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A new synthesis of (−)-epipyriculol: a phytotoxic metabolite

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Abstract

A convenient synthesis of the phytotoxic natural product epipyriculol has been accomplished in 17 steps from methyl L-tartrate. The synthetic strategy is based upon the use of a butanediacetal-protected scaffold as central core from which the alkenyl side chains were assembled.

Keywords: Epipyriculol; BDA methodology; Palladium catalysis; Natural product synthesis

1. Introduction

Pyriculol (**1**), first isolated in 1969 by Iwasaki et al. from a culture broth of *Pyricularia oryzae* Cavara,[1] is a phytotoxic metabolite that has been shown to cause dark necrotic spots on rice leaves. This is one of the symptoms of rice blast fungus, a crippling disease that also damages the collar, node and panicle of the plants and impairs the growth of seedlings.[2] A wide range of related structures have been isolated later,[3–6] many of which are known to be phytotoxic metabolites. Its *S*(C10)-epimer, epipyriculol (**2**), was obtained in 1991 from the same fungus and showed even stronger inhibition activity than pyriculol in spore germination bioassays (Fig. 1).[4]

To date, only one synthesis of epipyriculol has been described.[7,8] In that work, the syntheses of all four stereoisomers of pyriculol, including epipyriculol, were reported in 20 steps.[8]

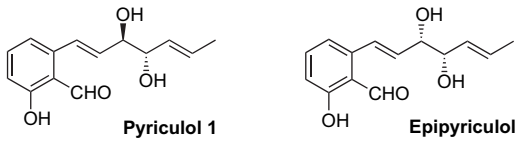
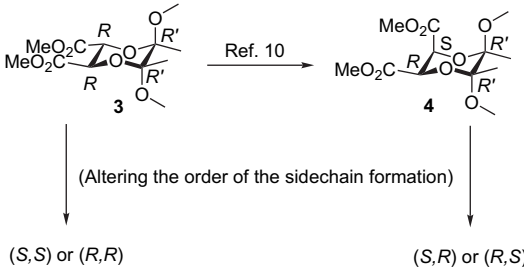


Figure 1. Phytotoxic metabolites that contribute to the symptoms of rice blast disease.

Here we describe a new route to epipyriculol that should also be general for the synthesis of all four stereoisomers. Our work starts from the single and cheap chiral source L-tartrate. The natural product **2** was obtained after 17 steps and only five chromatographic separations. The use of butanediacetal (BDA) as a 1,2-diol protecting group for methyl L-tartrate[9–12] (Scheme 1) allows us to have a convenient scaffold upon which to build the rest of the molecule by appropriate side chain modifications. BDA-protected 1,2-diols have shown particularly good flexibility and robustness as building blocks in other synthesis programmes.[13–19] Moreover, desymmetrisation of this common, now commercially available, precursor **3**[10] and interchange of the alkenyl side chains in principle determines the isomer that will be ultimately obtained, giving potential access to all four stereoisomers of pyriculol.



Scheme 1. Strategy to obtain all four isomers of **1** from the common precursor **3**.

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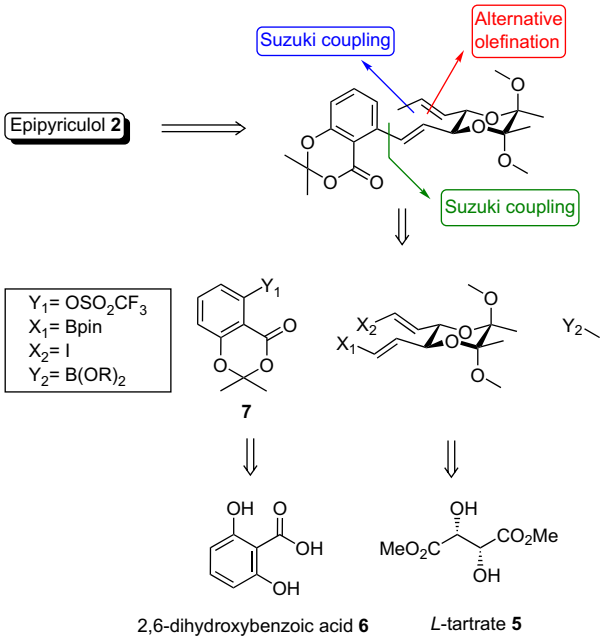
2. Results and discussion

Our proposed route to epipyriculol **2** is shown in Scheme 2. The strategy is based on the BDA protecting group method, developed in our laboratories[14,18,13] and by others,[11,12,20] in combination with Pd-catalysed cross-coupling reactions. It was anticipated that the introduction of the *E*-propenyl side chain would eventually proceed better using a Takai olefination rather than further Suzuki coupling.



Scheme 2. Proposed retrosynthesis to epipyriculol **2**.

Thus, starting from methyl L-tartrate **5**, we expected the boronate precursor (X_1=BPin) to engage in the first Suzuki coupling with the triflate **7** obtained from 2,6-dihydroxybenzoic acid **6**. After this coupling, the resulting product could be further functionalised (X_2=I) to obtain a second partner for another Suzuki reaction or, alternatively, directly olefinated through a Takai reaction. Epipyriculol **2** would be achieved after removal of the two protecting groups.

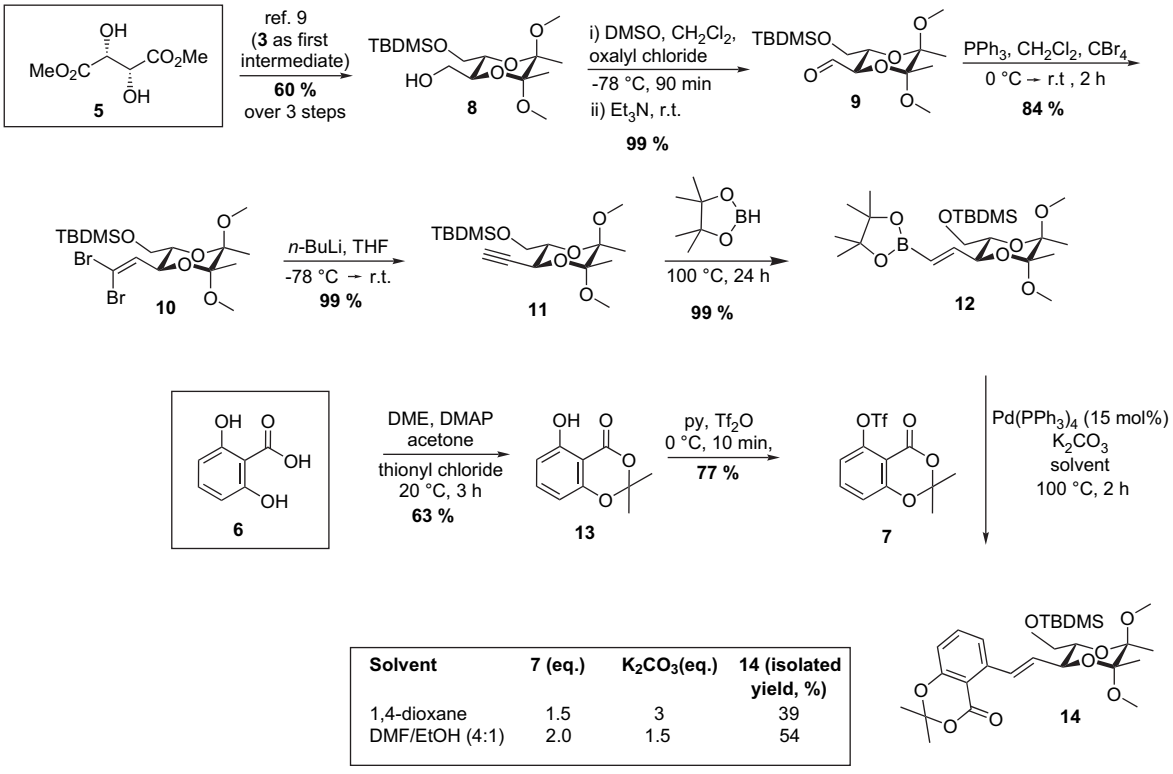
The synthesis also allows access to each isomer selectively early on in the pathway. A drawback in the previous reported route[8] relies on the enantiomeric differentiation. Diastereomeric mixtures (ca. 1:1), arising from nucleophilic addition of an acetylide anion to a chiral aldehyde, were chromatographically separated, each of which was further elaborated to give an isomer of pyriculol. Moreover, this chiral approach can be readily adapted to give access to the other three stereoisomers. Thus, desymmetrisation of the equatorial–equatorial precursor **3** to the corresponding equatorial–axial **4** would eventually give the (*S*,*S*)-isomer (**2**) and the (*S*,*R*)-isomer (Scheme 1). The other two stereoisomers (*R*,*R*)- and (*R*,*S*)-(**1**) would be obtained after reversing the coupling operations.

Following the analysis described above, we began the synthesis of epipyriculol **2** by installing the aromatic side chain. The results obtained are depicted in Scheme 3.

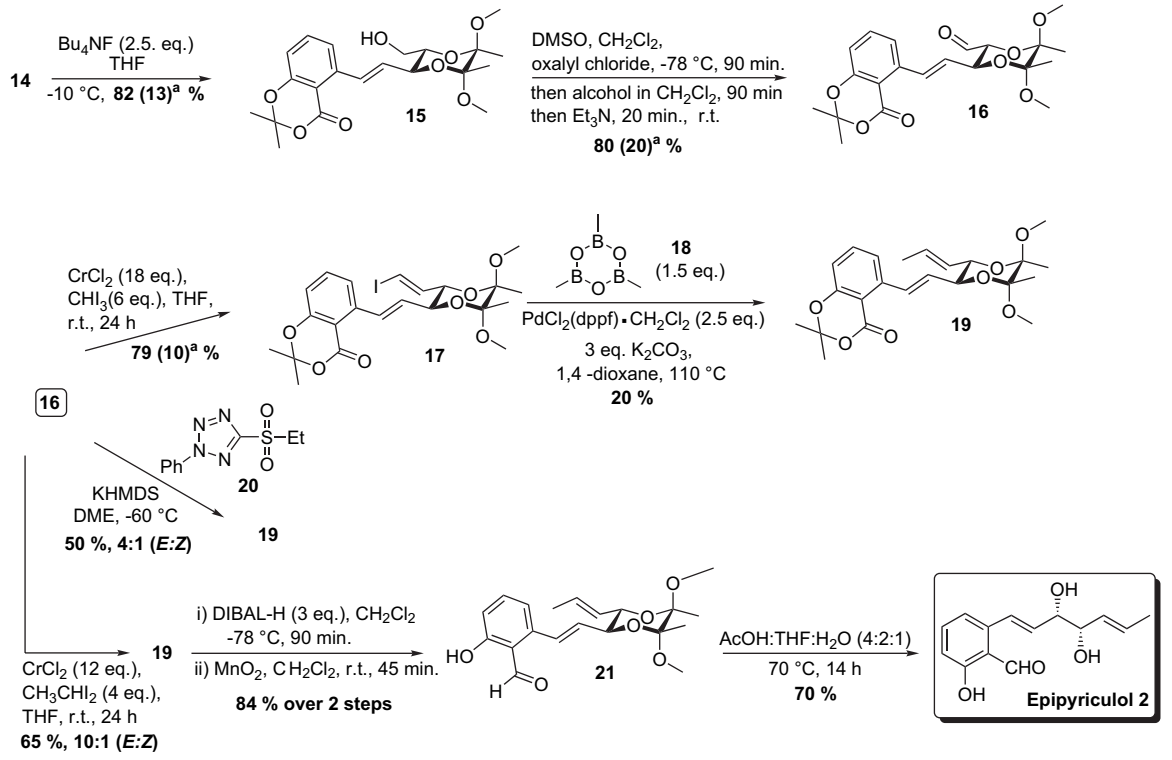
Accordingly, the BDA-protected boronate **12** was prepared from **5** in 47% overall yield over 7 steps and without need for column chromatography. Diol **5** was protected as butanediacetal **3**, which after reduction of the two ester groups to alcohols and mono-silyl protection of one of them afforded alcohol **8**. After forming aldehyde **9** by Swern oxidation, Corey–Fuchs homologation to obtain the alkyne **11** and hydroboration of this yielded the vinyl boronate **12** after removal of the pinacol by sublimation. The other partner for the first Suzuki reaction, namely triflate **7**, was obtained from **6** in 49% yield over two steps, using a more practical procedure to that previously reported,[21,22] and again without chromatographic purification. At this point, the Suzuki coupling between **12** and **7** was attempted. Not many examples of couplings between aromatic triflates and vinyl boronates can be found in the literature.[23,24] In general, the method of choice for the coupling of triflates with boronic derivatives involves a Pd-phosphine catalyst in combination with inorganic bases such as K_2CO_3 or K_3PO_4, in hot dioxane as solvent.[25,26] In our particular case, the following issues were addressed after experimentation under several conditions: (a) $Pd(PPh_3)_4$ was found to be a superior catalyst compared to $PdCl_2(dppf)\cdot CH_2Cl_2$ or $Pd(OAc)_2$–PCy_3 (CsF as base) under similar conditions; (b) longer reaction times than 2 h did not improve the yield; (c) when anhydrous dioxane was used as solvent, 3 equiv of base were necessary to bring the reaction to completion, however, amounts of phenol (coming from the hydrolysis of **7**, C–OSO_2CF_3 to C–OH) were found in the mixture; (d) when DMF (dry)/EtOH (4:1 volume)[24] was used, only 1.5 equiv of base were needed to complete the reaction. Curiously, the by-product formed exclusively from **7** under these conditions was the benzene-derivative (C–OSO_2CF_3 to C–H). The latter route gave the coupling product **14** in moderate yield after purification by column chromatography.

The final stages of the synthesis are shown in Scheme 4. In spite of the difficulties found in the first Suzuki coupling, we tested the possibility of forming the remaining *E*-alkenyl moiety by a better-known second Suzuki coupling, in this case with the methylboronic acid derivative **18**.[27]

The formation of the vinyl iodide **17** for the second Suzuki coupling was carried out in good yield by deprotection of the silyl protecting group of **14**, Swern oxidation of the resulting alcohol **15**[19] and Takai homologation[28] of the aldehyde **16** to obtain **17** as a 9:1 (*E*/*Z*) molar ratio mixture. It is important to note that the silyl deprotection of **14** has to be accomplished at −10 °C, otherwise isomerisation was observed. In a same way, quenching the Swern oxidation of **15** with Et_3N to obtain aldehyde **16** has to be addressed carefully, since reaction times longer than 20 min cause isomerisation. These two features suggest a particular sensitivity of the scaffold to isomerise. This behaviour could be explained by the increased acidity of the allylic proton due to the presence of a highly conjugated system. This fact could impart a certain instability to the system under basic conditions, which could be a drawback for the subsequent Suzuki coupling. Indeed, the coupling of **17** with trimethylboroxine proceeded as expected with total retention of configuration but in a poor 20% yield after column chromatography. A mixture of by-products coming from the BDA-scaffold, including



Scheme 3. Synthesis of **14**.



Scheme 4. Completion of the synthesis of epipyriculol **2**. [a]In brackets, recovered starting material.

homocoupling, were unavoidably formed in the reaction. Moreover, Pd loadings >2.5% generated significant amounts of terminal alkene. Therefore, other approaches were screened to install the *E*-propenyl chain.

In the literature, one of the most used methods to install a *E*-propenyl moiety is the Julia–Kociensky olefination, using the sulfone **20**.[29,30] However, the poor 4:1 (*E*/*Z*) molar ratio obtained under the optimal reaction conditions reported[30] forced

us to seek for other conditions. Given the fact that the Takai olefination proceeded smoothly to form the *E*-vinyl iodide **17**, and with high stereocontrol, we examined the same reaction[31] with the aldehyde **16** but using CH_3CHI_2.[32,33] Pleasingly, the reaction yielded a reasonable 65% of **19** with a 10:1 (*E*/*Z*) molar ratio. Although the presence of small amounts of the alcohol did not interfere in the formation of **17**, it was found that, in this particular case, the purification of the aldehyde (alcohol <5%) is crucial in order to obtain good yields of **19**.

With compound **19** in hand, we only needed to remove both the cyclic ester and the BDA to obtain the natural product. DIBAL-H reduction of the ester[34] and treatment of the resulting products with MnO_2[8] gave the desired aldehyde **21**. The removal of the BDA group was attempted under different conditions including: TFA,[16] $TiCl_4$[20] and BF_3/ethanedithiol,[10] all of them failed to give **2**. However, a combination of AcOH/THF/H_2O (4:2:1 in volume)[35] at 70 °C rendered our target compound epipyriculol **2** in satisfactory yields and identical in all respects to the reported natural product.

3. Conclusions

The synthesis of epipyriculol **2** has being completed. Our route involves 17 steps in a 9.1% overall yield for the longest linear sequence (14 steps). Only five chromatographic separations are needed throughout the synthesis. All other stereoisomers as well as derivatives could, in principle, be prepared using a related synthetic route.

4. Experimental

4.1. General methods

All reactions were performed in oven-dried glassware, under an inert argon atmosphere. All solvents used were reagent grade and distilled by standard procedures. All aqueous solutions were saturated unless otherwise indicated and all reactions were magnetically stirred and monitored by GC–MS, on a Perkin–Elmer AutoSystem XL GC/TurboMass GC–MS spectrometer. Where sealed microwave tubes were used, these were sealed with Suba-Seal septa. Analytical TLC was carried out with precoated glass-backed plates (Merck Keiselgel 60 F_{254} plates), visualised by UV fluorescence (λ=254 nm) and stained with aqueous acidic ammonium molybdate(IV). Flash column chromatography and purification through silica pads were carried out using Merck Keiselgel (230–400 mesh). P.E. refers to petroleum ether, 40–60 °C boiling point.

Optical rotations were measured, unless the compound could not be isolated in sufficient purity, on a Perkin–Elmer Model 343 Polarimeter with a sodium lamp at 25 °C. $[\alpha]_D^{25}$ are given in 10^{-1} deg cm^2 g^{-1} and concentrations, *c*, are reported in g/100 mL. IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IR Spectrometer and selected characteristic absorbances are reported neat, in cm^{-1} (abs). Proton magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz on a Bruker DPX-400 and are reported as follows: chemical shift δ in parts per million (number of protons, multiplicity, coupling constant *J* in hertz). Residual protic solvent was used as the internal reference, setting chloroform to δ 7.26. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz on a Bruker DPX-400. Chemical shifts are quoted in parts per million, referenced to the appropriate solvent peak, taking chloroform as δ 77.0. Assignments were made using DEPT 135 experiments. Elemental analysis was carried out, unless the compound could not be isolated in sufficient purity, at the Department of Chemistry, University of Cambridge. High-resolution mass spectrometry (HRMS) was carried out on a Waters LCT Premier XE Spectrometer using electrospray ionisation (ESI) at the Department of Chemistry, University of Cambridge.

4.1.1. 5-Hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (*13*)

Following the literature procedure,[21] a solution of 2,6-dihydroxybenzoic acid (16.28 g, 105.6 mmol) in DME (35 mL) was dried over $MgSO_4$ at rt overnight. To the filtered solution was added DMAP (665 mg, 5.5 mmol) and acetone (10 mL, 140 mmol). The solution was cooled to 20 °C and a solution of thionyl chloride (18 g, 151 mmol) in DME (5 mL) was added over 2 h. The solution was stirred for 1 h. The mixture was then passed through a pad of silica, eluting with CH_2Cl_2 (1 L) after which water (1 L) was added to the filtrate and the aqueous phase further extracted with CH_2Cl_2 (2×500 mL). The organic fractions were combined and washed with water (2×500 mL) and brine (500 mL), then dried over Na_2SO_4, filtered and concentrated in vacuo to give **13** as a brown oil, which crystallised upon cooling (12.81 g, 66.06 mmol, 63%).

^{1}H NMR δ: 10.04 (1H, br s), 7.32 (1H, dd, *J*=8, 8), 6.53 (1H, d, *J*=8), 6.35 (1H, d, *J*=8), 1.65 (6H, s). ^{13}C NMR δ: 165.3, 161.3, 155.5, 137.9, 110.68, 107.2, 107.1, 99.3, 25.5.

4.1.2. 2,2-Dimethyl-4-oxo-4H-benzo[1,3]dioxin-5-yl trifluoromethanesulfonate (*7*)

Following the procedure,[22] triflic anhydride (5.0 g, 17.72 mmol) was added to a solution of **13** (2.862 g, 14.75 mmol) in pyridine (25 mL) at 0 °C. The solution was stirred for 10 min then quenched with $NaHCO_3$ (aq) (15 mL). The mixture was repeatedly extracted with ether and the combined organic fractions were washed with water, dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in P.E. and the filtrate was concentrated in vacuo to give **7** as a pale orange solid (1.07 g, 3.28 mmol, 22%). The residue remaining from dissolution in P.E. was dissolved in ether and the filtrate was concentrated in vacuo to give additional **7** as an orange solid (2.64 g, 8.10 mmol, 55%).

^{1}H NMR δ: 7.60 (1H, dd, *J*=8, 8), 7.06 (1H, d, *J*=8), 7.00 (1H, d, *J*=8), 1.75 (6H, s). ^{13}C NMR δ: 157.4, 157.0, 148.7, 117.8, 116.6, 116.5, 108.3, 106.8, 25.5.

4.1.3. (2R,3S,5R,6R)-3-((tert-Butyldimethylsilyloxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carbaldehyde (*9*)

Prepared according to a previous procedure.[36] A solution of DMSO (1.58 mL, 22.31 mmol) in CH_2Cl_2 (30 mL) was added to a solution of oxalyl chloride (1.41 g, 11.13 mmol) in CH_2Cl_2 at −78 °C and stirred for 30 min. A solution of **8** (3.0 g,

8.57 mmol) in CH_2Cl_2 (65 mL) was added over 30 min. The solution was stirred at −78 °C for 90 min then Et_3N (4.17 mL, 29.94 mmol) was added over 15 min. The solution was allowed to warm to rt over 20 min, then diluted with CH_2Cl_2 (300 mL) and washed with water (2×250 mL) and brine (250 mL). The organic fractions were dried over $MgSO_4$ and concentrated in vacuo to give **9** as a yellow oil (2.98 g, 8.57 mmol, 100%).

^{1}H NMR δ: 9.64 (1H, d, J=1.5), 4.12 (1H, dd, J=10, 1.5), 3.76–3.85 (3H, m), 3.26 (6H, s), 1.36 (3H, s), 1.29 (3H, s), 0.87 (9H, s), 0.05 (6H, s).

*4.1.4. tert-Butyl(((2S,3S,5R,6R)-3-(2,2-dibromovinyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methoxy)-dimethylsilane (**10**)*

Carbon tetrabromide (5.697 g, 17.18 mmol) was added to a solution of triphenylphosphine (9.015 g, 34.37 mmol) in CH_2Cl_2 (120 mL) at 0 °C and stirred for 15 min. The ice-bath was removed and the mixture was stirred for another 15 min. A solution of **9** (2.99 g, 8.59 mmol) in CH_2Cl_2 (60 mL) was added and the mixture was stirred for 3 h. Hexane (120 mL) was added whereupon a precipitate was formed. The mixture was filtered and the filtrate was washed again with hexane (120 mL) and refiltered. The solvent was removed in vacuo and the resulting crude **10** was redissolved in hexane (120 mL) and placed in the fridge overnight, after which the mixture was filtered once more and the solvent removed again in vacuo to yield pure **10** as a brown oil (3.63 g, 7.22 mmol, 84%).

R_f (20% Et_2O in P.E.): 0.65. $[\alpha]_D^{25}$ −94.0 (c 0.205, $CDCl_3$). IR (neat, cm^{-1}): 2929, 1629, 1253, 1116, 1037. ^{1}H NMR δ: 6.45 (1H, d, J=9), 4.41 (1H, dd, J=9, 9), 3.69 (1H, dt, J=9, 5), 3.63 (2H, dd, J=5, 2), 3.33 (3H, s), 3.26 (3H, s), 1.29 (3H, s), 1.28 (3H, s), 0.89 (9H, s), 0.08 (3H, s), 0.06 (3H, s). ^{13}C NMR δ: 134.9, 98.8, 98.6, 95.2, 71.4, 70.9, 63.1, 48.3, 47.9, 25.8, 18.3, 17.5, 17.5, −5.4 (2C). E.A. Calcd for $C_{17}H_{32}Br_2O_5Si$: C 40.49, H 6.40, Br 31.69. Found: C 41.09, H 6.21, Br 31.77.

*4.1.5. tert-Butyl(((2R,3S,5R,6R)-2-ethynyl-5,6-dimethoxy-5,6-dimethyltetrahydro-2H-pyran-3-yl)methoxy)-dimethylsilane (**11**)*

n-BuLi (7.91 mL, 12.65 mmol, 1.6 M in hexanes) was added dropwise over 15 min to a solution of **10** (2.55 g, 5.06 mmol) in THF (70 mL) at −78 °C. The solution was allowed to warm up to rt over 30 min, after which NH_4Cl (aq) (40 mL) was added and the aqueous layer was extracted with ether (2×60 mL). The organic fractions were combined and washed with water (2×40 mL) and brine (40 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to give **11** as a yellow oil (1.741 g, 5.06 mmol, 100%).

$[\alpha]_D^{25}$ −93.0 (c 0.835, $CDCl_3$). IR (neat, cm^{-1}): 3260, 2929, 2344, 1252, 1118, 1036. ^{1}H NMR δ: 4.42 (1H, dd, J=10, 2), 3.77 (3H, m), 3.26 (3H, s), 3.24 (3H, s), 2.47 (1H, d, J=2), 1.30 (3H, s), 1.25 (3H, s), 0.88 (9H, s), 0.07 (3H, s), 0.06 (3H, s). ^{13}C NMR δ: 98.9, 98.7, 79.7, 75.0, 72.4, 62.9, 60.1, 48.1, 47.8, 25.8, 18.3, 17.5 (2C), −5.3 (2C). E.A. Calcd for $C_{17}H_{32}O_5Si$: C 59.27, H 9.36. Found: C 58.75, H 8.94.

*4.1.6. tert-Butyl(((2S,3S,5R,6R)-5,6-dimethoxy-5,6-dimethyl-3-((E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-vinyl)-1,4-dioxan-2-yl)methoxy)dimethylsilane (**12**)*

Alkyne **11** (1.741 g, 5.06 mmol) was added to pinacolborane (1.762 mL, 12.14 mmol) and the mixture was heated at 100 °C in a sealed tube for 24 h. Then, the crude mixture was heated to 110 °C under high vacuum (<2 Torr) overnight. After this treatment, pure **12** was obtained in the flask as a yellow oil (2.39 g, 5.06 mmol, 100%).

$[\alpha]_D^{25}$ −89.6 (c 0.875, $CDCl_3$). IR (neat, cm^{-1}): 2953, 1644, 1372, 1254, 1120, 1038. ^{1}H NMR δ: 6.59 (1H, dd, J=18, 6), 5.81 (1H, dd, J=18, 1), 4.12 (1H, ddd, J=9, 6, 1), 3.64 (2H, d, J=5), 3.56 (1H, dt, J=10, 5), 3.21 (3H, s), 3.19 (3H, s), 1.27 (3H, s), 1.24 (3H, s), 1.22 (12H, s), 0.85 (9H, s), 0.04 (3H, s), 0.03 (3H, s). ^{13}C NMR δ: 147.8, 132.0, 98.5, 83.2, 72.1, 71.5, 63.2, 47.7, 47.6, 25.9, 24.8, 18.2, 17.6, 17.5, −5.3 (2C). E.A. Calcd for $C_{23}H_{45}BO_7Si$: C 58.47, H 9.60. Found: C 58.32, H 8.96.

*4.1.7. 5-((E)-2-((2S,3S,5R,6R)-3-((tert-Butyldimethylsilyloxy)-methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)vinyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**14**)*

Vinyl boronate **12** (47.2 mg, 0.1 mmol), triflate **7** (65.2 mg, 2 equiv), $Pd(PPh_3)_4$ (17.3 mg, 15 mol %) and K_2CO_3 (19.8 mg, 1.5 equiv) were placed in a sealed tube under argon and dry DMF (0.4 mL) and absolute ethanol (0.1 mL) were added. The mixture was heated at 100 °C for 2 h. After this time the mixture was concentrated under vacuum and the crude was separated by column chromatography (7% Et_2O/P.E., then 15 and 30%) to obtain the coupling product **14** as an oil (28.2 mg, 0.054 mmol, 54%).

R_f (10% Et_2O in P.E.): 0.14. $[\alpha]_D^{25}$ −76.2 (c 1.56, $CHCl_3$). IR (neat, cm^{-1}): 2948, 1741, 1576, 1319, 1272, 1128, 1042, 836, 779. ^{1}H NMR δ: 7.76 (1H, d, J=16), 7.42 (1H, t, J=8), 7.26 (1H, dd, J=8, 1), 6.85 (1H, dd, J=8, 1), 6.17 (1H, dd, J=16, 7), 4.29 (1H, t, J=8), 3.71 (3H, m), 3.30 (3H, s), 3.29 (3H, s), 1.72 (3H, s), 1.70 (3H, s), 1.32 (3H, s), 1.30 (3H, s), 0.85 (9H, s), 0.04 (3H, s), 0.02 (3H, s) ^{13}C NMR δ: 160.0, 156.7, 141.1, 135.0, 132.3, 129.8, 121.6, 116.5, 111.0, 105.2, 98.6 (2C), 72, 5, 71.2, 63.3, 48.0, 47.8, 26.0, 25.8 (3C), 25.3, 18.2, 17.7, 17.6, −5.2, −5.3. HRMS (ESI) m/z 545.2569 [(M+Na)$^+$; calculated for $C_{27}H_{42}O_8SiNa$: 545.2547].

*4.1.8. 5-((E)-2-((2S,3S,5R,6R)-3-(Hydroxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)vinyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**15**)*

A solution of Bu_4NF 1.0 M in THF (2.97 mL, 2.975 mmol, 2.5 equiv) was added dropwise to **14** (620 mg, 1.19 mmol) dissolved in THF (12 mL) at −10 °C under argon. The solution was magnetically stirred for 3 h 30 min. After this time the solution was passed through a pad of silica, washing with a 1:1 solution of ether/petroleum ether and then pure ether. The solvents were removed under vacuum and the remaining mixture was purified by column chromatography (25% ether/P.E, then 50%) to give **15** as a white solid after complete solvent removal (400 mg, 0.98 mmol, 82%). The remaining starting material was recovered after washing the column with pure ether

(79 mg, 0.15 mmol, 13%) alongside some amounts of the silanol.

R_f(Et_2O): 0.51. $[\alpha]_D^{25}$ −86.6 (*c* 0.65, $CHCl_3$). IR (neat, cm^{-1}): 3508, 2949, 1734 (vs), 1600, 1578, 1477, 1378, 1320, 1272, 1208, 1124 (vs), 1081, 1040 (vs). ^1H NMR δ: 7.66 (1H, d, *J*=16), 7.45 (1H, t, *J*=8), 7.22 (1H, d, *J*=7), 6.88 (1H, dd, *J*=8, 1), 6.08 (1H, dd, *J*=16, 8), 4.39 (1H, t, *J*=9), 3.75 (3H, m), 3.32 (3H, s), 3.30 (3H, s), 2.20 (1H, O*H*, t, *J*=6), 1.72 (3H, s), 1.69 (3H, s), 1.35 (3H, s), 1.34 (3H, s). ^{13}C NMR δ: 160.3, 156.7, 140.9, 135.4, 133.3, 129.1, 121.8, 116.7, 111.0, 105.4, 98.8, 98.7, 71.4, 71.0, 62.3, 48.1, 48.0, 26.1, 25.1, 17.7, 17.6. HRMS (ESI) *m/z* 431.1665 [$(M+Na)^+$; calculated for $C_{21}H_{28}O_8Na$: 431.1682].

*4.1.9. (2R,3S,5R,6R)-3-((E)-2-(2,2-Dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)vinyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carbaldehyde (**16**)*

A solution of DMSO (102 μL, 1.44 mmol, 4.5 equiv) in CH_2Cl_2 (1 mL) was added dropwise to a solution of oxalyl chloride (84 μL, 0.96 mmol, 3 equiv) in CH_2Cl_2 (2 mL) at −78 °C and stirred for 90 min. A solution of **15** (130 mg, 0.32 mmol) in CH_2Cl_2 (2.5 mL) was added over 1 h. The solution was stirred at −78 °C for 1 h and then Et_3N (334 μL, 2.4 mmol, 7.5 equiv) was added over 10 min. The solution was allowed to warm to rt over 20 min, then diluted with CH_2Cl_2 (30 mL) and washed with water (30 mL). The aqueous phases were further extracted with CH_2Cl_2 (30 mL) and the combined organic phases washed with water (2×50 mL) and brine (50 mL). The organic fraction was dried over $MgSO_4$ and concentrated in vacuo to give a mixture 4:1 (determined by ^1H NMR) of the aldehyde **16** and the starting material alcohol **15** as an oil (128 mg, 98%). The mixture could be separated by column chromatography (40% Et_2O in P.E., then 60, 80 and 100% Et_2O).

R_f (80% Et_2O in P.E.)=0.24. ^1H NMR δ: 9.66 (1H, d, *J*=1), 7.76 (1H, d, *J*=16), 7.44 (1H, t, *J*=8), 7.25 (1H, d, *J*=8), 6.87 (1H, d, *J*=8), 6.19 (1H, dd, *J*=16, 7), 4.49 (1H, ddd, *J*=10, 7, 1), 4.16 (1H, dd, *J*=10, 4), 3.32 (3H, s), 3.29 (3H, s), 1.69 (3H, s), 1.68 (3H, s), 1.40 (3H, s). 1.35 (3H, s).

*4.1.10. 5-((E)-2-((2S,3S,5R,6R)-3-((E)-2-Iodovinyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)vinyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**17**)*

A mixture of aldehyde **16** and alcohol **15** (4:1 molar ratio, 205 mg, 0.42 mmol respect to aldehyde) and CHI_3 (993 mg, 2.52 mmol, 6 equiv) were dissolved in THF (2 mL) under argon. This solution was added dropwise to a magnetically stirred dispersion of $CrCl_2$ (930 mg, 7.56 mmol, 18 equiv) in THF (4 mL) at rt and the mixture was stirred for 24 h. After this time the mixture was poured into water (25 mL) and extracted with ether (25 mL). The aqueous phase was further extracted with ether (25 mL) and CH_2Cl_2 (25 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvents removed under vacuum. The remaining crude was purified by column chromatography (20% Et_2O in P.E., then 100% Et_2O) to give the iodide **17** as a 9:1 (*E*/*Z* molar ratio) mixture (177 mg, 0.33 mmol, 79%) and the starting mixture (22 mg, 10%).

R_f(20% Et_2O in P.E.): 0.29. $[\alpha]_D^{25}$ −119.3 (*c* 0.80, $CHCl_3$). IR (neat, cm^{-1}): 2992, 2949, 1732 (vs), 1600, 1578, 1477, 1377, 1318, 1271, 1208, 1141 (vs), 1120 (vs), 1078, 1040. ^1H NMR δ: 7.75 (1H, d, *J*=16), 7.45 (1H, t, *J*=8), 7.21 (1H, dd, *J*=7, 1), 6.88 (1H, dd, *J*=8, 1), 6.57 (2H, m), 6.04 (1H, dd, *J*=16, 8), 4.26 (1H, ddd, *J*=10, 8, 1), 4.14 (1H, dd, *J*=10, 4), 3.31 (3H, s), 3.28 (3H, s), 1.72 (3H, s), 1.70 (3H, s), 1.34 (6H, s). ^{13}C NMR δ: 160.1, 156.8, 141.1, 140.8, 135.2, 133.5, 128.3, 121.6, 116.8, 111.1, 105.4, 99.0, 98.7, 81.0, 73.7, 72.1, 48.3, 48.2, 25.9, 25.5, 17.7 (2C). HRMS (ESI) *m/z* 553.0724 [$(M+Na)^+$; calculated for $C_{22}H_{27}IO_7Na$: 553.0699].

*4.1.11. 5-((E)-2-((2S,3S,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-3-((E)-prop-1-enyl)-1,4-dioxan-2-yl)vinyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**19**)*

Heck coupling: vinyl iodide **17** (103 mg, 0.19 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.75 mg, 0.0046 mmol, 2.5 mol %) and K_2CO_3 (75 mg, 0.54 mmol, 3 equiv) were placed in a thick-glass sealed tube and purged with argon. 1,4-Dioxane (750 μL) and trimethylboroxine (38.5 μL, 0.28 mmol, 1.5 equiv) were added and the mixture was heated at 105 °C for 2 h. The completion of the reaction was judged by TLC. After this time the mixture was diluted in ether and filtered, the solvents were removed under vacuum and the crude was purified by column chromatography (30% Et_2O/P.E.) to give **19** as an oil (14.6 mg, 20%).

Julia–Kociensky olefination: a 0.5 M solution of KHMDS in toluene (1.920 mL, 0.96 mmol) was placed under vacuum. After removal of the toluene, the dry KHMDS was redissolved in DME (700 μL). A portion of this fresh solution (200 μL, 0.27 mmol, ca. 4 equiv) was added by syringe pump to a solution of the mixture aldehyde **16**/alcohol **15** (4:1 mol ratio, 26 mg, 0.064 mmol) and sulfone **20** (46 mg, 0.192 mmol, 3 equiv) in DME (300 μL) at −60 °C over 1 h. After this time water (100 μL) was added and the mixture left to reach rt. The mixture was eluted with Et_2O and extracted with water. The aqueous phase was further extracted with ether and the combined organic phases were washed water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (10% Et_2O/P.E., then 20% and pure ether) to give alkene **19** (12 mg, 44%) as a 4:1 (*E*/*Z* molar ratio) mixture (determined by ^1H NMR) alongside sulfone **19**; and the starting mixture aldehyde/alcohol (10 mg, 38%).

Takai olefination: pure aldehyde **16** (20 mg, 0.05 mmol) and CH_3CHI_2 (56.4 mg, 0.2 mmol, 4 equiv) were dissolved in THF (0.4 mL) under argon. This solution was added dropwise to a magnetically stirred dispersion of $CrCl_2$ (74 mg, 0.6 mmol, 12 equiv) in THF (0.4 mL) at rt and the mixture was stirred for 24 h. After this time the mixture was poured into water (4 mL) and extracted with ether (10 mL). The aqueous phase was further extracted with ether (6 mL) and CH_2Cl_2 (6 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvents removed under vacuum. The remaining crude was purified by column chromatography (10% Et_2O in P.E., then 20%) to give the alkene **19** as a 10:1 (*E*/*Z* molar ratio) mixture (14 mg, 0.033 mmol, 65%).

R_f (20% Et_2O in P.E.): 0.23. $[\alpha]_D^{25}$ −78.5 (*c* 1.00, $CHCl_3$). IR (neat, cm^{-1}): 1733 (vs), 1599, 1577, 1475, 1376, 1316, 1270,

1204, 1119 (vs), 1039. ^{1}H NMR δ: 7.72 (1H, d, J=16), 7.43 (1H, t, J=8), 7.22 (1H, d, J=8), 6.86 (1H, d, J=8), 6.05 (1H, dd, J=16, 7), 5.82 (1H, dq, J=15, 7), 5.49 (ddd, J=16, 8, 1), 4.28 (1H, dd, J=10, 8), 4.09 (1H, t, J=8), 3.33 (3H, s), 3.30 (3H, s), 1.71 (6H, m), 1.68 (3H, s), 1.35 (3H, s), 1.34 (3H, s). ^{13}C NMR δ: 160.1, 156.7, 141.2, 135.1, 132.4, 131.6, 129.5, 127.0, 121.6, 116.5, 111.0, 105.2, 98.7, 98.6, 72.7, 72.6, 48.1, 48.0, 26.0, 25.2, 18.0, 17.8 (2C). HRMS (ESI) *m/z* 441.1898 [(M+Na)$^+$; calculated for $C_{23}H_{30}O_7Na$: 441.1889].

*4.1.12. 2-((E)-2-((2S,3S,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-3-((E)-prop-1-enyl)-1,4-dioxan-2-yl)vinyl)-6-hydroxybenzaldehyde (**21**)*

DIBAL-H (1 M in CH_2Cl_2, 165 μL, 0.165 mmol, 3 equiv) was added to a solution of the alkene **19** (23 mg, 0.055 mmol) in CH_2Cl_2 (300 μL) at −78 °C and the solution was stirred for 90 min. After this time MeOH (150 μL) and aqueous 1 M HCl (165 μL) were added and the mixture was left to reach rt. The mixture was diluted with ether and washed with water. The aqueous phase was further extracted with ether (×3) and the combined organic phases were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. The resulting crude was redissolved in dry CH_2Cl_2 (1.2 mL) and added to activated MnO_2 (160 mg). The mixture was magnetically stirred at rt under argon for 45 min, then filtered through a pad of Celite under vacuum. After removal of the solvent, aldehyde **21** was obtained (17 mg, 0.046 mmol, 84% over two steps).

R_f (50% Et_2O in P.E.): 0.69. $[\alpha]_D^{25}$ −72.4 (*c* 0.50, $CHCl_3$). IR (neat, cm^{-1}): 1645, 1610, 1570, 1450, 1119. ^{1}H NMR δ: 11.84 (1H, s), 10.27 (1H, s), 7.44 (1H, t, J=8), 7.16 (1H, d, J=15), 6.89 (1H, d, J=7), 6.88 (1H, d, J=8), 5.97 (1H, dd, J=15, 7), 5.84 (1H, dq, J=15, 7), 5.48 (ddd, J=15, 8, 1), 4.26 (1H, ddd, J=10, 6, 1), 4.03 (1H, t, J=9), 3.31 (3H, s), 3.29 (3H, s), 1.73 (3H, dd, J=7, 1), 1.36 (3H, s), 1.34 (3H, s). ^{13}C NMR δ: 195.5, 162.7, 142.4, 137.1, 133.1, 132.4, 127.2, 126.8, 119.0, 117.3, 117.1, 98.8, 98.7, 73.2, 72.0, 48.1, 48.0, 18.1, 17.8, 17.7. HRMS (ESI) *m/z* 385.1629 [(M+Na)$^+$; calculated for $C_{20}H_{26}O_6Na$: 385.1627].

*4.1.13. Epipyriculol **2** (2-((1E,3S,4S,5E)-3,4-dihydroxyhepta-1,5-dienyl)-6-hydroxybenzaldehyde)*

AcOH (0.3 mL) and water (0.075 mL) were added to a solution of compound **21** (2 mg, 0.0055 mmol) in THF (0.15 mL) at rt and the mixture was heated at 70 °C for 14 h. The initial blurred solution became gradually transparent and the progress of the reaction was monitored by TLC. After completion, the solvents were removed under vacuum and the remaining mixture was purified by preparative TLC (70% Et_2O in P.E.) to give epipyriculol (0.95 mg, 0.0038 mmol, 70%). The characterisation data (^{1}H NMR, IR, optical rotation) are identical to those previously reported.[8]

R_f (80% Et_2O in P.E.): 0.27. $[\alpha]_D^{25}$ −50 (*c* 0.025, $CHCl_3$). IR (neat, cm^{-1}): 2925, 1643, 1450. ^{1}H NMR δ: 11.85 (1H, s), 10.30 (1H, s), 7.45 (1H, t, J=8), 7.19 (1H, d, J=15), 6.90 (1H, d, J=7), 6.89 (1H, d, J=8), 6.08 (1H, dd, J=16, 6), 5.84 (1H, dq, J=15, 6), 5.55 (ddq, J=15, 7, 1), 4.22 (1H, t, J=6), 4.03 (1H, t, J=7), 1.75 (3H, dd, J=7, 1).

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