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General strategy towards chiral methylene bis-pyrans: synthesis of the C2–C16 fragment of phorboxazole A☆

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Abstract—A chiral methylene bis-pyran fragment was synthesized by making efficient use of an oxy-anion intramolecular Michael addition, Brown's asymmetric allylation and Grubb's ring closing metathesis reactions in a stereoselective manner.

1. Introduction

There has been an increase in the isolation of macrolides comprising oxygen and nitrogen heterocycles as part of the structure. The pyran and oxazole rings are more common in these natural products with recent examples including halichondrin[1] B **1**, bryostatins[2] **2**, phorboxazoles[3] **3** amongst others (Fig. 1). All these natural products are mostly sourced from marine sponges and rare species, thus making them difficult to be obtained from natural sources. Accordingly, the synthesis would ultimately allow us to obtain these bioactivities in substantial quantities for further evaluation. The methylene bis-tetrahydropyran skeleton is present in these molecules and therefore, approaches towards the properly functionalized and enantiopure synthesis of bis-pyran skeleton have always been a challenging and rewarding task. As part of a major programme towards the synthesis of these macrolides, we herein report a practical approach for chirally substituted methylene bis-pyran synthesis. This synthesis also correlates to the C2–C16 fragment of phorboxazole A, isolated in 1995 by Searle and Molinski from the Indian Ocean sponge *Phorbas* sp.[4]

2. Results and discussion

Our synthetic strategy relied on the utilization of a natural chiral pool compound D-glucose, as starting material. The strategy for constructing the bis-oxane fragment **4**, is retrosynthetically outlined in Scheme 1. One pyran ring was constructed using an oxy anion intramolecular Michael addition while the second was obtained using Grubb's RCM approach to complete the methylene bis-pyran skeleton. We herein report, the synthesis of the C2–C16 bis-oxane portion of phorboxazole A.

We began with the conversion of D-glucose to the corresponding ene derivative **9** in four steps (33% overall yield) by following a literature protocol.[5] Deprotection of the acetonide of **9** was carried out using 50% aq acetic acid and cat. H_2SO_4 to afford the lactol, which was further reduced in its crude form with $NaBH_4$ in MeOH at 0 °C to give triol **10** in 67% overall yield. Selective protection of the triol afforded compound **12** in an overall yield of 72% for two steps. Hydroboration of **12** furnished the primary alcohol **13**, which was oxidized to the corresponding aldehyde and further subjected to a two-carbon extension following the Wittig olefination protocol to afford the α,β-unsaturated ester **14** in 89% yield. Deprotection of the acetonide in **14**, resulted in the formation of the diol **7**, which underwent an intramolecular oxy-anion Michael addition promoted by NaH at −78 °C to give a *cis*-oxane skeleton **15a** with good selectivity (20:1 *cis*:*trans*). We optimized the reaction conditions for enriching the diastereoselectivity by employing different bases such as NaHMDS, LiHMDS, LDA and NaH (Table 1). Amongst them NaH at −78 °C was found to be appropriate for good diastereoselectivity (20:1) and chemical yield. The primary hydroxyl function was protected as MOM ether **6** (Scheme 2).

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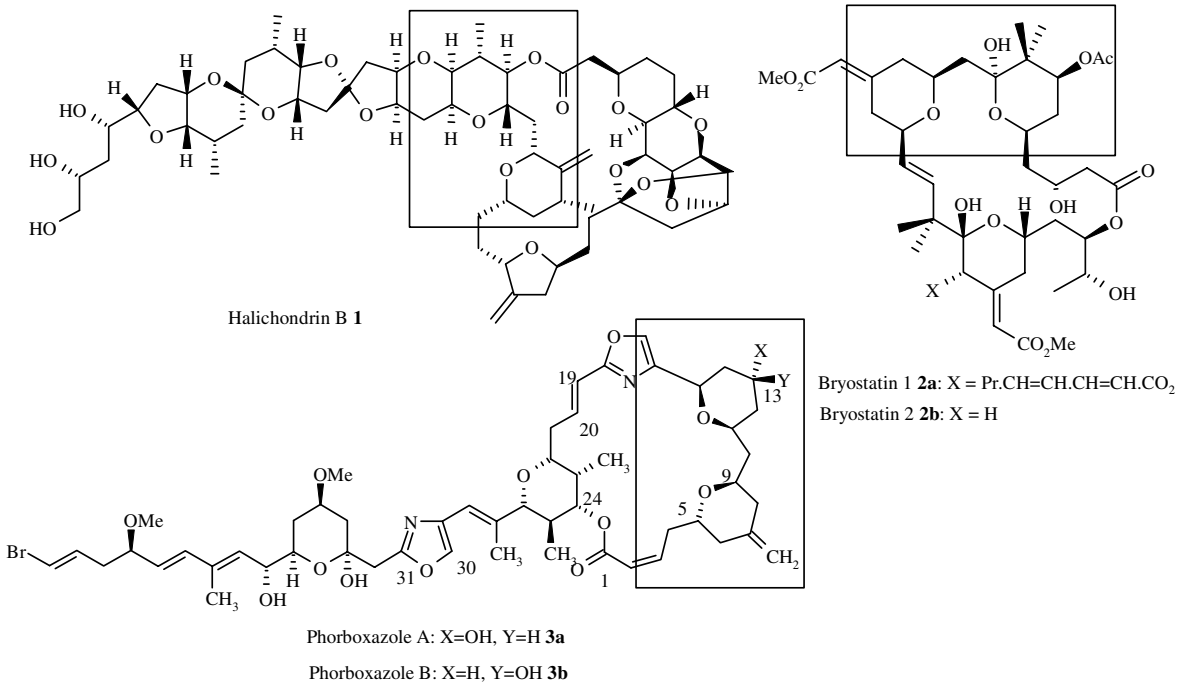
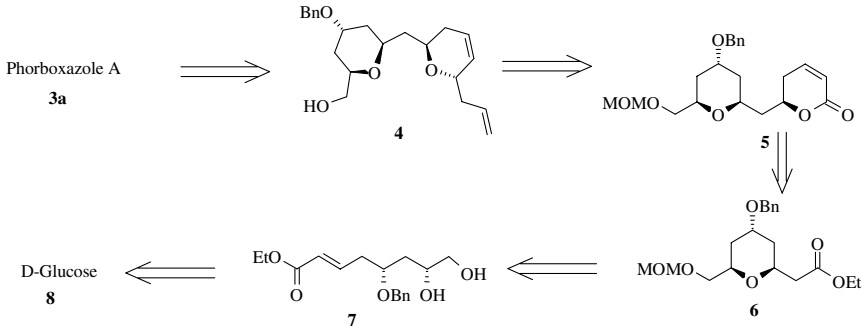


Figure 1.



Scheme 1. Retrosynthetic analysis.

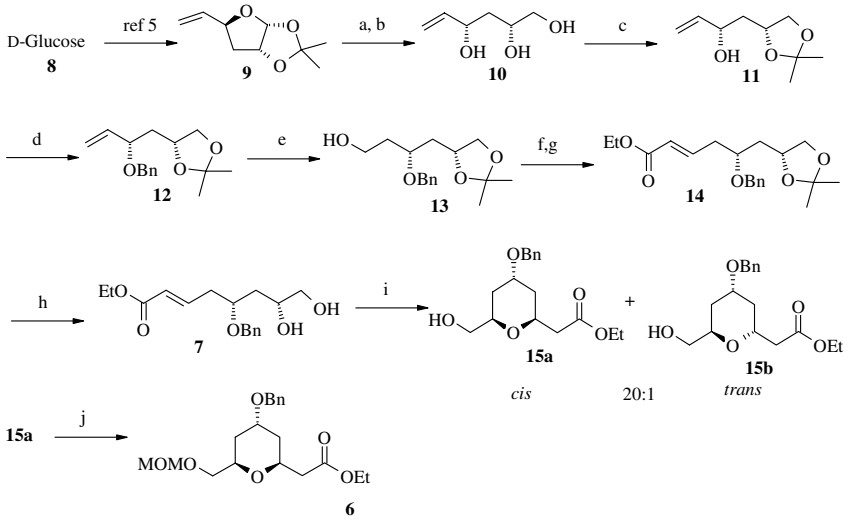
Introduction of the second *trans* (C5/C9) oxane ring in target **4** was intended to be accomplished via the Brown allylation and ring closing metathesis (RCM). Accordingly, compound **6** was subjected to partial reduction using DIBAL-H at −78 °C in CH_2Cl_2 to afford aldehyde **16** in 86% yield. The latter on treatment with Brown's (+)-allyl diisopinocampheylborane reagent[6] led to the homoallylic alcohol **17** in 78% yield. The stereochemistry of the newly generated hydroxy bearing carbon is assigned as *R* based on the literature precedence.[7] The chiral HPLC of this compound (chiralcel OD18) was found to show single isomer. Compound **17**, on treatment with acryloyl chloride in the presence of diisopropylethylamine afforded the corresponding acryloyl ester **18** in 93% yield. The compound was set for the construction of the *trans*-oxane skeleton by following RCM protocol. Accordingly, compound **18** was exposed to Grubb's catalyst (10 mol %) in CH_2Cl_2[8] to afford δ-lactone **5** in 94% yield. DIBAL-H reduction of **5** at −78 °C in CH_2Cl_2 followed by reaction with ethanol and CSA afforded the ethyl glycoside.[9] Reaction of this ethyl acetal with allyltrimethylsilane and TMSOTf as the Lewis acid in CH_2Cl_2 at 0 °C afforded the corresponding allyl substituted dihydropyran **4** as a single isomer in 85% yield (Scheme 3). This selectivity of anomeric ethoxy group followed by allylation has precedence.[10,11]

Table 1.

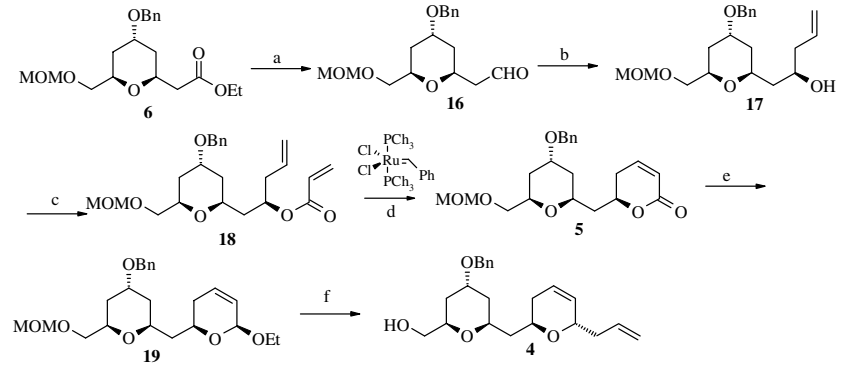
Entry	Base	Yield (%)	*cis*:*trans* (%)
1	NaHMDS	80	90:10
2	LiHMDS	75	85:15
3	LDA	71	70:30
4	NaH	82	95:05

3. Conclusion

In conclusion, chiral methylene bis-pyran skeleton was accomplished successfully by employing oxy-anion Michael addition, Brown's allylation and Grubb's



Scheme 2. Reagents and conditions: (a) 50% aq AcOH, H_2SO_4 (cat.), 50 °C, 2 h; (b) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 67% (overall yield for two steps); (c) PTSA (cat.), acetone, rt, 3 h, 76%; (d) NaH, BnBr, THF, reflux, 8 h, 96%; (e) BH_3·DMS, NaOH, H_2O_2, THF, 8 h, 80%; (f) IBX, THF, DMSO, rt, 2 h, 83%: (g) $Ph_3P{=}CH{-}CO_2Et$, benzene, rt, 12 h, 72% (overall yield for two steps); (h) CSA, MeOH, rt, 2 h, 91%; (i) NaH, THF, −78 °C, 4 h, 82%; (j) $^{i}Pr_2NEt$, MOMCl, CH_2Cl_2, 0 °C, 6 h.



Scheme 3. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 86%; (b) (+)-allyl diisopinocampheylborane, Et_3N, H_2O_2, 1 h, 78%; (c) $^{i}Pr_2NEt$, acryloyl chloride, CH_2Cl_2, 0 °C to rt, 4 h, 93%; (d) Grubb's catalyst (1st gene.), $Ti(^{i}OPr)_4$, CH_2Cl_2, 60 °C, 6 h, 94%; (e) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; then CSA, EtOH, 86%; (f) allyltrimethyl silane, TMSOTf, CH_2Cl_2, 0 °C, 1 h, 85%.

RCM reaction effectively. Studies directed towards the total synthesis of phorboxazole A, B, bryostatins and halichondrins B employing this approach are currently in progress in our group.

4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Jasco Dip 360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200, Brucker Avance 300 or Varian Unity 400. Chemical shifts are reported in ppm with respect to the internal TMS. Coupling constants (J) are quoted in hertz. Mass spectra were recorded on VG micromass-7070H (70 eV).

4.1.1. (2*R*,4*S*)-5-Hexene-1,2,4-triol 10. Ene derivative **9** (3.40 g, 170 mmol) was hydrolyzed using 50% aqueous acetic acid (12 mL) and a catalytic amount of concd H_2SO_4 (two drops) by heating at 50 °C for 2 h. The reaction mixture was cooled to room temperature, then ethyl acetate was added and neutralized with saturated sodium bicarbonate. The aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude lactol, which was as such used without any further purification. The above crude lactol (2.60 g, 20 mmol) was taken in methanol (30 mL), cooled to 0 °C and $NaBH_4$ (1.11 g, 30 mmol) then added in small portions under a nitrogen atmosphere. After complete addition, the reaction mixture was brought to room temperature and allowed to stir for 1 h. The reaction mixture was quenched with acidic resin (3 g) and stirred for an additional 1 h. It was then filtered through a Celite pad and concentrated under vacuum to yield the crude product, which was purified by column chromatography (chloroform/

EtOAc) to afford the pure product **10** (2.11 g, overall 67% yield) as a colourless liquid. $[\alpha]_D^{25} = -5.6$ (*c* 0.75, $CHCl_3$); IR: 3333, 3320, 3290, 2922, 1661, 1302, 1060, 927 cm^{-1}; ^1H NMR (200 MHz, D_2O): δ 5.96–5.77 (m, 1H), 5.36–5.15 (m, 2H), 4.30 (q, $J = 7.3$ Hz, 1H), 3.80–3.71 (m, 1H), 3.58–3.40 (m, 2H), 1.70 (t, $J = 4.8$ Hz, 2H); ^{13}C NMR (75 MHz, D_2O): 139.1, 116.0, 70.5, 69.1, 65.3, 39.0. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.49; H, 9.11.

4.1.2. 1-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-(2*S*)-3-buten-2-ol 11. To compound **10** (1.320 g, 10 mmol) in anhydrous acetone (20 mL) at room temperature was added a catalytic amount of *p*-toluenesulfonic acid in one portion. The mixture was stirred at room temperature for 3 h, then solid sodium hydrogen carbonate was added in one portion and the mixture stirred for 20 min. The mixture was filtered and the filtrate concentrated in vacuo to leave a light blue oil. Purification by column chromatography, using ethyl acetate–petroleum ether as eluent, gave the acetonide **11** (1.30 g, 76% yield) as a colourless oil. $[\alpha]_D^{25} = -7.6$ (*c* 2.35, $CHCl_3$); IR: 3457, 2924, 1644, 1370, 1247, 1054 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.97–5.80 (m, 1H), 5.30 (d, $J = 10.4$ Hz, 1H), 5.14 (d, $J = 10.4$ Hz, 1H), 4.22–4.11 (m, 2H), 4.10 (t, $J = 7.4$ Hz, 1H), 3.58 (t, $J = 7.4$ Hz, 1H), 2.95 (br s, 1H), 1.71–1.68 (m, 2H), 1.42 and 1.38 (2s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 141.5, 116.0, 110.5, 76.0, 72.6, 71.0, 41.8, 28.5, 27.2. Mass (EI): *m*/*z* 172 (M^+). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.81; H, 9.35.

4.1.3. 4-[2-Benzyloxy-(2*S*)-3-butenyl]-2,2-dimethyl-(4*R*)-1,3-dioxolane 12. To a well-stirred suspension of freshly activated NaH (0.8 g, 20 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (20 mL), a solution of alcohol **11** (1.72 g, 10 mmol) in dry THF (5 mL) was added dropwise at 0 °C. After 30 min, benzyl bromide (1.43 mL, 12 mmol) was added and the reaction mixture brought to room temperature and refluxed for 8 h. Then the solid ice pieces were added to quench the reaction and the THF layer separated with the aqueous layer extracted with ether (3×20 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. After removing the volatiles under reduced pressure, crude benzyl ether was purified by column chromatography with 10% EtOAc in hexane as an eluent to furnish **12** (2.51 g, 96% yield) as a colourless liquid. $[\alpha]_D^{25} = -32.9$ (*c* 3.15, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.28–7.16 (m, 5H), 5.82–5.66 (m, 1H), 5.28 (dd, $J = 14.2$, 1.1 Hz, 2H), 4.58 (d, $J = 13.4$ Hz, 1H), 4.30 (d, $J = 13.4$ Hz, 1H), 4.05 (m, 1H), 3.98–3.80 (m, 2H), 3.48 (t, $J = 8.6$ Hz, 1H), 2.10–1.95 (m, 1H), 1.76–160 (m, 1H), 1.37 and 1.30 (2s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 138.0, 128.2, 127.5, 127.4, 117.7, 115.2, 108.3, 72.7, 70.0, 69.7, 69.4, 39.1, 26.8, 25.7. Mass (FAB): *m*/*z* 263 (M^++1); HRMS: Calcd for $C_{16}H_{23}O_3$ (M^++1): 263.1647. Found: 263.1644.

4.1.4. 3-Benzyloxy-4-[2,2-dimethyl-(4*R*)-1,3-dioxolan-4-yl]-(3*R*)-butan-1-ol 13. To compound **12** (950 mg, 3.625 mmol) in dry THF was added BH_3·DMS (0.413 g, 5.438 mmol) for over a period of 15 min while maintaining the temperature at 0 °C. The reaction mixture was brought to room temperature and stirred for a period of 8 h. This was then treated with the very slow addition of 3 M NaOH until the reaction mixture was basic while maintaining the temperature at 0 °C. To this was added H_2O_2 (30% solution in H_2O, 0.82 mL, 7.25 mmol) and the reaction mixture stirred over a period of 3 h, and then extracted with ethyl acetate (6×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography to yield alcohol **13** (810 mg, 80%) as a colourless liquid. $[\alpha]_D^{25} = +18.1$ (*c* 0.85, $CHCl_3$); IR: 3485, 2988, 1380, 1266, 1056, 738 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.38–7.22 (m, 5H), 4.52 (Abq, $J = 11.8$ Hz, 2H), 4.21–4.08 (m, 1H), 3.95 (t, $J = 7.4$ Hz, 1H), 3.82–3.68 (m, 3H), 3.45 (t, $J = 7.4$ Hz, 1H), 2.05–1.90 (m, 1H), 1.88–1.65 (m, 3H), 1.38 and 1.30 (2s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 137.9, 128.3, 127.7, 127.6, 108.5, 75.0, 72.6, 70.8, 69.4, 59.9, 37.1, 35.9, 26.8, 25.5. Mass (FAB): *m*/*z* 281 (M^++1): HRMS: Calcd for $C_{16}H_{25}O_4$ (M^++1): 281.1752. Found: 281.1755.

4.1.5. Ethyl 5-benzyloxy-6-[2,2-dimethyl-(4*R*)-1,3-dioxolan-4-yl]-(*E*,5*R*)-2-hexenoate 14. To a well-stirred solution of IBX (1.12 g, 4 mmol) in DMSO (1 mL) was added alcohol **13** (0.56 g, 2 mmol) dropwise in THF (15 mL). The reaction mixture was stirred for 3 h at room temperature. The solid materials were filtered through a sintered funnel. The resulting filtrate was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the crude aldehyde, which was used as such without any further purification. The above crude aldehyde was taken in benzene (15 mL) and carboethoxy methylenetriphenylphosphorane (1.39 g, 4 mmol) then added with the resulting solution stirred for 12 h at room temperature. The solvent was removed under vacuum, the residue was diluted with dichloromethane and washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to yield the α,β-unsaturated ester **14** (0.61 g, 72% overall yield from alcohol) as a colourless oil. $[\alpha]_D^{25} = -20.1$ (*c* 2.7, $CHCl_3$); IR: 2975, 1713, 1656, 1263, 1053 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.40–7.30 (m, 5H), 7.05–6.90 (m, 1H), 5.90 (d, $J = 18.6$ Hz, 1H), 4.55 (Abq, $J = 11.8$ Hz, 2H), 4.28–4.12 (m, 3H), 3.95 (t, $J = 7.4$ Hz, 1H), 3.65 (m, 1H), 3.50 (t, $J = 7.4$ Hz, 1H), 2.50 (t, $J = 6.5$ Hz, 2H), 2.00–1.85 (m, 1H), 1.75–1.60 (m, 1H), 1.40 (s, 3H), 1.32–1.21 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 166.7, 144.6, 138.2, 128.7, 127.8, 124.0, 108.8, 99.8, 75.0, 72.8, 71.2, 69.5, 60.5, 37.8, 36.5, 27.0, 25.8, 14.2. Mass (FAB): *m*/*z* 349 (M^++1). HRMS: Calcd for $C_{20}H_{29}O_5$ (M^++1): 349.2014. Found: 349.2011.

4.1.6. Ethyl 5-benzyloxy-7,8-dihydroxy-(*E*,5*R*,7*R*)-2-octenoate 7. Camphor-10-sulfonic acid (23 mg, 0.1 mmol) was added in one portion to a stirred solution of the acetonide compound **14** (348 mg, 1 mmol) in methanol (10 mL) at 0 °C under nitrogen atmosphere. The mixture was warmed to room temperature and stirred at this temperature for 12 h before it was quenched with a

saturated aqueous solution of sodium hydrogen carbonate (5 mL). The methanol was removed in vacuo and the remaining aqueous layer was then extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to leave a yellow oil. Purification by column chromatography, using 80% ethyl acetate–petroleum ether, increasing to ethyl acetate as eluent, gave the diol **7** (280 mg, 91%) as a pale yellow oil. $[\alpha]_D^{25} = -16.2$ (*c* 0.4, $CHCl_3$); IR: 3446, 3424, 1733, 1647, 1216, 758 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.24 (m, 5H), 6.98–6.82 (m, 1H)), 5.85 (d, $J = 15.6$ Hz, 1H), 4.69 (d, $J = 11.1$ Hz, 1H), 4.46 (d, $J = 11.1$ Hz, 1H), 4.18 (q, $J = 7.4$ Hz, 2H), 3.86–3.78 (m, 2H), 3.50 (dd, $J = 11.1$, 5.9 Hz, 1H), 3.35 (dd, $J = 11.1$, 5.9 Hz, 1H), 2.52 (t, $J = 6.7$ Hz, 2H), 1.58–1.43 (m, 2H), 1.28 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 166.0, 143.9, 137.2, 128.7, 128.1, 127.8, 124.0, 77.6, 77.2, 71.1, 66.4, 60.5, 37.0, 36.5, 14.2. Mass (FAB): *m/z* 331 (M^++23), 309 (M^++1); HRMS: Calcd for $C_{17}H_{25}O_5$ (M^++1): 309.1701. Found: 309.1705.

4.1.7. Ethyl 2-[4-benzyloxy-6-hydroxymethyl-(2*S*,4*R*,6*R*)-dihydro-4*H*-2-pyranyl]acetate 15a. To a suspension of NaH (160 mg, 4 mmol, 60% w/v dispersion in mineral oil) in dry THF (20 mL) at −78 °C was added slowly compound **7** (308 mg, 1 mmol) in THF (3 mL). The reaction was stirred for 4 h, after which TLC showed complete conversion. Then solid ice pieces were added to quench the reaction and then the THF layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by column chromatography (hexane/EtOAc) to afford the pure product **15a** (252 mg, 82% yield) as a colourless liquid. $[\alpha]_D^{25} = -9.5$ (*c* 1.15, $CHCl_3$); IR: 3504, 2865, 1733, 1417, 1288, 1184, 905, 737 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.32–7.28 (m, 5H), 4.52 (Abq, $J = 8.2$ Hz, 2H), 4.30–4.22 (m, 1H), 4.14 (q, $J = 7.4$ Hz, 2H), 3.98–3.90 (m, 1H), 3.89–3.85 (m, 1H), 3.56 (dd, $J = 7.6$, 5.3 Hz, 1H), 3.40 (dd, $J = 7.6$, 5.3 Hz, 1H), 2.49 (dd, $J = 10.6$, 4.7 Hz, 1H), 2.35 (dd, $J = 10.6$, 4.7 Hz, 1H), 1.99–1.91 (m, 1H), 1.75–1.68 (m, 1H), 1.55–1.43 (m, 2H), 1.28 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.8, 138.2, 128.2, 127.6, 127.1, 72.6, 70.5, 70.0, 68.8, 65.8, 60.5, 41.2, 34.9, 31.0, 14.2. Mass (FAB): *m/z* 331 (M^++Na); HRMS: Calcd for $C_{17}H_{24}O_5Na$ (M^++Na): 331.1521. Found: 331.1520.

4.1.8. Ethyl 2-[4-benzyloxy-6-methoxymethoxymethyl-(2*S*,4*R*,6*R*)-dihydro-4*H*-2-pyranyl]acetate 6. To alcohol **15a** (280 mg, 0.909 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added diisopropylethylamine (234 mg, 1.818 mmol) and MOMCl (109 mg, 1.363 mmol) successively and the mixture stirred for 6 h. The reaction mixture was quenched by adding water (4 mL) and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by column chromatography (hexane/EtOAc) to afford the pure product **6** (287 mg, 90%) as a colourless liquid. $[\alpha]_D^{25} = -7.6$ (*c* 0.3, $CHCl_3$); IR: 2924, 1736, 1452, 1341, 1112, 1041 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.39–7.25 (m, 5H), 4.64 (s, 2H), 4.55 (Abq, $J = 8.1$ Hz, 2H), 4.32–4.23 (m, 1H), 4.18–4.02 (m, 3H), 3.94–3.88 (m, 1H), 3.53 (d, $J = 3.6$ Hz, 2H), 3.35 (s, 3H), 2.60 (dd, $J = 15.3$, 8.1 Hz, 1H), 2.48 (dd, $J = 15.3$, 8.1 Hz, 1H), 2.02–1.96 (m, 1H), 1.86–1.74 (m, 1H), 1.68–1.59 (m, 2H), 1.28 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 171.1, 138.6, 128.3, 127.8, 127.3, 96.4, 71.8, 70.7, 70.1, 69.8, 68.8, 60.1, 55.2, 41.3, 34.8, 31.8, 14.1. Mass (FAB): 353 (M^++1); HRMS: Calcd for $C_{19}H_{29}O_6$ (M^++1): 353.1964. Found: 353.1968.

4.1.9. 2-[4-Benzyloxy-6-methoxymethoxymethyl-(2*S*,4*R*,6*R*)-dihydro-4*H*-2-pyranyl]acetaldehyde 16. To a solution of **6** (200 mg, 0.568 mmol) in dry dichloromethane at −78 °C under a nitrogen atmosphere was added DIBAL-H (1 M solution in hexane, 0.568 mmol). The mixture was stirred at −78 °C for 1 h, and then 1 mL of CH_3OH added slowly, while maintaining the temperature at −78 °C for an additional 30 min. A mixture of 3 mL of EtOAc and 12 mL of saturated aqueous sodium potassium tartarate was added to the mixture and the temperature allowed to rise to 23 °C. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (petroleum ether/EtOAc) to afford **16** (150 mg) as a viscous liquid in 86% yield. IR: 2924, 1706, 1453, 1339, 1112, 1041 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.79–9.77 (m, 1H), 7.35–7.22 (m, 5H), 4.58 (s, 2H), 4.55 (s, 2H), 4.40–4.28 (m, 1H), 4.08–3.98 (m, 1H), 3.95–3.88 (m, 1H), 3.48 (d, $J = 6.5$ Hz, 2H), 3.36 (s, 3H), 2.65–2.38 (m, 2H), 1.88 (t, $J = 12.0$ Hz, 2H), 1.46 (t, $J = 12.0$ Hz, 2H).

4.1.10. 1-[4-Benzyloxy-6-methoxymethoxymethyl-(2*R*,4*R*,6*R*)-dihydro-4*H*-2-pyranyl]-(2*R*)-4-penten-2-ol 17. A solution of (+)-allyldiisopinocampheylborane (162 mg, 0.5 mmol) in dry diethyl ether was cooled to −78 °C and aldehyde **16** (154 mg, 0.5 mmol) in anhydrous diethyl ether was added dropwise over 5 min under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 1 h and then brought to room temperature (~1 h). This was then treated with a very slow addition of TEA (0.278 mL, 2 mmol), and hydrogen peroxide (0.113 mL, 30% w/v dispersion in H_2O, 1 mmol) successively while maintaining the temperature at 0 °C. Then the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The organic layer was separated and washed with water, brine and dried over Na_2SO_4, concentrated and purified by column chromatography to yield the homoallyl alcohol **17** (136 mg, 78% yield) as a colourless oil. $[\alpha]_D^{25} = -9.8$ (*c* 1.0, $CHCl_3$); IR: 3437, 2928, 1450, 1341, 1041 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H), 5.89–5.75 (m, 1H), 5.14–4.98 (m, 2H), 4.60 (s, 2H), 4.51 (s, 2H), 4.18–3.98 (m, 2H), 3.96–3.83 (m, 2H), 3.47 (d, $J = 4.9$ Hz, 2H), 3.33 (s, 3H), 2.31–2.20 (m, 2H), 1.90–1.74 (m, 2H), 1.57–1.40 (m, 4H). Mass (FAB): *m/z* 351 (M^++1); HRMS: Calcd for $C_{20}H_{31}O_5$ (M^++1): 351.2171. Found: 351.2173.

4.1.11. 1-[4-Benzyloxy-6-methoxymethoxymethyl-(2*S*,4*R*,6*R*)-dihydro-4*H*-2-pyranylmethyl]-(1*R*)-3-butenyl acrylate 18. To an ice-cold solution of alcohol **17** (155 mg, 0.442 mmol) and diisopropylethylamine (0.381 mL, 2.21 mmol) in CH_2Cl_2 (10 mL) was added a solution of acryloyl chloride (119 mg, 1.328 mmol) in CH_2Cl_2 (2 mL) dropwise. After 4 h of stirring at 0 °C, the solution was diluted with saturated $NaHCO_3$, the organic layer separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to afford a residue, which was purified by column chromatography on silica gel (hexane/EtOAc) to furnish ester **18** (166 mg, 93%) as a colourless liquid. $[\alpha]_D^{25} = -14.6$ (*c* 1.0, $CHCl_3$); IR: 2924, 1722, 1197, 1046, 771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.30–7.21 (m, 5H), 6.41–6.30 (m, 1H), 6.15–6.03 (m, 1H), 5.82–5.71 (m, 2H), 5.25–5.11 (m, 1H), 5.10–5.01 (m, 2H), 4.61 (s, 2H), 4.50 (s, 2H), 3.92–3.78 (m, 3H), 3.48 (d, $J = 4.9$ Hz, 2H), 3.32 (s, 3H), 2.41–2.32 (m, 2H), 2.00–1.89 (m, 1H), 1.85–1.55 (m, 5H). Mass (ESIMS): *m*/*z* 427 (M^++Na); HRMS: Calcd for $C_{23}H_{32}O_6Na$ (M^++Na): 427.2096. Found: 427.2093.

4.1.12. 6-[4-Benzyloxy-6-methoxymethoxymethyl-(2*S*,4*R*,6*R*)-2*H*,3*H*,4*H*,5*H*-2-pyranylmethyl]-(6*R*)-2*H*,5*H*-2-pyranone 5. To a solution of ester **18** (100 mg, 0.247 mmol) in CH_2Cl_2 (20 mL) were added $Ti(^iOPr)_4$ (21 mg, 0.074 mmol) in CH_2Cl_2 (5 mL) and $Cl_2(PCy_3)_2$-Ru=CHPh (20 mg, 0.024 mmol) in CH_2Cl_2 (5 mL) successively. The mixture was refluxed at 60 °C (oil bath temperature) overnight, and then concentrated to afford a residue, which was purified by column chromatography on silica gel (hexane/EtOAc) to furnish lactone **5** (87 mg, 94% yield) as a viscous liquid. $[\alpha]_D^{25} = -10.7$ (*c* 1.0, $CHCl_3$); IR: 2920, 1732, 1219, 1061 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.31–7.22 (m, 5H), 6.86–6.83 (m, 1H), 5.98 (d, $J = 12.5$ Hz, 1H), 4.66–4.61 (m, 1H), 4.58 (s, 2H), 4.51 (s, 2H), 4.08–3.88 (m, 2H), 3.86–3.82 (m, 1H), 3.48 (d, $J = 5.3$ Hz, 2H), 3.32 (s, 3H), 2.40–2.27 (m, 2H), 1.86–1.69 (m, 4H), 1.35–1.30 (m, 2H). Mass (FAB): *m*/*z* 399 (M^++Na). HRMS: Calcd for $C_{21}H_{28}O_6Na$ (M^++Na): 399.1783. Found: 399.1784.

4.1.13. 6-[4-Benzyloxy-6-methoxymethoxymethyl-(2*S*,4*R*,6*R*)-2*H*,3*H*,4*H*,5*H*-2-pyranylmethyl]-(6*R*)-2*H*,5*H*-2-pyranol 19. To a solution of lactone **5** (60 mg, 0.159 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added DIBAL-H (1 M in hexane, 0.159 mmol). The mixture was stirred at −78 °C for 30 min and then quenched with 10% Rochelle salt solution. The resulting mixture was warmed to 23 °C and stirred for 1 h. The layers were then separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was dissolved in EtOH (3 mL) and CSA (6 mg) was added. The resulting mixture was stirred at 23 °C for 30 min. The mixture was quenched with Et_3N (two drops) and concentrated. The residue was purified by silica gel column chromatography to afford the ethyl glycoside **19** (55 mg, 86% yield) as a colourless liquid. $[\alpha]_D^{25} = -1.7$ (*c* 0.75, $CHCl_3$); IR: 2924, 1380, 1046 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.36–7.32 (m, 5H), 6.02–5.96 (m, 1H), 5.76–5.71 (m, 1H), 4.95 (d, $J = 9.6$ Hz, 1H), 4.64 (s, 2H), 4.55 (Abq, $J = 11.8$ Hz, 2H), 4.24–4.19 (m, 1H), 4.12 (q, $J = 5.9$ Hz, 2H), 3.95–3.82 (m, 2H), 3.58–3.48 (m, 3H), 3.34 (s, 3H), 2.02–1.90 (m, 4H), 1.58–1.54 (m, 4H), 1.26 (t, $J = 5.9$ Hz, 3H). Mass (ESIMS): *m*/*z* 429 (M^++Na); HRMS: Calcd for $C_{23}H_{34}O_6Na$ (M^++Na): 429.2253. Found: 429.2252.

4.1.14. 4-Benzyloxy-2-[2-ethoxy-(2*S*,6*R*)-2*H*,5*H*-6-pyranylmethyl]-6-methoxymethoxymethyl-(2*R*,4*R*,6*R*)-2*H*,3*H*,4*H*,5*H*-pyran 4. A solution of **19** (30 mg, 0.73 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0 °C. To the cooled solution was added allyltrimethylsilane (16 mg, 0.147 mmol) in dichloromethane. After stirring for 10 min, trimethylsilyl triflate (3 mg, 0.014 mmol) in dichloromethane was added to the reaction mixture. The resulting mixture was stirred for 1 h and diluted with water and extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent evaporated. The residue was purified by column chromatography to give **4** (22 mg, 85%) as a colourless liquid. $[\alpha]_D^{25} = -8.23$ (*c* 1.15, $CHCl_3$); IR: 3480, 2922, 1384, 1061, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.36–7.32 (m, 5H), 5.88–5.78 (m, 2H), 5.73–5.67 (m, 1H), 5.10–5.02 (m, 2H), 4.54 (Abq, $J = 11.8$ Hz, 2H), 4.21–4.16 (m, 1H), 4.14–4.08 (m, 1H), 3.94–3.84 (m, 3H), 3.60 (dd, $J = 11.1$, 5.9 Hz, 1H), 3.42 (dd, $J = 11.1$, 5.9 Hz, 1H), 2.44–2.38 (m, 1H), 2.35–2.31 (m, 1H), 2.26–2.21 (m, 1H), 2.08–2.00 (m, 1H), 1.97–1.90 (m, 4H), 1.56–1.52 (m, 2H). Mass (ESIMS): *m*/*z* 381 (M^++Na). Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.72; H, 8.44. Found: C, 73.75; H, 8.46.

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