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Synthesis of the C1–C16 fragment of the ajudazols

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ABSTRACT

The synthesis of the C1–C16 framework of the ajudazols has been achieved taking advantage of a highly selective isobenzofuran oxidative rearrangement and a key Stille coupling to introduce the key C14–C15 bond.

1. Introduction

Myxobacteria have been widely recognized as a rich source of bioactive metabolites with significant biological activities. The myxobacterial strain *Chondromyces crocatus* is particularly noteworthy for having yielded extracts containing the chondramides A–D and the crocacins A–C.[1,2]

Ajudazols A **1** and B **2** were isolated by Jansen and co-workers by reverse phase chromatography from the acetone extracts of the wet mass of *C. crocatus*.[3] Structurally, the ajudazols showcase a number of exquisite, and in some cases, unique features, such as a 4,8-dihydroxy-7-methyl-isochroman-1-one, a 3-methoxybutenoic acid methyl amide as well as an internal oxazole and a *Z,Z*-diene unit. Biologically, the ajudazols have been identified as inhibitors of the bacterial mitochondrial electron transport at low nanomolar concentrations (Fig. 1).[3]

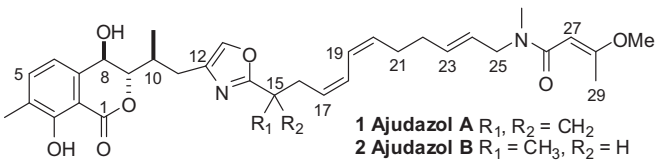

Fig. 1. Ajudazol A **1** and ajudazol B **2**.

Biosynthetic studies by Muller have determined that the ajudazols are assembled by a hybrid polyketide synthase (PKS) non-ribosomal peptide (NRPS) multienzyme, which efficiently puts together the ajudazol framework in a linear fashion.[4] Interestingly, the key isochromanone ring formation is promoted by a novel thioesterase domain rather than by an expected terminal cyclase.[4]

The exciting combination of unique structural features combined with a promising therapeutic profile makes the ajudazols highly attractive targets. Rizzacasa and Taylor have published elegant approaches towards the total synthesis of the ajudazols;[5,6] however, there have been no reported total syntheses of either ajudazol A or B.

As part of our own efforts towards the synthesis of the ajudazols, we envisioned the ajudazols as originating from the metal promoted coupling of vinyl halide **3** to oxazole **4** via C–H activation of the oxazole's C2 position. Vinyl halide **3** could be formed from the alkylation of bis-alkyne **5** and the condensation of the amine functionality with methoxybutenoic acid **6**. The key bis-alkyne **5** in turn was envisioned as originating from the bis-acetylene unit **7** (Scheme 1).

The oxazole substituted isochroman-1-one unit **4** on the other hand, was thought of as being obtained through the coupling of the isobenzofuran anion **8** and aldehyde **9** followed by oxidative rearrangement of the resulting α-hydroxyisobenzofuran intermediate. The isobenzofuran anion could be accessed readily through base treatment of methyl acetal **10**, whilst the oxazole containing aldehyde **9** was thought as having originated from oxazole ester **11**.

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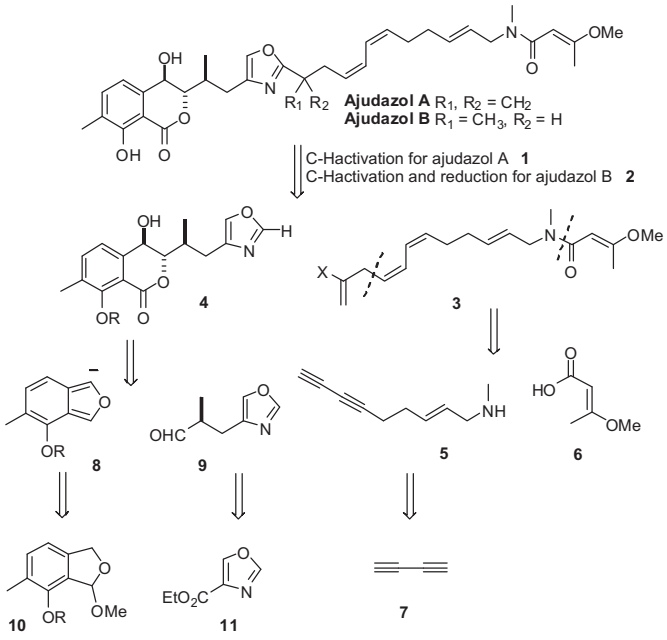
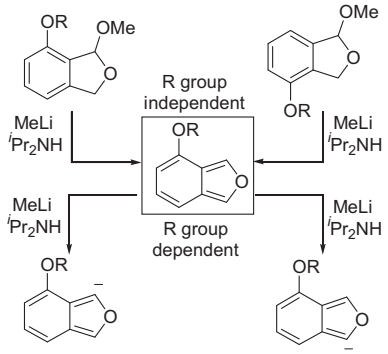


Scheme 1.

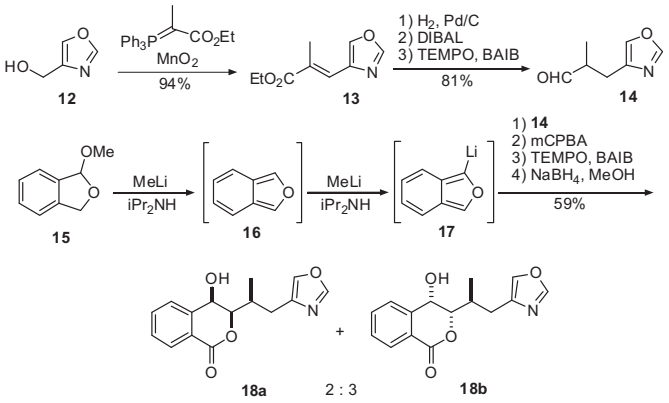
2. Results and discussion

We have recently reported the oxidative rearrangement of α-hydroxy-isobenzofurans, which allows the efficient generation of isochromanones quickly, efficiently, and with minimal purification.[7,8] The rearrangement can be directed to generate single regioisomers through the use of C4 or C7 substituents on the phthalan starting unit (Scheme 2). Furthermore, we have also shown that it is possible to couple isobenzofuran anions with highly functionalised C2-unsubstituted oxazole containing aldehydes without any cross-reactivity issues.



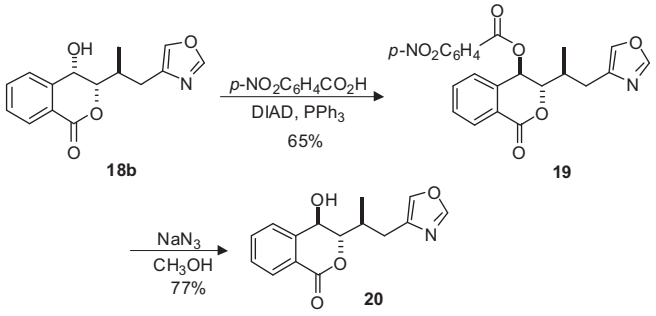
Scheme 2.

Having demonstrated the feasibility of using substituted isobenzofurans to generate isochromanones, it was decided to focus our efforts on the key oxazole C–H activation required to bring together the western **4** and eastern **3** sections of the ajudazols. Our initial model studies began with the known oxazole alcohol **12**, which was converted into the racemic homologated aldehyde **14** following our recently published procedure.[8] Aldehyde **14** was then coupled with the phthalan derived isobenzofuran anion **17**. Oxidative rearrangement, followed by oxidation of the lactol intermediate and selective ketone reduction yielded the desired ajudazol western section framework as a separable mixture of *syn*/*syn* and *syn*/*anti* diastereomers **18a** and **18b** (Scheme 3).



Scheme 3.

The *syn*/*anti* diastereomer **18b** was then converted to the desired *anti*/*anti* adduct **20** via Mitsunobu inversion of the C8 stereocentre followed by mild hydrolysis of the resulting *p*-nitrobenzoate ester **19** (Scheme 4).[9] The relative stereochemistry of the *anti*/*anti* isochromanone **20** was corroborated by X-ray crystallography (Fig. 2).[10]



Scheme 4.

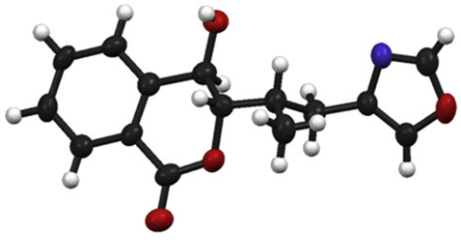
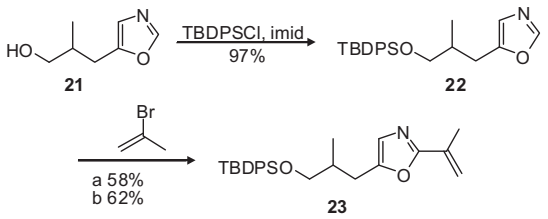


Fig. 2. Crystal structure of isochromanone **20**.

Having the three diastereomeric isochromanones at hand, the key C14–C15 bond formation by C–H activation of the oxazole C2 position was explored. Encouragingly, initial studies using the oxazole model system **22** resulted in selective C2 C–H activation under both palladium and copper mediated conditions to generate the desired sp^2–sp^2 coupled product **23** (Scheme 5).[11]

Unfortunately, to our disappointment, the reaction conditions used to generate alkene **23** could not be applied successfully to any of the oxazole containing isochromanones **18**–**20**. Modification of the C–H activation conditions proved fruitless with most of them resulting in the complete degradation of the isochromanone units.

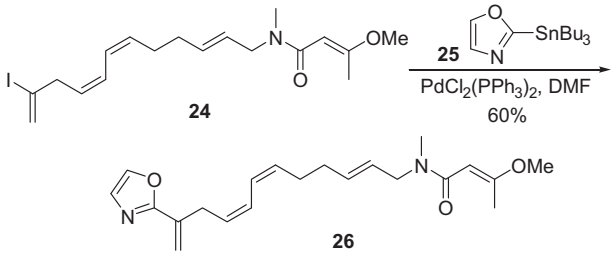
Faced with such a set-back, we referred to Taylor's synthesis of the ajudazol A's eastern section **26** as an alternative model through which C14–C15 bond formation could be achieved.[6] In Taylor's approach, the key sp^2–sp^2 bond was achieved cleanly and



Reagents and Conditions: a) $Pd(PPh_3)_4$, ^tBuOLi, Dioxane, 110 °C; b) CuI, ^tBuOLi, *trans- N, N'*- dimethylcyclohexane-1,2 diamine, Dioxane, 110 °C.

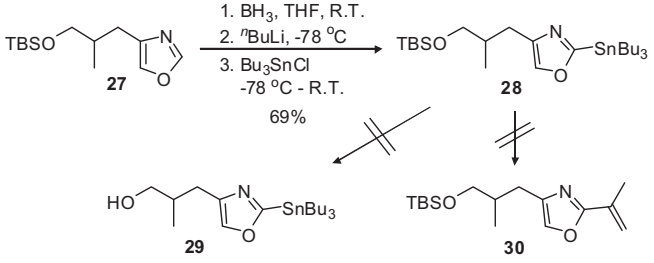
Scheme 5.

efficiently through the Stille coupling between vinyl iodide **24** and 2-(tributylstannyl)oxazole **25** (Scheme 6).



Scheme 6.

Prompted by the starting material decomposition observed during the attempted C–H activation of the isochromanone units, the introduction of the stannyl group onto a simpler oxazole, which could then be incorporated into the isochromanone core was initially attempted. Thus, the TBS silyl ether **27** was cleanly deprotonated and stannylated at the C2 position to yield the tributylstannane **28** in good yield (Scheme 7). It must be noted that pre-complexation of the oxazole with borane is essential for clean deprotonation at C2 to take place. In the absence of borane, degradation of the starting material through the well documented C-2 opening of oxazoles was the major product.[12]



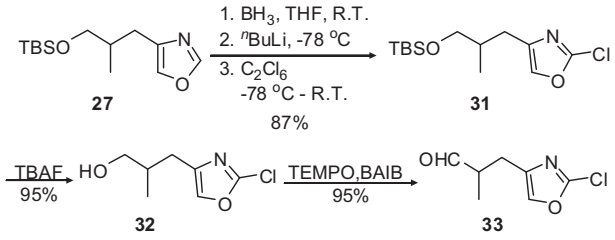
Scheme 7.

Unfortunately, all conditions attempted to remove the TBS group resulted in concomitant destannylation. In a number of cases, complete destannylation was observed before any desilylation had taken place. The highly unstable nature of the stannyl group made it clear that even if selective desilylation could have been achieved, it is unlikely that the stannane **29** would have survived coupling with the isobenzofuran anion and incorporation into the isochromanone core unit.

Furthermore, model Stille couplings of stannane **28** with 2-bromopropene failed to generate the expected alkenyl unit **30**, resulting instead in oxazole proto-destannylation. In any event, all attempts to introduce the tributylstannyl moiety directly onto any of the isochromanone units proved fruitless.

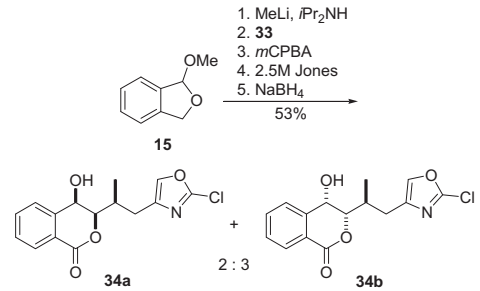
Hence, it was then decided to explore the use of the reverse Stille strategy in which the western section of ajudazol A, bearing a C-2 halogen substituted oxazole, could be coupled with a vinyl stannane containing eastern section. The use of 2-chloro oxazoles as Stille coupling partners has been recently described by Taylor as a way of generating 2-alkenyl oxazoles quickly and efficiently.[13]

Unfortunately, as in the case of the stannanes, direct chlorination of the isochromanone units **18**–**20** could not be achieved using a wide variety of reagents and conditions. However, using the borane complexation protocol, the TBS oxazole **27** was efficiently chlorinated at the C-2 position in excellent yield and with complete regio-selectivity to give chloride **31** (Scheme 8).[12] TBS removal then proceeded in near quantitative yield to provide the free alcohol **32**, which upon TEMPO oxidation yielded the key aldehyde precursor **33**.



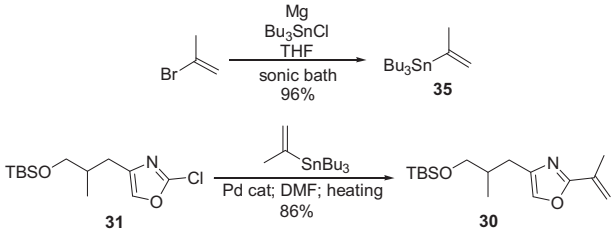
Scheme 8.

The chloro-aldehyde **33** was then coupled with phthalan **15** via our isobenzofuran based reaction sequence to yield the desired chloro-isochromanone unit as a 2:3 mixture of *syn*/*syn* and *anti*/*syn* diastereomers **34a** and **34b**. Significantly, no de-halogenated side products could be detected (Scheme 9).



Scheme 9.

With the key chloro-isochromanone units **34a** and **34b** at hand, the Stille coupling required to achieve the key C14–C15 bond formation was explored (Scheme 10). Initial model studies using the chlorooxazole intermediate **31** with vinyl stannane **35** as the coupling partner suggested that the coupling was highly dependent on the nature of the palladium ligands and the reaction temperature (Table 1).[14]



Scheme 10.

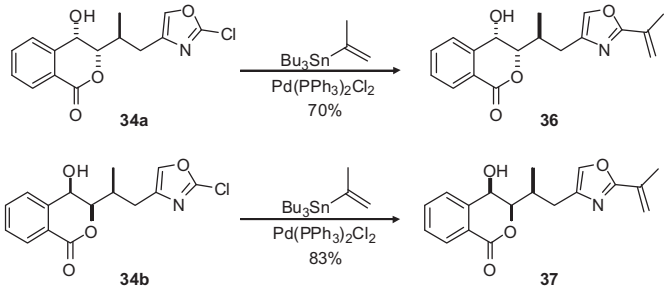
The optimised conditions (entry 3) proved to be robust and extremely reproducible, reliably affording the desired coupled oxazole **30** in high yields. More importantly, the same conditions were successfully used to couple both of the chloro-isochromanone units **34a** and **34b** with the vinyl stannane **35** to generate the

Table 1
Stille coupling optimisation conditions

	Heat source	Temp (°C)	Time (h)	Catalyst	Yield
1	Conv	60	72	$Pd(PPh_3)_2Cl_2$ (8%)	10 (25)
2	μwave	75	9	$Pd(PPh_3)_2Cl_2$ (8%)	17 (47)
3	μwave	130	12	$Pd(PPh_3)_2Cl_2$ (8%)	80
4	μwave	120	12	$Pd(PPh_3)_4$ (8%)	86
5	μwave	120	6	$Pd(PPh_3)_4$, TFP (20%)	78 (87)
6	μwave	120	2	$Pd_2(dba)_3$ (8%)	0
7	μwave	130	12	$Pd(PPh_3)_2Cl_2$ (8%), CuI (20%)	70

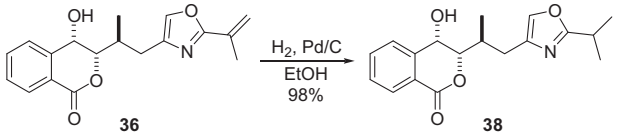
N.B Stille reactions carried out in anhydrous, degassed DMF; TFP: trifuryl phosphine (0.1 M) with 1.10 equiv of stannane **35**.
Yields in parenthesis are based on recovered starting material.

desired alkenyl units **36** and **37** incorporating the C1–C16 framework of ajudazol A in excellent yields (Scheme 11).



Scheme 11.

Furthermore, treatment of alkenyl oxazole **36** under standard hydrogenation conditions cleanly and efficiently reduced the methylene group into the corresponding methyl unit and thus completing the C1–C16 framework of ajudazol B **38** in excellent yield (Scheme 12).



Scheme 12.

In conclusion, we have completed the C1–C16 frameworks of both ajudazol A and ajudazol B taking advantage of a Stille coupling and an α-hydroxyisobenzofuran oxidative rearrangement to generate the key 4,8-dihydroxyisochroman-1-one and alkenyl oxazole units, respectively. Furthermore, we have shown that the isobenzofuran anion methodology is compatible with sensitive aldehydes. Efforts in our group are focussed on the application of this methodology to the total synthesis of the ajudazols.

3. Experimental

3.1. General

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether, dichloromethane (DCM), and toluene were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at ≤40 °C.

IR spectra were recorded using a JASCO FT/IR410 Fourier Transform spectrometer using a diamond gate. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}). Melting points were recorded using a Bibby Stuart Scientific Melting Point SMP1 and are uncorrected.

Proton magnetic resonance spectra (^1H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were, respectively, recorded either at 400 MHz and 100 MHz using a Bruker DPX Avance400 instrument or at 500 MHz and 125 MHz using a Bruker AvanceIII 500 Instrument. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, sext=sextet, sept=septet, m=multiplet, b=broad, dm=double multiplet), and (3) coupling constant (J) quoted in Hertz to the nearest 0.1 Hz. High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray and chemical ionisation mass spectrometer operating at a resolution of 15,000 full widths at half height. Flash chromatography was performed using silica gel (Fluorochem Scientific Silica Gel 60, 40–63 μ) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F_{254}) or aluminium oxide (Merck Aluminium Oxide 60 F_{254} neutral) where specified. The plates were visualised by the quenching of UV fluorescence (λ_{max} 254 nm) and/or by staining with either anisaldehyde, potassium permanganate, iodine or cerium ammonium molybdate followed by heating.

3.1.1. (±)-(3R,4R)-4-Hydroxy-3-((S)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one, ***18a*** *and (±)-(3S,4S)-4-hydroxy-3-((S)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one,* ***18b****.* A 0 °C solution of 1-methoxy-1,3-dihydroisobenzofuran **15** (1.47 g, 9.8 mmol) in anhydrous THF (50 mL), was treated with diisopropylamine (137 μL, 0.9 mmol) and stirred for 10 min. Methyllithium solution (1.6 M in diethyl ether, 12.9 mL, 20.5 mmol) was then added slowly, and the solution was stirred at 0 °C for 30 min. The reaction mixture was cooled to −78 °C, and 2-methyl-3-(oxazol-4-yl)propanal **14** (1.50 g, 10.8 mmol) was added dropwise. The resulting solution was then stirred for a further 90 min at −78 °C (until TLC analysis on alumina plates showed reaction completion) before being warmed up and quenched with water at 0 °C. The mixture was extracted with diethyl ether (3×100 mL) and the combined organic extracts were washed with water (50 mL), saturated brine solution (50 mL), and dried over sodium sulfate. The solvent was removed under reduced pressure at room temperature to afford the desired α-hydroxyisobenzofuran intermediate, which was used in the next step without further purification.

The crude α-hydroxyisobenzofuran unit was dissolved in anhydrous DCM (50 mL) and cooled to 0 °C. The resulting solution was then treated with 3-chloroperoxybenzoic acid (77%, 2.41 g, 10.8 mmol) and the reaction was stirred at 0 °C until completion by TLC analysis on alumina plates (2 h). The reaction was quenched with saturated sodium bicarbonate solution (40 mL), extracted with dichloromethane (3×100 mL) and the combined organic extracts were dried over sodium sulfate. The solvent was then removed under reduced pressure at room temperature to afford the crude keto–lactol as a yellow oil, which was taken on as crude immediately to the next step without further purification.

The freshly prepared keto–lactol unit was dissolved in anhydrous DCM (60 mL) and sequentially treated with (diacetoxyiodo) benzene (8.82 g, 27.4 mmol) and TEMPO (305 mg, 1.9 mmol) under argon. The reaction mixture was stirred at room temperature completion as indicated by TLC analysis (12 h). The reaction was then diluted with DCM (100 mL) and washed with saturated sodium thiosulfate solution (2×30 mL), water (2×30 mL), and brine (30 mL). The organic layer was dried over sodium sulfate and then concentrated under reduced pressure. The crude residue was

purified by flash column chromatography (silica gel, elution gradient 0–10% diethyl ether/petroleum ether) to afford the desired keto–lactone intermediate as a colourless oil.

The keto–lactone intermediate was dissolved in anhydrous methanol (50 mL) and treated with sodium borohydride (518 mg, 13.7 mmol). The resulting reaction mixture was then stirred at −78 °C until completion as indicated by TLC analysis (90 min). The reaction mixture was then warmed to 0 °C and quenched with water (20 mL) and 10% aq citric acid (20 mL). The biphasic solution was stirred at room temperature for 20 min before being extracted with DCM (3×70 mL). The combined organic extracts were washed with water (3×15 mL), saturated brine solution (15 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, elution gradient 0–50% diethyl ether in petroleum ether) to give (±)-(3*R*,4*R*)-4-hydroxy-3-((*S*)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one, **18a** (749 mg, 28%) as a colourless crystalline solid. Further elution afforded (±)-(3*S*,4*S*)-4-hydroxy-3-((*S*)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one, **18b** (1.12 g, 42%) as a colourless crystalline solid.

*3.1.2. (±)-(3R,4R)-4-Hydroxy-3-((S)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one, **18a**.* ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.23 (3H, d, J=6.7 Hz), 2.56–2.64 (1H, m), 2.69 (1H, dd, J=15.2, 5.5 Hz), 2.78 (1H, ddd, J=15.2, 5.4, 0.9 Hz), 4.23 (1H, dd, J=9.2, 1.7 Hz), 5.02 (1H, s), 7.49–7.55 (3H, m), 7.65 (1H, td, J=7.5, 1.4 Hz), 7.85 (1H, br s), 8.16–8.12 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.9, 28.5, 33.1, 65.0, 84.8, 124.6, 128.2, 129.8, 130.4, 134.4, 135.7, 137.7, 140.5, 151.4, 165.2; m/z [Cl^+ (+ve), isobutene] 274 $[M+H]^+$ (100%); HRMS found $[M+H]^+$ 274.1075, $C_{15}H_{16}NO_4$ requires 274.1079; ν_{max}/cm^{-1} (film): 3377, 2932, 1713; melting point: 160–162 °C.

*3.1.3. (±)-(3S,4S)-4-Hydroxy-3-((S)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one, **18b**.* ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.11 (3H, d, J=6.5 Hz), 2.59–2.68 (2H, m), 3.04 (1H, br d, J=5.6 Hz), 3.14 (1H, d, J=14.0 Hz), 4.23 (1H, dd, J=8.7, 1.3 Hz), 4.78 (1H, d, J=6.3 Hz), 7.45–7.50 (2H, m), 7.53 (1H, td, J=7.7, 1.3 Hz), 7.65 (1H, td, J=7.3, 1.0 Hz), 7.72 (1H, s), 8.13 (1H, d, J=7.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.5, 28.2, 33.6, 65.6, 84.0, 124.5, 128.2, 130.1, 130.6, 134.5, 135.8, 138.2, 140.4, 150.9, 164.8; m/z [Cl^+ (+ve), isobutene] 274 $[M+H]^+$ (100%); HRMS found $[M+H]^+$ 274.1082, $C_{15}H_{16}NO_4$ requires 274.1079; ν_{max}/cm^{-1} (film): 3187, 2984, 2971, 1707; melting point: 196–198 °C.

*3.1.4. (±)-(3S,4R)-3-((S)-1-(Oxazol-4-yl)propan-2-yl)-1-oxoisochroman-4-yl 4-nitrobenzoate, **19**.* A solution of (±)-(3*S*,4*S*)-4-hydroxy-3-((*S*)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one, **18b** (413 mg, 1.5 mmol) in anhydrous toluene (21 mL) was treated with triphenylphosphine (991 mg, 3.7 mmol) and 4-nitrobenzoic acid (480 mg, 3.8 mmol) and the resulting solution was cooled down to 0 °C. The solution was treated dropwise with diisopropylazodicarboxylate (744 μL, 3.8 mmol) before being warmed up and heated at reflux under argon for 16 h. The reaction mixture was cooled to room temperature before the solvent was evaporated under reduced pressure and the crude residue purified by flash column chromatography (silica gel, elution gradient 0–15% ethyl acetate in hexanes) to afford the desired nitrobenzoate ester **19** (415 mg, 65%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.04 (3H, d, J=6.9 Hz), 2.08–2.12 (1H, m), 2.63 (1H, dd, J=14.7, 8.2 Hz), 2.94 (1H, dd, J=14.6, 4.1 Hz), 4.71 (1H, dd, J=8.9, 2.9 Hz), 6.35 (1H, d, J=2.9 Hz), 7.49 (1H, s), 7.56–7.57 (1H, m), 7.60 (1H, td, J=7.6, 1.4 Hz), 7.67 (1H, td, J=7.5, 1.4 Hz), 7.79 (1H, s), 8.17–8.21 (3H, m), 8.25–8.28 (2H, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.2, 28.5, 35.0, 68.7, 84.3, 123.8, 128.7, 128.8, 128.9, 130.6, 130.9, 131.2, 132.2, 132.3, 134.2, 134.6, 136.0, 137.3, 151.0, 151.2, 163.1, 164.0; m/z [EI^+ (+ve)] 422 $[M]^+$ (100%); HRMS found $[M]^+$ 422.1119, $C_{22}H_{18}N_2O_7$ requires 422.1114; ν_{max}/cm^{-1} (film): 3115, 2970, 2936, 1722, 1607, 1528.

*3.1.5. (±)-(3S,4R)-4-Hydroxy-3-((S)-1-(oxazol-4-yl)propan-2-yl)isochroman-1-one, **20**.* A solution of (±)-(3*S*,4*R*)-3-((*S*)-1-(oxazol-4-yl) propan-2-yl)-1-oxoisochroman-4-yl 4-nitrobenzoate, **19** (117 mg, 0.3 mmol) in anhydrous methanol (2 mL) was treated with sodium azide (72 mg, 1.1 mmol) and stirred under argon at 40 °C for 24 h. The reaction mixture was then cooled down to room temperature and quenched by the addition of water (5 mL) before being extracted with ethyl acetate (3×20 mL). The combined organics were washed with water (5 mL) and saturated aqueous brine (5 mL) before being dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to yield a crude product, which was purified by flash column chromatography (silica gel, elution gradient 0–75% ethyl acetate in hexanes) to afford the desired product, (±)-(3*S*,4*R*)-4-hydroxy-3-((*S*)-1-(oxazol-4-yl)propan-2-yl) isochroman-1-one, **20** (58 mg, 77%) as a white crystalline solid.

^{1}H NMR (C_6D_6, 400 MHz) δ: 0.93 (3H, d, J=7.1 Hz), 2.06 (1H, dd, J=15.6, 6.1 Hz), 2.37–2.46 (1H, m), 2.69 (1H, ddd, J=15.6, 5.8, 1.4 Hz), 4.03 (1H, dd, J=10.5, 2.2 Hz), 4.68 (1H, dd, J=10.4, 4.9 Hz), 5.98 (1H, d, J=5.9 Hz), 6.62 (1H, s), 6.91 (1H, s), 7.00 (1H, t, J=7.6 Hz), 7.21 (1H, td, J=7.6, 1.3 Hz), 7.83 (1H, d, J=7.7 Hz), 8.21 (1H, dd, J=7.7, 1.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 18.2, 25.8, 32.3, 65.1, 86.0, 123.6, 124.6, 128.2, 130.1, 134.3, 135.3, 138.9, 143.4, 151.5, 165.3; m/z [EI^+ (+ve)] 273 $[M]^+$ (100%); HRMS found $[M]^+$ 273.1003, $C_{15}H_{15}O_4N$ requires 273.1001; ν_{max}/cm^{-1} (film): 3213, 2963, 2922, 2853, 1721, 1605, 1514, 1456; melting point: 158–160 °C.

*3.1.6. (±)-4-(3-(tert-Butyldiphenylsilyloxy)-2-methylpropyl)oxazole, **22**.* (±)-2-Methyl-3-(oxazol-4-yl)propan-1-ol **21** (959 mg, 6.8 mmol) was dissolved in anhydrous DMF (14 mL) and then sequentially treated with imidazole (924 mg, 13.6 mmol) and *tert*-butylchlorodiphenylsilane (2.12 mL, 8.2 mmol) and the resulting homogeneous solution was stirred under argon at room temperature for 150 min. The reaction mixture was then diluted with diethyl ether (300 mL) and washed with water (5×60 mL) followed by saturated brine solution (50 mL) before being dried over sodium sulfate. The solvent was evaporated under reduced pressure to afford a crude product that was purified by flash column chromatography (silica gel, elution gradient 0–10% diethyl ether in petroleum ether) to afforded the desired (±)-4-(3-(*tert*-butyldiphenylsilyloxy)-2-methylpropyl)oxazole **22** (2.51 g, 97%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.95 (3H, d, J=6.8 Hz), 1.06 (6H, s), 1.07 (3H, s), 2.05–2.13 (1H, m,), 2.38 (1H, dd, J=14.6, 8.0 Hz), 2.75 (1H, dd, J=14.5, 5.9 Hz), 3.53 (2H, d, J=5.6 Hz), 7.30 (1H, s), 7.36–7.45 (6H, m), 7.66 (3H, m), 7.71–7.73 (1H, m), 7.79 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.7, 19.5, 26.7, 27.0, 29.7, 35.3, 68.2, 127.8, 129.8, 133.9, 134.8, 135.8, 139.1, 150.8; m/z [Cl^+ (+ve), isobutane] 380 $[M+H]^+$ (100%); HRMS found $[M+H]^+$ 380.2050, $C_{23}H_{30}NO_2Si$ requires 380.2046; ν_{max}/cm^{-1} (film): 2959, 2932, 2859, 1427.

*3.1.7. (±)-4-(3-(tert-Butyldiphenylsilyloxy)-2-methylpropyl)-2-(prop-1-en-2-yl)oxazole, **23**. Method A: Pd catalyzed C–H activation.* A mixture of (±)-4-(3-(*tert*-butyldiphenylsilyloxy)-2-methylpropyl)oxazole, **21** (80 mg, 0.2 mmol), tetrakis-(triphenylphosphine)palladium (13 mg, 11 μmol), lithium *tert*-butoxide (34 mg, 0.4 mmol) and 2-bromopropene (38 μL, 0.4 mmol) in anhydrous 1,4-dioxane (0.6 mL) was stirred in a sealed tube at 110 °C for 24 h under an atmosphere of argon. The reaction was then cooled down to room temperature before being quenched with water (5 mL) and extracted with ethyl acetate (3×20 mL). The resultant organics were washed with water (2×7 mL) and saturated brine solution (10 mL) before being dried over sodium sulfate and solvent evaporated to afford the crude product. Purification by flash

column chromatography (silica gel elution gradient 0–0.5% ethyl acetate in pentane) of the crude residue afforded the desired product, (±)-4-(3-(*tert*-butyldiphenylsilyloxy)-2-methylpropyl)-2-(prop-1-en-2-yl)oxazole **23** (51 mg, 58%) as a colourless oil. Further elution with 5% ethyl acetate in pentane afforded the recovered starting material, (±)-4-(3-(*tert*-butyldiphenylsilyloxy)-2-methylpropyl)oxazole **22** (9 mg, 11%) as a colourless oil.

Method B: *Cu catalyzed C–H activation*. A suspension of (±)-4-(3-(*tert*-butyldiphenylsilyloxy)-2-methylpropyl)oxazole **21** (80 mg, 0.2 mmol), *trans-N,N′*-dimethylcyclohexane-1,2-diamine (6 mg, 4 μmol), copper iodide (4 mg, 21 μmol), lithium *tert*-butoxide (34 mg, 0.4 mmol) and 2-bromopropene (38 μL, 0.4 mmol) in anhydrous 1,4-dioxane (0.6 mL) was stirred in a sealed tube at 110 °C under an atmosphere of argon for 24 h. The reaction mixture was then cooled down to room temperature before being quenched with water (5 mL) and extracted with ethyl acetate (3×20 mL). The combined organics were washed with water (2×7 mL) and saturated brine solution (10 mL) before being dried over sodium sulfate and the solvent evaporated under reduced pressure. Purification of the crude residue by flash column chromatography (silica gel, elution gradient with 0–1% ethyl acetate in pentane) afforded the desired product, (±)-4-(3-(*tert*-butyldiphenylsilyloxy)-2-methylpropyl)-2-(prop-1-en-2-yl)oxazole **23** (55 mg, 62%) as a colourless oil. Further elution with 5% ethyl acetate in pentane afforded the recovered starting material, (±)-4-(3-(*tert*-butyldiphenylsilyloxy)-2-methylpropyl)oxazole **22** (10 mg, 12%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.00 (3H, d, J=6.7 Hz), 1.07 (9H, s), 2.05–2.12 (1H, m), 2.14–2.16 (3H, m), 2.39 (1H, ddd, J=14.6, 7.8, 0.9 Hz), 2.71 (1H, ddd, J=14.6, 6.3, 0.9 Hz), 3.54 (1H, dd, J=9.9, 5.6 Hz), 3.59 (1H, dd, J=9.9, 5.3 Hz), 5.32–5.33 (1H, m), 5.89–5.91 (1H, m), 7.20 (1H, br s), 7.36–7.44 (6H, m), 7.65–7.68 (4H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.9, 19.3, 19.5, 27.0, 30.0, 35.2, 68.1, 117.6, 127.7, 129.7, 132.0, 134.0, 134.5, 135.7, 140.6, 162.3; m/z [FAB$^+$ (+ve), NOBA] 420 $[M+H]^+$ (100%); HRMS found $[M+H]^+$ 420.2354, $C_{26}H_{34}NO_2Si$ requires 420.2359; ν_{max}/cm^{-1} (film): 2959, 2930, 2857, 1589, 1532, 1462, 1427.

3.1.8. (±)-4-(3-(tert-Butyldimethylsilyloxy)-2-methylpropyl)oxazole, ***27***. A solution of (±)-2-methyl-3-(oxazol-4-yl)propan-1-ol **21** (1.31 g, 9.3 mmol) in anhydrous DMF (15 mL) was treated with imidazole (1.26 g, 18.5 mmol) and *tert*-butylchlorodimethylsilane (1.66 g, 10.7 mmol) and the resulting homogeneous mixture was stirred under argon at room temperature for 16 h. The reaction mixture was then diluted with diethyl ether (300 mL) and washed sequentially with water (5×60 mL) and brine (50 mL) before being dried over sodium sulfate. The solvent was evaporated under vacuum to afford a crude residue that was purified by flash column chromatography (silica gel, elution gradient 0–10% diethyl ether in petroleum ether) to afford the desired product, (±)-4-(3-(*tert*-butyldimethylsilyloxy)-2-methylpropyl)oxazole **27** (2.09 g, 88%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.03 (6H, s), 0.89 (9H, s), 0.90 (3H, d, J=6.8 Hz), 1.98–2.02 (1H, m), 2.32 (1H, dd, J=14.6, 8.2 Hz), 2.68 (1H, ddd, J=14.6, 5.8, 1.0 Hz), 3.43–3.49 (2H, m), 7.40 (1H, m), 7.81 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: −5.3, −5.2, 16.6, 18.5, 26.1, 29.6, 35.3, 67.5, 135.0, 139.3, 150.8; m/z [CI$^+$ (+ve), isobutane] 256 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 256.1737, $C_{13}H_{26}NO_2Si$ requires 256.1733; ν_{max}/cm^{-1} (film): 2959, 2930, 2859.

3.1.9. (±)-4-(3-(tert-Butyldimethylsilyloxy)-2-methylpropyl)-2-(tributylstannyl)oxazole, ***28***. (±)-4-(3-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl)oxazole **27** (1.50 g, 5.9 mmol) was dissolved in anhydrous THF (35 mL) and treated with a 1 M solution of borane in tetrahydrofuran (6.18 mL, 6.2 mmol). The solution was stirred under argon at room temperature for 30 min and then cooled down to −78 °C. *n*-Butyllithium (2.5 M in hexanes, 2.47 mL, 6.2 mmol) was then added dropwise over 5 min and the resulting mixture was allowed to stir at −78 °C for a further 25 min before being quenched with the dropwise addition of tributyltin chloride (1.68 mL, 5.9 mmol). The resulting mixture was stirred for 30 min at −78 °C before being warmed up to 0 °C and quenched with water (4 mL). The biphasic mixture was diluted with diethyl ether (25 mL), the phases separated, and the organic fraction was sequentially washed with water (3×5 mL) and brine (8 mL) before being dried over sodium sulfate. The solvent was evaporated under reduced pressure to afford a crude residue that was purified by flash column chromatography (silica gel, elution gradient 0–2% diethyl ether in petroleum ether) to afford (±)-4-(3-(*tert*-butyldimethyllsilyloxy)-2-methylpropyl)-2-(tributylstannyl)oxazole, **28** (2.23 g, 69%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: −0.04 (6H, s), 0.88 (9H, s), 0.88–0.93 (9H, m), 0.94 (3H, d, J=6.7 Hz), 1.26–1.35 (12H, m), 1.55–1.61 (6H, m), 2.07–2.12 (1H, m), 2.49 (1H, ddd, J=15.4, 8.0, 0.9 Hz), 2.81 (1H, ddd, J=15.4, 6.2, 1.0 Hz), 3.46–3.51 (2H, m), 7.58 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: −5.3, −5.3, 12.1, 13.8, 16.8, 18.5, 26.1, 27.0, 27.2, 28.8, 34.1, 67.4, 137.4, 139.9, 177.5; m/z [CI$^+$ (+ve)] 670 $[M+H]^+$ (100%). HRMS found $[M+H]^+$ 670.3105, $C_{35}H_{56}NO_2Si^{118}Sn$ requires 670.3102; ν_{max}/cm^{-1} (film): 2959, 2932, 2857.

3.1.10. (±)-4-(3-(tert-Butyldimethylsilyloxy)-2-methylpropyl)-2-chlorooxazole, ***31***. A solution of (±)-4-(3-(*tert*-butyldimethylsilyloxy)-2-methylpropyl)oxazole **27** (2.2 g, 8.4 mmol) in anhydrous THF (40 mL) was treated with borane (1 M in THF, 8.86 mL, 8.9 mmol) and the resulting mixture was stirred under argon at room temperature for 30 min. The solution was cooled down to −78 °C, and *n*-butyllithium (2.5 M in hexane) (5.54 mL, 8.9 mmol) was added dropwise over 5 min. The reaction mixture was stirred for 25 min at −78 °C before being quenched with the dropwise addition of a solution of hexachloroethane (3.99 g, 16.9 mmol) in THF (15 mL). The reaction mixture was stirred for 60 min at −78 °C before being warmed up to 0 °C and stirred for a further 2 h before being quenched with water (50 mL). The mixture was diluted with diethyl ether (100 mL) and the phases separated. The organic fraction was sequentially washed with water (3×20 mL) and brine (30 mL) before being dried over sodium sulfate. The solvent was evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography (silica gel, elution gradient 0–5% diethyl ether in petroleum ether) to afford (±)-4-(3-(*tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-chlorooxazole, **31** (2.12 g, 87%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.02 (6H, s), 0.88 (9H, s), 0.89 (3H, d, J=6.5 Hz), 1.97–1.99 (1H, m), 2.25 (1H, ddd, J=14.7, 8.2, 0.9 Hz), 2.63 (1H, ddd, J=14.7, 5.8, 1.1 Hz), 3.42–3.47 (2H, m), 7.35 (1H, br t, J=1.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: −5.3, 16.5, 18.4, 26.0, 29.9, 35.0, 67.3, 137.2, 142.2, 146.4; m/z [CI$^+$ (+ve)] 290 $[M(^{35}Cl)+H]^+$ (100%), 292 $[M(^{37}Cl)+H]^+$ (35%); HRMS found $[M+H]^+$ 290.1350, $C_{13}H_{25}^{35}ClNO_2Si$ requires 290.1343; ν_{max}/cm^{-1} (film): 2957, 2930, 2886, 2857, 1520, 1472, 1464.

3.1.11. (±)-3-(2-Chlorooxazol-4-yl)-2-methylpropan-1-ol, ***32***. A 0 °C solution of (±)-4-(3-(*tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-chlorooxazole, **31** (2.00 g, 6.90 mmol) in anhydrous THF (28 mL) was treated with the dropwise addition of tetrabutylammonium fluoride (1 M in THF, 10.4 mL, 10.4 mmol). After 30 min, the reaction mixture was warmed up to room temperature and stirred for 16 h before being quenched with water (20 mL) and extracted with diethyl ether (3×50 mL). The combined organics were washed sequentially with water (3×10 mL) and brine (20 mL) before being dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a crude product that was purified by flash column chromatography (silica gel, elution gradient 0–50% diethyl

ether in petroleum ether) to yield (±)-3-(2-chlorooxazol-4-yl)-2-methylpropan-1-ol, **32** (1.15 g, 95%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.92 (3H, d, J=6.7 Hz), 1.97–2.06 (1H, m), 2.29 (1H, br s), 2.43 (1H, ddd, J=14.7, 7.0, 0.8 Hz), 2.58 (1H, ddd, J=14.7, 6.2, 1.1 Hz), 3.47 (1H, dd, J=11.0, 6.4 Hz), 3.54 (1H, dd, J=10.9, 5.4 Hz), 7.40 (1H, br t, J=0.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.6, 29.8, 35.0, 67.0, 137.4, 141.5, 146.6; m/z [EI$^+$ (+ve)] 175 [M(^{35}Cl)]$^+$ (100%), 177 [M(^{37}Cl)]$^+$ (100%); HRMS found [M]$^+$ 175.0404, $C_7H_{10}^{35}ClNO_2$ requires 175.0400; ν_{max}/cm^{-1} (film): 3390, 2963, 2930, 2875, 1520.

*3.1.12. (±)-3-(2-Chlorooxazol-4-yl)-2-methylpropanal, **33**.* A solution of (±)-3-(2-chlorooxazol-4-yl)-2-methylpropan-1-ol **32** (1.15 mg, 6.6 mmol) in anhydrous DCM (30 mL) was treated sequentially with (diacetoxyiodo)benzene (2.54 g, 7.9 mmol) and TEMPO (103 mg, 0.7 mmol). The resulting mixture was stirred at room temperature under an atmosphere of argon for 16 h before being diluted with DCM (250 mL) and washed with saturated sodium thiosulfate solution (2×60 mL), water (2×30 mL) and brine (30 mL). The organic fraction was then dried over sodium sulfate and concentrated under reduced pressure to afford a crude orange oil. Purification of the crude residue by flash column chromatography (silica gel, elution gradient 0–10% diethyl ether in petroleum ether) afforded (±)-3-(2-chlorooxazol-4-yl)-2-methylpropanal **33** (1.09 g, 95%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.15 (3H, d, J=7.2 Hz), 2.53 (1H, ddd, J=14.9, 7.1, 0.9 Hz), 2.76–2.84 (1H, m), 2.93 (1H, ddd, J=14.9, 6.6, 1.1 Hz), 7.42 (1H, t, J=1.0 Hz), 9.71 (1H, d, J=1.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.5, 27.1, 45.2, 137.7, 140.4, 146.9, 203.5; m/z [CI$^+$ (+ve), isobutane] 174 [M(^{35}Cl)+H]$^+$ (100%), 176 [M(^{37}Cl)+H]$^+$ (35%); HRMS found [M+H]$^+$ 174.0321, $C_7H_9NO_2^{35}Cl$ requires 174.0322; ν_{max}/cm^{-1} (film): 2967, 2930, 2884, 2856, 1724.

*3.1.13. (±)-(3R,4R)-3-((S)-1-(2-Chlorooxazol-4-yl)propan-2-yl)-4-hydroxyisochroman-1-one, **34a**, and (±)-(3S,4S)-3-((S)-1-(2-chlorooxazol-4-yl)propan-2-yl)-4-hydroxyisochroman-1-one, **34b**.* Using the same general procedure described for the synthesis of 4-hydroxy-3-isochroman-1-ones **18a** and **18b**, a solution (±)-1-methoxy-1,3-dihydroisobenzofuran **15** (1.36 mg, 9.08 mmol) in anhydrous THF (45 mL) was treated with diisopropylamine (2.67 mL, 19.1 mmol), *n*-butyllithium solution (1.6 M in hexanes, 11.9 mL, 19.1 mmol) and (±)-3-(2-chlorooxazol-4-yl)-2-methylpropanal **33** (1.67 g, 9.63 mmol) to generate the putative α-hydroxyisobenzofuran intermediate. Oxidative rearrangement of the crude intermediate was performed using 3-chloroperoxybenzoic acid (77%, 2.24 g, 9.99 mmol) in anhydrous DCM (45 mL) to afford the crude keto–lactols. Oxidation of the lactol unit was performed in acetone (45 mL) using 2.5 M Jones reagent (6 mL). Purification of the crude residue using flash chromatography (silica gel, elution gradient 0–20% diethyl ether in petroleum ether) afforded the keto–lactone intermediates (1.60 g, 58%) as a 2:3 ratio of *syn*/*anti* diastereoisomers as a yellow oil. Reduction of the keto–lactone intermediates was performed at −78 °C in methanol (25 mL) with sodium borohydride (243 mg, 6.68 mmol). The crude products were purified by flash column chromatography (silica gel, elution gradient 0–1% methanol in dichloromethane) to yield (±)-(3*R*,4*R*)-3-((*S*)-1-(2-chlorooxazol-4-yl)propan-2-yl)-4-hydroxyisochroman-1-one, **34a** (581 mg, 21%) as a colourless oil. Further elution afforded (±)-(3*S*,4*S*)-3-((*S*)-1-(2-chlorooxazol-4-yl)propan-2-yl)-4-hydroxyisochroman-1-one, **34b** (889 mg, 32%) also as a colourless oil.

Compound **34a**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.20 (3H, d, J=6.7 Hz), 2.56–2.65 (2H, m), 2.77–2.81 (1H, m), 3.05 (1H, br d, J=6.1 Hz), 4.25 (1H, dd, J=8.5, 1.7 Hz), 4.98 (1H, d, J=1.6 Hz), 7.47 (1H, s), 7.50 (1H, br d, J=7.6 Hz), 7.53 (1H, td, J=7.7, 1.2 Hz), 7.66 (1H, td, J=7.5, 1.3 Hz), 8.13 (1H, dd, J=7.8, 1.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.2, 28.9, 33.1, 65.3, 84.0, 124.3, 128.0, 129.8, 130.4, 134.4, 137.7, 140.2, 140.5, 146.9, 164.8; m/z [EI$^+$ (+ve)] 307 [M(^{35}Cl)]$^+$ (100%), 309 [M(^{37}Cl)]$^+$ (35%); HRMS found [M]$^+$ 307.0613, $C_{15}H_{14}^{35}ClNO_4$ requires 307.0611; ν_{max}/cm^{-1} (film): 3399, 3134, 2976, 2934, 1715, 1518, 1462.

Compound **34b**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.13 (3H, d, J=6.7 Hz), 2.27–2.28 (1H, m), 2.56–2.65 (2H, m), 3.08 (1H, dd, J=11.2, 1.0 Hz), 4.21 (1H, dd, J=9.1, 1.6 Hz), 4.76 (1H, d, J=3.8 Hz), 7.46–7.47 (2H, m), 7.54 (1H, td, J=7.6, 1.2 Hz), 7.66 (1H, td, J=7.5, 1.3 Hz), 8.13 (1H, dd, J=7.8, 1.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.1, 28.5, 33.1, 65.2, 83.7, 124.2, 128.1, 130.0, 130.5, 134.5, 137.9, 140.1, 140.9, 146.4, 164.6; m/z [EI$^+$ (+ve)] 307 [M(^{35}Cl)]$^+$ (100%), 309 [M(^{37}Cl)]$^+$ (35%). HRMS found [M]$^+$ 307.0616, $C_{15}H_{14}^{35}ClNO_4$ requires 307.0611; ν_{max}/cm^{-1} (film): 3399, 3129, 2974, 2934, 1717, 1518.

*3.1.14. Tributyl(prop-1-en-2-yl)stannane, **35**.* A round bottom flask charged with magnesium turnings (175 mg, 7.2 mmol), was treated with anhydrous THF (36 mL) followed by tributyltin chloride (1.50 mL, 5.5 mmol). The heterogeneous mixture was then sonicated at room temperature under an argon atmosphere for 2 min before being treated with the dropwise addition of 2-bromopropene (639 μL, 7.2 mmol). The reaction mixture was sonicated for a further 3 h by which time no magnesium turnings were longer visible. The reaction was quenched by the addition of water (50 mL) and extracted with diethyl ether (3×50 mL). The combined organics were washed with water (15 mL) and brine (20 mL) before being dried over sodium sulfate and concentrated under reduced pressure to afford a crude colourless oil. Purification of the crude residue by flash column chromatography (silica gel, petroleum ether) afforded tributyl(prop-1-en-2-yl)stannane **35** (1.95 g, 96%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.89–0.92 (15H, m), 1.30–1.35 (6H, m), 1.47–1.54 (6H, m), 1.97 (3H, app t, J=1.6 Hz), 5.09 (1H, dq, J=3.0, 1.4 Hz), 5.69 (1H, dq, J=3.1, 1.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 9.3, 13.9, 27.5, 27.6, 29.3, 125.7, 150.5. m/z [EI$^+$ (+ve)] 332 [M]$^+$ (100%). HRMS found [M]$^+$ 332.1534, $C_{15}H_{32}^{118}Sn$ requires 332.1529; ν_{max}/cm^{-1} (film): 2957, 2928, 2872, 2853, 1458.

*3.1.15. (±)-4-(3-(tert-Butyldimethylsilyloxy)-2-methylpropyl)-2-(prop-1-en-2-yl)oxazole, **30**.* (±)-4-(3-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl)-2-chlorooxazole (60 mg, 0.21 mmol), tributyl(prop-1-en-2-yl)stannane **31** (83 mg, 2.28 mmol) and bis(-triphenylphosphine)palladium(II)dichloride (12 mg, 17 μmol) were combined in an oven dried microwave vial and degassed anhydrous DMF (2 mL) was added. The resulting heterogeneous solution was heated under an atmosphere of argon under microwave irradiation at 130 °C for 12 h. The reaction was cooled and the crude mixture was passed through a pad of Celite and eluted with diethyl ether (10 mL). The organics were then washed with water (4×4 mL) and brine (5 mL) before being dried over sodium sulfate. The solvent was evaporated under reduced pressure to afford a crude colourless oil. Purification of the crude residue by flash column chromatography (silica gel, elution gradient 0–2% diethyl ether in petroleum ether) afforded (±)-4-(3-(*tert*-butyldimethylsilyloxy)-2-methylpropyl)-2-(prop-1-en-2-yl)oxazole, **30** (50 mg, 86%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.03 (6H, s), 0.89 (9H, s), 0.92 (3H, d, J=6.7 Hz), 1.96–2.04 (1H, m), 2.15 (3H, dd, J=1.5, 1.0 Hz), 2.32 (1H, ddd, J=14.6, 7.9, 0.9 Hz), 2.64 (1H, ddd, J=14.6, 6.1, 1.0 Hz), 3.45 (1H, dd, J=9.8, 5.9 Hz), 3.50 (1H, dd, J=9.9, 5.5 Hz), 5.32 (1H, quint, J=1.5 Hz), 5.87–5.90 (1H, m), 7.30 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: −5.2, 16.8, 18.5, 19.3, 26.1, 29.9, 35.2, 67.5, 117.6, 132.0, 134.5, 140.7, 162.4; m/z [CI$^+$ (+ve),] 296 [M+H]$^+$ (100%). HRMS found [M+H]$^+$ 296.2049, $C_{16}H_{30}NO_2Si$ requires 296.2046; ν_{max}/cm^{-1} (film): 2959, 2930, 2858, 1671, 1541, 1548, 1465.

*3.1.16. (±)-(3S,4S)-4-Hydroxy-3-((S)-1-(2-(prop-1-en-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one, **36**.* (±)-(3*S*,4*S*)-3-((*S*)-1-(2-Chlorooxazol-4-yl)propan-2-yl)-4-hydroxyisochroman-1-one **34a**

(197 mg, 0.64 mmol), tributyl(prop-1-en-2-yl)stannane (251 mg, 0.69 mmol) and bis(triphenylphosphine)palladium(II) dichloride (36 mg, 51 μmol) were combined together in an oven dried microwave vial with degassed, anhydrous DMF (3.2 mL) and heated 120 °C under microwave for 12 h under an atmosphere of argon for 12 h. The crude mixture was passed through a pad of Celite and eluted with diethyl ether (50 mL). The organics were then washed with water (2×10) and brine (10 mL) before being dried over sodium sulfate. The solvent was evaporated under reduced pressure to afford the crude product as a yellow oil. Purification by flash column chromatography (silica gel, elution gradient 0–10% diethyl ether in DCM) afforded (±)-(3*S*,4*S*)-4-hydroxy-3-((*S*)-1-(2-(prop-1-en-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one **36** (140 mg, 70%), as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.16 (3H, d, J=6.7 Hz), 2.12 (3H, br s), 2.53–2.63 (2H, m), 2.93 (1H, d, J=6.8 Hz), 3.13–3.16 (1H, m), 4.23 (1H, dd, J=8.5, 1.6 Hz), 4.79 (1H, d, J=5.4 Hz), 5.32 (1H, t, J=1.5 Hz), 5.89 (1H, s), 7.39 (1H, s), 7.46 (1H, d, J=7.7 Hz), 7.52 (1H, td, J=7.6, 1.2 Hz), 7,64 (1H, td, J=7.5, 1.4 Hz), 8.14 (1H, dd, J=7.7, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.9, 19.2, 28.4, 33.9, 65.7, 84.1, 117.9, 124.5, 128.1, 130.0, 130.6, 131.8, 134.5, 135.1, 139.7, 140.5, 162.5, 164.9; m/z [CI$^+$ (+ve)] 314 [M+H]$^+$ (100%). HRMS found [M+H]$^+$ 314.1390, $C_{18}H_{20}NO_4$ requires 314.1392; ν_{max}/cm^{-1} (film): 3372, 2961, 2928, 2880, 1713, 1666, 1605, 1556, 1463.

3.1.17. (±)-(3S,4S)-4-Hydroxy-3-((R)-1-(2-(prop-1-en-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one, ***37***. (±)-(3*S*,4*S*)-3-((*R*)-1-(2-Chlorooxazol-4-yl)propan-2-yl)-4-hydroxyisochroman-1-one **34b** (93 mg, 0.3 mmol), tributyl(prop-1-en-2-yl)stannane (127 mg, 0.3 mmol) and bis(triphenylphosphine)palladium(II) dichloride (17 mg, 24 μmol) were combined in an oven dried microwave vial and suspended in anhydrous, degassed DMF (3 mL). The heterogeneous suspension was heated to 120 °C under microwave irradiation under an atmosphere of argon for 12 h. The crude mixture was passed through a pad of Celite and eluted with diethyl ether (30 mL). The organics were then washed with water (2×5) and brine (5 mL) before being dried over sodium sulfate. The solvent was evaporated under reduced pressure to yield a crude yellow oil. Purification of the crude residue by flash column chromatography (silica gel, elution gradient 0–10% diethyl ether in DCM) afforded (±)-(3*S*,4*S*)-4-hydroxy-3-((*R*)-1-(2-(prop-1-en-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one, **37** (79 mg, 83%), as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.27 (3H, d, J=6.7 Hz), 2.10 (3H, s), 2.56–2.74 (3H, m), 4.18 (1H, d, J=9.5 Hz), 5.04 (1H, d, J=2.4 Hz), 5.36 (1H, d, J=4.6 Hz), 5.38 (1H, s), 5.93 (1H, s), 7.41 (1H, s), 7.48–7.53 (2H, m), 7.64 (1H, d, J=7.0 Hz), 8.13 (1H, d, J=7.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1, 19.0, 28.6, 33.0, 64.8, 85.3, 119.0, 124.8, 128.1, 129.6, 130.3, 131.2, 134.3, 134.8, 139.2, 140.5, 163.0, 165.2; m/z [FAB$^+$ (+ve)] 314 [M+H]$^+$ (100%). HRMS found [M+H]$^+$ 314.1397, $C_{18}H_{20}NO_4$ requires 314.1392; ν_{max}/cm^{-1} (film): 3342, 2964, 2934, 2919, 2877, 1710, 1606, 1532, 1456.

3.1.18. (±)-(3S,4S)-4-Hydroxy-3-((S)-1-(2-(prop-1-en-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one, ***38***. A solution of (±)-(3*S*,4*S*)-4-hydroxy-3-((*S*)-1-(2-(prop-1-en-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one **36** (72 mg, 230 μmol) in absolute ethanol (3 mL) was charged with palladium on carbon (10% Pd on activated carbon, 11 mg). The suspension was then stirred under an atmosphere of hydrogen at room temperature until TLC analysis indicated reaction completion (4 h). The suspension was filtered through a plug of Celite and silica and the filtrate concentrated under reduced pressure to afford (±)-(3*S*,4*S*)-4-hydroxy-3-((*S*)-1-(2-(prop-1-en-2-yl) oxazol-4-yl)propan-2-yl)isochroman-1-one **38** (71 mg, 98%) as a colourless oil without the need of any further purification.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.15 (3H, d, J=6.7 Hz), 1.30 (6H, d, J=6.9 Hz), 2.50–2.57 (2H, m), 3.02 (1H, sept, J=7.0 Hz), 3.11–3.16 (1H, m), 3.19 (1H, d, J=6.7 Hz), 4.23 (1H, dd, J=7.9, 1.7 Hz), 4.79 (1H, d, J=5.0 Hz), 7.34 (1H, s), 7.47 (1H, d, J=7.5 Hz), 7.52 (1H, td, J=7.5, 1.2 Hz), 7.64 (1H, td, J=7.5, 1.3 Hz), 8.14 (1H, dd, J=7.8, 1.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.2, 20.5, 20.6, 28.2, 28.6, 34.1, 65.9, 84.2, 124.5, 128.1, 129.9, 130.6, 134.4, 134.6, 138.3, 140.6, 165.0, 168.9; m/z [CI$^+$ (+ve)] 316 [M+H]$^+$ (100%); HRMS found [M+H]$^+$ 316.1551, $C_{18}H_{22}NO_4$ requires 316.1549; ν_{max}/cm^{-1} (film): 3374, 2972, 2936, 2878, 1717, 1605, 1566.

3.2. Crystallographic data collection and refinement details

X-ray data for **20** were collected at 100 K on a Rigaku R-Axis RAPID Image Plate diffractometer equipped with an Oxford Cryosystems Cryostream low-temperature device and using graphite monochromated Mo Kα radiation (λ=0.71075 Å) radiation. Data reduction and an empirical absorption correction were carried out using CrystalClear [CRYSTALCLEAR 1.4.0. Rigaku, 9009 New Trails Dr., The Woodlands, Texas 77381, USA, 1998]. The structure was solved by direct methods using the program SHELXS97 [SHELX, Sheldrick, G. M., 2008. *Acta Crystallogr. A64*, pp 112–122] and refined using full-matrix least-squares refinement on F^2 using SHELXL97 [SHELX Sheldrick, G. M., 2008. *Acta Crystallogr. A64*, pp 112–122] within the WinGX program suite [Farrugia, L. J., . *J. Appl. Cryst*. **1999**, *32*, pp 837–838]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms modelled as riding atoms and placed on calculated positions.

Crystal data for **20**: $C_{15}H_{15}NO_4$, M_r=273.28, monoclinic, $C2/c$, a=13.5059(9), b=9.3899(6), c=21.6502(17) Å, β=105.593(3)°, T=100(2) K, Z=8, R=0.0783 for 1726 data with $F_0>2\sigma(F)$, $wR2$=0.2634 for 3031 unique data (all data 18,041), GOF=1.132.

CCDC832199 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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