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Mevalonate analogues as substrates of enzymes in the isoprenoid biosynthetic pathway of *Streptococcus pneumoniae*

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ABSTRACT

Survival of the human pathogen *Streptococcus pneumoniae* requires a functional mevalonate pathway, which produces isopentenyl diphosphate, the essential building block of isoprenoids. Flux through this pathway appears to be regulated at the mevalonate kinase (MK) step, which is strongly feedback-inhibited by diphosphomevalonate (DPM), the penultimate compound in the pathway. The human mevalonate pathway is not regulated by DPM, making the bacterial pathway an attractive antibiotic target. Since DPM has poor drug characteristics, being highly charged, we propose to use unphosphorylated, cell-permeable prodrugs based on mevalonate that will be phosphorylated in turn by MK and phosphomevalonate kinase (PMK) to generate the active compound in situ. To test the limits of this approach, we synthesized a series of C_3-substituted mevalonate analogues to probe the steric and electronic requirements of the MK and PMK active sites. MK and PMK accepted substrates with up to two additional carbons, showing a preference for small substituents. This result establishes the feasibility of using a prodrug strategy for DPM-based antibiotics in *S. pneumoniae* and identified several analogues to be tested as inhibitors of MK. Among the substrates accepted by both enzymes were cyclopropyl, vinyl, and ethynyl mevalonate analogues that, when diphosphorylated, might be mechanism-based inactivators of the next enzyme in the pathway, diphosphomevalonate decarboxylase.

1. Introduction

Streptococcus pneumoniae kills over a million people a year, mostly children and the elderly, and is the primary cause of community-acquired pneumonia and bacterial meningitis.[1,2] Universal vaccination programs in the US have led to a reduction in the targeted serotypes of *S. pneumoniae*; however, this effort has resulted in serotype replacement by nonvaccinated strains that show substantial antimicrobial resistance.[3] Vancomycin, the antibiotic of last resort, has shown signs of weakness in some strains of *S. pneumoniae*,[4,5] and widespread resistance to beta-lactams and macrolides, including multiple-drug-resistance, makes treatment difficult and expensive.[6–9] The need for new strategies to combat this deadly pathogen in the short term is unequivocal.

A presently unexploited antibiotic target in *S. pneumoniae* is the mevalonate pathway (Fig. 1), which is required for the organism to survive in lung and serum.[10] This pathway converts mevalonate to isopentenyl diphosphate (IPP), the building block of isoprenoids, in three enzymatic steps, each carried out by a member of the GHMP kinase family. We recently discovered that the first enzyme, mevalonate kinase (MK), is feedback-inhibited by diphosphomevalonate (DPM) through binding at a high-affinity allosteric site at concentrations (K_i = 0.5 μM) where the human homolog of MK is unaffected.[11] The allosteric site is thought to lie at the MK dimer interface and appears to be absent from the MKs of mammals[12] and some bacteria,[13] raising the possibility that the effects of DPM inhibition would be limited to few species.

DPM is not expected to cross the cell membrane because of its high negative charge (4-); therefore, we have focused on a prodrug

Abbreviations: ATP, adenosine triphosphate; ADP, adenosine diphosphate; DPM-DC, diphosphomevalonate decarboxylase; DTT, dithiothreitol; GHMP, galactokinase, homoserine kinase, mevalonate kinase, phosphomevalonate kinase; HEPES, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid; IPTG, isopropyl-1-thio-β-D-galactopyranoside; LDH, lactate dehydrogenase; 2-ME, β-mercaptoethanol; Mev, mevalonate; Pmev, phosphomevalonate, DPM, diphosphomevalonate; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; IPP, isopentenyl diphosphate; MK, mevalonate kinase; NADH, nicotinamide adenine dinucleotide, reduced form; P_i, inorganic phosphate; PEP, phosphoenolpyruvate; PK, pyruvate kinase; PMK, phosphomevalonate kinase; Tris, tris(hydroxymethyl)aminomethane; unit, 1 μmol of product formed per minute at a saturating concentration of substrate(s).

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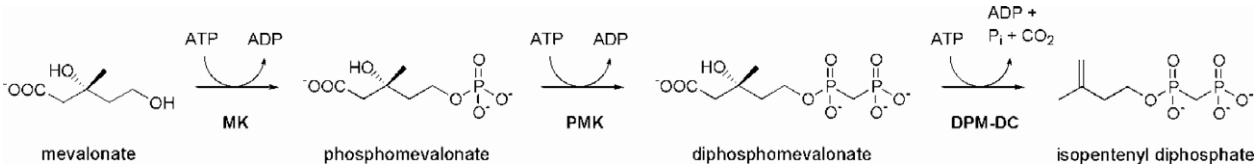


Figure 1. The mevalonate pathway. MK, mevalonate kinase; PMK, phosphomevalonate kinase; DPM-DC, diphosphomevalonate decarboxylase.

strategy in which mevalonate analogues are taken up by cells and phosphorylated by the mevalonate pathway enzymes to generate inhibitors in situ. An analogous strategy has been used to show that 6-fluoromevalonate inhibits isoprenoid biosynthesis in cultured human cells.[14,15] This result is consistent with the compound crossing the cell membrane and being converted in situ to the phosphorylated form; the diphosphorylated compound (6-fluoro-5-diphosphomevalonate) is a potent inhibitor of the human diphosphomevalonate decarboxylase (DPM-DC).[16] The present study seeks to expand the repertoire of DPM prodrugs with a series of compounds elaborating the C_3-methyl group with hydrocarbons of variable length, branching, and saturation (Scheme 1). Several mevalonate analogues were designed with an eye toward mechanism-based inhibition of DPM-DC, in addition to binding to the MK allosteric site, in a dual-acting antibiotic approach. In the present view of the DPM-DC transition state, substantial positive charge forms on C_3 during turnover.[17] To exploit this mechanism for inactivation, we synthesized DPM analogues (vinyl-, ethynyl-, and cyclopropyl-substituted) that delocalize this positive charge through resonance, transiently forming a strong electrophile that could undergo attack by a protein nucleophile in the vicinity of the putative substrate-binding pocket of DPM-DC.[18] An advantage of this strategy is that the potency of the antibiotic is enhanced because the inhibitor acts at two points in the same pathway. Because the human mevalonate pathway enzymes are closely related to those from *S. pneumoniae*, the specificity of antibiotics directed against DPM-DC is a concern. Whereas a functional mevalonate pathway is required for survival of the bacterium, the human pathway can be suppressed with minimal side-effects with the use of cholesterol-lowering drugs (statins, HMG-CoA reductase) and antiproliferative agents (bisphosphonates, farnesyl transferase).[19,20] Therapeutic benefits that arise by controlling flux through the human mevalonate pathway suggest that DPM-DC inhibitors may have additional clinical uses. In the present study, we assess the limitations on side chains for a prodrug strategy; binding of these analogues to the MK allosteric site and DPM-DC inactivation will be the subject of a future study.

2. Chemistry

The general synthetic route to the racemic vinyl, ethyl, *n*-propyl, *n*-butyl, *i*-butyl, 2-propenyl, allyl, ethynyl, and 1-propynyl mevalonate lactone analogues (**1a–e, g, i–k**) is shown in Scheme 2. Selective protection of the ketone functional group with ethylene glycol in the presence of BF_3–OEt_2, followed by LAH reduction provided diol **7** in a high yield. Next, selective protection of diol **7** using TBDPSCl gave mono-protected diol **8** in 86% yield. Then, the cyclic ketal group of **8** was readily cleaved using PPTS to give **9**. The other hydroxyl group of **9** was protected as a MOM ether to give bis-protected diol **10** in a quantitative yield. Diol **10** was treated with Grignard reagents in the presence of $CeCl_3$[21] to generate tertiary alcohols **11a–e, 11g, 11i–k** in good yields (77–99%). Selective deprotection of MOM group in **11a–g, 11i–k**, followed by an oxidation of the resulting primary alcohol using IBX and $NaClO_2$ provided the corresponding carboxylic acids **13a–e, 13g, 13i–k**. Finally, desilylation of the TBDPS group in **13a–e, 13g, 13i–k** coincidently led to an intramolecular cyclization to give the desired lactones **1a–e, 1g, 1i–k**.

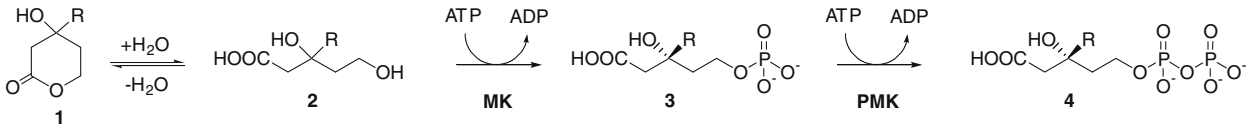
The cyclopropyl analogue (**1f**) had to be prepared by a slightly different route starting from the diprotected alcohol intermediate (**11f**) because of problems with the MOM ether deprotection step (Scheme 3).

The bulky isopropyl group could not be installed using standard Grignard reaction conditions to make **11h**, either with or without $CeCl_3$. Consequently, the 2-propenyl intermediate (**12g**) was hydrogenated to the isopropyl analogue (**12h**), and the synthesis of **11h** was completed as usual (Scheme 4).

To carry out the enzyme assays it was necessary to hydrolyze lactones **1a–k** prior to incubation with the enzyme. Hydrolysis was carried out smoothly in aqueous 2.0 M LiOH at room temperature for 1 h. It was found that re-lactonization occurred in water ($t_{1/2}$ = 14 days), methanol ($t_{1/2}$ = 7 days), or neat ($t_{1/2}$ = 3 days), but was suppressed in 50 mM Hepes/K^+ buffer containing 1 mM $MgCl_2$ at pH 8.0 (stable at least one week), which is the buffer used to assay MK and phosphomevalonate kinase (PMK).

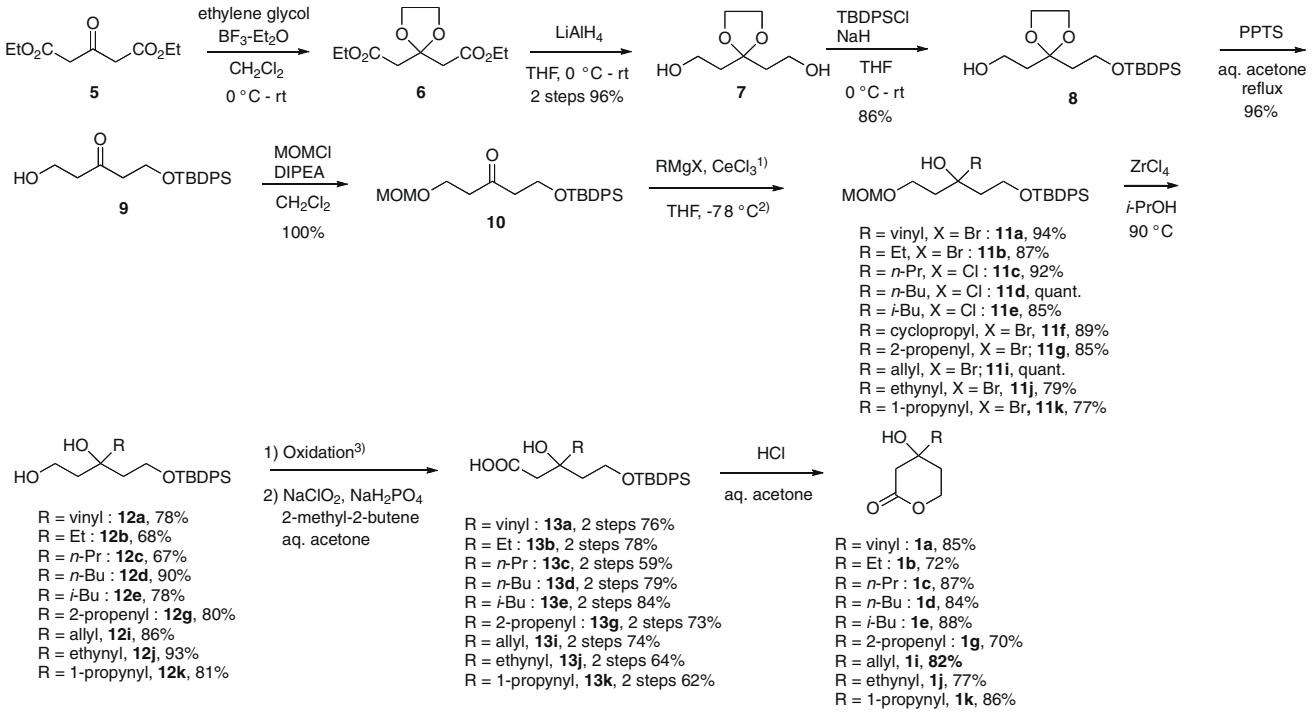
3. Results

To assess their viability as substrates of the enzymes in the mevalonate pathway, each of the mevalonate analogues was tested as a substrate for both MK and PMK. These activities are imperative for in vivo conversion of the alcohols to the corresponding diphosphorylated analogues. Reaction progress was monitored optically at 386 nm using a well-established pyruvate kinase/lactate dehydrogenase coupled enzyme system in which the ADP produced by phosphorylation of the mevalonate analogue is linked stoichiometrically (1:1) to NADH oxidation.[22] Reaction progress curves (Fig. 2) are the average of three assays done under identical conditions. The primary enzyme was varied from analogue to analogue to allow each progress curve to finish in a reasonable amount of time (see Fig. 2 legend). To compare the activity of compounds, the data were normalized to a 1.0 μM enzyme concentration, since



R = vinyl, Et, *n*-Pr, *i*-Pr, isopropenyl, cyclopropyl, *n*-Bu, *i*-Bu, allyl, ethynyl, 1-propynyl

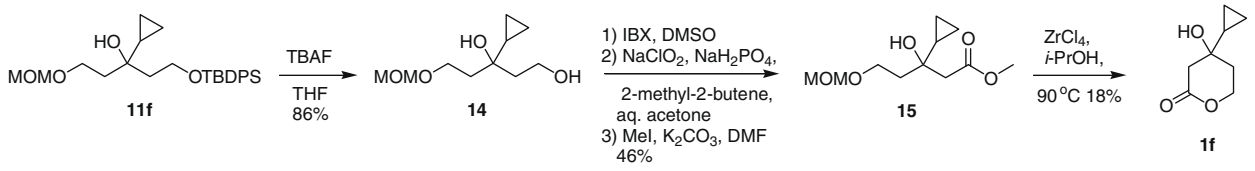
Scheme 1.



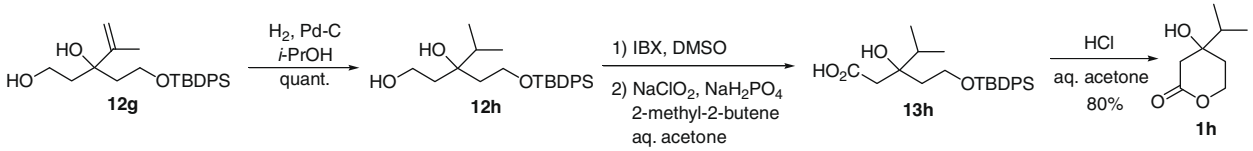
1) $CeCl_3$ was not used for the vinyl and allyl analogues. 2) The ethynyl and propynyl analogues did not react at -78 °C but did work at 0 °C - rt

3) Dess-Martin periodinane/CH_2Cl_2 0 °C to room temp. was used for the *n*-propyl analogue, and IBX/DMSO was used for the all other analogues.

Scheme 2.



Scheme 3.



Scheme 4.

activity was linear with enzyme concentration (data not shown). MK reactions were initiated by addition of analogue (Fig. 2A). The MK reactions were allowed to reach completion before adding PMK, resulting in the progress curves shown in Figure 2B. The endpoint of the MK reaction occurred at 50% of the initial concentration of the racemic compound, as would be expected for conversion of a single enantiomer.

4. Discussion

4.1. Synthetic approach

The yields of all of the steps in the synthetic route were excellent (see Schemes 2–4 for yields). The main complications came in the selection of protecting groups for the terminal alcohols. Initially, *p*-methoxybenzyl was selected as one of the alcohol protecting groups, but it caused problems later in the synthesis when it was removed; the methoxymethyl (MOM) protecting group was much more suitable. Steric hindrance seems to be the main cause for failure of the Grignard reaction; neither the isopropyl nor the *tert*-butyl analogue could be made directly by this route. However, the isopropyl analogue was prepared by catalytic hydrogenation of the 2-propenyl analogue.

4.2. Validation of the prodrug strategy

To evaluate their potential as prodrugs, eleven mevalonate analogues were tested as substrates for MK and PMK. Seven of

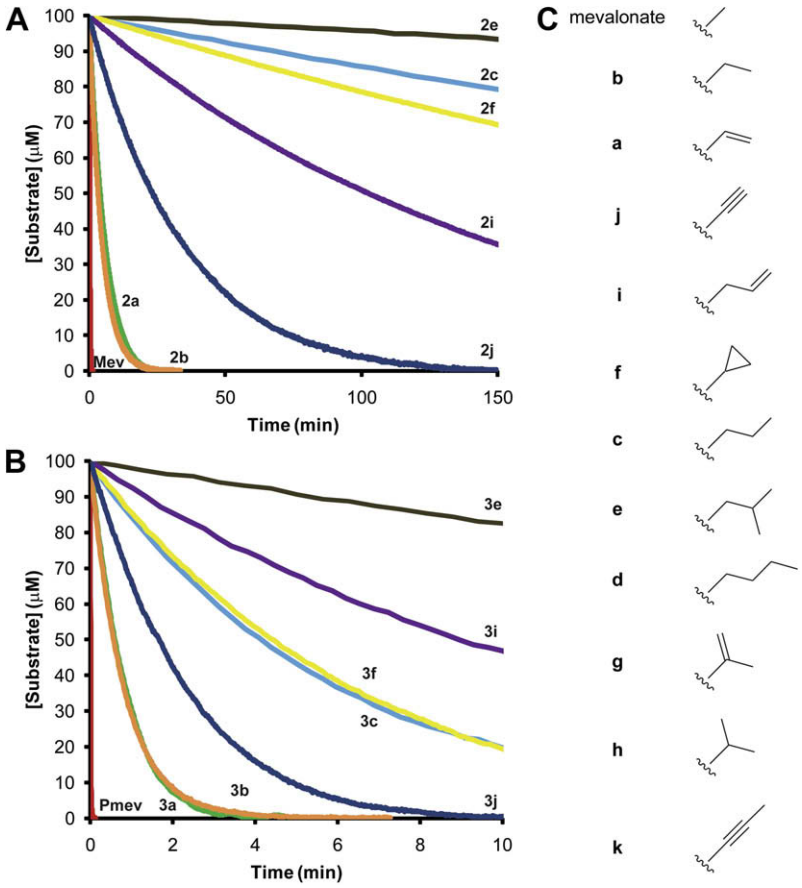


Figure 2. Mevalonate analogues as substrates for MK and PMK. Reaction progress curves for mevalonate kinase (A) and phosphomevalonate kinase (B). Color coding is identical in panels A and B. Reaction conditions: MK (Mev, 0.050 μM; **2a**, 1 μM; **2b**, 1 μM; **2c**, 20 μM; **2e**, 20 μM; **2f**, 20 μM; **2i**, 20 μM; **2j**, 10 μM) or PMK (Pmev, 0.005 μM; **3a**, 0.075 μM; **3b**, 0.150 μM; **3c**, 1.0 μM; **3e**, 2.0 μM; **3f**, 0.50 μM; **3i**, 2.0 μM; **3j**, 0.10 μM), pyruvate kinase (10.0 units/ml), lactate dehydrogenase (20.0 units/ml), ATP (4.0 mM), $MgCl_2$ (5.0 mM), NADH (0.82 mM), phosphoenolpyruvate (1.0 mM), KCl (50 mM), β-mercaptoethanol (20.0 mM), compounds **2a**–**2k** (200 μM, racemic mixture) or **3a**–**c**, **e**, **f**, **i**, **j** (100 μM), Hepes/K^+ (50 mM, pH 8.0), $T = 25 \pm 2$ °C. The activities of compounds **2d**, **2g**, **2h** and **2k** with MK were indistinguishable from background. (C) Mevalonate analogues (R-groups) listed in the order of their reaction rate with MK.

the analogues (**a**, **b**, **c**, **e**, **f**, **i**, and **j**) proved to be substrates for both enzymes, and are, therefore, viable prodrug candidates. The remaining four analogues (**d**, **g**, **h**, and **k**) were inactive with MK (<0.0025% of the activity of mevalonate).

The progress-curve based comparison of the reactivity of each active analogue reveals an inverse relationship between reaction rate and the size of the R-group (Fig. 2). For example, increasing the length of the mevalonate C_3 methyl group by a single methylene (**b**) has only a small effect on the reaction rate with MK and PMK. However, a two-carbon increase (**c**) significantly reduces reactivity, and a three-carbon increase (**e**) profoundly decreases the reactivity. The geometry of the R-group also has a dramatic effect on reactivity; branched compounds are excluded (cf., **2g** vs **2i**, or **2h** vs **2f**). The similar trend in reactivity for both enzymes is not surprising given their similar GHMP-kinase active-site architectures.[23,24] The changes in reaction rate may be due to alterations in V_{max} and/or K_m, and a full kinetic analysis of seven compounds with the three mevalonate pathway enzymes (as substrates, inhibitors, and allosteric regulators) will be reported in due course.

5. Conclusions

We have demonstrated the feasibility of using C_3-substituted mevalonates as prodrugs to generate DPM analogues in situ. By knowing which analogues are suitable substrates for these enzymes, we can synthesize the appropriate DPM analogues for testing as allosteric inhibitors of MK as well as potential inhibitors and mechanism-based inactivators of DPM-DC, the next enzyme in the isoprenoid biosynthetic pathway.

6. Experimental procedures

6.1. General methods

Flash chromatography was performed with 230–400 mesh silica gel. ^1H NMR, ^{13}C NMR and ^{31}P NMR spectra were obtained using Varian 300, 400 and 500 MHz spectrometers. NMR spectra were recorded in ppm (δ) relative to tetramethylsilane ($\delta = 0.00$) as an internal standard unless stated otherwise and are reported as follows; chemical shift, multiplicity (br = broad, s = singlet, t = triplet, q = quartet, m = multiplet), coupling constant, and integration. Solvents and liquid reagents were transferred using hypodermic syringes. All other reagents and solvents used were reagent grade. All glassware was dried in an oven at 150 °C prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone. Methylene chloride and triethylamine were dried over calcium hydride prior to use. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck precoated silica gel plate (60 F254). Small and medium scale purifications were performed by flash chromatography. Pyruvate kinase and lactate dehydrogenase were obtained from Roche Applied Science (Indianapolis, IN). Kinetic measurements of enzymatic reactions were made using a Cary 100 or 400 UV/Vis spectrophotometer (Varian Inc., Palo Alto, CA).

6.2. 1,5-Dihydroxy-3-pentanone-ethylideneacetal (7)

A mixture of diethyl acetone-1,3-dicarboxylate (**5**, 4.04 g, 20.0 mmol), ethylene glycol (4.46 mL, 80.0 mmol), and $BF_3{\cdot}Et_2O$ (3.80 mL, 30.0 mmol) in CH_2Cl_2 (40 mL) was stirred at 0 °C for 90 min and room temperature for 46 h. H_2O was added to the mixture at 0 °C, and the mixture was stirred at 0 °C for 30 min and extracted with AcOEt. The organic layer was washed with H_2O, brine, dried with Na_2SO_4, and evaporated. The residue was treated again as mentioned above and worked up the same way. A mixture of the crude product and $LiAlH_4$ (1.0 M in THF, 40 mL, 40 mmol) in THF (150 mL, HPLC grade) was stirred at 0 °C for 1 h and room temperature for 15 h, and aqueous 2.0 M NaOH was added to the mixture at 0 °C. The mixture was stirred at 0 °C for 30 min, and the resulting gel was filtered off with Celite and washed with acetone. The combined filtrate and washings were evaporated, and the residue was co-evaporated with *i*-PrOH (×2) and purified by silica gel column chromatography (5% MeOH in AcOEt) to give **7** (3.13 g, 96%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 4H, acetal-CH_2 × 2), 3.70–3.77 (m, 4H, CH_2OH × 2), 2.56 (br s, 2H, OH × 2), 1.97–2.05 (m, 4H, CH_2CH_2OH × 2) ^{13}C NMR (125 MHz, $CDCl_3$) δ 112.27, 64.78, 58.67, 38.32. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_7H_{14}NaO_4$: 185.07843. Found: 185.07876.

6.3. 1-*O*-(*tert*-Butyldiphenylsilyl)-1,5-dihydroxy-3-pentanone-ethylideneacetal (8)

A mixture of **7** (2.61 g, 16.1 mmol) and NaH (964 mg, 24.1 mmol) in THF (150 mL, HPLC grade) was stirred at 0 °C for 1 h, and TBDPSCl (6.27 mL, 24.1 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 30 min and room temperature for 69 h, and AcOH (500 μL) was added at 0 °C. The mixture was stirred at 0 °C for 10 min, and solid $NaHCO_3$ and MeOH were added. The mixture was stirred at 0 °C for 30 min, and the suspension was filtered through Celite and washed with acetone. The combined filtrate and washing were evaporated, and the residue was purified by silica gel column chromatography (25% AcOEt in hexane) to give **8** (5.57 g, 86%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.68 (m, 10H, Ph × 2), 3.69–3.98 (m, 8H, acetal-CH_2 × 2, CH_2OH, CH_2OTBDPS), 2.74–2.78 (m, 1H, OH), 1.91–1.95 (m, 4H, CH_2CH_2O × 2), 1.04 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.52, 133.55, 129.63, 127.65, 111.09, 64.50, 59.86, 58.76, 39.29, 38.61, 26.76, 19.04. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{23}H_{32}NaO_4Si$: 423.19621. Found: 423.19611.

6.4. 1-*O*-(*tert*-Butyldiphenylsilyl)-1,5-dihydroxy-3-pentanone (9)

A mixture of **8** (2.45 g, 6.11 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 6.14 g, 24.4 mmol) in acetone (55 mL) and H_2O (5.5 mL) was stirred with reflux for 4 h. The mixture was diluted with AcOEt and washed with H_2O, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (30% AcOEt in hexane) to give **9** (2.09 g, 96%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.66 (m, 10H, Ph × 2), 3.84–3.97 (m, 4H, CH_2OH, CH_2OTBDPS), 2.63–2.75 (m, 4H, CH_2CH_2O × 2), 2.49 (br s, 1H, OH), 1.03 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.61, 135.44, 133.15, 129.70, 127.66, 59.48, 57.71, 45.82, 45.26, 26.66, 19.03. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{21}H_{28}NaO_3Si$: 379.16999. Found: 379.16975.

6.5. 1-*O*-(*tert*-Butyldiphenylsilyl)-5-*O*-methoxymethyl-1,5-dihydroxy-3-pentanone (10)

A mixture of **9** (114 mg, 320 μmol), MOMCl (49 μl, 640 μmol), and DIPEA (223 μl, 1.28 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 90 min, and then MeOH was added. The mixture was stirred for 10 min and evaporated. The residue was partitioned between AcOEt and ice cooled aqueous 0.1 M HCl, and the organic layer was washed with H_2O, brine, dried with Na_2SO_4, and evaporated. The residue was dried under vacuum to give **10** (128 mg, 100%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.66 (m, 10H, Ph × 2), 4.60 (s, 2H, MOM-CH_2), 3.79–3.97 (m, 4H, CH_2OMOM, CH_2OTBDPS), 3.34 (s, 3H, MOM-CH_3), 2.66–2.76 (m, 4H, CH_2CH_2O × 2), 1.03 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.60, 135.41, 133.25, 129.58, 127.58, 96.39, 62.33, 59.40, 55.10, 45.79, 43.38, 26.62, 18.99. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{23}H_{32}NaO_4Si$: 423.19621. Found: 423.19487.

6.6. Grignard reaction

A mixture of ketone **10**, Grignard reagent (2.0 equiv for **11i**, 2.5 equiv for **11g**, 3.0 equiv for **11a**–**d**, **f**, **j**, **k**, 4.0 equiv for **11e**) and $CeCl_3$ (1.5 equiv) in dry THF (as a 1 mM solution) was stirred at −78 °C for 3–6 h (except for **11j** and **11k**) or at 0 °C for 2 h and room temperature for 4 h (for **11j** and **11k**). Aqueous saturated NH_4Cl was added to the mixture at −78 °C (except for **11j** and **11k**) or at room temperature (for **11j** and **11k**), and the mixture was stirred at room temperature for 30 min and extracted with AcOEt. The organic layer was washed with H_2O, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (5% AcOEt in hexane for **11g**, 10% AcOEt in hexane except for **11g**) to give the corresponding Grignard products.

6.7. 1-*O*-(*tert*-Butyldiphenylsilyl)-5-*O*-methoxymethyl-3-vinylpentan-1,3,5-triol (11a)

Compound **11a** (2.02 g, 94%) was obtained as a colorless oil from **10** (2.00 g, 5.00 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.68 (m, 10H, Ph × 2), 5.75–5.84 (m, 1H, CH_2=CH), 5.41–5.47, 5.19–5.23 (each m, each 1H, CH_2=CH), 4.60 (s, 2H, MOM-CH_2), 4.19 (s, 1H, OH), 3.59–3.94 (m, 4H, CH_2OMOM, CH_2OTBDPS), 3.35 (s, 3H, MOM-CH_3), 1.62–2.06 (m, 4H, CH_2CH_2O × 2), 1.04 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.51, 135.53, 135.51, 132.80, 129.81, 129.79, 127.75, 127.71, 113.80, 96.51, 75.26, 64.20, 61.49, 55.26, 41.54, 40.59, 26.72, 18.95. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{25}H_{36}NaO_4Si$: 451.22751. Found: 451.22721.

6.8. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-ethyl-5-*O*-methoxymethylpentan-1,3,5-triol (11b)

Compound **11b** (1.14 g, 87%) was obtained as a colorless oil from **10** (1.21 g, 3.02 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.69 (m, 10H, Ph × 2), 4.61 (s, 2H, MOM-CH_2), 3.65–3.88 (m, 5H, CH_2OMOM, CH_2OTBDPS, OH), 3.36 (s, 3H, MOM-CH_3), 1.76–1.85 (m, 4H, CH_2CH_2O × 2), 1.52–1.58 (m, 2H, Et-CH_2), 1.05 (s, 9H, *t*-Bu), 0.86 (t, 3H, Et-CH_3, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.48, 132.92, 129.73, 127.68, 96.42, 73.81, 64.18, 61.09, 55.24, 39.32, 37.59, 31.86, 26.69, 18.92, 8.19. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{25}H_{38}NaO_4Si$: 453.24316. Found: 453.24342.

6.9. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(2-methoxymethyloxyethyl)hexan-1,3,-diol (11c)

Compound **11c** (2.04 g, 92%) was obtained as a colorless oil from **10** (2.00 g, 5.00 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.69 (m, 10H, Ph × 2), 4.60 (s, 2H, MOM-CH_2), 3.65–3.87 (m, 5H, CH_2OMOM, CH_2OTBDPS, OH), 3.36 (s, 3H, MOM-CH_3), 1.76–1.85 (m, 4H, CH_2CH_2O × 2), 1.45–1.50 (m, 2H, $CH_3CH_2CH_2$), 1.26–1.41 (m, 2H, $CH_3CH_2CH_2$), 1.05 (s, 9H, *t*-Bu), 0.89 (t, 3H, $CH_3CH_2CH_2$, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.54, 132.96, 132.93, 129.79, 127.73, 96.47, 73.66, 64.26, 61.17, 55.29, 41.93, 39.86,

38.24, 26.76, 18.96, 17.05, 14.69. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{26}H_{40}NaO_4Si$: 467.25881. Found: 467.25863.

6.10. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(2-methoxymethyloxyethyl)heptan-1,3,-diol (11d)

Compound **11d** (248 mg, quant.) was obtained as a colorless oil from **10** (200 mg, 500 μmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.69 (m, 10H, Ph × 2), 4.60 (s, 2H, MOM-CH_2), 3.84–3.89, 3.63–3.70 (each m, each 2H, CH_2OTBDPS, CH_2OMOM), 3.78 (s, 1H, OH), 3.36 (s, 3H, MOM-CH_3), 1.73–1.88 (m, 4H, CH_2CH_2O × 2, $CH_3CH_2CH_2$), 1.45–1.51 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.21–1.29 (m, 4H, $CH_3CH_2CH_2CH_2$, $CH_3CH_2CH_2CH_2$), 1.05 (s, 9H, *t*-Bu), 0.89 (t, 3H, $CH_3CH_2CH_2CH_2$, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.54, 132.96, 132.94, 129.79, 127.74, 96.47, 73.68, 64.26, 61.18, 55.29, 39.87, 39.25, 38.23, 26.76, 25.99, 23.26, 18.96, 14.05. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{27}H_{42}NaO_4Si$: 481.27446. Found: 481.27322.

6.11. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(2-methoxymethyloxyethyl)-5-methylhexan-1,3,-diol (11e)

Compound **11e** (2.73 g, 85%) was obtained as a colorless oil from **10** (2.80 g, 7.00 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.69 (m, 10H, Ph × 2), 4.60 (s, 2H, MOM-CH_2), 3.84–3.87, 3.63–3.71 (each m, each 2H, CH_2OTBDPS, CH_2OMOM), 3.35 (s, 3H, MOM-CH_3), 1.71–1.89 (m, 5H, CH_2CH_2O × 2, $(CH_3)_2CHCH_2$), 1.39–1.42 (m, 2H, $(CH_3)_2CHCH_2$), 1.05 (s, 9H, *t*-Bu), 0.92–0.96 (m, 6H, $(CH_3)_2CHCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.44, 132.83, 132.82, 129.69, 127.64, 96.36, 74.10, 64.30, 61.16, 55.18, 47.90, 40.32, 38.81, 26.66, 24.68, 23.79, 18.86. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{27}H_{42}NaO_4Si$: 481.27446. Found: 481.27385.

6.12. 1-*O*-(*tert*-Butyldiphenylsilyl)-5-*O*-methoxymethyl-3-cyclopropyl-pentan-1,3,5-triol (11f)

Compound **11f** (0.43 g, 89%) was obtained as a colorless oil from **10** (0.96 g, 3.90 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.70 (m, 4H, *Ph*), 7.38–7.44 (m, 6H, *Ph*), 4.61 (s, 2H, MOM-CH_2), 3.83–3.89, 3.75–3.81 (each m, each 2H, CH_2OTBDPS, CH_2OMOM), 3.76 (s, 1H, *OH*), 3.36 (s, 3H, MOM-CH_3), 1.93–1.87 (m, 2H, CH_2CH_2O), 1.78–1.75 (m, 2H, CH_2CH_2O), 1.04 (s, 9H, *t*-Bu), 0.69 (m, 1H, *CH* of cyclopropyl), 0.52–0.43 (m, 2H, CH_2 of cyclopropyl), 0.34–0.32 (d, 2H, CH_2 of cyclopropyl, J = 8.5 Hz): ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.74, 133.14, 129.99, 127. 93, 96.71, 71.69, 64.82, 61.86, 60.56, 55.49, 42.25, 41.30, 26.98, 19.13. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{26}H_{38}NaO_4Si$: 465.24316. Found: 465.24308.

6.13. 1-*O*-(*tert*-Butyldiphenylsilyl)-5-*O*-methoxymethyl-3-(1-methylvinyl)pentan-1,3,5-triol (11g)

Compound **11g** (2.52 g, 85%) was obtained as a colorless oil from **10** (2.67 g, 6.66 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.67 (m, 10H, Ph × 2), 5.24, 4.99 (each s, each 1H, CH_2=C), 4.60 (s, 2H, MOM-CH_2), 4.28 (br s, 1H, OH), 3.53–3.87 (m, 4H, CH_2OTBDPS, CH_2OMOM), 3.35 (s, 3H, MOM-CH_3), 1.71–2.03 (m, 4H, CH_2CH_2O × 2), 1.61 (s, 3H, Me), 1.03 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.11, 135.43, 135.41, 132.72, 132.70, 129.68, 129.65, 127.63, 127.58, 112.20, 96.46, 77.34, 64.06, 61.32, 55.13, 39.89, 38.72, 26.60, 19.53, 18.84. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{26}H_{38}NaO_4Si$: 465.24316. Found: 465.24369.

6.14. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(2-methoxymethyloxyethyl)-5-hexen-1,3,-diol (11i)

Compound **11i** (1.78 g, quant.) was obtained as a light yellow oil from **10** (1.60 g, 4.00 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.69 (m, 10H, Ph × 2), 5.81–5.83 (m, 1H, CH_2=CH), 5.02–5.08 (m, 2H, CH_2=CH), 4.60 (s, 2H, MOM-CH_2), 3.83–3.91, 3.69–3.73 (each m, each 2H, CH_2OTBDPS or CH_2OMOM), 3.35 (s, 3H, MOM-CH_3), 2.31–2.32 (m, 2H, CH_2=CHCH_2), 1.75–1.87 (m, 4H, CH_2CH_2O × 2), 1.05 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.42, 134.06, 132.80, 129.71, 127.65, 117.79, 96.32, 73.27, 63.93, 60.94, 55.14, 44.22, 39.81, 38.21, 26.67, 18.86. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{26}H_{38}NaO_4Si$: 465.24316. Found: 465.24243.

6.15. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-ethynyl-5-*O*-methoxymethylpentan-1,3,5-triol (11j)

Compound **11j** (1.55 g, 79%) was obtained as a light yellow oil from **10** (1.83 g, 4.58 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.73 (m, 10H, Ph × 2), 4.80 (s, 1H, OH), 4.63 (s, 2H, MOM-CH_2), 4.20–4.25, 3.81–3.97 (each m, 1H and 3H, CH_2OTBDPS or CH_2O-MOM), 3.37 (s, 3H, MOM-CH_3), 2.50 (s, 1H, ethynyl-H), 2.06–2.12, 1.97–2.02, 1.83–1.87 (each m, 2H, 1H, and 1H, CH_2CH_2O × 2), 1.05 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.49, 135.42, 132.62, 129.73, 129.71, 127.66, 127.61, 96.36, 85.44, 73.04, 70.34, 64.43, 61.79, 55.19, 42.64, 41.43, 26.63, 18.87. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{25}H_{34}NaO_4Si$: 449.21186. Found: 449.21144.

6.16. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(2-methoxymethyloxyethyl)-4-hexyn-1,3,-diol (11k)

Compound **11k** (1.36 g, 77%) was obtained as a colorless oil from **10** (1.60 g, 4.00 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.74 (m, 10H, Ph × 2), 4.63 (s, 2H, MOM-CH_2), 4.18–4.23, 3.79–3.95 (each m, 1H and 3H, CH_2OTBDPS or CH_2OMOM), 3.37 (s, 3H, MOM-CH_3), 2.03–2.08, 1.92–1.96, 1.78–1.83 (each m, 2H, 1H, and 1H, CH_2CH_2O × 2), 1.85 (s, 3H, Me), 1.05 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.52, 135.47, 132.80, 132.71, 129.72, 129.68, 127.67, 127.64, 96.37, 81.00, 80.82, 70.52, 64.72, 62.03, 55.12, 43.03, 41.83, 26.65, 18.89, 3.47. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{26}H_{36}NaO_4Si$: 463.22751. Found: 463.22726.

6.17. Deprotection of the MOM group

A mixture of the Grignard products and $ZrCl_4$ (0.5 equiv) in *i*-PrOH (as a 1 mM solution) was stirred at 90 °C for 30 min. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (25% AcOEt in hexane) to give the corresponding alcohols.

6.18. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-vinylpentan-1,3,5-triol (12a)

Compound **12a** (1.42 g, 78%) was obtained as a colorless oil from **11a** (2.02 g, 4.72 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.68 (m, 10H, Ph × 2), 5.76 (dd, 1H, CH_2=CH, J_{trans} = 22.8 Hz, J_{cis} = 13.6 Hz), 5.56 (dd, 1H, CH_2=CH (trans), $J_{vicinal}$ = 22.8 Hz, $J_{geminal}$ = 1.6 Hz), 5.33 (dd, 1H, CH_2=CH (cis), $J_{vicinal}$ = 13.6 Hz, $J_{geminal}$ = 1.6 Hz), 4.72 (s, 1H, OH), 3.73–3.96 (m, 4H, CH_2OH, CH_2OTBDPS), 3.32 (br s, 1H, OH), 1.52–2.14 (m, 4H, CH_2CH_2O × 2), 1.04 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.01, 135.45, 135.42, 132.26, 132.22, 129.91, 129.87, 127.79, 127.71, 114.72, 78.04, 61.90, 59.50, 41.96, 40.71, 26.60, 18.82. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{23}H_{32}NaO_3Si$: 407.20129. Found: 407.20051.

6.19. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-ethylpentan-1,3,5-triol (12b)

Compound **12b** (1.09 g, 68%) was obtained as a light yellow oil from **11b** (1.79 g, 4.17 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.40–7.69 (m, 10H, Ph × 2), 3.81–3.93 (m, 4H, CH_2OTBDPS, CH_2OH), 1.65–1.93 (m, 6H, CH_2CH_2O × 2, Et-CH_2), 1.05 (s, 9H, *t*-Bu), 0.84 (t, 3H, Et-CH_3, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.52, 132.51, 132.43, 129.97, 129.96, 127.85, 127.84, 76.34, 61.41, 59.50, 38.74, 38.20, 31.68, 26.73, 18.92, 8.61. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{23}H_{34}NaO_3Si$: 409.21694. Found: 409.21610.

6.20. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(2-hydroxyethyl)hexan-1,3,-diol (12c)

Compound **12c** (1.20 g, 67%) was obtained as a light yellow oil from **11c** (1.99 g, 4.47 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.69 (m, 10H, Ph × 2), 4.31 (s, 1H, OH), 3.82–3.93 (m, 4H, CH_2OTBDPS, CH_2OH), 1.63–1.94 (m, 6H, CH_2CH_2O × 2, $CH_3CH_2CH_2$), 1.16–1.31 (m, 2H, $CH_3CH_2CH_2$), 1.05 (s, 9H, *t*-Bu), 0.91 (t, 3H, $CH_3CH_2CH_2$, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.54, 132.49, 132.40, 129.98, 127.84, 76.39, 61.44, 59.57, 41.68, 39.39, 38.73, 26.75, 18.92, 17.50, 14.67. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{24}H_{36}NaO_3Si$: 423.23259. Found: 423.23204.

6.21. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(2-hydroxyethyl)heptan-1,3,-diol (12d)

Compound **12d** (1.70 g, 90%) was obtained as a colorless oil from **11d** (2.10 g, 4.57 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.70 (m, 10H, Ph × 2), 3.83–3.93 (m, 4H, CH_2OTBDPS, CH_2OH), 1.58–1.95 (m, 6H, CH_2CH_2O × 2, $CH_3CH_2CH_2CH_2$), 1.28–1.33 (m, 4H, $CH_3CH_2CH_2CH_2$, $CH_3CH_2CH_2CH_2$), 1.05 (s, 9H, *t*-Bu), 0.88–0.92 (m, 3H, $CH_3CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.52, 132.48, 132.37, 129.96, 127.85, 127.83, 76.42, 61.44, 59.55, 39.37, 38.96, 38.70, 26.73, 26.41, 23.23, 18.91, 14.00. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{25}H_{38}NaO_3Si$: 437.24824. Found: 437.24760.

6.22. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(2-hydroxyethyl)-5-methylhexan-1,3,-diol (12e)

Compound **12e** (1.96 g, 82%) was obtained as a colorless oil from **11e** (2.65 g, 5.78 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.69 (m, 10H, Ph × 2), 3.86–3.97 (m, 4H, CH_2OTBDPS, CH_2OH), 1.65–1.99 (m, 5H, CH_2CH_2O × 2, $(CH_3)_2CHCH_2$), 1.48–1.60 (m, 2H, $(CH_3)_2CHCH_2$), 1.05 (s, 9H, *t*-Bu), 0.97, 0.92 (each d, each 3H, $(CH_3)_2CHCH_2$, each, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.55, 132.46, 132.37, 129.99, 127.87, 127.85, 76.86, 61.47, 59.63, 47.89, 40.07, 39.41, 26.74, 24.79, 24.75, 24.06, 18.92. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{25}H_{38}NaO_3Si$: 437.24824. Found: 437.24788.

6.23. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(1-methylvinyl)pentan-1,3,5-triol (12g)

Compound **12g** (251 mg, 80%) was obtained as a light yellow oil from **11g** (349 mg, 790 μmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.68 (m, 10H, Ph × 2), 5.41, 5.13 (each s, each 1H, CH_2=C), 4.84 (br s, 1H, OH), 3.71–3.87 (m, 4H, CH_2OTBDPS, CH_2OH), 3.37 (br s, 1H, OH), 1.70–2.11 (m, 4H, CH_2CH_2O × 2), 1.66 (s, 3H, Me), 1.04 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.83, 135.41, 135.38, 132.23, 132.17, 129.86, 129.81, 127.74, 127.70, 113.13, 80.41, 61.90, 59.56, 40.16, 38.96, 26.55, 19.50, 18.78. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{24}H_{34}NaO_3Si$: 421.21694. Found: 437.21606.

6.24. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-hydroxy-3-(1-methylethyl)pentan-1,5-diol (12h)

A mixture of **12g** (1.47 g, 3.68 mmol) and Pd–C (400 mg) in *i*-PrOH (35 mL) was stirred at room temperature for 18 h under a hydrogen atmosphere. The mixture was filtered off, and the filtrate was evaporated. The residue was purified by silica gel column chromatography (33% AcOEt in hexane) to give **12h** (1.51 g, quant.) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.69 (m, 10H, Ph × 2), 4.32 (br s, 1H, OH), 3.83–3.96 (m, 4H, CH_2OTBDPS, CH_2OH), 3.68 (br s, 1H, OH), 1.61–2.03 (m, 5H, CH_2CH_2O × 2, $(CH_3)_2CH$), 1.05 (s, 9H, *t*-Bu), 0.95, 0.88 (each d, each 3H, $(CH_3)_2$CH, each J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.53, 132.51, 132.42, 129.99, 129.96, 127.85, 127.83, 78.28, 61.32, 59.43, 35.40, 35.31, 34.68, 26.74, 17.25, 16.83. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{24}H_{36}NaO_3Si$: 421.23259. Found: 423.23154.

6.25. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(2-hydroxyethyl)-5-hexen-1,3,-diol (12i)

Compound **12i** (1.34 g, 86%) was obtained as a colorless oil from **11i** (1.74 g, 3.93 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.69 (m, 10H, Ph × 2), 5.69–5.77 (m, 1H, CH_2=CH), 5.03–5.08 (m, 2H, CH_2=CH), 3.82–3.98, (m, 4H, CH_2OTBDPS, CH_2OMOM), 2.47, 2.41 (each dd, each 1H, CH_2=CHCH_2, $J_{vicinal}$ = 7.5 Hz, $J_{geminal}$ = 14.0 Hz), 1.88–1.94, 1.65–1.83 (each m, 1H and 3H, CH_2CH_2O × 2), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.41, 133.70, 132.34, 132.24, 129.88, 127.76, 118.25, 75.83, 61.25, 59.32, 43.87, 39.45, 38.71, 26.64, 18.81. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{24}H_{34}NaO_3Si$: 421.21694. Found: 421.21837.

6.26. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-ethynylpentan-1,3,5-triol (12j)

Compound **12j** (1.40 g, 93%) was obtained as a light yellow oil from **11j** (1.67 g, 3.92 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.74 (m, 10H, Ph × 2), 5.19 (s, 1H, OH), 4.31–4.36, 4.10–4.18, 3.85–3.90 (each m, 1H, 1H, and 2H, CH_2OTBDPS or CH_2OMOM), 2.96 (br s, 1H, OH), 2.56 (s, 1H, ethynyl-H), 2.13–2.17, 2.03–2.08, 1.86–1.91, 1.69–1.74 (each m, each 1H, CH_2CH_2O × 2), 1.05 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.51, 135.41, 132.16, 132.13, 129.90, 129.85, 127.76, 127.67, 85.37, 73.46, 72.57, 62.29, 59.89, 43.75, 41.95, 26.58, 18.82. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{23}H_{30}NaO_3Si$: 405.18564. Found: 405.18531.

6.27. 1-*O*-(*tert*-Butyldiphenylsilyl)-3-(2-hydroxyethyl)-4-hexyn-1,3,-diol (12k)

Compound **12k** (1.12 g, 81%) was obtained as a light yellow oil from **11k** (1.53 g, 3.47 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.75 (m, 10H, Ph × 2), 5.01 (s, 1H, OH), 4.29–4.34, 4.11–4.15, 3.83–3.89 (each m, 1H, 1H, and 2H, CH_2OTBDPS or CH_2OMOM), 3.07 (br s, 1H, OH), 2.09–2.15, 1.99–2.04, 1.82–1.86, 1.65–1.71 (each m, each 1H, CH_2CH_2O × 2), 1.88 (s, 3H, Me), 1.05 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.60, 135.55, 132.45, 132.30, 129.96, 129.89, 127.84, 127.78, 81.64, 80.90, 72.83, 62.53, 60.17, 44.12, 42.44, 26.68, 18.90, 3.56. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{24}H_{32}NaO_3Si$: 419.20129. Found: 419.20104.

6.28. Oxidation from the alcohol to the carboxylic acid

A mixture of the alcohol and IBX (1.5 equiv) in DMSO (as a 0.1 M solution, except for **12c**) or the alcohol and Dess–Martin periodinane (3.0 equiv) in CH_2Cl_2 (as a 0.1 M solution, for **12c**) was stirred at room temperature for 15 h. Aqueous 0.1 M $Na_2S_2O_3$ was added to the mixture at room temperature, and the mixture was stirred for 10 min and extracted with AcOEt. The organic layer was washed with H_2O, brine, dried with Na_2SO_4, and evaporated. A mixture of the crude product, $NaClO_2$ (3.0 equiv), $NaH_2PO_4{\cdot}H_2O$ (1.0 equiv), and 2-methyl-2-butene (4.0 equiv) in acetone/H_2O = 3:1 (as a 0.1 M solution) was stirred at room temperature for 4 h. The mixture was

diluted with AcOEt, washed with ice cooled aqueous 0.1 M HCl, H_2O, and brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (25–75% AcOEt in hexane) to give the corresponding carboxylic acids.

6.29. 5-*O*-(*tert*-Butyldiphenylsilyl)-3,5-dihydroxy-3-vinylpentanoic acid (13a)

Compound **13a** (1.12 g, 76%) was obtained as a colorless oil from **12a** (1.42 g, 3.70 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.65 (m, 10H, Ph × 2), 5.83 (dd, 1H, CH_2=*CH*, J_{trans} = 16.8 Hz, J_{cis} = 10.4 Hz), 5.55 (d, 1H, *CH*$_2$=CH (trans), J = 16.8 Hz), 5.33 (d, 1H, *CH*$_2$=CH (cis), J = 10.4 Hz), 3.91–3.97, 3.78–3.80 (each m, each 1H, *CH*$_2$OTBDPS), 2.67, 2.58 (each d, each 1H, *CH*$_2$CO$_2$H, J = 15.6 Hz), 2.05–2.13, 1.66–1.70 (each m, each 1H, *CH*$_2$CH$_2$O), 1.05 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.58, 140.04, 135.45, 135.42, 131.96, 131.90, 130.18, 130.11, 127.97, 127.89, 115.52, 74.96, 61.70, 45.64, 39.48, 26.69, 18.89. HRMS (pos. ion ESI) *m/z* calcd for (M+Na)$^+$ $C_{23}H_{30}NaO_4Si$: 421.18056. Found: 421.18084.

6.30. 5-*O*-(*tert*-Butyldiphenylsilyl)-3,5-dihydroxy-3-ethylpentanoic acid (13b)

Compound **13b** (700 mg, 78%) was obtained as a colorless oil from **12b** (871 mg, 2.25 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.67 (m, 10H, Ph × 2), 3.85–3.98 (m, 2H, *CH*$_2$OTBDPS), 2.59, 2.53 (each d, each 1H, *CH*$_2$CO$_2$H, J = 15.6 Hz), 1.66–1.88 (m, 4H, *CH*$_2$CH$_2$O, Et-*CH*$_2$), 1.06 (s, 9H, *t*-Bu), 0.91 (t, 3H, Et-*CH*$_3$, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.85, 135.46, 135.42, 132.29, 132.22, 130.00, 129.98, 127.85, 127.82, 74.16, 61.09, 42.80, 38.15, 32.00, 26.69, 18.87, 8.08. HRMS (pos. ion ESI) *m/z* calcd for (M+Na)$^+$ $C_{23}H_{32}NaO_4Si$: 423.19621. Found: 423.19677.

6.31. 3-{2-(*tert*-Butyldiphenylsilyloxy)ethyl}-3-hydroxyhexanoic acid (13c)

Compound **13c** (447 mg, 59%) was obtained as a colorless oil from **12c** (739 mg, 1.84 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.67 (m, 10H, Ph × 2), 3.85–3.96 (m, 2H, *CH*$_2$OTBDPS), 2.59, 2.52 (each d, each 1H, *CH*$_2$CO$_2$H, J = 15.6 Hz), 1.76–1.92 (m, 2H, *CH*$_2$CH$_2$O), 1.57–1.67 (m, 2H, CH$_3$CH$_2$*CH*$_2$), 1.31–1.39 (m, 2H, CH$_3$*CH*$_2$CH$_2$), 1.06 (s, 9H, *t*-Bu), 0.92 (t, 3H, *CH*$_3$CH$_2$CH$_2$, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.31, 135.36, 135.33, 131.91, 131.79, 130.08, 130.05, 127.87, 127.83, 74.24, 61.23, 43.38, 41.64, 37.95, 26.63, 18.80, 17.02, 14.33. HRMS (pos. ion ESI) *m/z* calcd for (M+Na)$^+$ $C_{24}H_{34}NaO_4Si$: 437.21186. Found: 437.21247.

6.32. 3-{2-(*tert*-Butyldiphenylsilyloxy)ethyl}-3-hydroxyheptanoic acid (13d)

Compound **13d** (1.31 g, 79%) was obtained as a colorless oil from **12d** (1.60 g, 3.86 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.67 (m, 10H, Ph × 2), 5.38 (br s, 1H, OH), 3.85–3.97 (m, 2H, *CH*$_2$OTBDPS), 2.59, 2.53 (each d, each 1H, *CH*$_2$CO$_2$H, J = 15.2 Hz), 1.77–1.92 (m, 2H, *CH*$_2$CH$_2$O), 1.64–1.67 (m, 2H, CH$_3$CH$_2$CH$_2$*CH*$_2$), 1.28–1.31 (m, 4H, CH$_3$CH$_2$*CH*$_2$CH$_2$, CH$_3$*CH*$_2$CH$_2$CH$_2$), 1.06 (s, 9H, *t*-Bu), 0.90 (t, 3H, *CH*$_3$CH$_2$CH$_2$CH$_2$, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.14, 135.45, 135.43, 132.14, 132.04, 130.10, 130.08, 127.92, 127.89, 74.15, 61.24, 43.43, 39.15, 38.30, 26.71, 25.87, 23.00, 18.89, 13.91. HRMS (pos. ion ESI) *m/z* calcd for (M+H)$^+$ $C_{29}H_{33}O_4Si$: 429.24242. Found: 429.24286.

6.33. 3-{2-(*tert*-Butyldiphenylsilyloxy)ethyl}-3-hydroxy-5-methylhexanoic acid (13e)

Compound **13e** (1.63 g, 84%) was obtained as a colorless oil from **12e** (1.87 g, 4.51 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.68 (m, 10H, Ph × 2), 5.50 (br s, 1H, OH), 3.87–3.99 (m, 2H, *CH*$_2$OTBDPS), 2.54–2.62 (m, 2H, *CH*$_2$CO$_2$H), 1.73–1.92 (m, 3H, *CH*$_2$CH$_2$O, (CH$_3$)$_2$*CH*CH$_2$), 1.51–1.63 (m, 2H, (CH$_3$)$_2$CH*CH*$_2$), 1.06 (s, 9H, *t*-Bu), 0.99, 0.94 (each d, each 3H, *(CH*$_3$)$_2$CHCH$_2$, each J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.00, 135.37, 135.32, 131.80, 131.66, 130.12, 130.10, 127.90, 127.86, 74.77, 61.29, 47.50, 43.96, 38.42, 26.62, 24.49, 24.37, 23.87, 18.79. HRMS (pos. ion ESI) *m/z* calcd for (M+Na)$^+$ $C_{25}H_{36}NaO_4Si$: 451.22751. Found: 451.22784.

6.34. 5-*O*-(*tert*-Butyldiphenylsilyl)-3,5-dihydroxy-3-(1-methylvinyl)pentanoic acid (13g)

Compound **13g** (1.35 g, 73%) was obtained as a colorless oil from **12g** (1.79 g, 4.48 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.65 (m, 10H, Ph × 2), 5.32, 5.09 (each s, each 1H, *CH*$_2$=C), 3.84–3.89, 3.73–3.78 (each m, each 1H, *CH*$_2$OTBDPS), 2.72, 2.67 (each d, each 1H, *CH*$_2$CO$_2$H, J = 15.4 Hz), 2.01–2.08, 1.82–1.86 (each m, each 1H, *CH*$_2$CH$_2$O), 1.72 (s, 3H, Me), 1.05 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.30, 145.36, 135.35, 135.32, 131.86, 131.79, 130.05, 129.99, 127.86, 127.77, 113.32, 77.27, 61.58, 44.41, 37.80, 26.57, 19.13, 18.80. HRMS (pos. ion ESI) *m/z* calcd for (M+Na)$^+$ $C_{24}H_{32}NaO_4Si$: 435.19621. Found: 435.19619.

6.35. 5-*O*-(*tert*-Butyldiphenylsilyl)-3,5-dihydroxy-3-(1-methylethyl)pentanoic acid (13h)

Compound **13h** (1.51 g, 99%) was obtained as a light yellow oil from **12h** (1.48 g, 3.70 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.67 (m, 10H, Ph × 2), 3.95–3.99, 3.88–3.92 (each m, each 1H, *CH*$_2$OTBDPS), 2.58, 2.51 (each d, each 1H, *CH*$_2$CO$_2$H, J = 15.8 Hz), 2.01–2.06 (m, 1H, (CH$_3$)$_2$*CH*), 1.88–1.93, 1.78–1.83 (each m, each 1H, *CH*$_2$CH$_2$O), 1.07 (s, 9H, *t*-Bu), 0.99, 0.90 (each d, each 3H, *(CH*$_3$)$_2$CH, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.53, 135.35, 135.32, 131.88, 131.84, 130.11, 130.07, 127.89, 127.84, 76.72, 61.12, 39.90, 35.01, 34.89, 26.63, 18.81, 17.00, 16.80. HRMS (pos. ion ESI) *m/z* calcd for (M+Na)$^+$ $C_{24}H_{34}NaO_4Si$: 437.21186. Found: 437.21238.

6.36. 3-{2-(*tert*-Butyldiphenylsilyloxy)ethyl}-3-hydroxy-5-hexenoic acid (13i)

Compound **13i** (995 mg, 74%) was obtained as an yellow oil from **12i** (1.30 g, 3.27 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.67 (m, 10H, Ph × 2), 5.74–5.80 (m, 1H, CH$_2$=*CH*), 5.08–5.15 (m, 2H, *CH*$_2$=CH), 3.95–4.00, 3.86–3.91, (each m, each 2H, *CH*$_2$OTBDPS or *CH*$_2$OMOM), 2.60, 2.56 (each d, each 1H, *CH*$_2$CO$_2$H, J = 15.8 Hz), 2.47, 2.41 (each dd, each 1H, CH$_2$=CH*CH*$_2$, $J_{vicinal}$ = 7.5 Hz, $J_{geminal}$ = 14.0 Hz), 1.88–1.93, 1.78–1.83 (each m, each 1H, *CH*$_2$CH$_2$O), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.51, 135.29, 132.89, 132.38, 132.36, 129.76, 127.65, 118.79, 73.12, 60.69, 43.86, 42.80, 39.15, 26.57, 18.74. HRMS (pos. ion ESI) *m/z* calcd for (M+Na)$^+$ $C_{24}H_{32}NaO_4Si$: 435.19621. Found: 435.19639.

6.37. 5-*O*-(*tert*-Butyldiphenylsilyl)-3,5-dihydroxy-3-ethynylpentanoic acid (13j)

Compound **13j** (908 mg, 64%) was obtained as a light yellow oil from **12j** (1.36 g, 3.55 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.72 (m, 10H, Ph × 2), 4.22–4.27, 3.89–3.93 (each m, each 1H, *CH*$_2$OTBDPS), 2.89, 2.84 (each d, each 1H, *CH*$_2$CO$_2$H, J = 15.8 Hz), 2.55 (s, 1H, ethynyl-H), 2.14–2.16, 1.90–1.94 (each m, each 1H, *CH*$_2$CH$_2$O), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.71, 135.33, 135.28, 132.33, 129.73, 129.71, 127.72, 127.62, 84.08, 73.27, 68.17, 61.29, 45.96, 41.65, 26.54, 18.74. HRMS (pos. ion ESI) *m/z* calcd for (M+Na)$^+$ $C_{23}H_{28}NaO_4Si$: 419.16491. Found: 419.16488.

6.38. 3-{2-(*tert*-Butyldiphenylsilyloxy)ethyl}-3-hydroxy-4-hexynoic acid (13k)

Compound **13k** (686 g, 62%) was obtained as a light yellow oil from **12k** (1.07 g, 2.71 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.73 (m, 10H, Ph × 2), 4.25–4.30, 3.86–3.90 (each m, each 1H, CH_2OTBDPS), 2.89, 2.84 (each d, each 1H, CH_2CO_2H, J = 15.5 Hz), 2.11–2.15, 1.77–1.81 (each m, each 1H, CH_2CH_2O), 1.85 (s, 3H, Me), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.61, 135.41, 135.37, 132.42, 132.33, 129.79, 129.75, 127.68, 127.65, 81.60, 79.41, 68.67, 61.72, 46.52, 41.89, 26.57, 18.80, 3.41. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{24}H_{30}NaO_4Si$: 433.18056. Found: 433.18014.

6.39. Deprotection of the TBDPS group

A solution of the carboxylic acid in acetone/aqueous 1.0 M HCl = 1:1 (as a 1 mM solution) was stirred at room temperature for 24 h and evaporated. The residue was purified by silica gel column chromatography (75% AcOEt in hexane) to give the corresponding lactones.

6.40. 4-Hydroxy-2-oxo-4-vinyltetrahydropyrane (1a)

Compound **1a** (32 mg 85%) was obtained as a colorless oil from **13a** (104 mg, 261 μmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (dd, 1H, CH_2=CH, J_{trans} = 17.6 Hz, J_{cis} = 10.4 Hz), 5.33 (d, 1H, CH_2=CH (trans), J = 17.6 Hz), 5.22 (d, 1H, CH_2=CH (cis), J = 10.4 Hz), 4.61–4.68, 4.35–4.40 (each m, each 1H, CH_2O), 2.66 (s, 2H, CH_2CO_2), 1.93–2.06, 1.89–1.92 (each m, each 1H, CH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.50, 141.83, 114.03, 70.01, 65.88, 42.52, 33.93. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.33; H, 6.99.

6.41. 4-Ethyl-4-hydroxy-2-oxotetrahydropyrane (1b)

Compound **1b** (92 mg 72%) was obtained as a colorless oil from **13b** (354 mg, 883 μmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58–4.64, 4.33–4.38 (each m, each 1H, CH_2O), 2.61, 2.52 (each d, each 1H, CH_2CO_2H, J = 17.6 Hz), 1.83–1.91 (m, 2H, CH_2CH_2O), 1.59–1.66 (m, 2H, Et-CH_2), 0.98 (t, 3H, Et-CH_3, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.45, 70.18, 66.01, 42.61, 34.79, 33.41, 7.12. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_7H_{12}NaO_3$: 167.06787. Found: 167.06792.

6.42. 4-Hydroxy-2-oxo-4-propyltetrahydropyrane (1c)

Compound **1c** (124 mg 87%) was obtained as a light yellow oil from **13c** (372 mg, 897 μmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57–4.64, 4.32–4.37 (each m, each 1H, CH_2O), 2.62, 2.53 (each d, each 1H, CH_2CO_2, J = 17.6 Hz), 1.83–1.96 (m, 2H, CH_2CH_2O), 1.52–1.60 (m, 2H, $CH_3CH_2CH_2$), 1.38–1.43 (m, 2H, $CH_3CH_2CH_2$), 0.98 (t, 3H, $CH_3CH_2CH_2$, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.36, 70.06, 65.97, 44.60, 43.02, 33.89, 16.11, 14.24. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.32; H, 9.00.

6.43. 4-Butyl-4-hydroxy-2-oxotetrahydropyrane (1d)

Compound **1d** (144 mg 84%) was obtained as a light yellow oil from **13d** (429 mg, 1.00 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57–4.64, 4.32–4.37 (each m, each 1H, CH_2O), 2.62, 2.52 (each d, each 1H, CH_2COO, J = 17.2 Hz), 1.84–1.95 (m, 2H, CH_2CH_2O), 1.57–1.59 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.35–1.37 (m, 4H, $CH_3CH_2CH_2CH_2$, $CH_3CH_2CH_2CH_2$), 0.93 (t, 3H, $CH_3CH_2CH_2CH_2$, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.54, 69.80, 65.97, 42.88, 41.88, 33.73, 24.82, 22.73, 13.80. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.86; H, 9.50.

6.44. 4-Hydroxy-4-(2-methylpropyl)-2-oxotetrahydropyrane (1e)

Compound **1e** (149 mg 88%) was obtained as a light yellow oil from **13e** (421 mg, 982 μmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58–4.64, 4.32–4.37 (each m, each 1H, CH_2O), 2.66, 2.52 (each d, each 1H, CH_2COO, J = 17.2 Hz), 1.83–1.90 (m, 3H, CH_2CH_2O, $(CH_3)_2CHCH_2$), 1.48–1.58 (m, 2H, $(CH_3)_2CHCH_2$), 1.02, 1.00 (each s, each 3H, $(CH_3)_2CHCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.45, 70.25, 65.93, 50.63, 43.46, 34.28, 24.48, 24.44, 23.35. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_9H_{16}NaO_3$: 195.09917. Found: 195.09929.

6.45. 4-Hydroxy-4-(1-methylvinyl)-2-oxotetrahydropyrane (1g)

Compound **1g** (99 mg 70%) was obtained as an yellow oil from **13g** (371 mg, 899 μmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04, 4.96 (each s, each 1H, CH_2=C), 4.63 (ddd, 1H, CH_2O, J = 0.8, 3.8, 9.0 Hz), 4.36 (ddd, 1H, CH_2O, J = 4.0, 4.0, 5.5 Hz), 2.75, 2.68 (each d, each 1H, CH_2COO, J = 17.0 Hz), 2.08–2.14, 1.91–1.96 (each m, each 1H, CH_2CH_2O), 1.84 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.18, 147.58, 111.20, 71.73, 65.94, 42.01, 32.65, 18.09. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_8H_{12}NaO_3$: 179.06787. Found: 179.06769.

6.46. 4-Hydroxy-4-(1-methylethyl)-2-oxotetrahydropyrane (1h)

Compound **1h** (157 mg 80%) was obtained as a light yellow oil from **13h** (520 mg, 1.25 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (ddd, 1H, CH_2O, J = 4.0, 11.0, 11.0 Hz), 4.35 (ddd, 1H, CH_2O, J = 3.5, 3.5, 10.5 Hz), 2.60, 2.55 (each d, each 1H, CH_2COO, J = 17.0 Hz), 1.93(ddd, 1H, CH_2CH_2O, J = 4.0, 5.5, 10.5 Hz), 1.79–1.84 (m, 1H, $(CH_3)_2CH$), 1.70–1.77 (m, 1H, CH_2CH_2O), 0.98, 0.96 (each s, each 3H, $(CH_3)_2CH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.11, 72.37, 65.92, 40.52, 37.46, 31.30, 16.37, 16.13. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_8H_{14}NaO_3$: 181.08352. Found: 181.08354.

6.47. 4-Hydroxy-2-oxo-4-(2-propenyl)tetrahydropyrane (1i)

Compound **1i** (129 mg 82%) was obtained as a light yellow oil from **13i** (413 mg, 1.00 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81–5.89 (m, 1H, CH_2=CH), 5.17–5.34 (m, 2H, CH_2=CH), 4.57–4.65 (m, 1H, CH_2O), 4.35 (ddd, 1H, CH_2O, J = 3.5, 3.5, 5.5 Hz), 2.61, 2.55 (each d, each 1H, CH_2COO, J = 17.5 Hz), 2.31–2.49 (m, 1H, CH_2=$CHCH_2$), 1.91–1.97, 1.83–1.88 (each m, each 1H, CH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.26, 131.57, 120.13, 69.31, 65.85, 46.35, 42.49, 33.49. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_8H_{12}NaO_3$: 179.06787. Found: 179.06769.

6.48. 4-Ethynyl-4-hydroxy-2-oxotetrahydropyrane (1j)

Compound **1j** (109 mg 77%) was obtained as a colorless oil from **13j** (397 mg, 1.00 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.72 (m, 10H, Ph × 2), 4.55–4.61, 4.40–4.46 (each m, each 1H, CH_2O), 2.95, 2.86 (each d, each 1H, CH_2COO, J = 17.5 Hz), 2.64 (s, 1H, ethynyl-H), 2.21–2.27, 2.14–2.19 (each m, each 1H, CH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.33, 84.18, 73.54, 65.57, 63.58, 44.35, 35.42. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_7H_8NaO_3$: 179.03657. Found: 163.03694.

6.49. 4-Hydroxy-2-oxo-4-(2-propynyl)tetrahydropyrane (1k)

Compound **1k** (32 mg 85%) was obtained as a colorless oil from **13k** (104 mg, 261 μmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52–4.57, 4.40–4.44 (each m, each 1H, CH_2O), 2.91, 2.80 (each d, each 1H, CH_2COO, J = 17.5 Hz), 2.08–2.20 (m, 2H, CH_2CH_2O), 1.86 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.61, 81.67, 79.98, 65.84,

63.89, 44.98, 35.97, 3.25. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_8H_{10}NaO_3$: 177.05222. Found: 177.05199.

6.50. 3-Cyclopropyl-1-*O*-(methoxymethyl)pentan-1,3,5-triol (14)

A mixture of **11f** (885 mg, 2.00 mmol) and TBAF (1.0 M in THF, 2.40 mL, 2.40 mmol) in THF (10 mL) was stirred at room temperature for 5 h and evaporated. The residue was purified by silica gel column chromatography (75% AcOEt in hexane) to give **14** (350 mg, 86%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (s, 2H, MOM-CH_2), 3.80–4.02 (m, 4H, CH_2OH, CH_2OMOM), 3.49 (s, 1H, OH), 3.39 (s, 3H, MOM-CH_3), 3.21 (br s, 1H, OH), 1.75–2.10 (m, 4H, $CH_2CH_2O \times 2$), 0.40–0.75 (m, 5H, cyclopropyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 96.40, 72.72, 64.77, 59.44, 55.39, 41.86, 39.95, 18.68, −0.56, −0.60. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{10}H_{20}NaO_4$: 227.12538. Found: 227.12558.

6.51. Methyl 3-cyclopropyl-3-hydroxy-5-(methoxymethoxy)-pentanoate (15)

A mixture of **14** (490 mg, 2.40 mmol) and IBX (1.01 g, 3.60 mmol) in DMSO (24 mL) was stirred at room temperature for 15 h. Aqueous 0.1 M $Na_2S_2O_3$ was added to the mixture at room temperature, and the mixture was stirred for 10 min and extracted with AcOEt. The organic layer was washed with H_2O, brine, dried with Na_2SO_4, and evaporated. A mixture of the crude product, $NaClO_2$ (651 mg, 7.20 mmol), $NaH_2PO_4{\cdot}H_2O$ (331 mg, 2.40 mmol), and 2-methyl-2-butene (1.00 mL, 9.60 mmol) in acetone (18 mL) and H_2O (6 mL) was stirred at room temperature for 3 h. The mixture was diluted with AcOEt, and washed with ice cooled aqueous 0.1 M HCl, H_2O, and brine. The water layer was extracted with AcOEt/acetone = 1:1 (three times), and the combined organic layers were dried with Na_2SO_4, and evaporated. The crude mixture and K_2CO_3 (719 mg, 5.20 mmol) in anhydrous DMF (8.7 mL) was stirred at 0 °C for 20 min. MeI (0.16 mL, 2.60 mmol) was added to the mixture at 0 °C, and the mixture was stirred at room temperature for 8 h. MeOH (1 mL) was added to the mixture at 0 °C, and the mixture was stirred at room temperature for 10 min. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried with Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (10% AcOEt in hexane) to give **15** (257 mg, 46%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (s, 2H, MOM-CH_2), 3.82–3.86, 3.75–3.80 (each m, each 1H, CH_2OMOM), 3.70 (s, 3H, CO_2CH_3), 3.54 (br, 1H, OH) 3.37 (s, 3H, MOM-CH_3), 2.61 (s, 2H, $CH_2CO_2CH_3$), 1.93–2.02 (m, 2H, CH_2CH_2O), 0.85–0.90 (m, 1H, cycloproyl), 0.31–0.49 (m, 4H, cyclopropyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.71, 96.37, 70.12, 64.28, 55.25, 51.45, 45.02, 39.92, 18.89, 0.09, −0.57. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_{11}H_{20}NaO_5$: 255.12029. Found: 255.12039.

6.52. 4-Cyclopropyl-4-hydroxy-2-oxotetrahydropyrane (1f)

A mixture of **15** (85 mg, 0.37 mmol) and $ZrCl_4$ (43 mg, 0.18 mmol) in *i*-PrOH (37 mL) was stirred at 90 °C for 1.5 h and evaporated. The residue was purified by silica gel column chromatography (50% AcOEt in hexane) to give **1f** (10 mg,18%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56–4.62, 4.33–4.41 (each m, each 1H, CH_2O), 2.58, 2.51 (each, d, each 1H, CH_2COO, J = 17.6 Hz), 1.81–1.96 (m, 2H, CH_2CH_2O), 0.42–0.94 (m, 5H, cyclopropyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.15, 68.88, 65.99, 42.65, 33.81, 20.94, 0.38, −0.05. HRMS (pos. ion ESI) *m/z* calcd for $(M+Na)^+$ $C_8H_{12}NaO_3$: 179.06787. Found: 179.06762.

6.53. Recyclization analysis

A solution of the lactone in aqueous 2.0 M LiOH (1 mL) was stirred at room temperature for 1 h, and evaporated. The residue was purified by silica gel column chromatography (25% MeOH in CH_2Cl_2) to give the corresponding hydrolyzed carboxylic acids. They were kept as a dry form or a solution of MeOH, H_2O, or a buffer (50 mM HEPES and 1 mM $MgCl_2$, pH 8.0) at room temperature. Only the buffer solution resulted in no recyclization after a week.

6.54. Preparation of linearized mevalonate analogues

Lactones **1a–1h** were dissolved in 2.0 M aqueous LiOH and incubated for 1 h at 37 °C. Each solution was titrated to pH 7.0 using concentrated HCl to give **2a–2h**. Compounds were diluted to a final concentration of 2 mM for storage at −80 °C.

6.55. In vitro enzyme assay

Recombinant *S. pneumoniae* MK (Uniprot: Q8DR51) and PMK (Uniprot: Q8DR49) were overexpressed in *Escherichia coli* as dual-tagged His_6-GST fusion proteins. The purification and removal of affinity tags was carried out as previously described.[11] The phosphorylation of substrates generates ADP, which can be monitored continuously using the well-established pyruvate kinase/lactate dehydrogenase coupled assay system[11] (see Fig. 2 legend). MK reactions were initiated by the addition of racemic compound (**2a**–**2k**) to 200 μM (100 μM in each enantiomer), and reaction progress was monitored at 386 nm (ε_{386} = 0.61 mM^{-1}). Following completion of the MK reaction (0.2–4 h), PMK was added to the cuvette and phosphorylation of compounds **3a**–**c, e, f, i, j** was monitored. Three progress curves were obtained for each compound and were averaged to produce the traces shown in Figure 2. The reproducibility of the replicate curves was assessed statistically using the pooled standard deviation (Mev: 5.41, 243 points; **2a**: 6.23,1286 points; **2b**: 5.03, 1847 points; **2c**: 4.33, 484 points; **2e**: 1.82, 310 points; **2f**: 0.41, 3642 points; **2i**: 5.20, 242 points; **2j**: 2.51, 2894 points; Pmev: 2.05, 76 points; **3a**: 4.94, 493 points; **3b**: 0.83, 284 points; **3c**: 3.70, 301 points; **3e**: 3.26, 561 points; **3f**: 1.69, 508 points; **3i**: 2.58, 218 points; **3j**: 1.51, 847 points).

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