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Pd(II)-mediated synthesis of 2-deoxy- and rare-*C*-glycosides†

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Abstract—The synthesis of 2-deoxy-*C*-glycosides and rare-*C*-saccharides from the γ,δ-olefinic alcohols is described. In the presence of Pd(II) reagents these olefinic alcohols undergo an efficient intramolecular oxidative cyclisation to afford the target molecules.

1. Introduction

Bio-active carbohydrates play a prominent role in several life processes. The synthesis of glycosyl mimics,[1] where the acid labile *O*-glycosidic bond is replaced by a *C*-glycosidic bond, has attracted attention in the recent past. A variety of *C*-glycosides, 2-deoxy-*C*-glycosides and rare-*C*-glycosides are common structural elements in several natural products, especially antibiotics with antitumor activity such as daunorubicin,[2] calicheamycin[3] and olivomycin A,[4] and a number of compounds of the aureolic acid family. The synthesis of monosaccharides, which find widespread application as intermediates in natural product synthesis,[5] is therefore challenging to synthetic organic chemists.

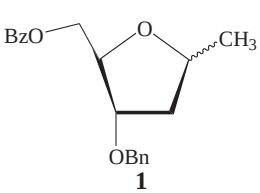
In continuation of our interest on the synthesis of rare saccharides[6], *C*-glycosides[7,8], *C*-saccharides[9,10] and pseudo saccharides,[11] and the prominent place occupied by the 2-deoxy and rare-*C*-saccharides, herein we describe the Pd(II)-mediated synthesis of these compounds from olefinic alcohols by an oxidative cyclisation protocol.

2. Results and discussion

2.1. Synthesis of 2-deoxy-*C*-methyl glycoside 1

The requisite olefinic alcohols for the synthesis of 2-deoxy-*C*-glycosides were prepared from 2,3-*O*-isopropylidene-(*R*)-glyceraldehyde. Accordingly, **4** on reaction with allyl bromide (Scheme 1) in the presence of zinc in THF[12] gave carbinol **5**. On reaction of **5** with benzyl bromide in the presence of sodium hydride the benzyl ether **6** formed cleanly. On hydrolysis with 60% aq. AcOH formation of the diol **7** was effected in 75% yield. Benzoylation of **7** with benzoyl chloride in the presence of pyridine in CH_2Cl_2 gave the mono-benzoate **8** along with minor amounts of di-benzoate.

The olefinic alcohol **8** on reaction with $PdCl_2$–$CuCl$–O_2 underwent oxidative cyclisation[13,14] and gave the 2-deoxy hemiketal **9** in 86% yield, which on reductive deoxygenation with triethylsilane[15] in the presence of boron trifluoride monoetherate, furnished the 2-deoxy-*C*-methyl glycoside **1** as an inseparable mixture of α- and β-isomers in a 1:1 ratio in 70% yield.



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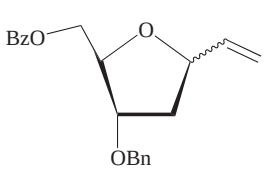

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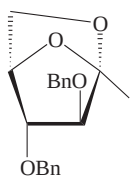

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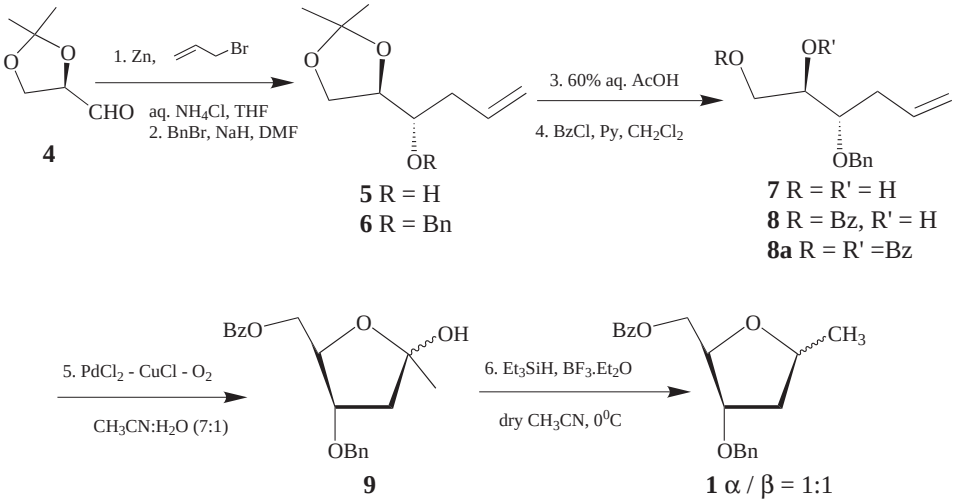


Scheme 1.

2.2. Synthesis of 2-deoxy-*C*-vinyl glycoside 2

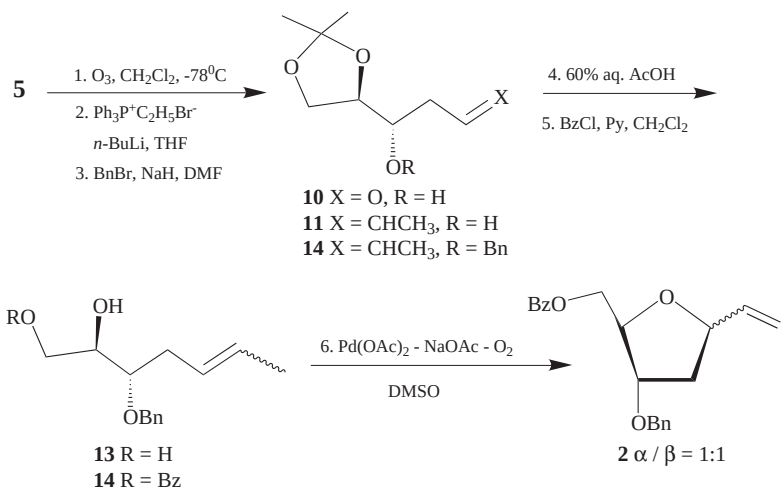
Carbinol **5** was subjected to ozonolysis in CH_2Cl_2 at −78°C to give the corresponding aldehyde **10** (Scheme 2), which on Wittig olefination with ethyl triphenylphosphorane gave olefin **11**. On reaction with benzyl bromide and sodium hydride **12** was formed in 78% yield, which on hydrolysis with 60% aq. AcOH gave diol **13** in 70% yield. Reaction of **13** with benzoyl chloride in the presence of pyridine in CH_2Cl_2 gave the mono-benzoate **14** along with traces of di-benzoate. Oxidative cyclisation of the olefinic alcohol **14** with $Pd(OAc)_2$–NaOAc–O_2 in DMSO then gave the 2-deoxy-*C*-vinyl glycoside **2** as a 1:1 ratio of inseparable α- and β-isomers in a 65% yield.

2.3. Synthesis of the rare-*C*-methyl glycoside 3

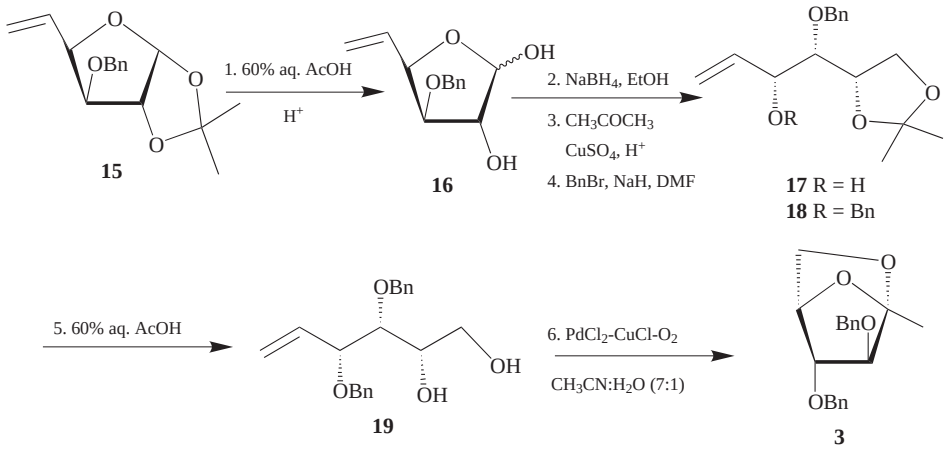
The rare saccharide synthesis was initiated from 'diacetone glucose' (DAG), where unlike the case of earlier allylic alcohols, the olefin was incorporated at the C-(5) of the sugar. The main strategy was to convert the 5, 6-diol of DAG into an olefin, where use of the C-(2) hydroxyl group as an internal nucleophile for oxidative cyclisation would result in an unusual *C*-methyl glycoside.

Olefin **15**, prepared (Scheme 3) through a known procedure,[16,17] was subjected to hydrolysis with 60% aq. AcOH in the presence of conc. H_2SO_4 (catalytic) to afford the diol **16**. Reduction of **16** with sodium borohydride in ethanol followed by further reaction of triol with acetone $CuSO_4$ gave **17** in 47% overall yield. The alcohol **17** was then reacted with benzyl bromide in the presence of sodium hydride to afford **18** in 85% yield. Hydrolysis of **18** with 60% aq. AcOH at room temperature gave the diol **19**, which finally on $PdCl_2$–$CuCl$–O_2-mediated oxidative cyclisation afforded the 1,6-anhydro rare-*C*-glycoside **3** (L-xylo derivative) in 70% yield.

Thus, in summary the protocol presented is a mild and efficient method for the synthesis of 2-deoxy-*C*-methyl



Scheme 2.



Scheme 3.

glycoside **1**, 2-deoxy-*C*-vinyl glycoside **2** and rare-*C*-methyl glycoside **3** using the Pd(II)-mediated oxidative cyclisation of γ,δ-olefinic alcohols by an internal oxygen nucleophile. The Markownikoff addition product, the hemiketal, was efficiently converted into 2-deoxy-*C*-methyl glycoside by reductive deoxygenation. The utility of the present methodology and the *C*-glycosides synthesised could find wide use in the synthesis of new glyco substances.

3. Experimental

Solvents were dried over standard drying agents and freshly distilled prior to use. ^{1}H (200 MHz, 500 MHz) and ^{13}C NMR (50 MHz, 125 MHz) spectra were recorded in deuteriochloroform solution with tetramethylsilane as an internal reference on Varian Gemini-200 MHz and INOVA-500 MHz spectrometers, and coupling constants (J) are given in Hz. Optical rotations were measured with a Jasco DIP-370 instrument and $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40°C in vacuo. The nomenclature used in the experimental section was adopted from ACD/Name version 1.0β, ACD Inc., Toronto, Canada.

3.1. 4-[1-Benzyloxy-(1*S*)-3-butenyl]-2,2-dimethyl-(4*R*)-1,3-dioxolane 6

To a stirred solution of **5** (1.0 g, 5.81 mmol) in dry DMF (3 mL), sodium hydride (60% dispersion in oil, 0.53 g, 11.62 mmol,) was added at 0°C and stirred for 30 min. Benzyl bromide (0.68 mL, 5.81 mmol) was added and further stirred for 3 h at room temperature. The reaction was quenched by adding aq. NH_4Cl solution (10 mL) and the compound was extracted into ether (2×15 mL). The combined ether layers were washed with water (20 mL), brine (20 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by column chromatography (60–120 mesh silica gel, ethyl acetate: petroleum ether 1:9) gave **6** as a syrup (0.99 g, 65%). $[\alpha]_D$ = +16.9 (c 2.88, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34, 1.55 (2s, 6H, CH_3), 2.20–2.52 (m, 2H, H-3,3′), 3.30–3.62 (m, 1H, H-4), 3.83–4.26 (m, 3H, H-5,6,6′), 4.58–4.70 (m, 2H, -OCH_2Ph), 5.00–5.20 (m, 2H, H-1,1′), 5.76–6.01 (m, 1H, H-2), 7.21–7.40 (m, 5H, -OCH$_2$*Ph*); EIMS (m/z, %): 247 (17), 171 (56), 155 (100), 91 (78). Anal. calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.19; H, 8.41%.

3.2. 3-Benzyloxy-(2*R*,3*S*)-5-hexene-1,2-diol 7

A solution of **6** (0.9 g, 3.43 mmol) in 60% aq. acetic acid (10 mL) was stirred at room temperature for 12 h. The reaction mixture was neutralised with excess solid $NaHCO_3$ (8 g) and the compound was extracted into ethyl acetate (3×15 mL). The combined ethyl acetate layers were washed with water (15 mL), brine (15 mL) and dried (Na_2SO_4). Evaporation of solvent and purification of the residue by column chromatography (60–120 mesh silica gel, ethyl acetate: petroleum ether 1:4) gave **7** as a syrup (0.57 g 75%). $[\alpha]_D$ = +3.95 (c 1.92, $CHCl_3$); IR (neat): 1080, 2936, 3400 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.08–2.65 (m, 3H, H-3,3′ -OH), 3.45–3.72 (m, 4H, H-4,5,6,6′), 4.40–4.74 (m, 2H, -OCH_2Ph), 5.02–5.20 (m, 2H, H-1,1′), 5.70–5.98 (m, 1H, H-2), 7.20–7.40 (m, 5H, -OCH$_2$*Ph*); EIMS (m/z, %): 222 (M$^+$, 3), 205 (19), 131 (100), 107 (58). Anal. calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.17; H, 8.09%.

3.3. Benzoylation of diol 7

To a stirred solution of **7** (1.2 g, 5.40 mmol) and pyridine (0.87 mL, 10.81 mmol) in CH_2Cl_2 (10 mL), was added dropwise benzoyl chloride (0.75 mL, 5.40 mmol) in CH_2Cl_2 (2 mL) at 0°C. The reaction mixture was stirred for 3 h at 0°C then diluted with cold water (20 mL) and extracted into CH_2Cl_2 (2×20 mL) and the combined CH_2Cl_2 layers were washed with 5% cold aq. HCl solution (25 mL), aq. $NaHCO_3$ solution (20 mL), water (20 mL), brine (20 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by column chromatography (60–120 mesh silica gel, ethyl acetate: petroleum ether 1:4) gave **8** and **8a** (total 1.37 g 75%) in two bands.

First eluted was 1-[1-[1,2-di(phenylcarbonyloxy)-(1*R*)-ethyl]-(1*S*)-3-butenyloxymethyl] benzene **8a** as a syrup (0.23 g, 10%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35–2.60 (m, 2H, H-3,3′), 3.80–3.92 (m, 1H, H-4), 4.60–4.80 (m, 4H, H-6,6′, -OCH_2Ph), 5.05–5.20 (m, 2H, H-1,1′), 5.50–5.65 (m, 1H, H-5), 5.76–5.98 (m, 1H, H-2), 7.20–7.40 (m, 5H, -OCH$_2$*Ph*), 7.42–7.64 (m, 6H, Ph), 7.90–8.10 (m, 4H, Ph); FABMS (*m*/*z*, %): 430 (M^+, 9), 220 (100), 210 (43), 107 (67).

Second eluted was 1-[1-[1-hydroxy-2-phenylcarbonyloxy-(1*R*)-ethyl]-(1*S*)-3-butenyloxy methyl]benzene **8** as a syrup (1.14 g, 65%). $[\alpha]_D = +12.4$ (*c* 1.50, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.42–2.57 (m, 2H, H-3,3′), 3.50–3.65 (m, 1H, H-4), 3.86–4.02 (m, 1H, H-5), 4.32–4.76 (m, 4H, H-6,6′-OCH_2Ph), 5.05–5.25 (m, 2H, H-1,1′), 5.71–6.01 (m, 1H, H-2), 7.20–7.34 (m, 5H, -OCH$_2$*Ph*), 7.36–7.60 (m, 3H, Ph), 7.94–8.05 (m, 2H, Ph); FABMS (*m*/*z*, %): 327 (M^++1, 19), 219 (15), 105 (72), 91 (100), 55 (45). Anal. calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.55; H, 6.71%.

3.4. 3-Benzyloxy-5-hydroxy-5-methyl-2-phenylcarbonyloxymethyl-(2*R*,3*S*)-tetrahydrofuran 9

To a stirred solution of **8** (0.2 g, 0.61 mmol), palladium(II) chloride (0.01 g, 0.06 mmol) and copper(I) chloride (0.06 g, 0.61 mmol) in aq. acetonitrile (3 mL, 1:7), oxygen gas was bubbled continuously for 2 h. The reaction mixture was filtered through a silicagel bed with ether eluent. Evaporation of solvent and purification of residue by column chromatography (60–120 mesh silica gel, ethyl acetate: petroleum ether 1:9) gave **9** (0.18 g, 86%) as an inseparable mixture of isomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50–1.60 (m, 3H, CH_3), 1.90–2.08 (m, 2H, H-2,2′), 3.85–4.00 (m, 1H, H-3), 4.04–4.20 (m, 1H, H-4), 4.23–4.75 (m, 4H, H-5,5′,-OCH_2Ph), 7.20–7.35 (m, 5H, -OCH$_2$*Ph*), 7.40–7.62 (m, 3H, Ph), 7.93–8.12 (m, 2H, Ph); FABMS (*m*/*z*, %): 327 (19), 325 (81), 105 (57), 91 (100), 55 (71). Anal. calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.11; H, 6.41%.

3.5. 3-Benzyloxy-5-methyl-2-phenylcarbonyloxymethyl-(2*R*,3*S*)-tetrahydrofuran 1

To a stirred solution of **9** (0.1 g, 0.29 mmol) and triethylsilane (0.09 mL, 0.58 mmol) in dry acetonitrile (3 mL), boron trifluoride etherate (0.036 mL, 0.29 mmol) was added under nitrogen atmosphere at 0°C and stirred for 15 min. The reaction mixture was diluted with aq. K_2CO_3 solution (2 mL), brought to room temperature and stirred for further 1 h. The mixture was extracted into ether (2×10 mL) and the combined ether extracts were washed with water (10 mL), brine (10 mL) and dried (Na_2SO_4). Evaporation of solvent and purification of residue by column chromatography (60–120 mesh silica gel, ethyl acetate: petroleum ether 1:9) gave **1** (0.066 g) in 70% yield as an inseparable mixture of isomers (1:1). $[\alpha]_D = +7.7$ (*c* 1.42, $CHCl_3$); IR (neat): 700, 1100, 1280, 1728, 2944 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (d, 3H, *J* 6.8 Hz, CH_3), 2.08–2.32 (m, 2H, H-2,2′), 3.98–4.08 (m, 1H, H-1), 4.16–4.70 (m, 6H, H-3,4,5,5′,-OCH_2Ph), 7.18–7.33 (m, 5H, -OCH$_2$*Ph*), 7.37–7.60 (m, 3H, Ph), 7.98–8.10 (m, 2H, Ph); FABMS (*m*/*z*, %): 311 (21), 309 (43), 105 (100), 91 (87). Anal. calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.56; H, 6.72%.

3.6. 1-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-(1*S*,3*E*)-3-penten-1-ol 11

A stirred solution of **5** (2.0 g, 11.62 mmol) in dry CH_2Cl_2 (20 mL), was bubbled with ozone continuously for 15 min (until the colour of the reaction mixture changed to blue) at −78°C and triphenylphosphine (3.3 g, 12.79 mmol) was added and stirred for 5 min. The reaction mixture was warmed to room temperature and evaporated under reduced pressure to give the crude aldehyde **10**.

To a stirred suspension of ethyl triphenylphosphonium bromide (5.1 g, 11.79 mmol) in dry THF (50 mL), potassium *tert*-butoxide (1.5 g, 13.79 mmol) in dry THF (10 mL) was added at room temperature over 10 min under nitrogen atmosphere. After 30 min a solution of the above aldehyde **10** in dry THF (10 mL) was added dropwise at room temperature and stirred for further 18h. The reaction mixture was quenched by adding aq. NH_4Cl solution (20 mL) and extracted into ether (2×25 mL). The combined ether layers were washed with water (20 mL), brine (20 mL) and dried (Na_2SO_4). Evaporation of solvent and purification of residue by column chromatography (60–120 mesh silica gel, ethyl acetate: petroleum ether 1:9) gave **11** as a syrup (1.03 g, 48% overall yield from **5**). $[\alpha]_D = +13.4$ (*c* 1.08, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34, 1.40 (2s, 6H, CH_3), 1.56–1.73 (m, 3H, CH_3), 2.17–2.30 (m, 2H, H-4,4′), 3.60–3.78 (m, 1H, H-7), 3.82–4.05 (m, 3H, H-5,6,7′), 5.32–5.74 (m, 2H, H-2,3); EIMS (*m*/*z*, %): 171 (17), 169 (29), 43 (100).

3.7. 4-[1-Benzyloxy-(1*S*,3*E*)-3-pentenyl]-2,2-dimethyl-(4*R*)-1,3-dioxolane 12

To a stirred solution of **11** (1.5 g, 8.06 mmol) in dry DMF (3 mL), was added sodium hydride (0.77 g, 16.12 mmol, 60% suspension), followed by benzyl bromide (1.14 mL, 9.67 mmol). The reaction was worked up and purified as described for **6**, to give **12** as a syrup (1.74 g 78%). $[\alpha]_D = +5.6$ (*c* 1.04, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30–1.45 (m, 6H, CH_3), 1.60–1.72 (m, 3H, CH_3), 2.20–2.42 (m, 2H, H-4,4′), 3.42–3.60 (m, 1H, H-7), 3.80–3.92 (m, 1H, H-7′), 3.96–4.10 (m, 2H, H-5,6), 4.48–4.72 (m, 2H, -OCH_2Ph), 5.40–5.66 (m, 2H, H-2,3), 7.20–7.42 (m, 5H, -OCH$_2$*Ph*); EIMS (*m*/*z*, %): 261 (27), 233 (43), 185 (100), 91 (78). Anal. calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.80; H, 8.69%.

3.8. 3-Benzyloxy-(2*R*,3*S*,5*E*)-5-heptene-1,2-diol 13

Compound **12** (1.7 g, 6.15 mmol) was taken in 60% aq. acetic acid (10 mL) and stirred for 12 h at room temperature, worked up and purified as described for **7**, to give **13** as a syrup (1.01 g, 70%). $[\alpha]_D = +17.8$ (*c* 1.40,

$CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.55–1.70 (m, 3H, CH_3), 2.22–2.50 (m, 2H, H-4,4′), 2.92–3.30 (br. s, 2H, -OH), 3.40–3.72 (m, 4H, H-5,6,7,7′), 4.40–4.70 (m, 2H, -O*CH*$_2$Ph), 5.32–5.64 (m, 2H, H-2,3), 7.18–7.36 (m, 5H, -OCH$_2$*Ph*); EIMS (*m*/*z*, %): 221 (9), 219 (14), 129 (53), 91 (100). Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.08; H, 8.46%.

3.9. 1-[1-[1-Hydroxy-2-phenylcarbonyloxy-(1*R*)-ethyl]-(1*S*,3*E*)-3-pentenyloxymethyl]benzene 14

To a stirred solution of **13** (0.65 g, 2.75 mmol) and pyridine (0.44 mL, 5.50 mmol) in dry CH_2Cl_2 (10 mL), benzoyl chloride (0.32 mL, 2.75 mmol) in dry CH_2Cl_2 (2 mL) was added drop wise at 0°C, worked up and purified as described for **8**, to give **14** (0.7 g) in 76% yield as a syrup. $[\alpha]_D$ = +21.95 (*c* 1.16, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.62–1.72 (m, 3H, CH_3), 2.36–2.60 (m, 2H, H-4,4′), 3.50–3.68 (m, 1H, H-5), 3.85–4.05 (m, 1H, H-6), 4.32–4.78 (m, 4H, H-7,7′–O*CH*$_2$Ph), 5.40–5.70 (m, 2H, H-2,3), 7.20–7.35 (m, 5H, -OCH$_2$*Ph*), 7.45–7.54 (m, 3H, -CO$_2$*Ph*), 8.00 (d, 2H, -CO$_2$*Ph*); FABMS (*m*/*z*, %): 340 (M^+, 5), 323 (32), 249 (43), 235 (100), 105 (87). Anal. calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.03; H, 7.05%.

3.10. 3-Benzyloxy-2-phenylcarbonyloxymethyl-5-vinyl-(2*R*,3*S*)-tetrahydrofuran 2

To a stirred solution of **14** (0.1 g, 0.28 mmol), palladium-(II) acetate (0.01 g, 0.002 mmol) and NaOAc (0.046 g, 0.56 mmol) in dry DMSO (3 mL), oxygen was bubbled for 12 h at 50°C. The reaction mixture was brought to room temperature, diluted with water (20 mL) and extracted into ether (2×15 mL). The combined ether layers were washed with water (15 mL), brine (20 mL) and dried (Na_2SO_4). Evaporation of solvent and purification of residue by column chromatography (60–120 mesh silica gel, ethyl acetate: petroleum ether 1:9), gave **2** (0.06 g) in 65% yield as an inseparable mixture (α/β = 1:1) as a syrup. $[\alpha]_D$ = +23.2 (*c* 2.01, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.70–2.00 (m, 1H H-4), 2.16–2.50 (m, 1H, H-4′), 4.04–4.16 (m, 1H, H-5), 4.22–4.42 (m, 2H, H-3,6), 4.42–4.72 (m, 4H, H-7,7′, -O*CH*$_2$Ph), 5.08–5.22 (m, 1H, H-1), 5.22–5.38 (m, 1H, H-1′), 5.74–6.08 (m, 1H, H-2), 7.20–7.34 (m, 5H, -OCH$_2$*Ph*), 7.45–7.56 (m, 3H, -CO$_2$*Ph*), 8.00 (d, 2H, -CO$_2$*Ph*); FABMS (*m*/*z*, %): 338 (M^+, 3), 324 (21), 231 (65), 105 (100), 91 (73). Anal. calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.47; H, 6.46%.

3.11. 4-Benzyloxy-5-vinyl-(3*R*,4*S*,5*R*)-tetrahydro-2,3-furandiol 16

A solution of **15** (5.0 g, 18.11 mmol) in 60% aq. AcOH (50 mL) containing conc. H_2SO_4 (catalytic) was stirred for 48 h at room temperature, worked up and purified as described for **7**, to give **16** (2.47 g) in 58% yield as a syrup. ^1H NMR (200 MHz, $CDCl_3$): δ 3.50 (br. s, 1H, -OH), 3.80–3.92 (m, 1H, H-3), 4.42–4.70 (m, 4H, H-2,4, -OCH$_2$*Ph*), 5.08–5.45 (m, 3H, H-1, 6,6′), 5.80–6.10 (m, 1H, H-5), 7.20–7.40 (m, 5H, -OCH$_2$*Ph*); EIMS (*m*/*z*, %): 219 (22), 145 (100), 107 (47), 91 (76).

3.12. 1-Benzyloxy[2,2-dimethyl-(4*S*)-1,3-dioxolan-4-yl]-methyl-(1*R*)-2-propenyl alcohol 17

To a solution of **16** (2.2 g, 9.32 mmol) in ethanol (15 mL) sodium borohydride (0.69 g, 18.64 mmol) was added in portions and stirred for 2 h at room temperature. Solvent was evaporated under reduced pressure and the crude triol was subjected to the next reaction.

To a solution of the above triol and dry $CuSO_4$ (5.0 g) in acetone (20 mL), conc. H_2SO_4 (catalytic) was added and stirred for 12 h at room temperature. The reaction mixture was filtered off, neutralised with solid $NaHCO_3$ (5.0 g) and extracted into ethyl acetate (2×20 mL). The combined ethyl acetate layers were washed with water (20 mL), brine (20 mL) and dried (Na_2SO_4). Evaporation of solvent and purification of residue by column chromatography (60–120 mesh silica gel, ethyl acetate: petroleum ether 1:9) gave **17** as a syrup (1.21 g, 47% yield from **16**). $[\alpha]_D$ = −3.8 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.34, 1.40 (2s, 6H, CH_3), 2.35 (br. d, 1H, -OH), 3.37 (dd, 1H, $J_{3,4}$ 6.0, $J_{4,5}$ 4.0 Hz, H-4), 3.74 (t, 1H, $J_{5,6}$ 8.0, $J_{6,6'}$ 8.0 Hz, H-6), 3.94–4.10 (m, 2H, H-5,6′), 4.28 (dd, 1H, $J_{3,4}$ 6.0, $J_{2,3}$ 16.0 Hz, H-3), 4.62, 4.80 (2d, 2H, -O*CH*$_2$Ph), 5.17 (d, 1H, *J* 10.0 Hz, H-1), 5.32 (d, 1H, *J* 16.0 Hz, H-1′), 5.78–5.95 (m, 1H, H-2), 7.20–7.36 (m, 5H, -OCH$_2$*Ph*); EIMS (*m*/*z*, %): 263 (31), 261 (25), 187 (100), 107 (54). Anal. calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.99; H, 7.93%.

3.13. 3,4-Dibenzyloxy-4-[2,2-dimethyl-(4*S*)-1,3-dioxolan-4-yl]-(3*R*)-1-butene 18

To a stirred solution of **17** (1.0 g, 3.59 mmol) in DMF (3 mL), NaH (60% suspension in mineral oil, 0.33 g, 7.19 mmol,) followed by benzyl bromide (0.42 mL, 3.59 mmol) were added, worked up and purified as described for **6**, to give **18** as a syrup (1.12 g, 85%). $[\alpha]_D$ = −25.66 (*c* 0.40, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.35, 1.40 (2s, 6H, CH_3), 3.41 (t, 1H, $J_{4,5}$ 5.4, $J_{5,6}$ 6.3 Hz, H-5), 3.65 (t, 1H, $J_{5,6}$ 6.3, $J_{6,6'}$ 9.0 Hz, H-6), 3.80 (t, 1H, $J_{5,6'}$ 6.3, $J_{6,6'}$ 9.0 Hz, H-6′), 3.94 (t, 1H, $J_{3,4}$ 4.5, $J_{4,5}$ 5.4 Hz, H-4), 4.22 (dd, 1H, $J_{2,3}$ 13.6, $J_{3,4}$ 4.5 Hz, H-3), 4.57 (s, 2H, -O*CH*$_2$Ph), 4.78 (s, 2H, -O*CH*$_2$Ph), 5.30 (s, 1H, H-1), 5.36 (d, 1H, *J* 8.0 Hz, H-1′), 5.81–5.61 (m, 1H, H-2), 7.22–7.40 (m, 10H, -OCH$_2$*Ph*); FABMS (*m*/*z*, %): 368 (M^+, 7), 353 (27), 187 (56), 181 (100), 91 (74). Anal. calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.93; H, 7.61%.

3.14. 3,4-Dibenzyloxy-(2*S*,3*S*,4*R*)-5-hexene-1,2-diol 19

A solution of **18** (1.0 g, 2.71 mmol) in 60% aqueous acetic acid (5 mL) was stirred for 12 h at room temperature, worked up and purified as described for **7**, to give **19** (0.55 g, 62%) as a syrup. $[\alpha]_D$ = −4.45 (*c* 1.24, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 2.62 (br. s, 2H, -OH), 3.40–3.51 (m, 3H, H-5,6,6′), 3.62–3.72 (m, 1H, H-4), 4.06 (t, 1H, $J_{2,3}$ 8.0, $J_{3,4}$ 5.5 Hz, H-3), 4.32 (d, 1H, -OCH(*H*)Ph), 4.56 (t, 2H, -O*CH*$_2$Ph), 4.80 (d, 1H, -OCH(*H*)Ph), 5.30 (s, 1H, H-1), 5.38 (d, 1H, *J* 7.8 Hz, H-1′), 5.72–5.92 (m, 1H, H-2), 7.14–7.31 (m, 10H, -OCH$_2$*Ph*); FABMS (*m*/*z*, %): 328 (M^+, 6), 311 (32),

181 (67), 147 (100), 91 (55). Anal. calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.16; H, 7.28%.

3.15. 5,6-Dibenzyloxy-1-methyl-(1*S*,4*S*,5*R*,6*S*)-2,7-dioxabicyclo[2.2.1]heptane 3

To a stirred solution of **19** (0.1 g, 0.30 mmol), palladium(II) chloride (0.005 g, 0.03 mmol) and copper(I) chloride (0.03 g, 0.30 mmol) in aq. acetonitrile (3mL, 1:7), oxygen gas was bubbled continuously for 48 h at room temperature, worked up and purified as described for **9**, to give **3** (0.069 g) in 70% yield as a syrup. $[\alpha]_D = +30.3$ (*c* 0.95, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.51 (s, 3H, CH_3), 3.38–3.46 (m, 2H, H-5,5′), 3.84 (br. d, 1H, $J_{2,3}$ 4.5 Hz, H-3), 4.00 (d, 1H, $J_{2,3}$ 4.5 Hz, H-2), 4.40 (s, 2H, -O*CH*$_2$Ph), 4.44–4.52 (m, 3H, H-4, -O*CH*$_2$Ph), 7.17–7.32 (m, 10H, -OCH$_2$*Ph*); FABMS (*m*/*z*, %): 309 (24), 257 (23), 181 (100), 143 (56). Anal. calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.53; H, 6.71%.

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