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Towards a simplified peloruside A: synthesis of C1–C11 of a dihydropyran analogue

Emma M. Casey [a,†], Febly Tho [a], Joanne E. Harvey [a], Paul H. Teesdale-Spittle [b,*]

[a] Centre for Biodiscovery, School of Chemical and Physical Sciences, Victoria University of Wellington, PO Box 600, Wellington, New Zealand
[b] Centre for Biodiscovery, School of Biological Sciences, Victoria University of Wellington, PO Box 600, Wellington, New Zealand

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ABSTRACT

A simplified analogue of the C1–C11 fragment of peloruside A has been synthesised starting from a monoprotected 2,2-dimethylpropane-1,3-diol. Oxidation, asymmetric allylation and acryloylation provided a substrate for ring-closing metathesis to a δ-lactone. Reduction, acylation and homologation with trimethyl(vinyloxy)silane provided a protected C3–C11 analogue in a stereoisomer manner. Introduction of the C1–C2 fragment and incorporation of the 2,3-*syn* stereochemistry was achieved by a boron-mediated Evans aldol reaction.

1. Introduction

Microtubule stabilisers such as the taxanes and epothilones are among the most successful anti-cancer drugs in current use.[1] With one in four deaths in the United States during 2010 attributed to cancer,[2] there is an ongoing need for improved clinical agents. Peloruside A (**1**, Fig. 1) is a microtubule stabilising agent[3] that was first reported by Northcote et al. in 2000[4] and has sparked a flurry of biological and chemical endeavour. It has high potency against cancer cells, low susceptibility towards resistance through P-glycoprotein-mediated efflux,[5] synergistic activity with taxoid site binders,[6] interactions with a previously uncharacterised binding site on tubulin,[5] and a unique mode of microtubule stabilisation.[7] In vivo animal study data show that peloruside A has good pharmacokinetic and pharmacodynamic profiles,[8] indicating that compounds based on its structure will be especially useful agents in cases where resistance to existing drugs forces the termination of treatment.

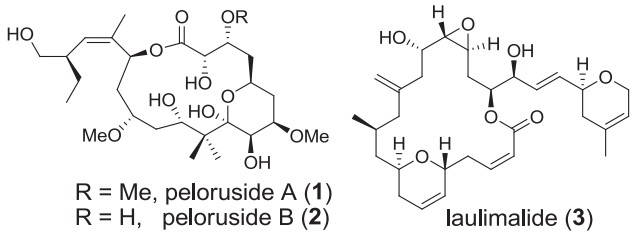

Fig. 1. Structures of peloruside A (**1**), peloruside B (**2**) and laulimalide (**3**).

To date there have been six total syntheses of peloruside A,[9–15] along with a number of syntheses of fragments and analogues, including the C1–C11[16,17] and C12–C24 fragments,[18] the unexpected synthesis of (−)-2-*epi*-peloruside A,[19] a monocyclic analogue,[20] and the naturally occurring congener peloruside B (**2**, Fig. 1).[21]

There is experimental evidence pointing to a peloruside A binding site on β-tubulin that coincides with that of laulimalide (**3**, Fig. 1),[5] a highly potent macrolide isolated from the sponge *Cacospongia mycofijiensis* that also stabilises microtubules.[22] However, uncertainty remains about the exact binding mode of peloruside A within this site.[7]

There are a number of structural changes that might be explored in seeking an analogue that is as potent as, and synthetically more tractable than, peloruside A. It is noticeable that with existing analogues or congeners of peloruside A, removal or modification of the pyran impacts severely on cytotoxicity, suggesting that the presence and position of the pyran ring are crucial to the binding/activity.[20,23] In order to probe this further, we have chosen to

* Corresponding author. Tel.: +64 4 463 6094; fax: +64 4 463 5339; e-mail address: paul.teesdale-spittle@vuw.ac.nz (P.H. Teesdale-Spittle).
† Current address: Department of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, UK.

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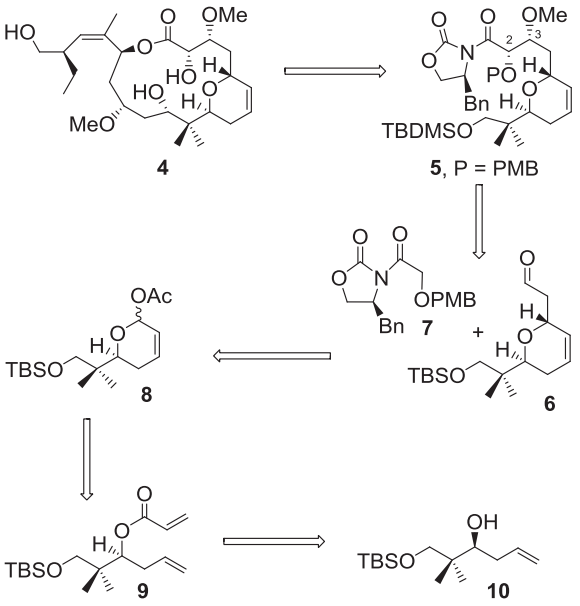
replace the pyranose ring of peloruside A with the dihydropyran of laulimalide, leading conceptually to analogue **4** (Scheme 1). The laulimalide-like dihydropyran presents the advantages over the peloruside A tetrahydropyran of having two fewer chiral centres and no hemiacetal functionality, thereby allowing greater ease of synthesis and higher metabolic stability. Several syntheses of laulimalide have been undertaken, with the most relevant to our work being that of Ghosh and Wang who prepared the dihydropyran using ring-closing methathesis.[24]



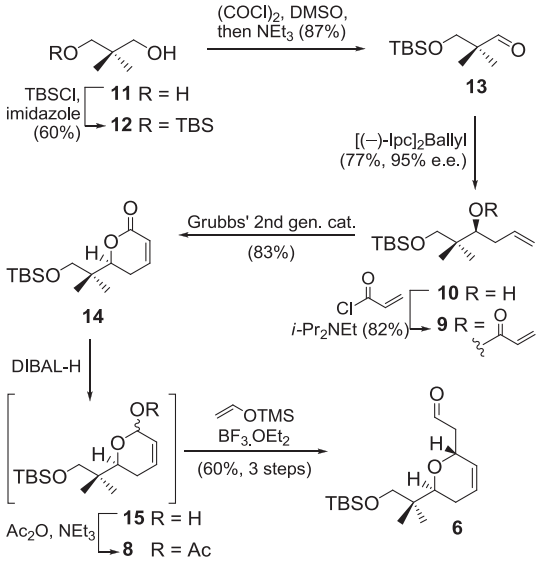
Scheme 1. Retrosynthetic strategy for the synthesis of simplified peloruside A analogue, **4**.

For optimal convergence in a synthetic strategy, precedent has shown it to be ideal to disconnect the macrocycle of peloruside A at both the lactone and a bond in the C9–C13 region. Two of the prior total syntheses have selected the C11–C12 bond for this latter purpose,[12,14] and the same strategy was implicit in the reported synthesis of the C12–C24 fragment by Stocker, Hoberg and ourselves.[18,25] We have thus targeted the synthesis of a C1–C11 analogue in the work presented here.

Our retrosynthetic analysis of the C1–C11 fragment of analogue **4** (viz. compound **5**) is shown in Scheme 1. A 1,2-*syn*-aldol reaction between aldehyde **6** and an Evans oxazolidinone **7** was envisaged to set the C2–C3 stereochemistry. Aldehyde **6** would be obtained by substitution of lactol acetate **8** with a vinyl enol ether nucleophile. Lactol acetate **8** would be synthesised by ring-closing metathesis of diene **9**, followed by reduction and acetylation. Diene **9** would ultimately be derived from acryloyl chloride and alcohol **10**, the product of an asymmetric Brown allylation of an unsymmetrically oxidised 1,3-propanediol.

2. Results and discussion

The synthesis of the C5–C11 fragment of analogue **4** proceeded as described in Scheme 2. Synthesis of allylic alcohol **10** began with monoprotection of 1,3-propanediol (**11**) to provide **12** in reasonable yield. Formation of the accompanying bis-protected product was minimised by using a slight excess of **11** over the protecting group. While several possible protecting groups were considered, ultimately the TBS group was chosen to provide stability through the synthesis of the C1–C11 fragment, whilst allowing orthogonal deprotection prior to oxidation and subsequent aldol coupling to a C12–C24 fragment. Alcohol **12** was subsequently oxidised in a reliably high yield under Swern conditions to provide aldehyde **13**. Allylation using Brown's boron-mediated asymmetric methodology provided secondary alcohol **10**. Although removal of magnesium salts created during the standard preparation of the allyldiisopinocampheylborane has been reported to improve enantioselectivity,[26] we found this to be unnecessary and we were able to obtain an ee of at least 95% according to Mosher ester analysis. Alcohol **10** was esterified with acryloyl chloride; subsequent ring-closing metathesis of the resulting diene **9** using Grubbs' second generation catalyst provided lactone **14**. Although a single step conversion equivalent to transformation of aldehyde **13** to lactone **14** via a vinylogous aldol reaction has been achieved,[27] our three-step approach allowed us to obtain good stereochemical control and a higher overall yield than reported for the single step transformation.



Scheme 2. Synthesis of C3–C11 fragment **6** via lactone **14**.

Synthesis of the C3–C11 fragment was completed in three further steps without purification of the intermediates in order to minimise degradation. Thus, careful reduction of **14** with DIBAL-H provided the hemiacetal **15** as a ca. 5:1 mixture of diastereomers, accompanied by about 10% of the ring-open aldehyde congener. This material was immediately acetylated under mild conditions to provide lactol acetate **8**, again as a mixture of diastereomers. Treatment with trimethyl(vinyloxy)silane under Lewis acidic conditions provided the C3–C11 aldehyde **6** in good overall yield, now as a single diastereomer. The laulimalide-like trans substitution across the dihydropyran of aldehyde **6** was confirmed by the observation of NOE correlations between H9 and H4a (Fig. 2). This stereochemical control presumably arises from steric shielding of one face of the conjugated oxonium intermediate by the bulky C9 substituent.

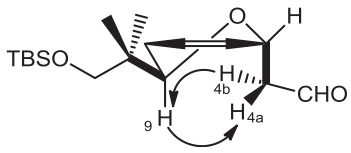
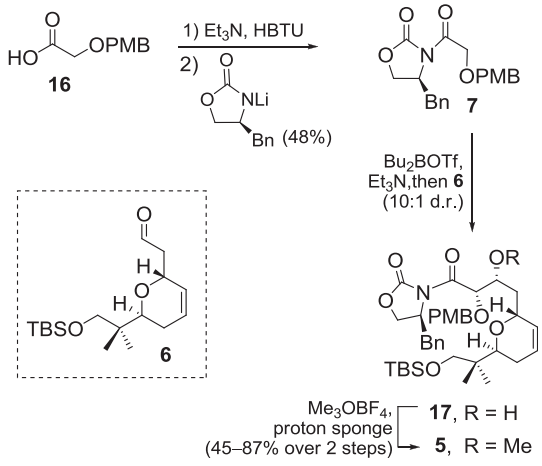


Fig. 2. NOE correlations within **6** confirming the trans-orientation of the ring substituents.

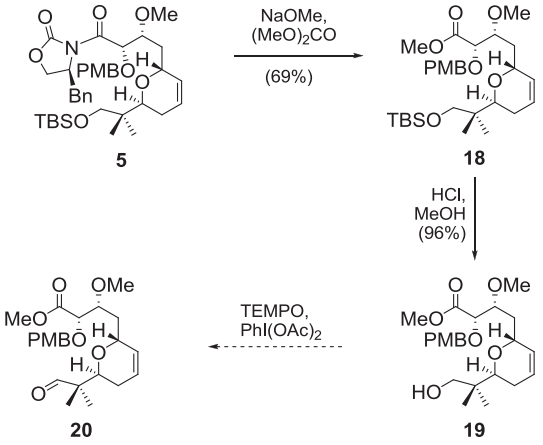
The required *syn*-relationship between the C2 and C3 substituents was set using an Evans' oxazolidinone-directed 1,2-*syn*-aldol reaction.[28] Oxazolidinone glycolate **7** is well known.[29]

However, we found the literature preparation via a pivaloyl mixed anhydride was prone to formation of the undesired pivaloylated Evans auxiliary as a persistent contaminant. For this reason, **7** was generally prepared by acylation of the lithium salt of benzyl oxazolidinone through HBTU-mediated coupling with commercially available glycolic acid derivative **16**, albeit in modest yield (Scheme 3). Reaction of the boron enolate of **7** with aldehyde **6** proceeded smoothly to give the 1,2-*syn*-adduct in excellent yield with a diastereomeric ratio of 10:1 (according to NMR analysis of the crude material). We noted a tendency for **17** to undergo a retro-aldol reaction, so although **17** could be synthesised in yields of up to 90%, methyl ether **5** was most reliably prepared when the resulting alcohol was methylated without significant delay using Meerwein's salt to produce the fully protected C1–C11 fragment **5**. The use of no more than 2 equiv of fresh, high grade Meerwein's salt was optimal for this transformation. Retro-aldol products were noted when using older bottles of reagent, while loss of the auxiliary and formation of the methyl ester provided a competing reaction that was promoted by use of larger excesses of Meerwein's salt.



Scheme 3. Synthesis of protected C1–C11 oxazolidinone **5**.

Conversion of oxazolidinone **5** into a C11 aldehyde that would undergo aldol reaction with the C12–C24 portion of the analogue **4** was then explored. It was deemed necessary at this stage to remove the Evans auxiliary, in order to improve the solubility of the C1–C11 fragment for further reactions. Unfortunately, formation of the methyl ester from the above-mentioned reaction of **5** with excess Meerwein's salt was not sufficiently reliable or high yielding to be useful. Instead, conversion of the auxiliary-bound **5** into the methyl ester **18** was achieved with sodium methoxide in the presence of dimethyl carbonate following the methodology of Kanomata et al. (Scheme 4).[30] Formation of methyl ester **18** was typically accompanied, in yields of around 30%, by the methyl carbonate produced from ring opening of the Evans auxiliary. This competing reaction is likely to result from nucleophile attack at the carbamate carbonyl due to hindered access for the methoxide to the desired carbonyl group. Nonetheless, the Kanomata method provided significantly better results than those obtained without dimethyl carbonate and reasonable to good yields of **18** were obtained (typically ranging between 59 and 69%). Removal of the silyl protecting group with methanolic HCl afforded alcohol **19**. The reaction time was critical as concurrent loss of the PMB group was observed if left longer than 5 min. Thus alcohol 19 has been prepared and is ready for future coupling studies with the C12–C24 fragment. Preliminary studies on oxidation of **19** to aldehyde **20**, which will be required for aldol coupling with an appropriate C12–C24 fragment, suggest that the Dess–Martin periodinane oxidation gives variable yields depending on scale (ca. 70–75%). However, use of TEMPO and the co-oxidant $PhI(OAc)_2$ at room temperature appears to provide the desired aldehyde in high yield (ca. 85%) without the requirements for inert atmosphere, anhydrous conditions or low temperatures.



Scheme 4. Completion of the C1-C11 fragment **20**.

3. Conclusion

The C1–C11 fragment of a novel peloruside A-laulimalide analogue has been completed. Successful synthesis of the C3–C11 fragments using a ring-closing metathesis reaction was followed by incorporation of the C1–C2 moiety, utilising a boron-mediated Evans aldol reaction to set the desired 1,2-*syn* stereochemistry at C2 and C3. Protecting group manipulation allowed the synthesis of the C1–C11 alcohol, oxidation of which completed the fragment.

4. Experimental section

4.1. General

Unless otherwise stated, the following conditions apply. All reactions were performed under argon in oven-dried or flame-dried glassware using dry solvents and standard syringe techniques. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from the sodium benzophenone ketyl radical ion. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), and acetonitrile (MeCN) were by Stocker, Hoberg and ourselves distilled from calcium hydride. Toluene, hexanes and methanol (MeOH) were distilled from sodium. Diisopropylethylamine (i-Pr_2NEt) and pyridine were distilled from sodium hydroxide. Acetone was distilled from potassium carbonate. Anhydrous dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were purchased from Aldrich Chemical Company and were used without further purification. Sodium hydride (NaH) was obtained as a 60% suspension in mineral oil, washed three times with dry hexanes and dried under vacuum immediately prior to use. All other reagents were of commercial quality and distilled prior to use if necessary.

Reaction progress was monitored using aluminium-backed thin layer chromatography (TLC) plates pre-coated with silica UV254 and visualised by either UV radiation (254 nm), ceric ammonium molybdate dip or potassium permanganate dip. Purification of products via flash chromatography was conducted using a column filled with silica gel 60 (220–240 mesh) with solvent systems as indicated. ^1H and ^{13}C NMR spectra were recorded on either a Varian Unity Inova 300 (300 MHz for ^1H and 75 MHz for ^{13}C), a Varian Unity Inova 500 (500 MHz for ^1H and 125 MHz for ^{13}C), or a Varian DirectDrive 600 (600 MHz for ^1H and 150 MHz for ^{13}C) spectrometer. All chemical shifts (δ) were referenced to solvent peaks

(^{1}H—residual $CHCl_3$, ^{13}C—$CDCl_3$). Infrared spectra were obtained on either a Biorad FTS-7 spectrometer or a Bruker Tensor 27 FTIR spectrometer. High-resolution mass spectrometry (HRMS) was recorded on a Mariner 5158 time of flight spectrometer. Diastereoselectivies were determined by averaging the ^{1}H NMR peak heights for the diastereotopic signals of the crude product.

Compounds **12** and **13** were prepared following the methodology of Richter et al.[31] and compound **10** was prepared as described by Zhan et al.[32]

4.2. (3*S*)-1-*tert*-Butyldimethylsilyloxy-2,2-dimethylhex-5-ene-3-yl propenoate (9)

To a solution of the allylic alcohol (4.52 g, 17.5 mmol) in CH_2Cl_2 (96 mL) at 0 °C was added *i*-Pr_2NEt (7.6 mL, 46.6 mmol) followed by acryloyl chloride (2.8 mL, 34.5 mmol). The reaction mixture was warmed to rt, stirred overnight and then quenched with satd aq NH_4Cl (50 mL). The phases were then separated, the aqueous phase was extracted with CH_2Cl_2 (3×50 mL) and the organic fractions combined. The organic fractions were then washed with satd aq brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Flash chromatography (20:1 hexanes/EtOAc) of the crude orange product provided diene **9** as a colourless oil (4.50 g, 82%); R_f (10:1 hexane/EtOAc) 0.64; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (dd, *J*=17.3, 1.5 Hz, 1H), 6.10 (dd, *J*=17.3, 10.5 Hz, 1H), 5.79 (dd, *J*=10.5, 1.5 Hz, 1H), 5.77–5.70 (m, 1H), 5.09 (dd, *J*=10.3, 2.9 Hz, 1H), 5.02 (d, *J*=18.6 Hz, 1H), 4.97 (d, *J*=10.3 Hz, 1H), 3.33 (d, *J*=5.6 Hz, 2H), 2.46–2.41 (m, 1H), 2.29–2.22 (m, 1H), 0.91 (s, 6H), 0.89 (s, 12H), 0.01 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 135.3, 130.2, 128.9, 116.8 76.7, 69.2, 39.5, 34.7, 25.8, 20.9, 20.6, 18.2, −5.6, −5.7. IR (KBr disc) 2957, 2930, 2897, 2858, 1728, 1642, 1473, 1404, 1266, 1191, 1100, 984, 850, 775, 669 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{33}O_3Si^+$ (M+H$^+$) 313.2199, found 313.2189.

4.3. (2*S*,6*R*)-2-(2-*tert*-Butyldimethylsilyloxy-1,1-dimethylethyl)-6-oxoethyl-2,3-dihydro-6*H*-pyran (6)

To a solution of diene **9** (4.50 g, 14.4 mmol) in CH_2Cl_2 (1440 mL) was added Grubbs' second generation catalyst (0.63 g, 0.74 mmol) at rt. The reaction mixture was stirred overnight at rt then the solvent was removed under reduced pressure. The resulting residue was then redissolved in a 10:1 hexanes/EtOAc solvent mixture and filtered through a short pad of silica gel. The solvent was removed under reduced pressure and flash chromatography (10:1 hexanes/EtOAc) provided lactone **14** as a pale yellow oil (3.68 g, 90%); R_f (10:1 hexane/EtOAc) 0.18; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (ddd, *J*=9.8, 6.6, 2.2 Hz, 1H), 6.01 (dd, *J*=9.8, 1.0 Hz), 4.36 (dd, *J*=12.9, 3.9 Hz), 3.54 (d, *J*=9.8 Hz, 1H), 3.37 (d, *J*=9.8 Hz, 1H), 2.44 (ddd, *J*=18.3, 12.9, 2.2 Hz, 1H), 2.27 (dddd, *J*=18.3, 6.6, 3.9, 1.0 Hz, 1H), 0.98 (s, 3H), 0.91 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 145.9, 121.2, 81.3, 68.4, 38.6, 25.8, 24.5, 20.5, 19.9, 18.2, −5.6. IR (neat) 2955, 2930, 2884, 2857, 1721, 1200–600. Freshly prepared lactone **14** (3.68 g, 12.9 mmol) was then dissolved in CH_2Cl_2 (182 mL) at −23 °C and DIBAL-H was added dropwise (20.0 mL of a 1.0 M solution in hexanes, 20.0 mmol). The resulting mixture was stirred for 45 min then quenched with methanol (10 mL) and warmed to rt. A saturated solution of Rochelle's salt (100 mL) was added to the reaction mixture. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organic fractions were combined and dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to provide the lactol **15** as well as the corresponding ring opened aldehyde (10:1 by ^{1}H NMR analysis) and was used directly without further purification; R_f (10:1 hexane/ethyl acetate) 0.22; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07–6.04 (m, 1H), 5.79 (d, *J*=10.0 Hz, 1H), 5.37–5.35 (m, 1H), 3.87 (dd, *J*=3.0, 11.5 Hz, 1H), 3.45 (d, *J*=9.5 Hz, 1H), 3.34 (d, *J*=9.5 Hz, 1H), 2.17–2.09 (m, 1H), 1.92–1.87 (m, 1H), 0.89 (s, 9H), 0.85 (s, 6H), 0.03 (s, 6H). The resulting lactol was redissolved in CH_2Cl_2 (104 mL) and Et_3N (4.5 mL, 32.3 mmol) was added followed by Ac_2O (2.0 mL, 31.2 mmol) and catalytic DMAP (0.02 g, 0.16 mmol). The mixture was stirred at rt overnight then washed successively with satd aq $KHSO_4$ (25 mL), $NaHCO_3$ (25 mL) and satd aq brine (25 mL). The organic fraction was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to provide the acetate **8**. The crude material was dried under vacuum (0.2 mmHg, 2 h) to remove excess Ac_2O; R_f (10:1 hexane/ethyl acetate) 0.19; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27–6.26 (m, 1H), 6.18–6.13 (m, 1H), 5.75–5.74 (m, 1H), 3.82 (dd, *J*=3.3, 11.6 Hz, 1H), 3.42 (d, *J*=9.5 Hz, 1H), 3.30 (d, *J*=9.5 Hz, 1H), 2.22–2.18 (m, 1H), 2.12 (s, 3H), 1.97–1.93 (m, 1H), 0.89 (s, 9H), 0.87 (s, 3H), 0.83 (s, 3H), 0.02 (s, 6H). The crude acetate was then redissolved in MeCN (130 mL) and trimethyl(vinyloxy)silane (2.9 mL, 19.4 mmol) was added followed by $BF_3\cdot OEt_2$ (0.16 mL, 1.3 mmol). The resulting solution was stirred at rt for 3.5 h and was then quenched with satd aq $NaHCO_3$ (100 mL). The phases where separated and the aqueous phase was extracted with CH_2Cl_2 (3×100 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Flash chromatography (20:1 hexanes/EtOAc) provided aldehyde **6** (2.39 g, 53% over four steps from diene **9**) as a colourless oil; R_f (10:1 hexane/EtOAc) 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 [dd (app. t), *J*=2.7, 2.2 Hz, 1H, H-15], 5.96–5.89 (m, 1H), 5.71–5.65 (m, 1H), 4.79–4.77 (m, 1H), 3.57 (dd, *J*=11.0, 3.2 Hz, 1H), 3.43 (d, *J*=9.5 Hz, 1H), 3.24 (d, *J*=9.5 Hz, 1H), 2.82 (ddd, *J*=16.4, 9.5, 2.7 Hz, 1H), 2.45 (ddd *J*=16.4, 4.4, 2.2 Hz, 1H), 2.18–2.05 (m, 1H), 1.91–1.83 (m, 1H), 0.89 (s, 9H), 0.83 (s, 3H), 0.82 (s, 3H), 0.02 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 127.9, 126.4, 70.3, 69.2, 68.9, 47.3, 38.5, 25.9, 24.8, 20.9, 19.5, 18.3, −5.5, −5.6. IR (neat) 2956, 2857, 1724, 1472, 1390, 1362, 1252, 1216, 1094, 906, 837, 730 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{33}O_3Si^+$ (M+H$^+$) 313.2199, found 313.2195.

4.4. (4*S*)-3-[1-Oxo-2-(4-methoxybenzyloxy)ethyl]-4-benzyl-2-oxazolidinone (7)

To a solution of acid **16** (3.87 g, 19.7 mmol) in MeCN (159 mL) was added Et_3N (3.50 mL, 25.1 mmol) at rt. HBTU (8.24 g, 21.7 mmol) was then added and the resulting solution was stirred for 30 min. In a separate flask, (*S*)-4-benzyloxazolidin-2-one (3.50 g, 19.8 mmol) was dissolved in THF (20 mL), cooled to −78 °C and *n*-BuLi (11.0 mL of a 2.0 M solution in cyclohexane, 22 mmol) was added dropwise. This mixture was stirred for 15 min and the activated acid mixture was cannulated into the lithium salt of the oxazolidinone. The reaction mixture was warmed to rt and stirred for 2 h before being quenched with satd aq brine (50 mL). The phases were separated and the aqueous was extracted with CH_2Cl_2 (3×50 mL). The organic fractions were combined and washed with 10% HCl (100 mL), satd aq $NaHCO_3$ (100 mL) and water (100 mL), then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resulting oil was purified by gradient flash chromatography (5:1 to 1:1 hexanes/EtOAc) to provide **7** as a white solid (3.34 g, 48%); R_f (2:1 hexane/EtOAc) 0.21; spectral data matched those reported in the literature.[33]

4.5. (4*S*)-4-Benzyl-3-{(2*S*,3*R*)-4-[(2*S*,6*R*)-2-(2-*tert*-butyldimethylsilyloxy-1,1-dimethylethyl)-2,3-dihydro-6*H*-pyran-6-yl]-3-methoxy-2-(4-methoxybenzyloxy)-1-oxobutyl}-oxazolidin-2-one (5)

To a solution of the acylated oxazolidinone **7** (3.34 g, 9.4 mmol) in toluene (50 mL) at −50 °C was added Et_3N (1.5 mL, 10.8 mmol), causing the solution to turn orange. This was followed by the addition of Bu_2BOTf (10.0 mL of a 1 M solution in CH_2Cl_2, 10.0 mmol),

upon which the orange colour disappeared. The solution was stirred at −50 °C for 1.5 h, then a solution of the aldehyde **6** (2.39 g, 7.65 mmol) in toluene (23 mL) was added by cannula and the reaction mixture was warmed to −30 °C over 30 min. The solution was stirred at −30 °C for a further 2 h and the reaction was quenched with pH 7.0 sodium phosphate buffer (0.5 mL), MeOH (5.0 mL) and THF (5.0 mL). The resulting mixture was stirred for 5 min then a 30% solution of H_2O_2 was added (5.0 mL), the mixture was warmed to 0 °C and stirred for a further 1 h. The solvent was removed under reduced pressure and the resulting residue was dissolved in satd aq $NaHCO_3$ (50 mL) and EtOAc (50 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3×50 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to provide a yellow oil. Flash chromatography (1% Et_3N in 2:1 hexane/EtOAc) provided alcohol **17** (2.66 g, 52%) as a colourless oil in a mixture of diastereoisomers, dr=10:1 (by ^1H NMR analysis); R_f (2:1 hexane/EtOAc) 0.31 and used without delay for conversion to **5**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.27 (m, 5H), 7.22–7.11 (m, 2H), 6.91–6.87 (m, 2H), 5.83–5.80 (m, 1H), 5.68 (br d, J=9.4 Hz, 1H), 5.18 (d, J=2.7 Hz, 1H), 4.67–4.64 (m, 1H), 4.64 (d, J=11, 1H), 4.50 (d, J=11 Hz, 1H), 4.49–4.45 (m, 1H), 4.19–4.16 (m, 1H), 4.16–4.11 (m, 2H), 3.78 (s, 3H), 3.43 (d, J=9.8 Hz, 1H), 3.41 (dd, J=10.5, 2.9 Hz, 1H), 3.30 (d, J=9.8 Hz, 1H), 3.25 (dd, J=13.4, 3.2 Hz, 1H), 2.67 (dd, J=13.4, 9.8 Hz, 1H), 2.17–2.07 (m, 1H), 1.90–1.83 (m, 2H), 1.68 (ddd, J=13.9, 10.3, 3.7 Hz, 1H), 0.91 (s, 3H), 0.87 (s, 9H), 0.82 (s, 3H), 0.01 (d, J=4.2, 6H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 159.6, 153.3, 135.1, 130.1, 129.8, 129.4, 129.3, 129.1, 129.0, 127.4, 124.9, 113.9, 79.2, 72.8, 71.7, 69.7, 69.2, 69.1, 66.8, 55.6, 55.2, 38.8, 37.7, 37.0, 25.9, 25.3, 21.3, 20.2, 18.2, −5.5, −5.6. IR (neat) 3750, 3649, 2900, 1772, 1701, 1513, 1392, 1361, 1246, 1210, 1071, 1031, 908, 833, 728, 647 cm^{-1}. To a solution of freshly prepared **17** (2.66 g, 3.98 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added 1,8-bis(dimethylamino)naphthalene (proton sponge) (1.71 g, 7.96 mmol) followed by $Me_3O^+BF_4^-$ (1.18 g, 8.0 mmol). The resulting suspension was stirred for 3 h at 0 °C, quenched with satd aq $NaHCO_3$ (50 mL) and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL), the organic fractions were combined, washed with satd aq brine (75 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Gradient flash chromatography (5:1 to 2:1 hexanes/EtOAc) provided **5** (2.37 g, 87% from **17**) as a colourless oil; R_f (10:1 hexane/EtOAc) 0.52; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 5H), 7.20 (d, J=7.0 Hz, 2H), 6.86 (dd, J=6.8, 2.1 Hz, 2H), 5.84–5.79 (m, 1H), 5.64 (d, J=10.3 Hz, 1H), 5.50 (d, J=4.7 Hz, 1H), 4.61–4.54 (m, 1H), 4.57 (s, 2H), 4.36 (br d, J=10.3 Hz, 1H), 4.16–4.11 (m, 2H), 3.86–3.80 (m, 1H), 3.76 (s, 3H), 3.50 (d, J=9.4 Hz, 1H), 3.45 (s, 3H), 3.41 (dd, J=10.5, 2.7 Hz, 1H), 3.30 (d, J=9.4 Hz, 1H), 3.18 (dd, J=13.2, 3.2 Hz, 1H), 2.58 (dd, J=13.2, 10.0 Hz, 1H), 2.17–2.07 (m, 1H), 2.02–1.92 (m, 1H), 1.86 (dd, J=17.0, 2.7 Hz, 1H), 1.52–1.42 (m, 1H), 0.95 (s, 3H), 0.88 (s, 9H), 0.84 (s, 3H), 0.02 (s, 3H), 0.015 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 159.4, 153.1, 135.3, 130.1, 129.6, 129.44, 129.37, 129.9, 127.3, 124.8, 113.7, 78.2, 76.3, 72.9, 71.7, 69.4, 66.5, 59.9, 55.8, 55.2, 38.8, 37.8, 33.6, 30.9, 25.9, 25.3, 21.2, 20.2, 18.3, −5.5, −5.6. IR (neat) 2837, 1780, 1705, 1626, 1596, 1574, 1510, 1462, 1421, 1379, 1303, 1246, 1194, 1162, 1105, 1031, 977, 834, 776, 732, 703, 596. HRMS (ESI) calcd for $C_{38}H_{55}O_8NSiNa^+$ (M+Na^+) 704.3595, found 704.3547.

4.6. Methyl (2*S*,3*R*)-4-[(2*S*,6*R*)-2-(2-*tert*-butyldimethylsilyloxy-1,1-dimethylethyl)-2,3-dihydro-6H-pyran-6-yl]-3-methoxy-2-(4-methoxybenzyloxy) butyrate (18)

To a solution of the oxazalidinone **5** (1.09 g, 1.6 mmol) in CH_2Cl_2 (17 mL) was added dimethyl carbonate (0.74 g, 8.2 mmol) followed by sodium methoxide (0.44 g, 8.15 mmol). The resulting reaction mixture was stirred at rt for 1.5 h then quenched with H_2O (20 mL). The phases were separated and the aqueous fraction was extracted with CH_2Cl_2 (3×20 mL). The organic fractions were combined and acidified with 10% aq HCl (20 mL), then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Gradient flash chromatography (5:1 hexanes/EtOAc to neat EtOAc) provided methyl ester **18** (0.59 g, 69%) as a colourless oil; R_f (2:1 hexane/EtOAc) 0.53; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.23 (m, 2H), 6.87–6.83 (m, 2H), 5.85–5.80 (m, 1H), 5.65–5.62 (m, 1H), 4.69 (d, J=11.6 Hz, 1H), 4.39–4.34 (m, 1H), 4.36 (d, J=11.6 Hz, 1H), 3.91–3.89 (m, 1H), 3.86–3.80 (m, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.44 (s, 3H), 3.45–3.42 (m, 1H), 3.39–3.36 (m, 1H), 3.30–3.29 (m, 1H), 2.17–2.05 (m, 1H), 1.86–1.80 (m, 1H), 1.69–1.60 (m, 2H), 0.90 (s, 3H), 0.86 (s, 9H), 0.81 (s, 3H), 0.00 (s, 6H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 159.3, 130.0, 129.7, 129.4, 129.3, 124.8, 124.9, 113.7, 79.5, 78.6, 78.1, 72.4, 71.1, 69.6, 69.3, 59.7, 55.2, 51.8, 38.8, 34.7, 25.9, 25.2, 20.7, 20.5, 18.2, 14.2, −5.6. IR (neat) 2954, 2930, 2856, 1751, 1613, 1514, 1463, 1249, 1091, 835, 730 cm^{-1}. HRMS (ESI) calcd for $C_{29}H_{52}NO_7Si^+$ (M+NH_4^+) 554.3513, found 554.3506.

4.7. Methyl (2*S*,3*R*)-4-[(2*S*,6*R*)-(2-hydroxy-1,1-dimethylethyl)-2,3-dihydro-6*H*-pyran-6-yl]-3-methoxy-2-(4-methoxybenzyloxy) butyrate (19)

To a solution of silyl ether **18** (560 mg, 1.0 mmol) in MeOH (10 mL) at rt was added HCl (1 mL of a 1 mmol solution in CH_2Cl_2, 1 mmol). The resulting solution was stirred for 10 min, then quenched with satd aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Flash chromatography was used to purify the residue. Flash chromatography (2:1 hexanes/EtOAc) provided **19** (270 mg, 62%) as a colourless oil; R_f (2:1 hexane/EtOAc) 0.16; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.26 (m, 2H), 6.89–6.86 (m, 2H), 5.84–5.81 (m, 1H), 5.61 (dtd, J=10.3, 2.9, 1.2 Hz, 1H), 4.70 (d, J=11.7 Hz, 1H), 4.40 (d, J=11.7 Hz, 1H), 4.41–4.39 (m, 1H), 4.03 (d, J=4.6 Hz, 1H), 3.80 (s, 3H), 3.80–3.73 (m, 1H), 3.76 (s, 3H), 3.68 (d, J=10.9 Hz, 1H), 3.51 (dd, J=10.9, 2.9 Hz, 1H), 3.44 (s, 3H), 3.26 (d, J=11.0 Hz, 1H), 2.78 (br s, 1H), 2.17–2.11 (m, 1H), 1.87–1.82 (m, 2H), 1.45 (ddd, J=14.9, 11.0, 2.4 Hz, 1H), 0.96 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 159.4, 129.9, 129.2, 128.9, 124.5, 113.7, 78.1, 77.9, 72.8, 72.3, 70.0, 69.9, 59.3, 55.2, 51.9, 37.8, 34.4, 25.1, 22.5, 19.4. IR (neat) 3488, 3033, 2953, 2836, 1740, 1612, 1514, 1247, 1092, 1030, 909, 728 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{35}O_7^+$ (M+H^+) 423.2383, found 423.2375.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.09.131.

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