Tetrahydropyran Synthesis by Intramolecular Conjugate Addition to Enones: Synthesis of the Clavosolide Tetrahydropyran Ring

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Abstract: The synthesis of a tetrahydropyran intermediate for clavosolide A is reported, employing a combination of cross-metathesis and intramolecular oxa-Michael addition. The intramolecular oxa-Michael addition to α,β-unsaturated esters requires the use of strong bases and can result in either modest yields or stereoisomeric mixtures, and can be highly variable according to the substrate structure. In contrast, the corresponding ketones cyclise under very mild conditions to give the 2,6-*cis*-isomers directly. The use of appropriately substituted ketones allows efficient conversion into esters.

Key words: Michael addition, tandem reaction, cyclisation

There are numerous examples of the synthesis of tetrahydropyrans by the intramolecular conjugate addition of an oxygen nucleophile to a Michael acceptor, such as an α,β-unsaturated ester or ketone.[1] This method has recently been made more convenient by the application of cross-metathesis for the installation of the Michael acceptor.[2] The structures of several natural products would indicate that oxa-Michael addition to an α,β-unsaturated ester would be the obvious procedure. One such natural product is clavosolide A (**1**) (Figure 1). This marine natural product, isolated from *Myriastra clavosa*, is a symmetrical diolide. Other members of the clavosolide family lack one or more methyl groups and are not symmetrical.[3,4] The structure of clavosolide A was ultimately determined by synthesis.[4b,c] Structural features include a methylated xylose, a cyclopropane, and a tetrasubstituted tetrahydropyran.

The use of the intramolecular oxa-Michael addition to form the tetrahydropyran ring has been reported by Lee[4b] and by Gurjar.[4g] In both cases, strong base was required to obtain the tetrahydropyran as a single 2,6-*cis*-isomer and the synthetic sequence was lengthened by the choice of Wittig or Horner–Wadsworth–Emmons chemistry to install the Michael acceptor. The stereoselective synthesis of the tetrahydropyran moiety under mild conditions in a short and efficient reaction sequence is the subject of this paper.

Tetrahydropyran **2** is an intermediate in Willis' syntheses of clavosolide[4a] and polycavernoside,[5a] and also, as its TIPS ether, an intermediate in White's synthesis of polycavernoside.[5b] We intended to synthesise this compound by the cross-metathesis–intramolecular Michael strategy. We initially carried out a model study in the racemic series lacking the ring methyl group (Scheme 1). The substrate was prepared by alkylation of the dianion of methyl acetoacetate with BOMCl.[6] Reduction of ketone **3** and conversion of the ester into a Weinreb amide **5** allowed addition of allylmagnesium bromide to give the β,γ-unsaturated ketone **6**. This material, which would rapidly isomerise on storage to the corresponding α,β-unsaturated isomer, was stereoselectively reduced using tetramethylammonium triacetoxyborohydride, according to the method of Evans,[7] to give the *anti*-diol **7**.[8] Cross-metathesis with methyl acrylate proceeded smoothly in the presence of Grubbs' second-generation catalyst to give the α,β-unsaturated ester **8**, exclusively as the *E*-isomer, in good yield, accompanied by dimethyl fumarate from self-metathesis of the acrylate. A better yield of 89% for the α,β-unsaturated ester **8** was obtained by employing methyl crotonate.[9]

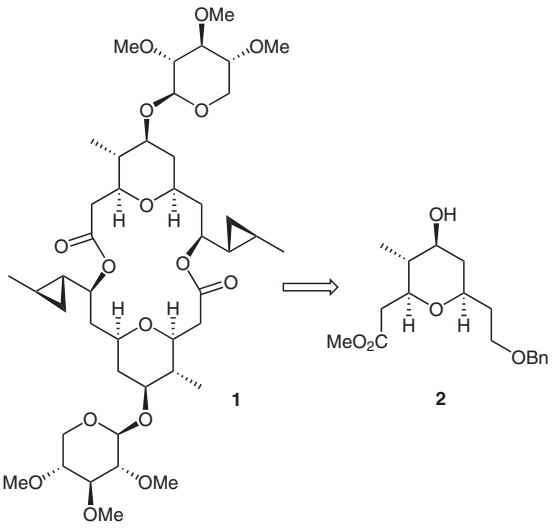

Figure 1 Clavosolide A

α,β-Unsaturated ester **8** was treated with several bases in order to determine the mildest conditions for cyclisation. No reaction was observed using potassium carbonate. The use of sodium methoxide in methanol resulted in slow cyclisation to give the tetrahydropyran **9** as a mixture of stereoisomers (*ca* 1:1). Treatment with a stronger base,

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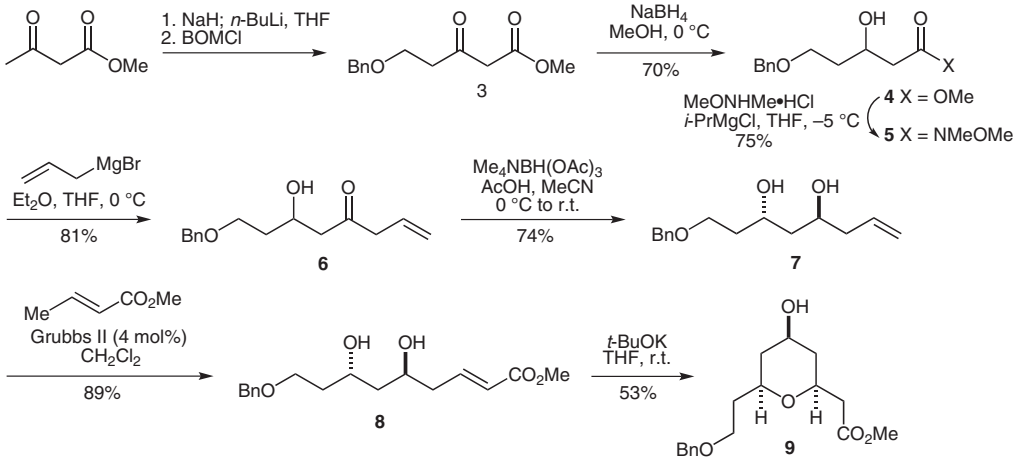
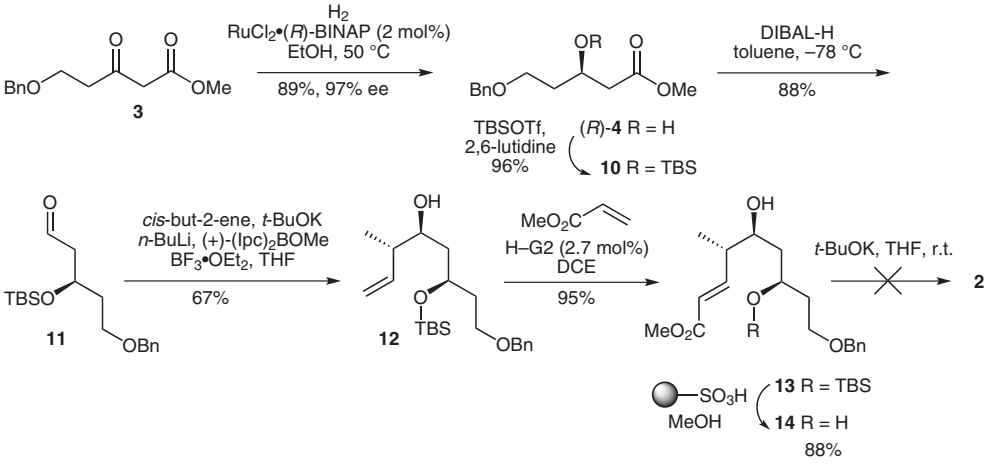


Scheme 1 Model study for clavosolide THP synthesis

potassium *tert*-butoxide in THF, gave **9** exclusively as the 2,6-*cis* isomer, but in moderate yield (53%).

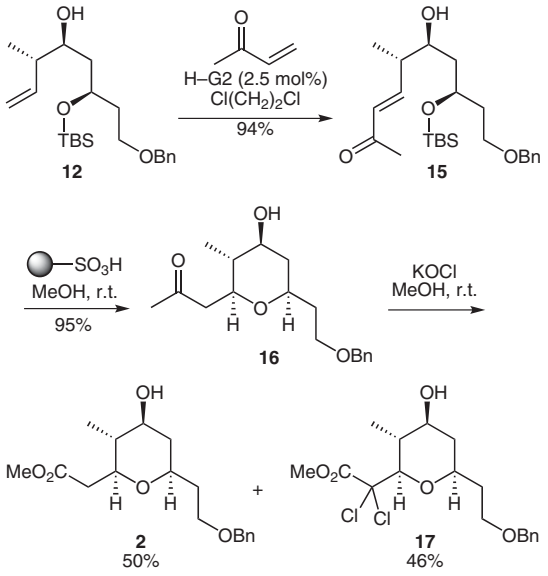
With the model system completed, we turned to the real system with the additional methyl group, employing the sequence devised by White (Scheme 2), with minor modifications.[5b] Asymmetric reduction of the β-keto ester **3** using Genet's convenient modification[10] of Noyori's system gave the alcohol (*R*)-**4** in excellent yield and an ee of 97%, as determined by chiral HPLC. This alcohol was protected as its TBS ether and reduced to the aldehyde **11** using DIBAL-H. Crotylation was then achieved using the Brown reagent derived from *cis*-but-2-ene and (+)-Ipc_2BOMe.[11] The desired homoallylic alcohol **12** could be obtained in up to 67% yield as a single stereoisomer after chromatography. Cross-metathesis of this more hindered alkene **12** with methyl acrylate gave the desired α,β-unsaturated ester in 89% yield, but required a high catalyst loading (20 mol%). A slightly better yield (95%) and a much lower catalyst loading (5 mol%) could be achieved using the Hoveyda–Grubbs second-generation catalyst[12] (H–G2) in dichloroethane at reflux. The use of this higher boiling solvent was found to be advantageous. Cross-metathesis with methyl crotonate was too slow to be of use. Deprotection using Amberlyst 15 in methanol cleanly removed the TBS group to give alcohol **14**, but did not result in the oxa-Michael addition. In our synthesis of diospongin A, it was possible to achieve deprotection–cyclisation in tandem fashion.[2b] In that case the Michael acceptor was an α,β-unsaturated ketone. The ester in the present case is a less effective activator of the alkene. Addition of sodium methoxide to the deprotected material to induce cyclisation resulted in the formation of the desired tetrahydropyran **2** but, as in the model study, as a *cis*/*trans* mixture (ca. 1.3:1).[13] In contrast, use of potassium *tert*-butoxide resulted in decomposition. It appears that the additional bulk provided by the methyl group promotes fragmentation, possibly by some form of retro aldol process.

While the use of strong base with appropriate protection of functional groups could be a solution to this problem, we sought a milder method. From experience with α,β-unsaturated ketones in the synthesis of diospongin A, it is apparent that ketones are more effective electron-withdrawing groups. With this in mind, the cross-metathesis between the alkene **12** and methyl vinyl ketone (MVK) was carried out to give the α,β-unsaturated ketone **15** in



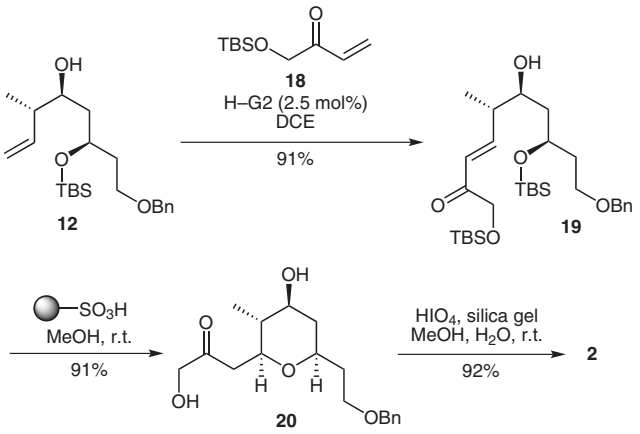
Scheme 2 Methyl acrylate metathesis–Michael chemistry

excellent yield (Scheme 3). Tandem deprotection–intramolecular Michael addition was then achieved upon treatment with Amberlyst 15 in methanol. The tetrahydropyran **16** was obtained exclusively as its 2,6-*cis* isomer. Cleavage of the methyl group by means of the haloform reaction was carried out using freshly prepared potassium hypochlorite in methanol.[14] The desired methyl ester **2** was obtained in 50% yield, accompanied by a similar yield of the corresponding α,α-dichloro ester **17** due to overhalogenation during the haloform reaction.



Scheme 3 MVK metathesis-Michael chemistry

To solve this problem, an alternative strategy for the ketone-into-ester conversion was adopted (Scheme 4). The alkene **12** underwent cross-metathesis with the TBS ether of 1-hydroxybut-3-en-2-one[15] (**18**) to give the metathesis product **19** in excellent yield (91%), again employing the Hoveyda–Grubbs catalyst at 5 mol% loading in dichloroethane. As anticipated, treatment of the metathesis product **19** with Amberlyst 15 in methanol resulted in the removal of both protecting groups and cyclisation to yield exclusively the 2,6-*cis*-isomer of the tetrahydropyran **20**.



Scheme 4 Completion of the formal synthesis

Following the example of Heathcock, who employed α-oxygenated ketones as ester surrogates in stereoselective aldol chemistry,[16] treatment with periodic acid in reagent grade methanol yielded the desired ester **2** in 92% yield. This material was spectroscopically identical to that reported by Willis and White.[4a,5]

The intramolecular oxa-Michael addition to α,β-unsaturated esters is complicated by the need to use relatively strong basic conditions to achieve both the addition and conversion into the 2,6-*cis*-isomer. Intramolecular addition to α,β-unsaturated ketones proceeds highly efficiently under very mild conditions to give the 2,6-*cis*-isomers directly, and can be carried out in a tandem fashion with O-desilylation. The use of α-oxygenated ketones allows for subsequent facile, mild, and efficient cleavage to esters. The synthesis of an intermediate for clavosolide demonstrates the usefulness of this method.

THF was distilled from Na/benzophenone; CH_2Cl_2 and MeCN were dried by distillation from CaH_2 immediately prior to use. MeOH was distilled from activated Mg. All other solvents and reagents were used as received. IR spectra were recorded on a Bio-Rad FTS 165 spectrometer either neat or as Nujol mulls using NaCl plates. ^{1}H NMR spectra were recorded on a Bruker Avance DPX at 300, 400, or 500 MHz with residual protic solvent as the reference. ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz on the same instruments. Chemical shifts (δ) are in ppm and coupling constants (*J*) are in Hz. Mass spectra were recorded on a Finnigan LCQ DECA XP MAX Ultra instrument. High-resolution mass spectra were recorded on a Waters Q-Tof premier instrument or Finnigan MAT95XP instrument. Specific rotations, $[\alpha]_D$, were recorded on an Jasco P-1030 polarimeter and are given with units of 10^{-1} deg·cm^2·g^{-1}. Enantiomeric excess was determined with chiral HPLC analysis, performed on a Shimadzu HPLC and Daicel Chemical Industries Chiralcel OD-H column, eluting with *i*-PrOH–hexane.

Methyl (±)-5-(Benzyloxy)-3-hydroxypentanoate (4)

$NaBH_4$ (9 mg, 0.25 mmol) was added to a solution of the β-keto ester **3** (0.12 g, 0.50 mmol) in MeOH (3 mL) cooled in an ice bath. The mixture was stirred for 1 h before sat. aq NH_4Cl (5 mL) was added at r.t. The volatiles were evaporated and the mixture was extracted with EtOAc (2 × 8 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (85:15 hexane–EtOAc) on silica gel (5 g) to give **4** as a colourless oil (0.09 g, 70%).

IR (neat): 3450, 2951, 2918, 2850, 1732, 1453, 1203, 1077, 1026, 735, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77–1.84 (2 H, m), 2.50 (2 H, d, *J* = 6.3 Hz), 3.5 (1 H, d, *J* = 3.3 Hz), 3.64–3.74 (5 H, m), 4.20–4.30 (1 H, m), 4.66 (1 H, d, *J* = 15.8 Hz), 4.74 (1 H, d, *J* = 15.8 Hz), 6.88 (1 H, dq, *J* = 15.5, 6.9 Hz), 7.28–7.38 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 137.9, 128.3, 127.6, 127.5, 73.1, 67.8, 66.8, 51.6, 41.3, 35.9.

MS (EI): *m*/*z* = 261 (M + Na), 239 (M + H).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{19}O_4$ (M + H): 239.1283; found: 239.1280.

(±)-5-(Benzyloxy)-3-hydroxy-*N*-methoxy-*N*-methylpentanamide (5)

i-PrMgCl (6.25 mL of a 2 M solution in THF, 13.5 mmol) was added slowly to a solution of the β-hydroxy ester **4** (0.60 g, 2.5 mmol)

and *N*,*O*-dimethylhydroxylamine hydrochloride (0.60 g, 6.3 mmol) in THF (8 mL) at –5 °C under N_2. The mixture was allowed to warm to r.t. and stirred for 3 h., followed by the addition of sat. aq NH_4Cl (10 mL) at 0 °C. The volatiles were evaporated and the residue was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (1:1.5 hexane–EtOAc) to give the Weinreb amide **5** (0.59 g, 75%) as a colourless solid; mp 40–41 °C.

IR (neat): 3449, 2937, 2866, 1640, 1453, 1421, 1387, 1099, 998, 739, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.79–1.86 (2 H, m), 2.56 (1 H, dd, *J* = 16.6, 8.7 Hz), 2.67 (1 H, dd, *J* = 16.6, 4.9 Hz), 3.19 (3 H, s), 3.66 (3 H, s), 3.68–3.90 (2 H, m), 3.89 (1 H, d, *J* = 2.8 Hz), 4.21–4.28 (1 H, m), 4.52 (2 H, s), 7.27–7.32 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 138.3, 128.3, 127.6, 127.6, 73.2, 67.7, 66.3, 61.2, 38.4, 36.3, 31.8.

MS (EI): *m*/*z* = 290 (M + Na), 268 (M + H).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{22}NO_4$ (M + H): 268.1549; found: 268.1542.

(±)-8-(Benzyloxy)-6-hydroxyoct-1-en-4-one (6)

Freshly prepared allylmagnesium bromide (2.0 mL of a 0.45 M solution in Et_2O, 0.9 mmol) was added slowly to a solution of the Weinreb amide **5** (0.20 g, 0.75 mmol) in THF (6 mL) under N_2 cooled in an ice bath. The mixture was stirred at 0 °C for 2 h and treated with sat. aq NH_4Cl (5 mL). The THF was evaporated and the mixture was extracted with EtOAc (3 × 6 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). The solvent was evaporated to give the ketone **6** (0.15 g, 81%) as a colourless oil, which was used directly in the next step.

IR (neat): 3506, 2928, 2883, 1631, 1453, 1103, 1039, 917, 848, 739, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.73–1.83 (2 H, m), 2.60 (1 H, dd, *J* = 16.6, 6.6 Hz), 2.65 (1 H, dd, *J* = 16.6, 10.65 Hz), 3.19 (2 H, d, *J* = 8.9 Hz), 3.39 (1 H, d, *J* = 4.7 Hz), 3.62–3.70 (2 H, m), 4.24–4.30 (1 H, m), 4.51 (2 H, s), 5.13 (1 H, dd, *J* = 16.1, 2.1 Hz), 5.18 (1 H, d, *J* = 9.7, 2.1 Hz), 5.92 (1 H, ddt, *J* = 16.1, 9.1, 7.4 Hz), 7.27–7.56 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.0, 138.0, 130.0, 128.4, 127.7, 127.6, 119.2, 73.2, 67.9, 66.6, 48.8, 48.4, 36.0.

MS (EI): *m*/*z* = 271 (M + H), 249 (M + H), 141.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{21}O_3$ (M + H): 249.1491; found: 249.1490.

(±)-(3*R*,5*R*)-1-(Benzyloxy)oct-7-ene-3,5-diol (7)

AcOH (1.7 mL) was added to a solution of $Me_4NBH(OAc)_3$ (0.80 g, 3.2 mmol) in MeCN (6 mL) at 0 °C under N_2. The mixture was stirred at r.t. for 30 min. A solution of **6** (80 mg, 0.40 mmol) in MeCN (2 mL) was added to the solution. The mixture was stirred for 3 h at r.t. and then neutralised with aq 2 M NaOH. The MeCN was evaporated and the mixture was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (1:1 hexane–EtOAc) on silica gel (3 g) to give the diol **7** (60 mg, 74%) as a colourless oil.

IR (neat): 3442, 2917, 2850, 1452, 1403, 1336, 1288, 915, 736, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.66 (2 H, dt, *J* = 5.3, 3.0 Hz), 1.88 (1 H, ddd, *J* = 8.9, 8.7, 4.8 Hz), 1.92 (1 H, ddd, *J* = 9.2, 8.8, 5.4 Hz), 2.26 (2 H, t, *J* = 6.9 Hz), 3.66 (1 H, dt, *J* = 9.7, 4.1 Hz), 3.73 (1 H, dt, *J* = 9.4, 5.0 Hz), 3.95–4.02 (1 H, m), 4.13–4.20 (1 H, m), 4.52 (2H , s), 5.12 (1 H, dd, *J* = 10.5, 1.4 Hz), 5.13 (1 H, dd, *J* = 16.9, 1.4 Hz), 5.82 (1 H, ddt, *J* = 16.9, 10.5, 7.1 Hz), 7.28–7.37 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.7, 134.7, 128.5, 127.8, 127.7, 117.8, 73.4, 72.4, 71.6, 68.8, 42.4, 42.3, 36.9.

MS (EI): *m*/*z* = 273 (M + Na), 251 (M + 1).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{23}O_3$ (M + H): 251.1647; found: 251.1649.

Methyl (5*R,7*R**,*E*)-9-(Benzyloxy)-5,7-dihydroxynon-2-enoate (8)**

Methyl crotonate (0.13 mL, 0.96 mmol) was added to a solution of the diol **7** (0.10 g, 0.40 mmol) in CH_2Cl_2 (6 mL) under N_2. Grubbs' second-generation catalyst (12 mg, 0.016 mmol) dissolved in CH_2Cl_2 (1 mL) and added to the mixture and the mixture was heated at reflux for 3 h. The solvent was evaporated and the residue was purified by flash chromatography (85:15 hexane–EtOAc) on silica gel (5 g) to give the α,β-unsaturated ester **8** (0.11 g, 89%) as a colourless oil.

IR (neat): 3411, 2915, 2866, 1657, 1436, 1275, 1168, 1092, 739, 676 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.69 (3 H, m), 1.91–1.99 (1 H, m), 2.33–2.47 (2 H, m), 3.73 (1 H, td, *J* = 4.6, 8.6 Hz), 3.69–3.77 (4 H, m), 4.06–4.19 (2 H, m), 4.52 (2 H, s), 5.90 (1 H, d, *J* = 15.6 Hz), 6.99 (1 H, dt, *J* = 15.6, 7.4 Hz), 7.28–7.37 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 145.6, 137.6, 128.5, 127.9, 127.7, 123.2, 73.4, 69.6, 69.5, 67.7, 51.4, 42.1, 40.2, 36.0.

MS (EI): *m*/*z* = 331 (M + Na), 309 (M + H), 223, 179.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{27}O_5$ (M + H): 309.1702; found: 309.1702.

Methyl (2*R,4*R**,6*S**)-[6-(2-Benzyloxyethyl)-4-hydroxytetrahydropyran-2-yl]acetate (9)**

t-BuOK (10 mg, 0.098 mmol) was added to a solution of **8** (30 mg, 0.098 mmol) in THF (2 mL) under N_2. The mixture was stirred overnight at r.t. and quenched with sat. aq NH_4Cl (2 mL). THF was evaporated and the residue was extracted with EtOAc (6 mL). The organic layer was washed with brine (5 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (1:1 hexane–EtOAc) on silica gel (2 g) to give the tetrahydropyran **9** (16 mg, 53%) as a colourless oil.

IR (neat): 3477, 2950, 2921, 2854, 1776, 1453, 1264, 1081, 1029, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (1 H, ddd, *J* = 11.5, 11.5, 4.8 Hz), 1.20 (1 H, ddd, *J* = 11.5, 11.5, 4.8 Hz), 1.49 (1H, d, *J* = 4.2 Hz), 1.75–1.84 (2 H, m), 1.94 (1 H, ddt, *J* = 12.1, 4.5, 2.5 Hz), 2.01 (1 H, ddt, *J* = 12.1, 4.5, 2.5 Hz), 2.43 (1 H, dd, *J* = 15.1, 9.6 Hz), 2.58 (1 H, dd, *J* = 15.1, 7.8 Hz), 3.50–3.60 (3 H, m), 3.66 (3 H, s), 3.72–3.87 (2 H, m), 4.48 (2 H, s), 7.27–7.35 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5, 138.5, 128.4, 127.7, 127.6, 73.1, 72.6, 72.0, 67.8, 66.6, 51.7, 41.0, 40.9, 40.7, 36.1.

MS (EI): *m*/*z* = 309 (M + H), 235.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{24}O_5$ + Na (M + Na): 331.1521; found: 331.1520.

Methyl (*R*)-(–)-5-(Benzyloxy)-3-hydroxypentanoate [(*R*)-4]

(*R*)-BINAP (25 mg, 0.04 mmol) and bis(2-methylallyl)(1,5-cyclooctadiene)ruthenium(II) (12 mg, 0.04 mmol) were dissolved in degassed anhyd acetone (6 mL) under N_2. The solution was cooled with an ice bath. HBr (0.33 mL, 29% in aq MeOH) was added to the solution and the mixture was stirred at r.t. for 0.5 h. The solvent was evaporated in vacuo. A solution of the β-keto ester **3** (0.47 g, 2 mmol) in EtOH (8 mL) was added to the freshly prepared catalyst

and the mixture was placed under H_2 (balloon) and stirred overnight at 50 °C. The solvent was evaporated and the residue was purified by flash chromatography (85:15 hexane–EtOAc) on silica gel (12 g) to give the alcohol (*R*)-**4**[10] as a colourless oil (0.42 g, 89%); $[\alpha]_D^{25}$ –5.9 (*c* 1.55, CH_2Cl_2).

Methyl (*R*)-5-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)pentanoate [(*R*)-10]

2,6-Lutidine (0.13 mL, 1.3 mmol) and TBSOTf (0.28 mL, 1.2 mmol) were added sequentially to a solution of (*R*)-**4** (0.24 g, 1 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2. The mixture was stirred at –78 °C for 1 h and then the solvent was evaporated. Sat. aq NH_4Cl (5 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL), and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (95:5 hexane–EtOAc) on silica gel (10 g) to give **10** (0.33 g, 96%) as a colourless oil, which was used directly in the next step.

(*R*)-(+)-5-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)pentanal (11)

DIBAL-H (3.7 mL of a 1 M solution in hexane, 3.7 mmol) was added to a solution of **10** (1.0 g, 2.8 mmol) in toluene (18 mL) at –78 °C under N_2. The mixture was stirred for 30 min at –78 °C. A few drops of H_2O were added and the mixture was stirred for 30 min. Na_2SO_4 was added and the mixture was stirred until a crystalline precipitate formed. The mixture was filtered through Celite and the solvent was evaporated to give the aldehyde **11**[16] as a colourless oil (0.84 g, 92%), which was used in the next step without purification; $[\alpha]_D^{25}$ +9.8 (*c* 1.36, CH_2Cl_2).

IR (neat): 2952, 2923, 2851, 1725, 1493, 1264, 1097, 1041, 836, 735, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (3 H, s), 0.07 (3 H, s), 0.86 (9 H, s), 1.82–1.90 (2 H, m), 2.50 (1 H, dd, *J* = 2.5, 6.0 Hz), 2.54 (1 H, dd, *J* = 2.9, 6.0 Hz), 3.52 (2 H, t, *J* = 6.0 Hz), 4.38 (1 H, quint, *J* = 6.0 Hz), 4.45 (1 H, d, *J* = 12.2 Hz), 4.50 (1 H, d, *J* = 12.2 Hz), 7.26–7.37 (5 H, m), 9.79 (1 H, t, *J* = 2.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.1, 138.2, 128.4, 127.6, 127.6, 73.0, 66.3, 65.6, 51.0, 37.6, 25.7, 17.9, –4.7, –4.6.

MS (EI): *m*/*z* = 345 (M + Na), 322 (M), 214.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{31}O_3Si$ (M + H): 323.2042; found: 323.2043.

(3*S*,4*S*,6*R*)-(–)-8-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-3-methyloct-1-en-4-ol (12)

t-BuOK (0.31 mL of a 1 M solution in THF, 0.31 mmol) was added dropwise to a solution of *cis*-but-2-ene (83 mL, 0.93 mmol) in THF (2 mL) under N_2 while maintaining the temperature below –65 °C. *n*-BuLi (0.19 mL of a 1.6 M solution in hexane, 0.31 mmol) was slowly added by a syringe pump maintaining the temperature below –65 °C. The mixture was stirred at –78 °C for 0.5 h and then warmed up to –25 °C and stirred for another 15 min. The orange mixture was recooled to –78 °C. A solution of (+)-*B*-methoxydiisopinocampheylborane (0.13 g, 0.40 mmol) in THF (2 mL) was added dropwise to the reaction mixture by a syringe pump at –78 °C over 20 min. $BF_3{\cdot}OEt_2$ (0.46 mL, 3.5 mmol) was added dropwise over 1 h. A solution of the aldehyde **11** (0.1 g, 0.31 mmol) in THF (3 mL) was added to the Brown reagent and the mixture was stirred overnight at –78 °C. H_2O_2 (8 mL, 30% aq) and aq 2 M NaOH (12 mL) were added and the mixture was stirred at r.t. for 2 h. The volatiles were evaporated and the mixture was extracted with Et_2O (3 × 6 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (95:5 hexane–EtOAc) on silica gel (12 g) to give **12**[17] (80 mg, 67%) as a colourless oil; $[\alpha]_D^{25}$ –17.1 (*c* 0.43, CH_2Cl_2).

IR (neat): 3451, 2954, 2928, 2856, 1455, 1361, 1253, 1091, 834, 774, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.07 (3 H, s), 0.10 (3 H, s), 0.88 (9 H, s), 1.06 (3 H, d, *J* = 6.8 Hz), 1.60 (2 H, t, *J* = 4.2 Hz), 1.85 (1 H, dq, *J* = 12.1, 6.7 Hz), 1.96 (1 H, dq, *J* = 12.1, 6.7 Hz), 2.19 (1 H, m), 3.37 (1 H, d, *J* = 2.0 Hz), 3.50 (2 H, t, *J* = 6.5 Hz), 3.77 (1 H, ddd, *J* = 6.9, 5.4, 2.0 Hz), 4.20 (1 H, ddt, *J* = 10.9, 6.2, 4.1 Hz), 4.45 (1 H, d, *J* = 11.2 Hz), 4.52 (1 H, d, *J* = 11.2 Hz), 4.98–5.05 (2 H, m), 5.72 (1 H, ddd, *J* = 17.6, 10.4, 7.6 Hz), 7.28–7.36 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.1, 138.2, 128.4, 127.7, 127.6, 114.8, 73.0, 71.6, 69.1, 66.8, 44.2, 38.9, 36.1, 25.8, 17.9, 15.1, –4.7, –4.8.

MS (EI): *m*/*z* = 392 (M + Na), 379 (M + H), 288, 206.

HRMS (EI): *m*/*z* calcd for $C_{22}H_{39}O_3Si$ (M + H): 379.2668; found: 379.2668.

(4*R*,5*R*,7*S*,*E*)-Methyl 9-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-methylnon-2-enoate (13)

Methyl acrylate (0.07 mL, 0.80 mmol) was added to a solution of **12** (0.10 g, 0.26 mmol) in DCE (8 mL) under N_2. The second-generation Hoveyda–Grubbs catalyst (4 mg, 0.007 mmol) was dissolved in DCE (1 mL) and added to the solution. The mixture was heated at reflux for 12 h, and additional catalyst (4 mg, 0.007 mmol) in DCE (1 mL) was added and the mixture was heated overnight at reflux. The solvent was evaporated and the residue was purified by flash chromatography (85:15 hexane–EtOAc) on silica gel (12 g) to give **13** (0.11 g, 95%) as a colourless oil; $[\alpha]_D^{25}$ –11.0 (*c* 1.54, CH_2Cl_2).

IR (neat): 3494, 2952, 2929, 2856, 1725, 1461, 1435, 1255, 1145, 808, 776, 735, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.07 (3 H, s), 0.10 (3 H, s), 0.88 (9 H, s), 1.06 (3 H, d, *J* = 6.8 Hz), 1.53 (1 H, ddd, *J* = 14.6, 4.0, 2.0 Hz), 1.63 (1 H, ddd, *J* = 14.6, 10.7, 4.0 Hz), 1.84 (1 H, dq, *J* = 13.8, 6.7 Hz), 1.96 (1 H, dq, *J* = 11.7, 6.7 Hz), 2.37 (1 H, m), 3.49 (2 H, t, *J* = 5.2 Hz), 3.68 (1 H, br), 3.72 (3 H, s), 3.89–3.91 (1 H, m), 4.18–4.21 (1 H, m), 4.44 (1 H, d, *J* = 11.9 Hz), 4.50 (1 H, d, *J* = 11.9 Hz), 5.83 (1 H, d, *J* = 15.8 Hz), 6.94 (1 H, dd, *J* = 15.8, 7.8 Hz), 7.26–7.35 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 151.2, 138.2, 128.4, 127.7, 127.6, 121.0, 73.0, 71.2, 69.1, 66.6, 51.4, 42.9, 38.7, 35.8, 25.8, 17.9, 14.5, –4.7, –4.9.

MS (EI): *m*/*z* = 459 (M + Na), 437 (M + H).

HRMS (EI): *m*/*z* calcd for $C_{24}H_{40}O_4Si$ + Na (M + Na): 459.2594; found: 459.2586.

Methyl (4*R*,5*R*,7*S*,*E*)-(–)-9-(Benzyloxy)-5,7-dihydroxy-4-methylnon-2-enoate (14)

The α,β-unsaturated ester **13** (0.22 g, 0.50 mmol) was dissolved in MeOH (6 mL). Amberlyst 15 (0.15 g) was added and the mixture was stirred overnight at r.t. The suspension was filtered through Celite and the solvent was evaporated. The residue was purified by flash chromatography (3:1 hexane–EtOAc) on silica gel (5 g) to afford **14** (0.14 g, 88%) as a colourless oil that solidified during refrigeration; $[\alpha]_D^{25}$ –35.2 (*c* 0.85, CH_2Cl_2).

IR (neat): 3494, 2952, 2929, 2856, 1725, 1461, 1435, 1255, 1145, 808, 776, 735, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 (3 H, d, *J* = 6.2 Hz), 1.57–1.62 (2 H, m), 1.64–1.69 (1 H, m), 1.93 (1 H, ddt, *J* = 15.1, 8.0, 5.2 Hz), 2.46 (1 H, ddq, *J* = 10.0, 8.0, 5.0 Hz), 3.14 (1 H, d, *J* = 5.2 Hz), 3.58 (1 H, s), 3.67 (1 H, td, *J* = 3.6, 9.4 Hz), 3.72–3.77 (4 H, m), 3.83–3.89 (1 H, m), 4.13–4.2 (1 H, m), 4.5 (1 H, d, *J* = 11.9 Hz),

4.52 (1 H, d, *J* = 11.9 Hz), 5.86 (1 H, d, *J* = 16.0 Hz), 6.94 (1 H, dd, *J* = 17.0, 8.9 Hz), 7.29–7.37 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 151.2, 137.6, 128.5, 127.9, 127.7, 121.1, 73.5, 71.6, 70.0, 69.7, 51.5, 42.8, 39.8, 35.9, 15.0.

MS (EI): *m*/*z* = 345 (M + Na), 323 (M + H).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{27}O_5$ (M + H): 323.1858; found: 323.1863.

(5*R*,6*R*,8*S*,*E*)-(–)-10-(Benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-6-hydroxy-5-methyldec-3-en-2-one (15)

Methyl vinyl ketone (0.20 mL, 2.4 mmol) was added to a solution of the alcohol **14** (0.3 g, 0.80 mmol) in DCE (6 mL) under N_2. The second-generation Hoveyda–Grubbs catalyst (13 mg, 0.02 mmol) was dissolved in DCE (1 mL) and added to the solution. The mixture was heated at reflux for 14 h, and additional catalyst (4 mg, 0.007 mmol) in DCE (1 mL) was added and the mixture was heated overnight at reflux. The solvent was evaporated and the residue was purified by flash chromatography (85:15 hexane–EtOAc) on silica gel (5 g) to give **15** (0.31 g, 94%) as a colourless oil; $[\alpha]_D^{25}$ –17.4 (*c* 1.2, CH_2Cl_2).

IR (neat): 3478, 2953, 2885, 2856, 1673, 1454, 1414, 1254, 1092, 984, 835, 775 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (3 H, s), 0.09 (3 H, s), 0.88 (9 H, s), 1.05 (3 H, d, *J* = 6.8 Hz), 1.48–1.52 (1 H, m), 1.62 (1 H, ddd, *J* = 12.4, 4.6, 4.0 Hz), 1.83–2.03 (2 H, m), 2.21 (3 H, s), 2.39–2.48 (1 H, m), 3.49 (2 H, t, *J* = 5.9 Hz), 3.80 (1 H, d, *J* = 5.5 Hz), 3.94 (1 H, dd, *J* = 9.4, 5.3 Hz), 4.20–4.23 (1 H, m), 4.43 (1 H, d, *J* = 11.9 Hz), 4.49 (1 H, d, *J* = 11.9 Hz), 6.05 (1 H, d, *J* = 16.2 Hz), 6.81 (1 H, dd, *J* = 16.2, 7.4 Hz), 7.26–7.35 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.8, 150.2, 138.1, 131.1, 128.3, 127.6, 73.0, 71.2, 69.2, 66.6, 42.8, 38.3, 35.7, 26.7, 25.7, 17.8, 14.2, –4.8, –4.9.

MS (EI): *m*/*z* = 443 (M + Na), 421 (M + H), 403, 377.

HRMS (EI): *m*/*z* calcd for $C_{24}H_{40}O_4Si$ + Na (M + Na): 443.2594; found: 443.2586.

1-{(2*R*,3*S*,4*S*,6*S*)-(+)-6-[2-(Benzyloxy)ethyl]-4-hydroxy-3-methyltetrahydro-2*H*-pyran-2-yl}propan-2-one (16)

Amberlyst 15 (70 mg) was added to a solution of **15** (0.10 g, 0.24 mmol) in MeOH (4 mL). The mixture was stirred overnight at r.t. The suspension was filtered through Celite and the solvent was evaporated. The residue was purified by flash chromatography (1:1 hexane–EtOAc) on silica gel (3 g) to give **16** (69 mg, 95%) as a colourless oil; $[\alpha]_D^{25}$ +23.1 (*c* 0.6, CH_2Cl_2).

IR (neat): 3049, 2953, 2919, 2849, 1642, 1529, 1249, 1040, 745 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (3 H, d, *J* = 6.5 Hz), 1.24–1.32 (2 H, m), 1.55 (1 H, m,), 1.73–1.78 (2 H, m), 1.95 (1 H, ddd, *J* = 12.4, 4.7, 1.8 Hz), 2.16 (3 H, s), 2.54 (1 H, dd, *J* = 14.7, 9.1 Hz), 2.59 (1 H, dd, *J* = 14.7, 3.6 Hz), 3.38 (1 H, ddd, *J* = 10.8, 10.4, 4.7Hz), 3.46 (1 H, td, *J* = 9.5, 3.7 Hz), 3.50–3.57 (3 H, m), 4.45 (1 H, d, *J* = 11.9 Hz), 4.49 (1 H, d, *J* = 11.9 Hz), 7.26–7.34 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.8, 138.4, 128.4, 127.7, 127.6, 77.8, 73.2, 73.1, 72.4, 66.6, 47.4, 44.0, 41.2, 36.1, 30.9, 12.9.

MS (EI): *m*/*z* = 329 (M + Na), 307 (M + H), 251.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{26}O_4$ + Na (M + Na): 329.1729; found: 329.1725.

Methyl (2*S*,3*S*,4*S*,6*R*)-(+)-[6-(2-Benzyloxyethyl)-4-hydroxy-3-methyltetrahydropyran-2-yl]acetate (2) and Methyl {(2*S*,3*S*,4*S*,6*S*)-(+)-6-[2-(Benzyloxy)ethyl]-4-hydroxy-3-methyltetrahydro-2*H*-pyran-2-yl}-2,2-dichloroacetate (17)

Freshly prepared KOCl solution[14] (1.5 mL) was added to a solution of **16** (0.15 g, 0.49 mmol) in MeOH (3 mL). The mixture was stirred for 30 min at r.t. The volatiles were evaporated and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (85:15 hexane–EtOAc) on silica gel (6 g) to give **17** (89 mg, 46%) and **2** (80 mg, 50%) as colourless oils.

Dichloroester 17

$[\alpha]_D^{25}$ +33.7 (*c* 1.0, CH_2Cl_2).

IR (neat): 3405, 2951, 2919, 2864, 1765, 1454, 1365, 1245, 1075, 1019, 845, 738, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (3 H, d, *J* = 6.6 Hz), 1.36 (1 H, dt, *J* = 12.6, 11 Hz), 1.66 (1 H, d, *J* = 3.2 Hz), 1.74–1.88 (3 H, m), 1.99 (1 H, ddd, *J* = 12.4, 4.9, 2.6 Hz), 3.46–3.50 (3 H, m), 3.64–3.68 (1 H, m), 3.77 (1 H, d, *J* = 7.9 Hz), 3.81 (3 H, s), 4.46 (1 H, d, *J* = 10.3 Hz), 4.49 (1 H, d, *J* = 10.3 Hz), 7.26–7.33 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 138.3, 128.4, 127.6, 127.6, 85.1, 84.7, 73.4, 73.0, 72.6, 66.4, 54.2, 42.0, 40.8, 35.8, 12.5.

MS (EI): *m*/*z* = 413 (M + Na), 391 (M + H), 332, 250.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{25}O_5{}^{35}Cl_2$ (M + H): 391.1079; found: 391.1090.

Ester 2

For spectral data of **2**, see below.

1-(*tert*-Butyldimethylsilyloxy)but-3-en-2-one (18)

Dess–Martin periodinane (4.16 g, 9.80 mmol) was added to a solution of 1-(*tert*-butyldimethylsilyloxy)but-3-en-2-ol[15] (1.0 g, 4.9 mmol) in CH_2Cl_2 (10 mL) cooled in an ice bath. The mixture was stirred for 2 h at r.t., before filtration through Celite. The volatiles were evaporated and the residue was purified by flash chromatography (95:5 hexane–EtOAc) on silica gel (30 g) to give **18** (0.73 g, 75%) as a colourless oil.

IR (neat): 2955, 2887, 1702, 1605, 1362, 1154, 990, 822, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.6 (6 H, s), 0.89 (9 H, s), 4.33 (2 H, s), 5.74 (1 H, d, *J* = 10.7 Hz), 6.30 (1 H, d, *J* = 17.6 Hz), 6.63 (1 H, dd, *J* = 17.6, 10.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6, 131.6, 128.7, 68.5, 25.7, 18.3, –5.6.

MS (EI): *m*/*z* = 223 (M + Na), 201 (M).

HRMS (EI): *m*/*z* calcd for $C_{10}H_{20}O_2Si$ + Na (M + Na): 223.1130; found: 223.1127.

(5*R*,6*R*,8*S*,*E*)-(–)-10-Benzyloxy-6-hydroxy-5-methyl-1,8-bis(*tert*-butyldimethylsilyloxy)dec-3-en-2-one (19)

A solution of the second-generation Hoveyda–Grubbs catalyst (13 mg, 0.020 mmol) in DCE (1 mL) was added to a solution of the alcohol **12** (0.3 g, 0.80 mmol) and ketone **18** (0.48 g, 2.4 mmol) in DCE (10 mL) under N_2. The mixture was heated at reflux for 12 h, and additional catalyst (13 mg, 0.020 mmol) in DCE (1 mL) was added and the mixture was heated overnight at reflux. The solvent was evaporated and the residue was purified by flash chromatography (85:15 hexane–EtOAc) on silica gel (10 g) to give **19** (0.40 g, 91%) as a colourless oil; $[\alpha]_D^{25}$ –12.3 (*c* 1.0, CH_2Cl_2).

IR (neat): 3475, 2954, 2929, 2884, 2856, 1719, 1621, 1461, 1253, 1097, 835, 776 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06–0.09 (12 H, m), 0.88 (9 H, s), 0.92 (9 H, s), 1.06 (3 H, d, *J* = 6.8 Hz), 1.50–1.53 (1 H, m), 1.59–1.62 (1 H, m), 1.81–1.97 (2 H, m), 2.38 (1 H, dd, *J* = 13.3, 6.7 Hz), 3.47–3.49 (2 H, m), 3.70 (1 H, s), 3.89–3.91 (1 H, m), 4.18–4.22 (1 H, m), 4.33 (2 H, s), 4.44 (1 H, d, *J* = 11.9 Hz), 4.50 (1 H, d, *J* = 11.9 Hz), 6.38 (1 H, d, *J* = 16.0 Hz), 6.94 (1 H, dd, *J* = 16.0, 7.6 Hz), 7.26–7.35 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.5, 149.7, 138.2, 128.4, 127.7, 127.6, 125.3, 73.0, 71.3, 69.1, 68.6, 66.6, 43.2, 38.6, 35.8, 25.8, 25.7, 18.4, 17.9, 14.5, –4.7, –4.9, –5.4, –5.5.

MS (EI): *m*/*z* = 573 (M + Na), 419.

HRMS (EI): *m*/*z* calcd for $C_{30}H_{55}O_5Si_2$ (M + H): 551.3588; found: 551.3596.

1-{(2*R*,3*S*,4*S*,6*S*)-(+)-6-[2-(Benzyloxy)ethyl]-4-hydroxy-3-methyltetrahydro-2*H*-pyran-2-yl}-3-hydroxypropan-2-one (20)

Amberlyst 15 (0.2 g) was added to a solution of **19** (0.30 g, 0.55 mmol) in MeOH (8 mL). The mixture was stirred overnight at r.t. and filtered through Celite. The solvent was evaporated and the residue was purified by flash chromatography (1:1 hexane–EtOAc) on silica gel (9 g) to give **20** (0.16 g, 91%) as a colourless oil; $[\alpha]_D^{25}$ +3.9 (*c* 0.95, CH_2Cl_2).

IR (neat): 3402, 2954, 2864, 1760, 1454, 1232, 1076, 1014, 843, 732, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (3 H, d, *J* = 6.5 Hz), 1.12–1.25 (2 H, m), 1.72 (2 H, quint, *J* = 6.2 Hz), 1.87 (1 H, ddd, *J* = 12.4, 4.6, 1.7 Hz), 2.50 (1 H, dd, *J* = 14.0, 8.8 Hz), 2.55 (1 H, dd, *J* = 14.7, 3.8 Hz), 3.08 (1 H, t, *J* = 3.7 Hz), 3.15 (1 H, d, *J* = 12.6 Hz), 3.33–3.35 (1 H, m), 3.36 (1 H, ddd, *J* = 9.6, 10.4, 3.9 Hz), 3.42 (2 H, t, *J* = 6.2 Hz), 3.48 (1 H, dt, *J* = 11.1, 6.1 Hz), 4.20 (1 H, d, *J* = 10.0 Hz), 4.23 (1 H, d, *J* = 10.0 Hz), 4.35 (1 H, d, *J* = 12.0 Hz), 4.46 (1 H, d, *J* = 12.0 Hz), 7.36–7.50 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.1, 138.4, 128.4, 127.8, 127.6, 77.9, 73.2, 73.0, 72.5, 69.5, 66.3, 43.9, 42.5, 41.0, 36.0, 12.8.

MS (EI): *m*/*z* = 345 (M + Na), 323 (M + H), 305, 251, 214.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{26}O_5$ + Na (M + Na): 345.1678; found: 345.1677.

Methyl (2*S*,3*S*,4*S*,6*R*)-(+)-[6-(2-Benzyloxyethyl)-4-hydroxy-3-methyltetrahydropyran-2-yl]acetate (2)

HIO_4 (380 mg, 2.0 mmol), silica gel (1 g), and H_2O (0.5 ml) were added sequentially to a solution of hydroxyl ketone **20** (160 mg, 0.50 mmol) in MeOH (6 mL). The mixture was stirred overnight at r.t. vigorously and then filtered through Celite. The filtrate was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (1:1 hexane–EtOAc) on silica gel (5 g) to give **2** (150 mg, 92%) as a colourless oil; $[\alpha]_D^{25}$ +8.5 (*c* 0.5, $CHCl_3$).

IR (neat): 3054, 2952, 2926, 2855, 1714, 1434, 1315, 1200, 1177, 1098, 898 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (3 H, d, *J* = 6.5 Hz), 1.19–1.33 (2 H, m), 1.47 (1 H, d, *J* = 5.5 Hz), 1.72–1.83 (2 H, m), 1.95 (1 H, ddd, *J* = 12.4, 4.6, 1.6 Hz), 2.41 (1 H, dd, *J* = 14.7, 9.6 Hz), 2.64 (1 H, dd, *J* = 14.7, 3.3 Hz), 3.38 (1 H, ddd, *J* = 10.5, 9.5, 4.5 Hz), 3.46 (1 H, td, *J* = 9.5, 3.3 Hz), 3.52–3.57 (3 H, m, CH), 3.65 (3 H, s), 4.45 (1 H, d, *J* = 11.9 Hz), 4.49 (1 H, d, *J* = 11.9 Hz), 7.26–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 138.5, 128.4, 127.6, 127.5, 77.8, 73.3, 73.1, 72.4, 66.7, 51.6, 43.9, 41.2, 39.1, 36.0, 12.8.

MS (EI): *m*/*z* = 345 (M + Na), 323 (M + H), 214.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{27}O_5$ (M + H): 323.1858; found: 323.1863.

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(13) Data for the *trans*-isomer of tetrahydropyran **2**: $[\alpha]_D^{25}$ +90.6 (*c* 0.28, CH_2Cl_2). IR (neat): 3054, 2952, 2926, 2855, 1714, 1434, 1315, 1200, 1177, 1098, 898 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.99 (3 H, d, *J* = 6.9 Hz), 1.20–1.32 (2 H, m), 1.47 (1 H, d, *J* = 3.0 Hz), 1.75–1.91 (2 H, m), 1.99 (1 H, ddd, *J* = 12.5, 4.3, 2.6 Hz), 2.44 (1 H, dd, *J* = 14.5, 4.4 Hz), 2.65 (1 H, dd, *J* = 14.5, 11.0 Hz), 3.48–3.62 (3 H, m), 3.66 (3 H, s), 3.85–3.89 (1 H, m), 4.43 (1 H, ddd, *J* = 10.8, 5.1, 4.9 Hz), 4.48 (1 H, d, *J* = 11.8 Hz), 4.54 (1 H, d, *J* = 11.8 Hz), 7.26–7.36 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 138.5, 128.4, 127.7, 127.5, 73.9, 73.1, 69.7, 66.9, 66.7, 51.7, 41.0, 40.4, 36.0, 33.4, 13.1. MS (EI): *m*/*z* = 345 (M + Na), 323 (M + H), 214. HRMS (EI): *m*/*z* calcd for $C_{18}H_{27}O_5$ (M + H): 323.1858; found: 323.1859.

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