Synthesis of the C1 to C13 tetrahydropyranyl-resorcylate core of paecilomycin B

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Abstract

A D-Glucose derived tetrahydropyran was converted into the C1 to C13 tetrahydropyranyl-resorcylate core of paecilomycin B in seven steps. Key transformations included the synthesis of a diketo-ester dioxinone, which upon thermolysis underwent a retro-hetero-Diels-Alder fragmentation to generate an acyl ketene. This was subsequently trapped by a secondary alcohol affording a triketo-ester, which was efficiently aromatized to produce the advanced resorcylate intermediate.

Keywords: Biomimetic synthesis; Resorcylic acid lactone; Retro-Diels-Alder; Ketene; Macrocycle

1 Introduction

Paecilomycin B (**2**) was isolated in 2010 by Wei and coworkers, along with a further five, novel resorcylic acid lactones (A-F; **1**–**6**) from a mycelial solid culture of *Paecilomyces* sp. SC0924 (Fig. 1).[1] This class of natural products contains the 6-alkyl-2,4-dihydroxybenzoic acid or β-resorcylate unit, which forms part of a macrolactone ring. These natural products were assessed for their antiplasmodial activity and paecilomycin B (**2**) was shown to have activity (IC$_{50}$ 3.8 μM) against *Plasmodium falciparum* lines 3D7, a chloroquine-susceptible line. Further to this, results from a cytotoxicity assay showed paecilomycin B to be relatively non-cytotoxic (IC$_{50}$ > 50 μM). There has been one reported total synthesis of paecilomycin B (**2**) (longest sequence 24 steps) by Ohba and Nakata in 2015.[2] In this paper, 2,4,6-tri*iso*propylphenyllithium mediated functionalization of a key aryl intermediate, based on the earlier work of Brimble,[3] and Fürstner[4] macrocyclization by ring closing metathesis (RCM) were used as key transformations.

(1) paecilomycin A **(2)** paecilomycin B **(3)** R^1 = H; R^2 = OH paecilomycin C **(4)** R^1 = OH; R^2 = H paecilomycin D **(5)** R^1 = H; R^2 = OH paecilomycin E **(6)** R^1 = OH; R^2 = H paecilomycin F
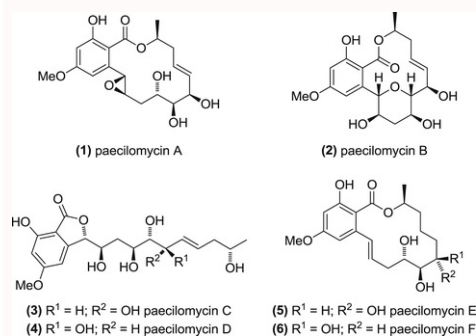
Fig. 1 Paecilomycins A-F.

alt-text: Fig. 1

The Barrett group has previously developed a biomimetic synthesis of such resorcylate natural products.[5] This work, which was inspired by the seminal work of Hyatt,[6] Harris[7] and Boeckman,[8] utilizes the dioxinone moiety to

generate triketo-ketene intermediates. These were trapped by reaction with an appropriate alcohol; sequential aromatization of the resultant β,δ,ζ-triketo-esters of lactones gave the corresponding resorcylates (**10**) (Scheme 1). This methodology has been applied in the total synthesis of natural products including the estrogen agonist (S)-(−)-zearalenone, the antimalarial aigialomycin D and antibiotics 15G256 π, ι, and β.[9-11] However, in order to expand the methodology further, the group was interested in the synthesis of paecilomycin B (**2**) as a result of the presence of its unique transannular tetrahydropyran functionality.
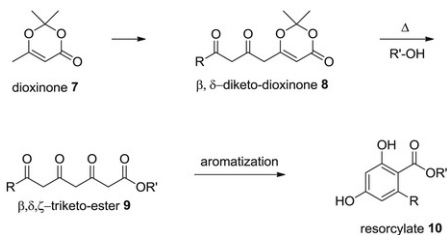

**Scheme 1** Barrett group synthesis of resorcylates.

alt-text: Scheme 1

2 Results and discussion

Wei reported that upon treatment of paecilomycin A (**1**) with 20% H_2SO_4, paecilomycin B (**2**) was formed as the major product.[1] We therefore sought to exploit this reasonable possible biomimetic transformation, thereby accessing both natural products. The retrosynthetic analysis of paecilomycin B (**2**), where it was proposed that a ring closing metathesis could be used for macrocyclization, is shown in Scheme 2. Resorcylate **11** would in turn be prepared from dioxinone **15** *via* diketo-dioxinone **13** (see Scheme 3).
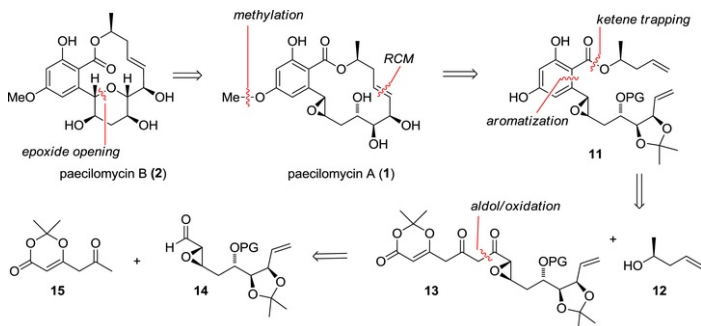
Scheme 2 Retrosynthetic analysis of paecilomycin B (**2**).
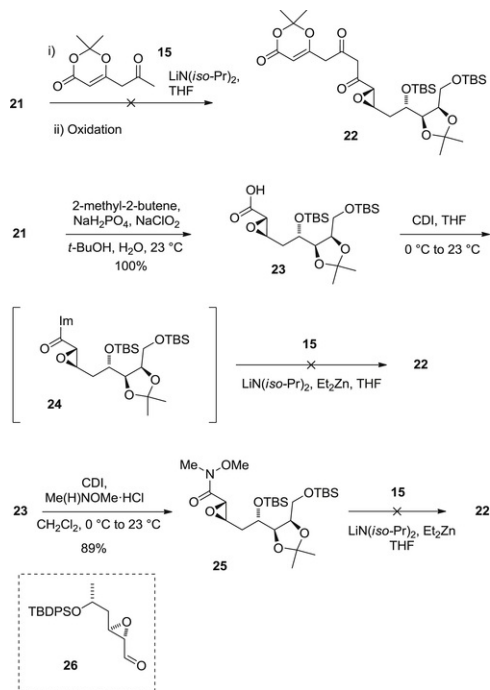
alt-text: Scheme 2
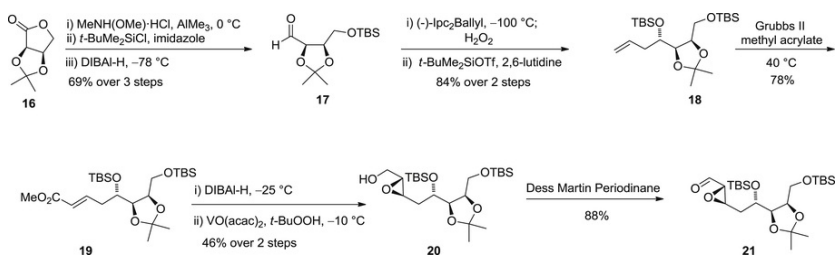
Scheme 3 Synthesis of aldehyde **21**.

alt-text: Scheme 3

Commercially available D-erythrolactone **16** was converted into the Weinreb amide, which was protected and reduced with DIBAl-H to give aldehyde **17** in 69% yield over three steps (Scheme 3). Subsequent Brown

allylboration with a hydrogen peroxide work up and silyl protection gave alkene **18**, which was subject to a cross metathesis with methyl acrylate thereby generating enoate **19**. Further DIBAl-H reduction gave the allylic alcohol, which was subject to diastereoselective epoxidation using *t*-butyl hydroperoxide catalyzed by VO(acac)$_2$ to provide epoxy-alcohol **20** (46%, two steps) as a single diastereoisomer. The alternative Sharpless epoxidation reaction was found to be low yielding, however gave the same epoxide as the major diastereoisomer thereby tentatively establishing its stereochemistry. This was confirmed by X-ray crystal structure determination (see Supporting Information). Subsequent Dess Martin periodinane oxidation of alcohol **20** gave aldehyde **21**.

Unfortunately, it was found at this stage that addition of the keto-dioxinone functionality by aldol[12] or *C*-acylation[13,14] reactions of the dianion derived from dioxinone **15**[9] with the aldehyde **21**, acyl imidazole **24** or Weinreb amide **25**, all proved to be untenable (Scheme 4) and gave only intractable mixtures of products. Furthermore, when these conditions were applied to a model aldehyde **26**,[12] no useful product was obtained thereby confirming that all our dioxinone homologation reactions[5] were incompatible with the α,β-epoxy-aldehyde functionality. As a result, an alternative route was examined.

Scheme 4 Attempts towards the synthesis of diketo-dioxinone **22**.

Considering these problems, a second retrosynthetic analysis of paecilomycin B (**2**) was proposed. This incorporated the tetrahydropyranyl ring prior to generation of the diketo-dioxinone moiety (Scheme 5). As with the previous approach, a ring closing metathesis was envisaged as the key macrocyclization process. Given the fact that the functionality and stereochemistry of the tetrahydropyranyl ring substituents in intermediate **27** closely resembled those of D-glucose, we sought to use this sugar as an inexpensive starting material.
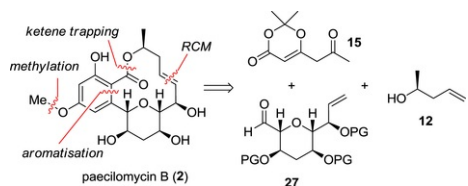

Scheme 5 Retrosynthetic analysis of paecilomycin B (**2**).

C-3 Deoxygenation of 1,6-anhydro-β, D-glucose **28** was carried out by selective double *p*-chlorobenzylation (68%), a process known for related benzylation reactions.[15] Subsequent Barton McCombie[16] deoxygenation of the imidazolylthiocarbonyl derivative of alcohol **29** provided the deoxy-glucose derivative **30** (84%) (Scheme 6). Subsequent boron trifluoride catalyzed reaction with acetic anhydride gave diacetate **31** (97%) with an anomeric selectivity of 3.3:1 (α: β). For a mechanistically similar reaction see the work of Zhao.[17] This ester was converted to nitriles **32** and **33** by reaction with trimethylsilyl cyanide catalyzed by trimethylsilyl triflate, and these products were separated by chromatography. Unfortunately, all attempts to convert the undesired nitrile **32** into its anomer **33** under either basic reaction conditions or resubmitting to further reaction with trimethylsilyl cyanide and trimethylsilyl triflate failed. Methanolysis of nitrile **33** in the presence of potassium carbonate gave the primary alcohol **34** (86%), which was protected as its *p*-bromo-benzyl ether **35** (93%). Our use of both the *p*-chlorobenzyl and *p*-bromobenzyl protecting groups was based on the expected preferential deprotection of the later by palladium catalyzed amination, a method introduced by Buchwald and Seeberger.[18] Finally, nitrile **35** was converted into the carboxylic acid **36** (97%) required for subsequent *C*-acylation reactions.
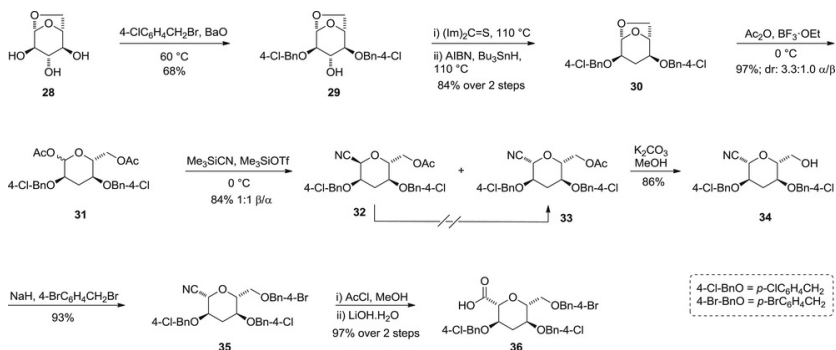
Scheme 6 Synthesis of tetrahydropyran **36**.

Attempts to condense the aldehyde, acyl chloride, imidazolide or Weinreb amide derived from carboxylic acid **36** with the dianion generated from keto-dioxinone **15**[5] failed to produce characterizable products. However, the methodology introduced during our total syntheses of 15G256 π, ι, and β[11] was successful in this key homologation. Thus sequential reaction of carboxylic acid **36** with thionyl chloride to provide acyl chloride **37**, keto-ester **38**[11] in the presence of *iso*-propylmagnesium bromide, morpholine in the presence of Pd(PPh₃)₄, and alcohol **12** at 110 °C followed by cesium acetate and methyl iodide, without the isolation of any intermediates (Scheme 7), gave the methylated resorcylate **41** in 32% yield over the four steps. In this process it was possible to directly remove the allyl ester functionality with ester **39** without a work-up, solely by concentration of the THF and dissolution of the residue in dichloromethane (the solvent required for the subsequent step). This was found to be necessary since, upon addition of water or MeOH to the reaction mixture following the acylation (**37** to **39**), either acid **36** or methyl ester **46** were regenerated as the major product respectively and not the required resorcylate precursor **40**. Presumably these were formed *via* retro-Claisen condensation reactions. At this stage, selective ether deprotection was carried out by Buchwald-Hartwig amination of the *p*-bromobenzyl ether using palladium, (2-biphenyl)di-*tert*-butylphosphine (**42**) and *N*-phenyl *N*-methyl aniline,[18] to give the aniline derivative **43**. Subsequent removal of the anilino-benzyl group with stannic chloride gave the key intermediate, the C1 to C13 core of paecilomycin B (**45**) (Scheme 7).
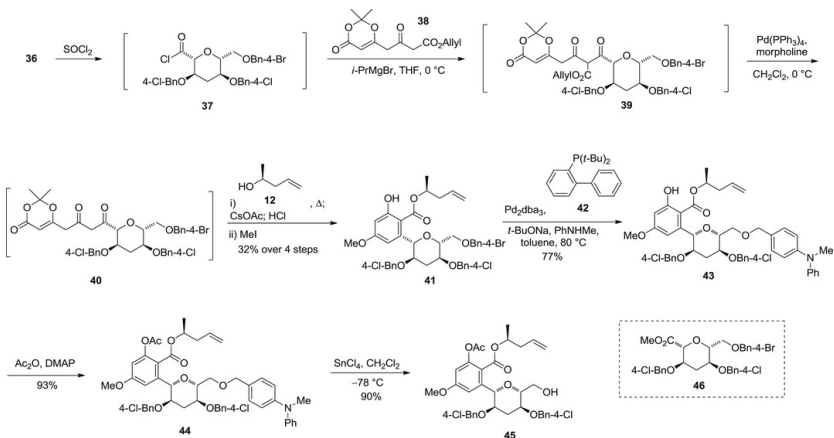
Scheme 7 Synthesis of methylated resorcylate **45**.

alt-text: Scheme 7

3 Conclusions

Two distinct routes were investigated towards the synthesis of paecilomycin B (**2**). The first was aimed at exploiting a proposed biosynthetic step for paecilomycin B (**2**) by generating the tetrahydropyranyl moiety *via* ring opening of the epoxide in paecilomycin A (**1**). For this synthesis, it was ultimately found that aldol addition of the key dioxinone fragment to an α,β-epoxy-aldehyde functionality was untenable. Revision of the route to include the tetrahydropyranyl portion prior to addition of dioxinone allowed for the synthesis of the C1 to C13 core of paecilomycin B (**2**) in 15 steps from 1,6-anhydro-β, D-glucose (**28**). The key transformations in this synthesis were to functionalize the tetrahydropyranyl acid **36** through formation of a diketo-dioxinone intermediate **40** and subsequent ketene generation, trapping with an alcohol, aromatization and selective mono-methylation, which gave key resorcylate **41** in 32% yield over four steps.

4 Experimental section

4.1 General remarks

All reactions were carried out in oven-dried glassware under dry N_2 or Ar, unless otherwise stated. All solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. The following reaction solvents were distilled under nitrogen: Et2O and THF from Ph2CO/Na; PhMe from Na; CH2Cl2 and Et3N from CaH2. MeOH was dried by reflux over Mg/I2, followed by distillation from CaH2 under N2. H_2O refers to redistilled H_2O. Flash column chromatography was performed using silica gel 60, and compounds were visualized by UV light (254 nm and 350 nm) and by staining with aqueous potassium permanganate or vanillin followed by gentle heating with a heat gun. IR spectra were recorded neat.

4.1.1 (4R,5R)-5-{[(tert-Butyldimethylsilyl)oxy]methyl}-N-methoxy-N,2,2-trimethyl-1,3-dioxolane-4-carboxamide

AlMe3 (2.0 M in hexanes; 35 mL, 70.2 mmol) was added slowly with stirring to a mixture of *N,O*-dimethylhydroxylammonium chloride (6.8 g, 70.2 mmol) in CH2Cl2 (130 mL) at 0 °C and then allowed to warm 23 °C. After 15 min, the solution was cooled to 0 °C and (−)-2,3-*O*-isopropylidene-D-erythronolactone (5.6 g, 35.1 mmol) in CH2Cl2 (130 mL) was added. After 25 min, reaction was quenched with aqueous HCl (0.5 M, 170 mL) and the mixture was allowed to warm to 23 °C. The phases were separated and the aqueous phase was extracted with CH2Cl2 (3 × 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude, unprotected alcohol was dissolved in CH2Cl2 (34 mL) and imidazole (3.7 g, 54.9 mmol) and Me3SiCl (5.5 g, 36.6 mmol) were sequentially added with stirring at 23 °C. After 16 h, the mixture was washed with saturated aqueous NH4Cl (150 mL). The aqueous layer was extracted with CH2Cl2 (3 × 200 mL) and the organic layers were dried (Na_2SO_4), concentrated *in vacuo* and chromatographed (5: 1 hexanes: EtOAc) to give (4*R*,5*R*)-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (7.2 g, 21.6 mmol, 71%) as a white solid. **mp**: 54–56 °C (CHCl3). **¹H NMR** (400 MHz, CDCl3) δ: 5.00 (1H, d, *J* = 6.6 Hz), 4.44 (1H, app. q, *J* = 6.1 Hz), 3.73 (3H, s), 3.72 (1H, dd, *J* = 10.4, 6.1 Hz), 3.61 (1H, dd, *J* = 10.4, 5.8 Hz), 3.19 (3H, s), 1.60 (3H, s), 1.42 (3H, s), 0.90 (9H, s), 0.07 (3H, s), 0.06 (3H, s). **¹³C NMR** (126 MHz, CDCl3) δ: 169.3, 109.9, 78.2, 73.9, 62.6, 61.3, 32.4, 27.5, 26.0 (3C), 25.6, 18.5, −5.3 (2C). **HRMS**: (ES⁺) Calculated for $C_{15}H_{31}NO_5SiNa$ [M + Na]⁺: 356.1869; Found: 356.1878. **IR ν_{max}/cm⁻¹ (neat)**: 1697, 1463, 1380, 1255, 1213, 1091, 992. **[α]³⁰_D**: +40.7 (*c* = 1.2, CHCl3).

4.1.2 (4R,5R)-5-{[(tert-Butyldimethylsilyl)oxy]-methyl}-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 17

DIBAl-H (1.0 M in PhMe, 60 mL; 59.7 mmol) was added with stirring over 20 min to (4R,5R)-5-{[($tert$-butyldimethylsilyl)oxy] methyl}-N-methoxy-N,2,2-trimethyl-1,3-dioxolane-4-carboxamide (10 g, 29.8 mmol) in THF (270 mL) at −78 °C. After 30 min saturated aqueous Rochelle's salt (300 mL) was added and the mixture warmed to 23 °C. The two phases were separated and the aqueous phase was extracted with Et$_2$O (2 × 250 mL). The combined organic layers were washed with brine (250 mL), dried (MgSO$_4$) and concentrated *in vacuo*. Chromatography (9: 1 hexanes: EtOAc) gave aldehyde **17** (7.8 g, 28.9 mmol, 97%) as a colorless oil. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 9.68 (1H, d, J = 2.0 Hz), 4.49–4.45 (1H, m), 4.43 (1H, dd, J = 7.8, 2.0 Hz), 3.78 (1H, dd, J = 11.4, 8.3 Hz), 3.69 (1H, dd, J = 11.4, 2.8 Hz), 1.57 (3H, s), 1.38 (3H, s), 0.88 (9H, s), 0.05 (3H, s), 0.04 (3H, s). **^{13}C NMR** (125 MHz, CDCl$_3$) δ: 200.2, 110.6, 80.8, 79.8, 60.5, 26.8, 25.7 (3C), 25.0, 18.2, −5.5, −5.7. **HRMS**: (CI$^+$) Calculated for C$_{13}$H$_{30}$NO$_4$Si [M + NH$_4$]$^+$: 292.1944; Found: 292.1953. **IR ν_{max}/cm^{-1} (neat)**: 1733, 1473, 1463, 1381, 1252, 1214, 1144, 1086, 1004. **[α]$^{28}_D$**: +39.8 (c = 1.2, CHCl$_3$).

4.1.3 tert-Butyl{[(4R,5R)-5-{(S)-1-[(tert-butyldimethylsilyl)oxy]but-3-en-1-yl}-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dimethylsilane 18

Aldehyde **17** (7.9 g, 28.7 mmol) in Et$_2$O (72 mL) was added with stirring to (−)-Ipc$_2$B(allyl)borane (1.0 M in pentane, 35 mL, 34.4 mmol) in Et$_2$O (200 mL) at −100 °C. After 3 h, aqueous NaOH (2.0 M, 19 mL) and H$_2$O$_2$ (50% v/v in H$_2$O, 8.7 mL) were added and the solution allowed to warm to 23 °C overnight. The mixture was diluted with water (200 mL), the phases were separated and the aqueous phase extracted with Et$_2$O (2 × 200 mL). The organic layers were washed with brine (200 mL), dried (MgSO$_4$) and concentrated *in vacuo*. Chromatography (95: 5 hexanes: Et$_2$O) gave the impure alcohol. The crude material was dissolved in CH$_2$Cl$_2$ (100 mL) at 0 °C and 2,6-lutidine (7.6 mL, 65.4 mmol) and t-BuMe$_3$SiOTf (7.5 mL, 32.7 mmol) were sequentially added with stirring. After 1 h at 0 °C and 23 °C for 30 min, the solution was diluted with CH$_2$Cl$_2$ (150 mL) and washed with saturated aqueous NaHCO$_3$ (200 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 200 mL) and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Chromatography (98: 2 hexanes: EtOAc) gave alkene **18** (7.9 g, 24.1 mmol, 84% over 2 steps) as a colorless oil. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 5.85 (1H, tdd, J = 17.3, 10.2, 7.1 Hz), 5.13–5.06 (2H, m), 4.16 (1H, ddd, J = 7.4, 5.9, 3.8 Hz), 4.06 (1H, app. t, J = 4.9 Hz), 4.05–4.02 (1H, m), 3.87 (1H, dd, J = 10.9, 3.8 Hz), 3.68 (1H, dd, J = 11.0, 7.4 Hz), 2.44–2.29 (2H, m), 1.45 (3H, s), 1.32 (3H, s), 0.91 (9H, s), 0.89 (9H, s), 0.09 (6H, s), 0.07 (3H, s), 0.07 (3H, s). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 134.3, 117.5, 107.7, 78.7, 78.5, 70.3, 63.4, 38.8, 27.8, 26.0 (3C), 25.9 (3C) 25.5, 18.4, 18.1, −3.9, −4.5, −5.1, −5.2. **HRMS**: (ES$^+$) Calculated for C$_{22}$H$_{47}$O$_4$Si$_2$ [M+H]$^+$: 431.3013; Found: 431.3015. **IR ν_{max}/cm^{-1} (neat)**: 1473, 1255, 1095, 836. **[α]$^{25}_D$**: +24.3 (c = 1.1, CHCl$_3$).

4.1.4 (S,E)-Methyl 5-[(tert-butyldimethylsilyl)oxy]-5-[(4R,5R)-5-{[(tert-butyldimethylsilyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]pent-2-enoate 19

Alkene **18** (6.0 g, 13.9 mmol), methyl acrylate (3.7 mL, 41.6 mmol) and [1,3-bis(2,4,6-trimethylphenyl)-2-imidazo-lidinylidene]dichloro(phenylmethylene) (tricyclohexylphosphine)ruthenium (590 mg, 0.695 mmol) were added to CH$_2$Cl$_2$ (250 mL) and heated to 40 °C for 3 h. The solution was concentrated *in vacuo* and chromatographed (8: 1 hexanes: Et$_2$O) to yield enoate **19** (5.3 g, 10.8 mmol, 78%) as a yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 7.01 (1H, td, J = 15.4, 7.5 Hz), 5.89 (1H, td, J = 15.6, 1.3 Hz), 4.17–4.10 (2H, m), 4.04–4.01 (1H, m), 3.83 (1H, dd, J = 10.9, 4.3 Hz), 3.72 (3H, s), 3.68 (1H, dd, J = 10.9, 6.7 Hz), 2.61–2.53 (1H, m), 2.49–2.42 (1H, m), 1.43 (3H, s), 1.31 (3H, s), 0.90 (9H, s), 0.88 (9H, s), 0.08 (6H, s), 0.07 (3H, s), 0.06 (3H, s). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 166.7, 145.4, 123.4, 108.0, 79.0, 78.1, 69.8, 62.9, 51.4, 37.0, 27.6, 26.0 (3C), 25.9 (3C), 25.3, 18.4, 18.1, −3.9, −4.5, −5.2, −5.3. **HRMS**: (ES$^+$) Calculated for C$_{24}$H$_{49}$O$_6$Si$_2$ [M + H]$^+$: 489.3068; Found: 489.3072. **IR ν_{max}/cm^{-1} (neat)**: 1729, 1256, 1171, 1094, 837. **[α]$^{25}_D$**: +18.1 (c = 1.6, CHCl$_3$).

4.1.5 (S,E)-5-[(tert-Butyldimethylsilyl)oxy]-5-[(4R,5R)-5-{[(tert-butyldimethylsilyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]pent-2-en-1-ol

DIBAl-H (1.0 M in PhMe; 1.0 mL, 0.990 mmol) was added with stirring to enoate **19** (220 mg, 0.450 mmol) in CH$_2$Cl$_2$ (3.7 mL) at −20 °C. After 1 h, the solution was allowed to warm to 23 °C and, after 1 h, was quenched with saturated aqueous NH$_4$Cl (0.4 mL) and stirred for a further 15 min. Et$_2$O (7.0 mL) and MgSO$_4$ (150 mg) were added and the mixture was filtered through Celite®, washing the solids with additional Et$_2$O. The combined filtrates were concentrated *in vacuo* and chromatographed (2: 1 pentane: Et$_2$O) to give (S,E)-5-[($tert$-butyldimethylsilyl)oxy]-5-[(4R,5R)-5-{[($tert$-butyldimethylsilyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]pent-2-en-1-ol (200 mg, 0.428 mmol, 95%) as a colorless oil. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 5.79–5.68 (2H, m), 4.17–4.02 (5H, m), 3.88 (1H, dd, J = 11.0, 3.7 Hz), 3.67 (1H, dd, J = 11.1, 7.3 Hz), 2.43–2.30 (2H, m), 1.45 (3H, s), 1.33 (3H, s), 0.90 (9H, s), 0.89 (9H, s), 0.08 (6H, s), 0.07 (3H, s), 0.07 (3H, s). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 132.0, 128.2, 107.7, 78.7, 78.5, 70.3, 63.5, 63.4, 37.0, 27.7, 26.0 (3C), 25.8 (3C), 25.4, 18.4, 18.0, −4.0, −4.5, −5.2, −5.3. **HRMS**: (ES$^+$) Calculated for C$_{23}$H$_{49}$O$_5$Si$_2$ [M + H]$^+$: 461.3119; Found: 461.3109. **IR ν_{max}/cm^{-1} (neat)**: 3392 br, 1473, 1463, 1380, 1253, 1094, 1005. **[α]$^{26}_D$**: +32.0 (c = 4.5, CHCl$_3$).

4.1.6 [(2R,3R)-3-{(S)-2-[(tert-Butyldimethylsilyl)oxy]-2-[(4R,5R)-5-{[(tert-butyldimethyl silyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}oxiran-2-yl]methanol 20

t-Butyl hydroperoxide (5.5 M in decane; 1.3 mL, 7.04 mmol) was added with stirring to (S,E)-5-[($tert$-butyldimethylsilyl)oxy]-5-[(4R,5R)-5-{[($tert$-butyldimethylsilyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]pent-2-en-1-ol (1.0 g, 2.20 mmol) and VO(acac)$_2$ (41 mg, 0.154 mmol) in CH$_2$Cl$_2$ (22 mL) at −10 °C. After 16 h, reaction was quenched with saturated aqueous Na$_2$SO$_3$ (30 mL) and the separated aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic layers were dried (MgSO$_4$) concentrated *in vacuo* and chromatographed (2: 1 pentane: Et$_2$O) to give epoxide **20** (500 mg, 10.5 mmol, 48%) as a yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 4.23–4.16 (2H, m), 4.12 (1H, dd, J = 6.3, 4.9 Hz), 3.90 (1H, m), 3.81 (1H, dd, J = 10.9,

4.6 Hz), 3.68 (1H, dd, J = 10.9, 6.6 Hz), 3.66–3.60 (1H, m), 3.13 (1H, td, J = 6.0, 2.2 Hz), 2.98 (1H, dt, J = 4.5, 2.4 Hz), 1.93–1.87 (1H, m), 1.80–1.73 (1H, m), 1.43 (3H, s), 1.34 (3H, s), 0.9 (18H, s), 0.12 (3H, s), 0.11 (3H, s), 0.07 (6H, s). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 108.0, 79.5, 78.71, 68.6, 62.8, 61.5, 59.0, 52.8, 36.4, 27.4, 26.0 (3C), 25.9 (3C), 25.3, 18.4, 18.1, −4.2, −4.5, −5.3, −5.2. **HRMS**: (ES$^+$) Calculated for C$_{23}$H$_{49}$O$_6$Si$_2$ [M + H]$^+$: 477.3068; Found: 477.3069. **IR ν_{max}/cm^{-1} (neat)**: 3460 br, 1473, 1380, 1254, 1215, 1097. **[α]$^{25}_D$**: +5.38 (c = 1.5, CH$_2$Cl$_2$).

4.1.7 (2S,3R)-3-{(S)-2-[(tert-Butyldimethylsilyl)oxy]-2-[(4R,5R)-5-{[(tert-butyldimethylsilyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}oxirane-2-carbaldehyde 21

Dess-Martin periodinane (1.2 g, 2.86 mmol) was added with stirring to alcohol **20** (1.1 g, 2.38 mmol) in CH$_2$Cl$_2$ (44 mL) at 23 °C. After 1 h, the mixture was filtered through Celite® and the resulting filtrate was washed with saturated aqueous NaHCO$_3$ (50 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 50 mL) and the combined organic layers were dried (Na$_2$SO$_4$), concentrated *in vacuo* and chromatographed (7: 1 pentane: Et$_2$O) to give aldehyde **21** as a white solid. Recrystallization from CH$_2$Cl$_2$ gave aldehyde **21** (1.0 g, 2.35 mmol, 88%) as white crystals. **mp**: 84–86 °C (CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 9.02 (1H, d, J = 6.4 Hz), 4.32–4.23 (1H, m), 4.23–4.08 (2H, m), 3.78 (1H, dd, J = 11.0, 4.9 Hz), 3.69 (1H, dd, J = 10.8, 5.8 Hz), 3.43 (1H, td, J = 5.8, 1.9 Hz), 3.22 (1H, dd, J = 6.5, 2.0 Hz), 2.02 (1H, dt, J = 14.5, 5.8 Hz), 1.92–1.83 (1H, m), 1.44 (3H, s), 1.36 (3H, s), 0.92 (9H, s), 0.91 (9H, s), 0.14 (3H, s), 0.15 (3H, s), 0.09 (6H, s). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 198.2, 108.2, 79.5, 77.7, 68.3, 62.4, 59.6, 53.7, 35.9, 27.3, 25.9 (3C), 25.8 (3C), 25.1, 18.3, 18.0, −4.1, −4.5, −5.3 (2C). **HRMS**: (ES$^+$) Calculated for C$_{23}$H$_{46}$O$_6$Si$_2$ [M + H]$^+$: 475.2911; Found: 475.2915. **IR ν_{max}/cm^{-1} (neat)**: 1732, 1473, 1381, 1257, 1215, 1095, 1006, 836. **[α]$^{25}_D$**: +63.4 (c = 1.3, CH$_2$Cl$_2$).

4.1.8 (2S,3R)-3-{(S)-2-[(tert-Butyldimethylsilyl)oxy]-2-[(4R,5R)-5-{[(tert-butyldimethylsilyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}oxirane-2-carboxylic acid 23

NaClO$_2$ (580 mg, 6.36 mmol) and NaH$_2$PO$_4$·H$_2$O (880 mg, 6.36 mmol) in water (12 mL) were added with stirring to aldehyde **21** (500 mg, 1.06 mmol) in 2-methyl-2-butene (6.8 mL) and *t*-BuOH (12 mL) at 23 °C. After 1 h, the mixture was diluted with H$_2$O (25 mL) and Et$_2$O (30 mL) and the two phases were separated. The aqueous phase was extracted with Et$_2$O (2 × 30 mL) and the combined organic phases were washed with water (30 mL), brine (2 × 30 mL), dried (MgSO$_4$) and concentrated *in vacuo*. Excess *t*-BuOH was removed by azeotrope with PhMe under reduced pressure to give acid **23** (520 mg, 1.06 mmol, 100%) as a colorless, thick syrup. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 4.24 (1H, q, J = 5.4 Hz), 4.21–4.13 (2H, m), 3.77 (1H, dd, J = 10.9, 4.5 Hz), 3.68 (1H, dd, J = 10.9, 5.8 Hz), 3.39–3.36 (2H, m), 2.00–1.94 (1H, m), 1.90–1.84 (1H, m), 1.43 (3H, s), 1.36 (3H, s), 0.90 (18H, s), 0.13 (3H, s), 0.12 (3H, s), 0.07 (6H, s). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 174.2, 108.3, 79.2, 77.8, 68.3, 62.5, 55.7, 53.1, 36.2, 27.3, 25.9 (3C), 25.8 (3C), 25.1, 18.3, 18.0, −4.1, −4.6, −5.3 (2C). **HRMS**: (ES$^+$) Calculated for C$_{23}$H$_{47}$O$_7$Si$_2$ [M + H]$^+$: 491.2869; Found: 491.2871. **IR ν_{max}/cm^{-1} (neat)**: 3158 br, 1729, 1463, 1275, 1096. **[α]$^{25}_D$**: +3.07 (c = 2.3, CH$_2$Cl$_2$).

4.1.9 (2S,3R)-3-{(S)-2-[(tert-Butyldimethylsilyl)oxy]-2-[(4R,5R)-5-{[(tert-butyldimethylsilyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}-N-methoxy-N-methyloxirane-2-carboxamide 25

Carbonyl diimidazole (16 mg, 97.3 μmol) was added with stirring to acid **23** (42 mg, 88.5 μmol) in CH$_2$Cl$_2$ (0.8 mL) at 0 °C. After 45 min at this temperature and 45 min at 23 °C. *N,O*-dimethylhydroxylammonium chloride (10 g, 97.3 μmol) was added and the mixture stirred for 16 h at 23 °C. The mixture was diluted with EtOAc (10 mL) and washed sequentially with aqueous HCl (1.0 M, 10 mL), saturated aqueous NaHCO$_3$ (10 mL) and brine (10 mL), dried (MgSO$_4$) and concentrated *in vacuo* to give Weinreb amide **25** (42 mg, 78.8 μmol, 89%) as a colorless oil. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 4.23–4.14 (3H, m), 3.83 (1H, dd, J = 10.9, 4.5 Hz), 3.77 (3H, s), 3.70–3.65 (2H, m), 3.35–3.32 (1H, m), 3.23 (3H, s), 2.07–2.00 (1H, m), 1.79–1.73 (1H, m), 1.42 (3H, s), 1.32 (3H, s), 0.89 (18H, s), 0.13 (3H, s), 0.11 (3H, s), 0.07 (6H, s). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 168.4, 107.9, 79.5, 78.2, 68.7, 62.7, 62.0, 55.0, 52.4, 36.4, 32.6, 27.5, 26.0 (3C), 25.9 (3C), 25.2, 18.4, 18.0, −4.2, −4.5, −5.3 (2C). **HRMS**: (ES$^+$) Calculated for C$_{25}$H$_{51}$NNaO$_7$Si$_2$ [M + Na]$^+$: 556.3102; Found: 556.3093. **IR ν_{max}/cm^{-1} (neat)**: 1679, 1464, 1381, 1255, 1215, 1095, 1005. **[α]$^{27}_D$**: +4.20 (c = 2.0, CH$_2$Cl$_2$).

4.1.10 (1R,2S,3S,4R)-2,4-bis[(4-Chlorobenzyl)oxy]-6,8-dioxabicyclo[3.2.1]octan-3-ol 29

(1*R*,2*S*,3*S*,4*R*)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (10 g, 61.7 mmol), 4-chlorobenzyl bromide (50.7 g, 247 mmol) and BaO (28 g, 185 mmol) in DMF (250 mL) was heated at 60 °C for 3 h. After cooling to 23 °C, the reaction was quenched with MeOH (130 mL) and the resulting mixture stirred for 30 min, diluted with CHCl$_3$ (500 mL) and filtered through Celite®. The filtrate was concentrated *in vacuo* and chromatographed (2: 1 pentane: EtOAc) to give sugar **29** (17 g, 42.1 mmol, 68%) as an off-white, amorphous solid. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 7.30–7.27 (8H, m), 5.45 (1H, s), 4.65 (2H, s), 4.63 (2H, s), 4.58 (1H, d, J = 5.1 Hz), 3.85–3.83 (2H, m), 3.68 (1H, dd, J = 7.5, 5.3 Hz), 3.32 (1H, d, J = 4.0 Hz), 3.24 (1H, d, J = 3.7 Hz), 2.33 (1H, d, J = 4.9 Hz). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 136.3, 136.2, 133.7, 133.6, 129.1 (2C), 129.0 (2C), 128.6 (4C), 101.1, 79.7, 79.4, 75.0, 71.3, 70.9, 70.4, 66.4. **HRMS**: (ES$^+$) Calculated for C$_{22}$H$_{23}$Cl$_2$NNaO$_5$ [M + CH$_3$CN + Na]$^+$: 474.0851; Found: 474.0831. **IR ν_{max}/cm^{-1} (neat)**: 3474 br, 1492, 1089, 1015, 892, 807. **[α]$^{24}_D$**: −24.6 (c = 1.1, CHCl$_3$).

4.1.11 O-{(1R,2R,3S,4R)-2,4-bis[(4-Chlorobenzyl)oxy]-6,8-dioxabicyclo[3.2.1]octan-3-yl}-1H-imidazole-1-carbothioate

Alcohol **29** (2.0 g, 4.87 mmol) and 1,1-thiocarbonyldiimidazole (1.3 g, 7.30 mmol) were heated at reflux in PhMe (47 mL) for 6 h. The solution was concentrated *in vacuo* and chromatographed (1: 2 pentane: EtOAc) to give *O*-{(1*R*,2*R*,3*S*,4*R*)-2,4-bis[(4-chlorobenzyl)oxy]-6,8-dioxabicyclo[3.2.1]octan-3-yl)-1*H*-imidazole-1-carbothioate (2.5 g, 4.68 mmol, 96%) as a yellow solid. **mp**: 96–98 °C (CHCl$_3$). **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 8.26 (1H, s), 7.53 (1H, s), 7.34–7.26 (8H, m), 7.02 (1H, s), 5.69 (1H, s),

5.47 (1H, s), 4.79–4.62 (5H, m), 3.84–3.76 (2H, m), 3.39 (1H, s), 3.35 (1H, s). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 182.0, 136.9, 135.5, 135.5, 133.9, 133.9, 131.3, 129.2 (4C), 128.7 (4C), 117.8, 99.9, 75.9, 74.1, 73.7, 73.6, 71.5, 70.7, 65.1. **HRMS**: (ES$^+$) Calculated for C$_{24}$H$_{23}$Cl$_2$N$_2$O$_5$S [M + H]$^+$: 521.0705; Found: 521.0714. **IR ν_{max}/cm^{-1} (neat)**: 1738, 1465, 1492, 1391, 1332, 1295, 1284, 1228, 1091, 1014, 986. **[α]^{24}$_D$**: −62.0 (c = 1.3, CHCl$_3$).

4.1.12 (1R,2S,4R)-2,4-bis[(4-Chlorobenzyl)oxy]-6,8-dioxabicyclo[3.2.1]octane 30

AIBN (1.8 g, 11.0 mmol) and Bu$_3$SnH (15 mL, 55.0 mmol) in PhMe (35 mL) were added with stirring over 1 h to O-{(1R,2R,3S,4R)-2,4-bis[(4-chlorobenzyl)oxy]-6,8-dioxabicyclo-[3.2.1]octan-3-yl}-1H-imidazole-1-carbothioate (5.8 g, 11.0 mmol) in PhMe (340 mL) at reflux. After a further 30 min, the solution was cooled to 23 °C and the solvent evaporated in vacuo. Chromatography (9: 1 silica gel: KF by weight; 10: 1 CH$_2$Cl$_2$: Et$_2$O) gave tetrahydropyran 30 (3.8 g, 9.60 mmol, 87%) as a colorless, viscous syrup. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.32–7.26 (8H, m), 5.46 (1H, s), 4.63–4.53 (5H, m), 3.78 (1H, dd, J = 7.7, 5.5 Hz), 3.68 (1H, d, J = 7.7 Hz), 3.34–3.20 (2H, m), 2.01 (1H, dt, J = 15.8, 1.8 Hz), 1.88–1.82 (1H, m). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 136.9, 136.8, 133.5 (2C), 129.0 (2C), 128.9 (2C), 128.5 (2C), 128.5 (2C), 100.7, 74.5, 72.3, 72.2, 70.5, 69.8, 65.4, 24.7. **HRMS:** (ES$^+$) Calculated for C$_{20}$H$_{20}$Cl$_2$NaO$_4$ [M + Na]$^+$: 417.0636; Found: 417.0645. **IR ν_{max}/cm^{-1} (neat)**: 1492, 1144, 1121, 1090, 1016, 922, 906. **[α]^{26}$_D$**: −35.9 (c = 1.0, CHCl$_3$).

4.1.13 {(2R,3S,5R)-6-Acetoxy-3,5-bis[(4-chlorobenzyl)oxy]tetrahydro-2H-pyran-2-yl}methyl acetate 31

Tetrahydropyran 30 (6.6 g, 16.8 mmol), Ac$_2$O (22 mL, 235 mmol) and BF$_3$·OEt$_2$ (1.0 mL, 8.40 mmol) were stirred at 0 °C for 30 min. The mixture was poured on to saturated aqueous NaHCO$_3$ (300 mL) and stirred until gas evolution ceased. If required, further solid NaHCO$_3$ was added. The aqueous phase was extracted with CHCl$_3$ (3 × 300 mL) and the combined organic phases were dried (MgSO$_4$) and concentrated in vacuo. Chromatography (4: 1 pentane: EtOAc) gave diacetate 31 (8.1 g, 16.3 mmol, 97%) as a colorless, thick syrup containing an inseparable mixture of diastereoisomers 3.3: 1.0 α: β. **α-anomer:** ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.33–7.22 (8H, m), 6.31 (1H, d, J = 3.2 Hz), 4.62–4.38 (4H, m), 4.31–4.22 (2H, m), 3.86 (1H, ddd, J = 9.8, 4.5, 2.4 Hz), 3.56 (1H, dt, J = 12.2, 4.2 Hz), 3.47–3.40 (1H, m), 2.39 (1H, dt, J = 11.7, 4.7 Hz), 2.15 (3H, s) 1.85 (3H, s), 1.85 (1H, app. q, J = 11.8 Hz). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 170.7, 169.4, 136.1, 136.0, 133.8, 133.8, 129.2 (2C), 129.1 (2C), 128.7 (4C), 88.6, 72.6, 71.2, 71.0, 70.7, 69.9, 62.8, 30.2, 21.1, 20.8. **β-anomer:** ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.34–7.20 (8H, m), 5.59 (1H, d, J = 7.9 Hz), 4.62–4.22 (6H, m), 3.68 (1H, ddd, J = 9.4, 4.6, 2.8 Hz) 3.47–3.37 (2H, m), 2.58 (1H, dt, J = 12.4, 4.8 Hz), 2.11 (3H, s) 2.01 (3H, s), 1.60 (1H, app. q, J = 11.4 Hz). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 170.7, 169.1, 136.5, 136.0, 133.8, 133.6, 129.1 (2C), 128.8 (2C), 128.7 (2C), 128.6 (2C), 95.4, 77.0, 74.0, 71.5, 71.1, 70.3, 62.8, 34.2, 21.1, 20.8. **HRMS:** (ES$^+$) Calculated for C$_{24}$H$_{26}$Cl$_2$NaO$_7$ [M + Na]$^+$: 519.0953; Found: 519.0947. **IR ν_{max}/cm^{-1} (neat)**: 1740, 1370, 1492, 1225, 1152, 1083, 970.

4.1.14 {(2R,3S,5R,6S)-3,5-bis[(4-Chlorobenzyl)oxy]-6-cyanotetrahydro-2H-pyran-2-yl}methyl acetate 33 and {(2R,3S,5R,6R)-3,5-bis[(4-chlorobenzyl)oxy]-6-cyanotetrahydro-2H-pyran-2-yl}methyl acetate 32

Me$_3$SiOTf (1.1 mL, 6.18 mmol) was added with stirring to diacetate 31 (5.1 g, 10.3 mmol) and Me$_3$SiCN (3.4 mL, 33.9 mmol) in CH$_3$CN (51 mL) at 0 °C. After 45 min, the solution was diluted with CH$_2$Cl$_2$ (200 mL) and washed with ice-cold saturated aqueous NaHCO$_3$ (100 mL). The organic phase was washed a further 3 times with saturated aqueous NaHCO$_3$ (100 mL) and dried (MgSO$_4$). The solvent was concentrated and the residue chromatographed (5: 1 to 3: 1 pentane: EtOAc) to give the β-anomer 33 (2.0 g, 4.32 mmol, 42%) as a white amorphous solid and the α-anomer 32 (2.0 mg, 4.32 mmol, 42%) as a colorless oil. **33:** ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.37–7.19 (8H, m), 4.71 (1H, d, J = 11.6 Hz), 4.66 (1H, d, J = 11.6 Hz), 4.55 (1H, d, J = 11.6 Hz), 4.38 (1H, d, J = 11.6 Hz), 4.33 (1H, dd, J = 12.2, 2.0 Hz), 4.17 (1H, dd, J = 12.2, 5.4 Hz), 4.03 (1H, d, J = 9.7 Hz), 3.66–3.57 (1H, m), 3.48–3.41 (1H, m), 3.39–3.30 (1H, m), 2.65 (1H, dt, J = 12.3, 4.5 Hz), 2.04 (3H, s), 1.45 (1H, app. q, J = 11.2 Hz). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 170.6, 135.6, 135.3, 134.1, 134.0, 129.3 (2C), 129.1 (2C), 128.8 (2C), 128.7 (2C), 116.8, 78.8, 73.6, 71.6, 70.6, 70.3, 69.0, 62.7, 35.3, 20.7. **HRMS:** (ES$^+$) Calculated for C$_{23}$H$_{24}$Cl$_2$NO$_5$ [M+H]$^+$: 464.1032; Found: 464.1037. **IR ν_{max}/cm^{-1} (neat)**: 1736, 1492, 1368, 1352, 1232, 1085, 1043, 1015, 807. **[α]^{26}$_D$**: +43.2 (c = 1.5, CHCl$_3$). **32:** ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.36–7.21 (8H, m), 4.79 (1H, d, J = 5.4 Hz), 4.62–4.54 (3H, m), 4.39 (1H, d, J = 11.7 Hz), 4.34–4.24 (2H, m), 3.82 (1H, ddd, J = 9.6, 4.8, 2.3 Hz), 3.60 (1H, ddd, J = 11.8, 5.3, 4.5 Hz), 3.34 (1H, ddd, J = 11.1, 9.7, 4.6 Hz), 2.62–2.50 (1H, m), 2.03 (3H, s), 1.80 (1H, app. q, J = 11.9 Hz). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 170.6, 135.7, 135.4, 134.1, 133.9, 129.1 (2C), 129.0 (2C), 128.9 (2C), 128.7 (2C), 114.9, 74.9, 71.4, 70.9, 70.3, 69.9, 67.2, 62.4, 32.3, 20.7. **HRMS:** (ES$^+$) Calculated for C$_{23}$H$_{24}$Cl$_2$NO$_5$ [M + H]$^+$: 464.1032; Found: 464.1038. **IR ν_{max}/cm^{-1} (neat)**: 1737, 1491, 1366, 1232, 1086, 1016, 807. **[α]^{26}$_D$**: +107.5 (c = 1.4, CHCl$_3$).

4.1.15 (2S,3R,5S,6R)-3,5-bis[(4-Chlorobenzyl)oxy]-6-(hydroxymethyl)tetrahydro-2H-pyran-2-carbonitrile 34

Nitrile 33 (690 mg, 1.49 mmol) and K$_2$CO$_3$ (205 mg, 1.49 mmol) were stirred in MeOH (130 mL) for 30 min. The solution was washed with saturated aqueous NH$_4$Cl (200 mL) and the aqueous phase was extracted with CHCl$_3$ (5 × 100 mL). The organic layers were dried (MgSO$_4$) and concentrated in vacuo. Chromatography (5:2 pentane/EtOAc) gave alcohol 34 (540 mg, 1.29 mmol, 86%) as an off-white oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.36–7.21 (8H, m), 4.67 (2H, s), 4.57 (1H, d, J = 11.6 Hz), 4.45 (1H, d, J = 11.7 Hz), 4.05 (1H, d, J = 9.7 Hz), 3.89 (1H, dd, J = 12.4, 2.6 Hz), 3.72 (1H, dd, J = 12.4, 4.5 Hz), 3.60 (1H, ddd, J = 11.2, 9.6, 4.6 Hz), 3.47 (1H, ddd, J = 11.0, 9.2, 4.5 Hz), 3.32–3.28 (1H, m), 2.62 (1H, dt, J = 12.2, 4.6 Hz), 1.46 (1H, app. q, J = 11.4 Hz). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 135.9, 135.3, 134.1, 133.9, 129.3 (2C), 129.0 (2C), 128.8 (2C), 128.7 (2C), 116.9, 81.2, 73.9, 71.5, 70.7 (2C), 69.0, 61.6, 32.5. **HRMS:** (ES$^-$) Calculated for C$_{22}$H$_{22}$Cl$_2$NO$_6$ [M + CO$_2$H]$^-$: 466.0824; Found: 466.0814. **IR ν_{max}/cm^{-1} (neat)**: 3443 br, 1492, 1351, 1087, 1015, 807. **[α]^{26}$_D$**: +19.3 (c = 1.0, CHCl$_3$).

4.1.16 (2S,3R,5S,6R)-6-{[(4-Bromobenzyl)oxy]methyl}-3,5-bis[(4-chlorobenzyl)oxy]tetrahydro-2H-pyran-2-carbonitrile 35

NaH (60% dispersion in oil; 71 mg, 1.76 mmol) and 4-bromobenzyl bromide (440 mg, 1.76 mmol) were added with stirring to alcohol 34 (500 mg, 1.12 mmol) in DMF (9 mL) at 23 °C. After 30 min, the solution was diluted with CHCl$_3$ (50 mL), washed

with water (4 × 50 mL), dried (MgSO$_4$) and concentrated *in vacuo*. Chromatography (2: 1 pentane: Et$_2$O) gave nitrile **35** (610 mg, 1.00 mmol, 93%) as a white amorphous solid. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 7.47–7.11 (12H, m), 4.70 (1H, d, *J* = 11.6 Hz), 4.66 (1H, d, *J* = 11.6 Hz), 4.55–4.33 (4H, m), 4.01 (1H, d, *J* = 9.7 Hz), 3.71–3.58 (3H, m), 3.48 (1H, ddd, *J* = 11.1, 9.4, 4.6 Hz), 3.35 (1H, ddd, *J* = 9.7, 4.1, 2.0 Hz), 2.60 (1H, dt, *J* = 12.2, 4.5 Hz), 1.43 (1H, app. q, *J* = 11.4 Hz). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 136.8, 135.9, 135.4, 134.1, 133.8, 135.6 (2C), 129.4 (2C), 129.3 (2C), 128.9 (2C), 128.8 (2C), 128.7 (2C), 121.6, 116.9, 80.9, 73.8, 72.8, 71.5, 70.6, 70.6, 69.1, 68.3, 35.7. **HRMS**: (ES$^+$) Calculated for C$_{28}$H$_{27}$BrCl$_2$NO$_4$ [M + H]$^+$: 590.0501; Found: 590.0521. **IR ν_{max}/cm^{-1} (neat)**: 1492, 1462, 1348, 1088, 1048, 1011, 972. **[α]$^{23}_D$**: +25.2 (*c* = 1.0, CHCl$_3$).

4.1.17 (2R,3R,5S,6R)-Methyl 6-{[(4-bromobenzyl)oxy]methyl}-3,5-bis[(4-chlorobenzyl)oxy]tetrahydro-2H-pyran-2-carboxylate

AcCl (0.50 mL) was added with stirring to nitrile **35** (290 mg, 0.496 mmol) in MeOH (10 mL) at 0 °C and the mixture was subsequently heated at 65 °C. After 24 h, the solution was cooled to 0 °C and further AcCl (0.20 mL) was added. After additional heating at 65 °C for 24 h, the solution was evaporated and the residue chromatographed (2: 1 pentane: Et2O) to give (2*R*,3*R*,5*S*,6*R*)-methyl 6-{[(4-bromobenzyl)oxy]methyl}-3,5-bis[(4-chlorobenzyl)oxy]tetrahydro-2*H*-pyran-2-carboxylate (310 mg, 0.492 mmol, 99%) as a white solid. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 7.45–7.12 (12H, m), 4.56–4.33 (6H, m), 3.84 (1H, d, *J* = 9.6 Hz), 3.76 (3H, s), 3.73–3.62 (3H, m), 3.50–3.41 (2H, m), 2.63 (1H, dt, *J* = 12.2, 4.3 Hz), 1.50 (1H, app. q, *J* = 11.2 Hz). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 169.9, 137.2, 136.2 (2C), 133.7, 131.4 (2C), 129.4 (2C), 129.0 (2C), 128.9 (2C), 128.6 (4C), 121.5, 80.4, 79.8, 74.0, 72.7, 71.6, 70.8, 70.4, 68.9, 52.3, 35.2. N.B.: One carbon unseen due to overlap of peaks. **HRMS**: (ES$^+$) Calculated for C$_{31}$H$_{32}$BrCl$_2$NNaO$_6$ [M + CH$_3$CN + Na]$^+$: 686.0688; Found: 686.0681. **IR ν_{max}/cm^{-1} (neat)**: 1748, 1491, 1365, 1216, 1088, 1015. **[α]$^{23}_D$**: +12.5 (*c* = 1.0, CHCl$_3$).

4.1.18 (2R,3R,5S,6R)-6-{[(4-Bromobenzyl)oxy]methyl}-3,5-bis[(4-chlorobenzyl)oxy]tetrahydro-2H-pyran-2-carboxylic acid 36

(2*R*,3*R*,5*S*,6*R*)-Methyl 6-{[(4-bromobenzyl)oxy]methyl}-3,5-bis[(4-chlorobenzyl)oxy]tetrahydro-2*H*-pyran-2-carboxylate (460 mg, 0.740 mmol) and LiOH·H$_2$O (62 mg, 1.48 mmol) were stirred in MeOH and water (20:1; 14 mL) for 24 h. The resultant solution was diluted with CHCl$_3$ (100 mL) and washed with aqueous citric acid (10%, 100 mL). The phases were separated and the organic phase was dried (MgSO$_4$) and concentrated *in vacuo* to give the acid **36** (440 mg, 0.729 mmol, 98%) as a colorless oil, which was used in subsequent reactions without further purification. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 7.44–7.12 (12H, m), 4.56–4.45 (5H, m), 4.34 (1H, d, *J* = 11.6 Hz), 3.89 (1H, d, *J* = 9.3 Hz), 3.75–3.62 (3H, m), 3.50–3.44 (2H, m), 2.62 (1H, dt, *J* = 12.0, 4.0 Hz), 1.57 (1H, app. q, *J* = 11.2 Hz). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 172.5, 136.7, 136.1, 136.0, 133.7 (2C), 131.5 (2C), 129.5 (2C), 129.1 (2C), 128.9 (2C), 128.6 (4C), 121.7, 79.8, 79.0, 73.7, 72.6, 71.4, 70.8, 70.3, 68.8, 35.1. **HRMS**: (ES$^+$) Calculated for C$_{28}$H$_{28}$BrCl$_2$O$_6$ [M + H]$^+$: 609.0446; Found: 609.0420 **IR ν_{max}/cm^{-1} (neat)**: 3101 br, 1746, 1491, 1220, 1088, 1014. **[α]$^{22}_D$**: +18.8 (*c* = 1.0, CHCl$_3$).

4.1.19 (S)-Pent-4-en-2-yl 2-{(2S,3R,5S,6R)-6-{[(4-bromobenzyl)oxy]methyl}-3,5-bis[(4-chloro benzyl)oxy]tetrahydro-2H-pyran-2-yl}-6-hydroxy-4-methoxybenzoate 41

SOCl$_2$ (0.22 mL, 2.91 mmol) was added with stirring to acid **36** (220 mg, 0.363 mmol) in CH$_2$Cl$_2$ (3.5 mL) at 23 °C. After 16 h, further SOCl$_2$ (0.12 mL, 1.46 mmol) was added and, after a further 1 h, the mixture was concentrated *in vacuo* and excess thionyl chloride was removed as its azeotrope with dry PhMe (3 × 1.0 mL) under reduced pressure to give the acid chloride **37**. While acid chloride **37** was drying under reduced pressure, allyl ester **38** (97 mg, 0.363 mmol) was dissolved in THF (3.5 mL) at 0 °C and *i*-PrMgBr (0.8 M in THF; 0.43 mL, 0.345 mmol) was added with stirring. After 30 min, the acid chloride **37** in CH$_2$Cl$_2$ (0.5 mL) was added with stirring at 0 °C. After 1 h, the mixture was concentrated *in vacuo*, the residue dissolved in CH$_2$Cl$_2$ (8.0 mL) and purged with Ar. To this, a degassed solution of Pd(PPh$_3$)$_4$ (42 mg, 36.3 μmol) and morpholine (63 μL, 0.726 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added and the mixture stirred for 30 min at 0 °C. The mixture was washed with aqueous 10% citric acid (25 mL) and extracted with CHCl$_3$ (3 × 25 mL). The organic phase was dried (MgSO$_4$) and concentrated *in vacuo* to give the crude diketo-dioxinone **40**, which was used in the subsequent reaction without further purification. Diketo-dioxinone **40** was heated in PhMe (10 mL) with (*S*)-4-penten-2-ol (0.30 mL, 2.90 mmol) at 110 °C for 1 h. The resultant solution was concentrated *in vacuo* and redissolved in CH$_2$Cl$_2$ and *i*-PrOH (1:1; 16 mL) and CsOAc (210 mg, 1.09 mmol) was added at room temperature. After stirring for 2 h, HCl in MeOH (1.25 M; 2.9 mL, 3.63 mmol) was added and the mixture was stirred for a further 16 h. The resulting mixture was washed with saturated aqueous NaHCO$_3$ (50 mL), extracted with Et$_2$O (3 × 50 mL) and the combined organic phases were dried (MgSO$_4$) and concentrated *in vacuo*. Chromatography gave crude resorcylate **40** as an inseparable mixture of products, which was used directly in the next step without purification. MeI (90 μL, 1.45 mmol) in Me$_2$CO (1.2 mL) was added with stirring to the crude of resorcylate **40** and K$_2$CO$_3$ (100 mg, 0.726 mmol) in Me$_2$CO (15 mL) and the mixture was heated at 45 °C for 2 h. The mixture was washed with H$_2$O (25 mL) and the aqueous phase was extracted with Et$_2$O (3 × 25 mL). The combined organic phases were dried (MgSO$_4$), concentrated *in vacuo* and chromatographed (2: 1 pentane: Et$_2$O) to give the methylated resorcylate **41** (92 mg, 0.115 mmol, 32% over 4 steps) as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 11.50 (1H, s), 7.46–7.16 (10H, m), 6.88–6.86 (2H, m), 6.71 (1H, d, *J* = 2.6 Hz), 6.44 (1H, d, *J* = 2.6 Hz), 5.78 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz), 5.49 (1H, d, *J* = 9.1 Hz), 5.21–5.08 (3H, m), 4.60 (1H, d, *J* = 11.7 Hz), 4.58 (1H, d, *J* = 12.7 Hz), 4.50 (1H, d, *J* = 12.7 Hz), 4.42 (1H, d, *J* = 11.7 Hz), 4.18 (1H, d, *J* = 11.8 Hz), 3.97 (1H, d, *J* = 11.8 Hz), 3.81 (3H, s), 3.76–3.71 (2H, m), 3.58–3.51 (2H, m), 3.06 (1H, ddd, *J* = 11.3, 8.8, 4.1 Hz), 2.64 (1H, dt, *J* = 12.1, 4.1 Hz), 2.49–2.32 (2H, m), 1.60 (1H, app q, *J* = 11.2 Hz), 1.26 (3H, d, *J* = 6.2 Hz). **^{13}C NMR** (101 MHz, CDCl$_3$) δ: 170.9, 164.0, 164.0, 143.9, 137.4, 136.5, 136.2, 133.6, 133.3, 133.3, 131.5 (2C), 129.2 (2C), 129.2 (2C), 129.0 (2C), 128.6 (2C), 128.3 (2C), 121.4, 118.3, 106.9, 106.1, 100.1, 80.7, 79.2, 78.1, 72.6 (2C), 72.0, 71.0, 70.5, 69.4, 55.3, 40.3, 36.4, 19.2. **HRMS:** (ES$^+$) Calculated for C$_{40}$H$_{42}$BrCl$_2$O$_8$ [M + H]$^+$: 799.1440; Found: 799.1460. **IR ν_{max}/cm^{-1} (neat)**: 1646, 1615, 1578, 1491, 1357, 1318, 1254, 1204, 1160, 1087, 1013. **[α]$^{25}_D$**: +37.7 (*c* = 1.0, CHCl$_3$).

4.1.20 (S)-Pent-4-en-2-yl 2-{(2S,3R,5S,6R)-3,5-bis[(4-chlorobenzyl)oxy]-6-[({4-[methyl(phenyl) amino]benzyl}oxy)methyl]tetrahydro-2H-pyran 2-yl}-6-hydroxy-4-methoxybenzoate 43

Resorcylate **41** (50 mg, 62.7 µmol) was dried by azeotrope with PhMe (3 × 1 mL) under reduced pressure, dissolved in PhMe (0.60 mL) and *N*-methylaniline (8.0 µL, 75.2 µmol) was added with stirring. Tris(dibenzylideneacetone)dipalladium(0) (2.9 mg, 3.14 µmol), (*o*-biphenyl)P(*t*-Bu)$_2$ (**42**) (1.9 mg, 6.27 µmol) and *t*-BuONa (8.0 mg, 87.8 µmol) were added to a Schlenk flask, which was evacuated and back filled with Ar. Resorcylate **41** and *N*-methylaniline was added and the mixture was heated for at 80 °C for 2 h. The mixture was cooled to 23 °C, diluted with Et$_2$O (10 mL) and filtered through Celite®. The filtrate was concentrated *in vacuo* and chromatographed to give aniline **43** (40 mg, 48.3 µmol, 77%) as a colorless oil. **¹H NMR** (400 MHz, CDCl$_3$) δ: 11.49 (1H, s), 7.31–7.17 (10H, m), 7.05–6.95 (5H, m), 6.89–6.87 (2H, m), 6.76 (1H, d, *J* = 2.7 Hz), 6.43 (1H, d, *J* = 2.7 Hz), 5.79 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz), 5.50 (1H, d, *J* = 9.1 Hz), 5.21–5.08 (3H, m), 4.62–4.43 (4H, m), 4.18 (1H, d, *J* = 11.8 Hz), 3.98 (1H, d, *J* = 11.8 Hz), 3.81–3.77 (2H, m), 3.77 (3H, s), 3.64–3.53 (2H, m), 3.31 (3H, s), 3.08 (1H, ddd, *J* = 11.2, 8.9, 4.0 Hz), 2.63 (1H, dt, *J* = 11.8, 4.3 Hz), 2.50–2.33 (2H, m), 1.57 (1H, app. q, *J* = 11.3 Hz), 1.27 (3H, d, *J* = 6.3 Hz). **¹³C NMR** (101 MHz, CDCl$_3$) δ: 170.8, 164.0, 163.9, 148.9, 148.5, 144.0, 136.6, 136.2, 133.5, 133.3, 130.6, 129.2 (2C), 129.2 (2C), 129.1 (2C), 129.0 (2C), 128.6 (2C), 128.2 (2C), 121.6, 121.0 (2C), 119.6 (2C), 118.3, 106.7, 106.1, 100.2, 80.8, 79.2, 78.2, 73.1, 72.6, 72.0, 71.0, 70.6, 68.9, 55.3, 40.3, 40.2, 36.5, 19.2. N.B: one C$_{Ar}$ unseen due to overlap. **HRMS**: (ES⁺) Calculated for C$_{47}$H$_{50}$Cl$_2$O$_8$N [M + H]⁺: 826.2913; Found: 826.2916. **IR ν$_{max}$/cm⁻¹ (neat)**: 1644, 1613, 1595, 1578, 1513, 1493, 1345, 1317, 1252, 1203, 1159, 1114, 1083, 1015. **[α]²⁶$_D$**: +36.2 (*c* = 1.0, CHCl$_3$).

4.1.21 (S)-Pent-4-en-2-yl 2-acetoxy-6-{(2S,3R,5S,6R)-3,5-bis[(4-chlorobenzyl)oxy]-6-[({4-[methyl(phenyl)amino]benzyl}oxy)methyl]tetrahydro-2H-pyran-2-yl}-4-methoxy benzoate 44

DMAP (1.4 mg, 11.6 µmol) was added with stirring to resorcylate **43** (48 mg, 58.2 µmol) and Ac$_2$O (10 µL, 0.175 mmol) in THF (0.8 mL) at 23 °C. After 30 min, the solution was washed with saturated aqueous NaHCO$_3$ (10 mL) and the aqueous phase was extracted with Et$_2$O (3 × 10 mL). The combined organic phases were dried (MgSO$_4$), concentrated *in vacuo* and chromatographed (1: 1 pentane: Et$_2$O) to give aniline **44** (47 mg, 54.1 µmol, 93%) as a colorless oil. **¹H NMR** (400 MHz, CDCl$_3$) δ: 7.30–7.15 (10H, m), 7.04–6.92 (7H, m), 6.89 (1H, d, *J* = 2.5 Hz), 6.58 (1H, d, *J* = 2.5 Hz), 5.75 (1H, ddt, *J* = 17.2, 10.3, 7.0 Hz), 5.17–5.03 (3H, m), 4.80 (1H, d, *J* = 9.1 Hz), 4.57 (1H. d, *J* = 11.8 Hz), 4.50–4.37 (3H, m), 4.16 (1H, d, *J* = 12.4 Hz), 4.12 (1H, d, *J* = 12.4 Hz), 3.78–3.71 (2H, m), 3.73 (3H, s), 3.63–3.54 (1H, m), 3.54–3.48 (1H, m), 3.30 (3H, s), 3.19 (1H, ddd, *J* = 11.0, 9.1, 4.3 Hz), 2.58 (1H, dt, *J* = 11.8, 4.5 Hz), 2.41–2.32 (1H, m), 2.29 (3H, s), 2.24–2.17 (1H, m), 1.52 (1H, app. q, *J* = 11.4 Hz), 1.28 (3H, d, *J* = 6.3 Hz). **¹³C NMR** (101 MHz, CDCl$_3$) δ: 169.0, 165.3, 161.1, 149.7, 148.9, 148.5, 141.3, 136.7, 136.3, 133.5, 133.4, 133.2, 130.7, 129.5 (2C), 129.2 (2C), 129.0 (4C), 128.5 (2C), 128.2 (2C), 121.6, 121.0 (2C), 119.7 (2C), 119.3, 117.9, 110.5, 108.1, 80.7, 78.8, 77.2, 73.1, 72.2, 71.1, 70.5, 70.5, 68.8, 55.5, 40.2, 40.0, 36.2, 21.0, 19.2. **HRMS:** (ES⁺) Calculated for C$_{49}$H$_{52}$Cl$_2$O$_9$N [M+H]⁺: 631.1865; Found: 631.1860. **IR ν$_{max}$/cm⁻¹ (neat)**: 1771, 1717, 1613, 1596, 1513, 1493, 1262, 1203, 1191, 1153, 1083. **[α]²⁶$_D$**: +27.8 (*c* = 1.0, CHCl$_3$).

4.1.22 (S)-Pent-4-en-2-yl 2-acetoxy-6-{(2S,3R,5S,6R)-3,5-bis[(4-chlorobenzyl)oxy]-6-(hydroxy methyl)tetrahydro-2H-pyran-2-yl}-4-methoxybenzoate 45

SnCl$_4$ in heptane (1.0 M; 25 µL, 25.4 µmol) was added with stirring to aniline **44** (20 mg, 23.1 µmol) in CH$_2$Cl$_2$ (0.8 mL) at −78 °C. After 30 min, the mixture was diluted with CH$_2$Cl$_2$ (10 mL) and washed successively with water (10 mL), saturated aqueous NaHCO$_3$ (10 mL) and brine (10 mL). The organic phase was dried (MgSO$_4$) and concentrated *in vacuo*. Chromatography (1: 2 pentane: Et$_2$O) gave alcohol **45** (14 mg, 20.8 µmol, 90%) as a colorless oil. **¹H NMR** (400 MHz, CDCl$_3$) δ: 7.34–7.31 (2H, m), 7.26–7.24 (2H, m), 7.19-7.16 (2H, m), 6.98–6.94 (2H, m), 6.77 (1H, d, *J* = 2.5 Hz), 6.61 (1H, d, *J* = 2.5 Hz), 5.76 (1H, ddt, *J* = 17.3, 10.4, 7.1 Hz), 5.14–5.07 (3H, m), 4.68 (1H, d, *J* = 9.1 Hz), 4.61 (1H, d, *J* = 11.7 Hz), 4.46 (1H, d, *J* = 11.7 Hz), 4.22 (1H, d, *J* = 12.2 Hz), 4.13 (1H, d, *J* = 12.2 Hz), 3.89 (1H, dd, *J* = 11.8, 2.5 Hz), 3.76 (3H, s), 3.69 (1H, dd, *J* = 11.8, 4.3 Hz), 3.50–3.41 (2H, m), 3.33 (1H, ddd, *J* = 11.1, 9.2, 4.4 Hz), 2.62 (1H, dt, *J* = 12.2, 4.2 Hz), 2.47–2.36 (1H, m), 2.28 (3H, s), 2.28–2.21 (1H, m), 1.54 (1H, app. q, *J* = 11.2 Hz), 1.27 (3H, d, *J* = 6.2 Hz). **¹³C NMR** (101 MHz, CDCl$_3$) δ: 168.8, 165.8, 160.7, 149.6, 140.2, 136.4, 136.1, 133.7, 133.3, 129.4 (2C), 129.0 (2C), 128.7 (2C), 128.3 (2C), 125.5, 119.4, 118.1, 111.2, 108.0, 80.7, 79.4, 76.7, 72.3, 71.5, 70.6, 70.3, 62.4, 55.6, 40.0, 35.8, 30.0, 19.2. **HRMS:** (ES⁺) Calculated for C$_{35}$H$_{39}$Cl$_2$O$_9$ [M+H]⁺: 673.1971; Found: 673.1971. **IR ν$_{max}$/cm⁻¹ (neat)**: 3517 br, 1772, 1717, 1614, 1491, 1367, 1320, 1264, 1192, 1153, 1086, 1041, 1015. **[α]²⁶$_D$**: +24.9 (*c* = 1.0, CHCl$_3$).

Acknowledgments

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.05.083.

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Appendix A. Supplementary data

The following is the supplementary data related to this article:

Multimedia Component 1

Multimedia component 1

alt-text: Multimedia component 1

Graphical abstract

alt-text: Image 1