature was raised to –20 °C and stirred for 14 h. The reaction was quenched at 0 °C by addition of MeOH (10 mL) and $p^H$ 7 buffer (10 mL), $H_2O_2$ (5 mL, 30%) was then added and the stirring continued for 1 h and extracted with EtOAc (3x50mL).

The combined organic extracts were washed with water (10 mL), brine (5 mL) and dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, 8% EtOAc/hexanes) to afford **8** (2.06 g, 96% yield) as a colourless solid. $R_f$ 0.7 (20% EtOAc in hexanes); $[\alpha]_D^{25}$ +30.0 (c 0.75, $CHCl_3$). IR (neat): $\nu_{max}$ 2945, 1720, 1515, 1454, 1262, 1116, 1003, 707 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.08 (m, 2H), 7.58 (m, 1H), 7.45-7.44 (m, 2H), 5.44 (q, *J* 7.1 Hz, 1H), 3.98 (dq, *J* 13.7, 6.4 Hz, 1H), 2.80 (p, *J* 7.3 Hz, 1H), 2.16 (brs, 1H), 1.57 (d, *J* 7.1 Hz, 3H), 1.25 (d, *J* 7.3 Hz, 3H), 1.22 (d, *J* 6.2 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 211.72, 165.86, 133.36, 129.77, 129.39, 128.45, 74.48, 69.45, 49.91, 20.84, 15.87, 14.40; HRMS (ESI) *m/z* [M + Na]$^+$ calcd. for $C_{14}H_{18}O_4Na$ 273.1093, found 273.1097.

**(2*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-methyl-3-oxohexan-2-yl benzoate (18).** To a stirred solution of compound **8** (1.9 g, 7.59 mmol) in $CH_2Cl_2$ (30 mL) at 0 °C, 2,6-lutidine (2.64 mL, 22.7 mmol) was added followed by TBSOTf (1.9 mL, 8.35 mmol) and stirred for 15 min. The reaction was quenched with saturated aqueous $NH_4Cl$ solution (20 mL), the reaction mixture was extracted with EtOAc (2 x 30 mL), washed with saturated aqueous $CuSO_4$ solution (20 mL), brine (20 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, 5% EtOAc/hexanes) to afford **18** (2.57 g, 92% yield) as a colourless liquid. $R_f$ 0.8 (20% EtOAc in hexanes); $[\alpha]_D^{25}$ –14.00 (c 0.68, $CHCl_3$). IR (neat): $\nu_{max}$ 2975, 1720, 1515, 1454, 1262, 1116, 1003, 771, 707 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.09-8.06 (m, 2H), 7.57 (m, 1H), 7.47-7.43 (m, 2H), 5.41 (q, *J* 6.8 Hz, 1H), 4.05 (m, 1H), 2.84 (dq, *J* 8.4, 7.1 Hz, 1H), 1.51 (d, *J* 7.0 Hz, 3H), 1.14 (d, *J* 6.2 Hz, 3H), 1.10 (d, *J* 7.0 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), -0.03 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 209.40, 165.78, 133.19, 129.81, 128.39, 75.08, 70.12, 50.58, 25.81, 21.15, 17.87, 15.24, 13.76, -4.69, -4.84; HRMS (ESI) *m/z* [M + Na]$^+$ calcd. for $C_{20}H_{32}O_4SiNa$ 388.2049, found 388.2052.

**(2*S*,4*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-methylhexane-2,3-diol (19).** To a stirred solution of the protected aldol product **18** (6.3 mmol) in THF (25 mL) at –78 °C was added $LiBH_4$ (2.74 g, 126.18 mmol). The reaction mixture was warmed slowly to room temperature and stirred for 21 h. Then the reaction mixture was cooled to 0 °C and quenched with the careful addition of $H_2O$. The mixture was extracted with EtOAc (2 x 25 mL) and the combined organic extracts were washed with brine (20 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, 18% EtOAc/hexanes) to afford **19** (1.52 g, 92% yield) as a colourless viscous liquid. $R_f$ 0.3 (20% EtOAc in hexanes); $[\alpha]_D^{25}$ –11.27 (c 1.1, $CHCl_3$). IR (neat): $\nu_{max}$ 3360, 2958, 2893, 1612, 1465, 1251, 1062, 838, 775, 688 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.89 (p, *J* 6.2 Hz, 1H), 3.80 (m 1H), 3.58 (dd, *J* =8.2, 3.9 Hz, 1H), 3.42 (s, 1H), 2.64 (brs, 1H), 1.64 (m, 1H), 1.58 (m, 1H), 1.20 (d, *J* 6.2 Hz, 3H), 1.16 (d, *J* 6.3 Hz, 3H), 0.90 (s, 9H), 0.81 (d, *J* 6.9 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 73.17, 67.97, 42.98, 25.79, 21.40, 17.93, 16.24, 12.27, -4.22, -4.87; HRMS (ESI) *m/z* [M + H]$^+$ calcd. for $C_{13}H_{31}O_3Si$ 263.2048, found 263.2045.

***tert*-Butyl((2*R*,3*S*,*E*)-5-iodo-3-methylpent-4-en-2-yloxy)dimethylsilane (20).** To a stirred solution of 1,2-diol **19** (5.33 mmol) in MeOH (10 mL) and $H_2O$ (5 mL) at 0 °C was added $NaIO_4$ (3.42 g, 15.99 mmol). The reaction mixture was stirred at room temperature for 30 min. Then it was diluted with $H_2O$ (15 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$, concentrated in vacuo. The aldehyde ($R_f$ 0.5, 3% EtOAc in petroleum ether), thus obtained, was directly used, after flash chromatography, for the next reaction without any further characterization.

To a stirred solution of anhydrous $CrCl_2$ (1.9 g, 31.98 mmol) in THF (20 mL) under argon atmosphere was added a solution of crude aldehyde and iodoform (4.19 g, 10.66 mmol) in THF (15 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h before being quenched with water (15 mL). The reaction mixture was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, hexanes) to afford **20** (1.45 g, 80% yield) as a colourless viscous liquid. $R_f$ 0.9 (5% EtOAc in hexanes);

$[\alpha]_D^{25}$ –16.91 (c 1.2, $CHCl_3$). IR (neat): $\nu_{max}$ 2957, 2931, 2853, 1463, 1373, 1254, 1110, 954, 836, 774, 671 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.47 (dd, *J* 14.4, 8.6 Hz, 1H), 5.97 (dd, *J* 14.4, 0.9 Hz, 1H), 3.64 (dq, *J* 6.1, 4.8 Hz, 1H), 2.16 (m, 1H), 1.07 (d, *J* 6.1 Hz, 3H), 0.89 (d, *J* 7.0 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 149.01, 74.73, 71.19, 48.35, 25.83, 21.23, 18.04, 15.70, -4.38, -4.81; HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{12}H_{25}IOSiNa$ 363.0612, found 363.0616.

**(2*R*,3*S*,*E*)-5-Iodo-3-methylpent-4-en-2-ol (21).** To a stirred solution of compound **20** (1.2 g, 3.52 mmol) in dry THF (25 mL), TBAF (1M solution in THF 3.87 mL, 3.87 mmol) was added at 0 °C. Reaction mixture was warmed to room temperature and stirred for 12 h. saturated aqueous $NH_4Cl$ solution (15 mL) was used to quench the reaction mixture, and extracted with EtOAc (2 x 20 mL), washed with brine (15 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, 8% EtOAc/hexanes) to afford **21** (0.725 g, 91% yield) as a colourless viscous liquid. $R_f$ 0.2 (10% EtOAc in hexanes); $[\alpha]_D^{25}$ +10.00 (c 0.25, $CHCl_3$). IR (neat): $\nu_{max}$ 3403, 2956, 2857, 1253, 1095, 837, 776 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.49 (dd, *J* 14.4, 8.7 Hz, 1H), 6.12 (dd, *J* 14.4, 0.6 Hz, 1H), 3.62 (p, *J* 6.1 Hz, 1H), 2.19 (m, 1H), 1.17 (d, *J* 6.3 Hz, 3H), 1.03 (d, *J* 6.9 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 148.09, 76.17, 70.52, 48.32, 20.48, 15.63; HRMS (ESI) *m/z* $[M + H]^+$ calcd. for $C_6H_{12}IO$ 226.9928, found 226.9924.

**(2*R*,3*S*,*E*)-5-Iodo-3-methylpent-4-en-2-yl 2-(diethoxyphosphoryl)acetate (5).** Diethyl phosphonoacetic acid (1.06 mL, 6.63 mmol) and DMAP (0.05 g, 0.44 mmol) were added sequentially to a stirred solution of **21** (0.500 g, 2.21 mmol) which was previously azeotroped with benzene, in dry $CH_2Cl_2$ (10 mL) at 0 °C under argon atmosphere. After stirring for 10 min at 0 °C, EDCI (1.27g, 6.63 mmol) was added to it and stirred at rt for another 4 h. Then reaction mixture was quenched with water and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (5 mL) and dried over $Na_2SO_4$ and concentrated under vacuo. The residue was purified by column chromatography ($SiO_2$, 30% EtOAc/hexanes) to afford **5** (0.84 g, 85%) as a yellow oil. $R_f$ 0.2 (40% EtOAc /hexanes); $[\alpha]_D^{25}$ +0.8 (c 1.25, $CHCl_3$). IR (neat): $\nu_{max}$ 2938, 2861, 1739, 1470, 1395, 1260, 1105, 1055, 1027, 971, 839, 778, 669 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.46 (dd, *J* 14.4, 8.6 Hz, 1H), 6.09 (dd, *J* 14.4, 0.9 Hz, 1H), 4.87 (m, 1H), 4.22-4.11 (m, 4H), 2.96 (d, *J* 21.6 Hz, 2H), 2.37 (m, 1H), 1.36-1.31 (m, 6H), 1.17 (d, *J* 6.4 Hz, 3H), 1.03 (d, *J* 6.9 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 165.29, 146.56, 76.45, 74.04, 62.62, 62.56, 45.17, 35.15, 33.82, 17.20, 16.36, 15.39; HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{12}H_{22}IO_5PNa$ 427.0141, found 427.0145.

**(4*S*,5*S*,6*S*,8*R*,*E*)-((2*R*,3*S*,*E*)-5-Iodo-3-methylpent-4-en-2-yl)-9-(tert-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-4,6,8-trimethylundeca-2,10-dienoate (3).** To a stirred solution of compound **5** (0.100 g, 0.22 mmol) and LiCl (0.02 g, 0.44 mmol) in MeCN (6 mL) at 0 °C, was added DBU (0.16 mL, 0.22 mmol) under argon atmosphere. After stirring at room temperature for 15 min, the mixture was again cooled to 0 °C. Then a solution of aldehyde **4** in MeCN (5 mL) was added dropwise. After stirring at room temperature for 12 h, the reaction mixture was quenched by addition of water and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated under vacuo. The residue was purified by column chromatography ($SiO_2$, 60-120 mesh, 6% EtOAc/hexanes) to afford **3** (0.119 g, 77% two steps) as a colorless oil. $R_f$ 0.5 (10% EtOAc /hexanes); $[\alpha]_D^{25}$ –5.10 (c 0.75, $CHCl_3$). IR (neat): $\nu_{max}$ 2924, 2855, 1713, 1649, 1513, 1458, 1248, 1179, 1071, 1036, 989, 821, 583 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) mixture of two diastereomers at C9 center: $\delta$ 7.26 (d, *J* 7.39 Hz, 2H), 6.94-6.85 (m, 3H), 6.47 (ddd, *J* 15.4, 9.5, 1.0 Hz, 1H), 6.09 (dt, *J* 14.4, 1.1 Hz, 1H), 5.84-5.71 (m, 2H), 5.15-5.04 (m, 2H), 4.91 (m, 1H), 4.55-4.46 (m, 2H), 3.90 (m, 1H), 3.80 (s, 3H), 3.17 (tt, *J* 7.5, 2.9 Hz, 1H), 2.64 (m, 1H), 2.40 (m, 1H), 1.76-1.68 (m, 2H), 1.61 (m, 1H), 1.27 and 1.25 (two d, *J* 7 and 7.1 Hz, 3H), 1.19 (d, *J* 6.3 Hz, 3H), 1.15 and 1.13 (two d, *J* 7.0 and 7.4 Hz, 3H), 1.02 (d, *J* 6.9, 3H), 0.97-0.89 (m, 4H), 0.89 and 0.88 ( two s, 9H), 0.84 (d, *J* 6.8 Hz, 3H), 0.02 and 0.01 (two s, 3H), -0.002 and -0.009 (two s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) mixture of two diastereomers at C9 center: $\delta$ 165.99,

159.10, 152.10, 152.02, 147.05, 140.11, 139.07, 130.97, 130.88, 129.19, 129.15, 120.70, 115.17, 114.82, 113.72, 84.81, 77.79, 77.11, 76.11, 74.69, 74.62, 72.36, 55.26, 45.49, 40.30, 40.08, 37.67, 37.12, 36.97, 33.48, 33.34, 25.92, 25.88, 18.26, 18.20, 17.36, 16.38, 15.97, 15.57, 15.43, 15.28, 15.04, -4.17, -4.35, -4.82; HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{34}H_{55}IO_5SiNa$ 721.2753, found 721.2755.

**Experimental procedure for the attempted Heck cyclization reaction (22)**

1. To a stirred solution of **3** (0.02 g, 0.028 mmol) in DMF (5 mL) were added $Cs_2CO_3$ (0.016 g, 0.05 mmol), $Et_3N$ (0.005 mL, 0.033 mmol) and $Pd(OAc)_2$ (0.01 g, 0.045 mmol) sequentially at rt under argon atmosphere. After stirring for 48 h at rt, the reaction mixture was quenched with water and extracted with EtOAc (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over $Na_2SO_4$ and concentrated under vacuo.

2. To a stirred solution of **3** (0.02 g, 0.028 mmol) in MeCN (5 mL) was added $Et_3N$ (0.03 mL, 0.221 mmol), followed by $PdCl_2(MeCN)_2$ (0.001 g, 0.46mmol) and formic acid (0.001 mL, 0.027 mmol) at rt under argon atmosphere. After stirring for 1 h at rt, the reaction mixture was quenched by the addition of water (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (5 mL) and dried over $Na_2SO_4$ and concentrated under vacuo.

3. To a stirred solution of **3** (0.02 g, 0.028 mmol) in DMF (5 mL) were added $Pd(OAc)_2$ (0.008 g, 0.035 mmol) and dry $K_2CO_3$ (0.032 g, 0.233 mmol) sequentially at rt under argon atmosphere. The resulting mixture was stirred at 80 °C for 2 h before being quenched by the addition of water (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure gave crude mass.

4. To a stirred and degassed solution of **3** (0.02 g, 0.028 mmol) in DMF (5 mL) were added $Pd(OAc)_2$ (0.006 g, 0.028 mmol), dry $K_2CO_3$ (0.038 g, 0.28 mmol), and $Bu_4NCl$ (0.023 g, 0.084 mmol) and the mixture was once again degassed. The solution was stirred under argon atmosphere and heated to 60 °C for 50 min. After cooling to room temperature, diethyl ether (5 mL) was added, and the solution was washed with water (5 mL) and extracted with EtOAc (2x10 mL). The combined organic extracts were washed with brine (5 mL) and dried over $Na_2SO_4$ and concentrated under vacuo.

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## Supplementary Material

$^1H$ & $^{13}C$ NMR spectra of compound **3**, **4a**, **5**, **6**, **8**, **10**, **12**-**21**.

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