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Facile access to new C-glycosides and C-glycoside scaffolds incorporating functionalised aromatic moieties

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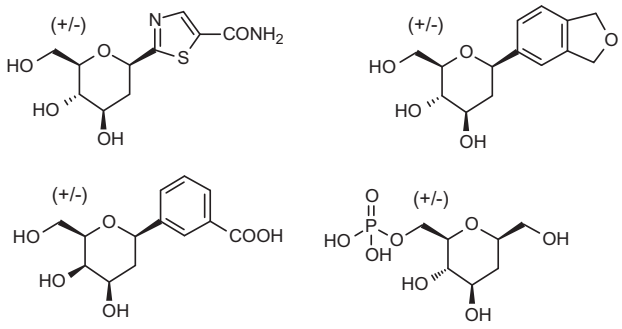
ABSTRACT

The tandem ene/intramolecular Sakurai cyclisation (IMSC) reaction has been successfully applied to the synthesis of a range of C-glycosides, with key intermediates offering opportunities for functionalisation of the glycon moiety. To demonstrate the versatility of the approach to access the 2-deoxy-C-glycoside series, we synthesised diastereomerically pure C-glucoside and galactoside derivatives incorporating functionalised aromatic, heteroaromatic and bicyclic aromatic moieties, in addition to the C-homologue of (±)-β-2-deoxy-glucose 6-phosphate.



1. Introduction

Carbohydrate and nucleoside mimetics have attracted a considerable attention in synthetic chemistry owing to their biological and chemotherapeutic properties.[1–8] These studies have led to the development of C-nucleosides and C-glycosides[9–11] as antibiotic, anticancer and antiviral agents.[12–14] Well known examples of antiproliferative C-nucleosides include formycin, tiazofurin and benzamide riboside **1** (Scheme 1).[15–17]

In the process of producing chemically stable C-nucleosides to probe the cellular biochemical space of nicotinamide adenine dinucleotide (NAD),[18–25] we have developed synthetic approaches based on ene-cyclisation chemistry and prepared a number of mimics of benzamide riboside **1**. As such, we reported the synthesis of a series of diastereomerically pure D- and L-pyranosyl phenyl and benzamide C-glycosides **3–6**[26] using Markó's tandem ene/IMSC and transmetallation methodologies (Scheme 1).[27,28] Similarly, we reported the synthesis of racemic 2-deoxy benzamide riboside **2** and analogues using an intramolecular ene-cyclisation.[29,30] We therefore aimed to establish whether the tandem ene-IMSC sequence offers means to access synthetic intermediates poised for a wider range of modifications. We report here such key

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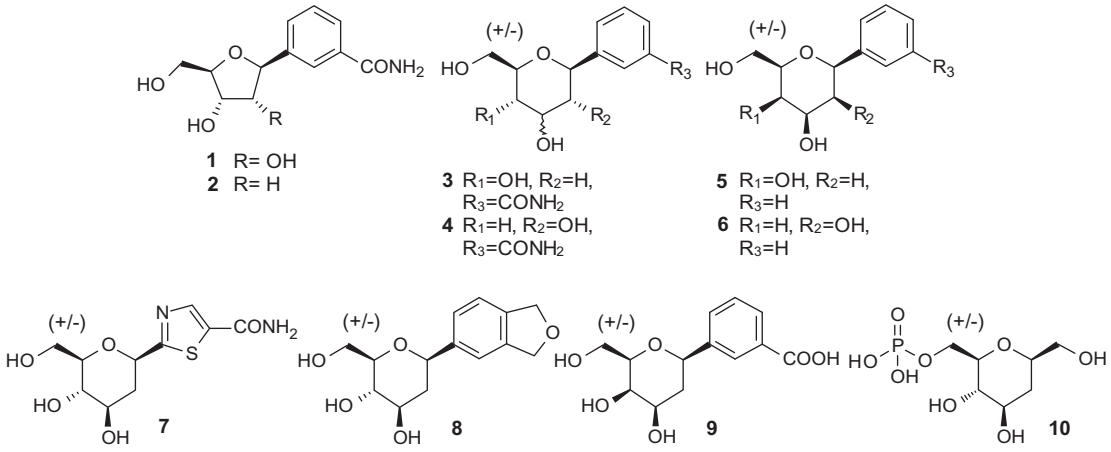


Scheme 1. Benzamide riboside **1**, 2-deoxy benzamide riboside **2**, benzamide and phenyl pyranosyl C-nucleosides **3**–**6**, a novel class of pyranosyl C-nucleosides **7**–**9** and 2-deoxy C-glucoside **10**.

intermediates which give access to three C-glycoside representatives (**7**–**9**), as well as access to the racemic mixture of the non-isomerisable homologue of β-2-deoxy glucose 6-phosphate, **10**.

2. Results and discussion

2.1. Synthesis of tiazofurin pyranosyl C-nucleoside 7

There are three classical routes to C-nucleosides and C-pyranosides. The first approach involves a direct attachment of a preformed nucleophilic aglycon to a protected carbohydrate moiety. This chemistry includes the reaction of heterocyclic organometallic compounds with pyranosyl[31,32] or furanosyl halides,[33] 1,2-anhydro-furanoses or -pyranoses,[34] functionalised lactones[35] and Heck-type coupling onto glycal moieties.[36–41] The second most common methodology consists in building-up the sugar moiety upon an aglycon unit and includes the tandem ene-IMSC sequence. This latter approach allows the introduction, in some cases, of up to four stereogenic centres in a one-step synthesis.[26,42] Finally, the last strategy consists of introducing a functional group at the anomeric position of the sugar derivative with the subsequent building-up of the aromatic moiety.[43] This typically involves the stereoselective introduction of a nitrile or alkyne group at the anomeric position followed by a cycloaddition reaction to build-up the heterocyclic base and generate the C-nucleoside or C-glycoside.

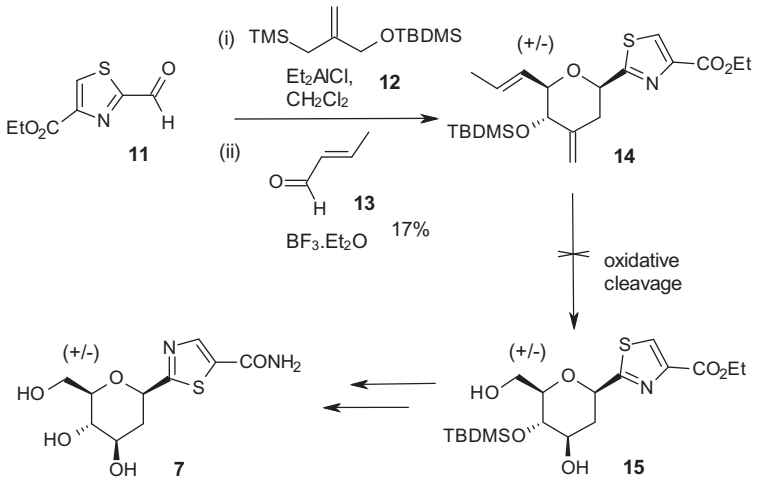
We seek to increase the scope of the two latter methodologies by combining the diastereoselective control we have optimised for the (D/L)-C-nucleoside syntheses using the tandem ene-IMSC sequence with the use of a functionalisable substituent at the C-1 position.

Key to a successful implementation of the tandem ene-IMSC sequence is the oxidative cleavage of the *exo*-alkene functionality, for example, compound **14**, generated upon cyclisation and the reduction of the resulting carbonyl. Firstly, we wished to determine if the tandem ene-IMSC sequence was suitable for the preparation of C-glycosides that incorporate electron rich heteroaryl moieties, such as compound **7**. Although it was possible to access the diastereomerically pure *exo*-methylene heteroaromatic pyran **14** (Scheme 2) from thiazolylaldehyde **11**, yields remained very low. Crucially, the oxidative cleavage of the *exo*-alkene **14** also proved problematic due to the presence of the oxidatively sensitive thiazolyl ring, which remained unstable to most oxidative cleavage conditions, ranging from ozonolysis to epoxidation/oxidation and *cis*-diol oxidations.

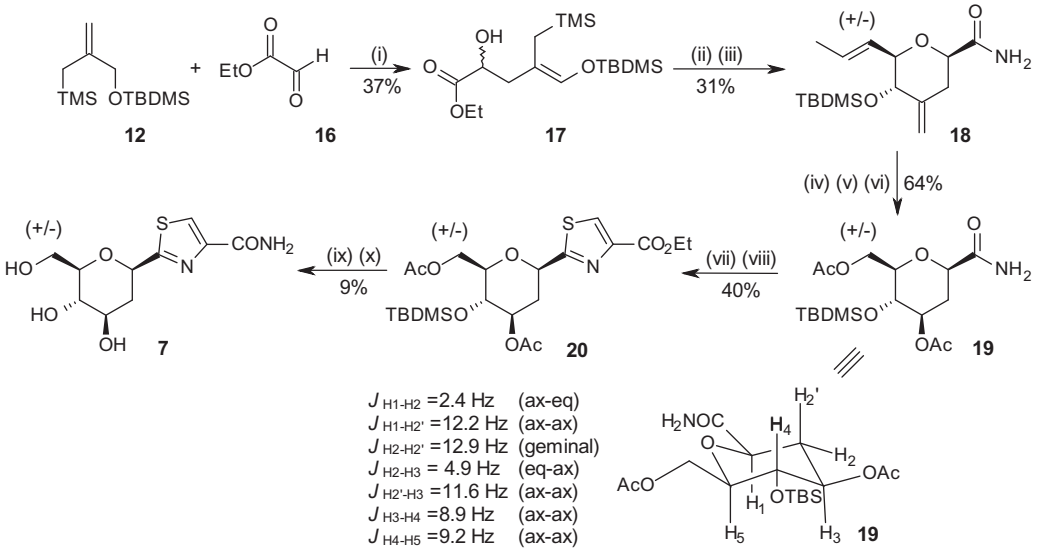
Therefore, it became apparent that designing a route in which aromatic and heteroaromatic rings could be built up in the late stages of the synthetic sequence would provide functional diversity at the aglycon unit. This would overcome the synthetic limitations caused by any harsh deprotection conditions and oxidative functionalisations of the glycon moiety. Using the tandem ene/IMSC protocol, we adopted a strategy that involved the synthesis of two *exo*-alkene pyranosyl intermediates **18** and **23** (Scheme 3 and Scheme 4, respectively), which could then be readily converted to their heteroaromatic and aromatic C-glycoside parents, for example, **7** and **8**, respectively.

Using allylsilane **12**, previously obtained via Trost's chemistry,[44] an ene-reaction was carried out with freshly distilled ethyl glyoxylate **16** in moderate yields (37%) (Scheme 3). The (*Z*)-geometric isomer of homoallylic alcohol **17** was obtained as the major product with the major side-product resulting from the competing intermolecular Sakurai condensation with aldehyde **16**, as was the case with all ene-reactions presented here-in. The characterisation of the (*Z*)-isomer **17** was consistent with the literature.[27] The IMSC step followed by aminolysis of the C-1 ester group, furnished the diastereomerically pure *exo*-methylene tetrahydropyran **18** in 31% yield over two steps, with the exclusive equatorial disposition of all the substituents (Scheme 3).[45] The stereocentres of **18**, as with all the pyran containing compounds, were defined by the coupling constants from the ^{1}H NMR and the typical axial and equatorial relationship that they represented. The moderate yield of these two steps was attributed to the ester hydrolysis that was observed upon work-ups. However, attempts at improving yields by using glyoxylamide instead of ethyl glyoxalate **16** for the IMSC were compromised by the difficulties encountered in preparing the glyoxylamide itself.

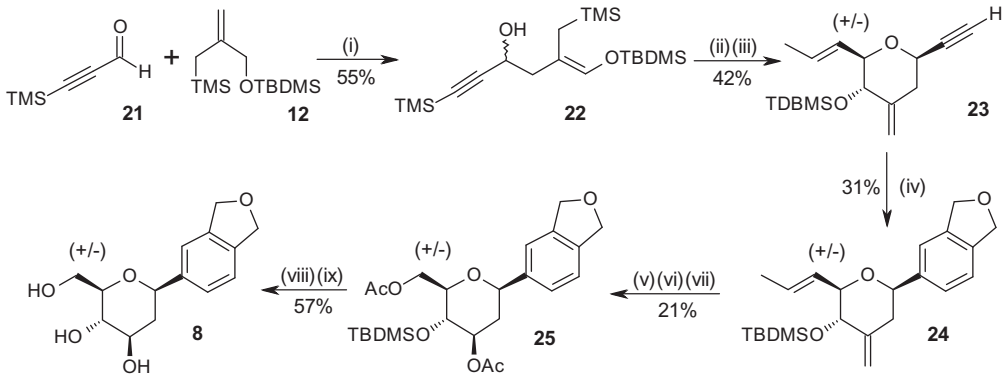
The cyclisation reaction and generation of the *exo*-alkene **18** was then followed by ozonolysis, reduction and acetylation to afford compound **19** in 64% yield over three steps. The ^{1}H NMR of **19** provided strong evidence to suggest that the $NaBH_4$ reduction of the C-3 ketone favoured an axial approach which led to an equatorially positioned hydroxyl group, as evident from the coupling constants, (Scheme 3). The derivative **19** was then reacted with phosphorous pentasulfide and led to a thioamide intermediate which was then reacted with ethyl bromopyruvate in Hantzsch reaction to afford the corresponding thiazole derivative **20**, in 40% over two steps.[46] Desilylation using TBAF in THF and the subsequent one-pot aminolysis of the ester functionality and deacetylation using saturated ammonia in methanol provided the fully



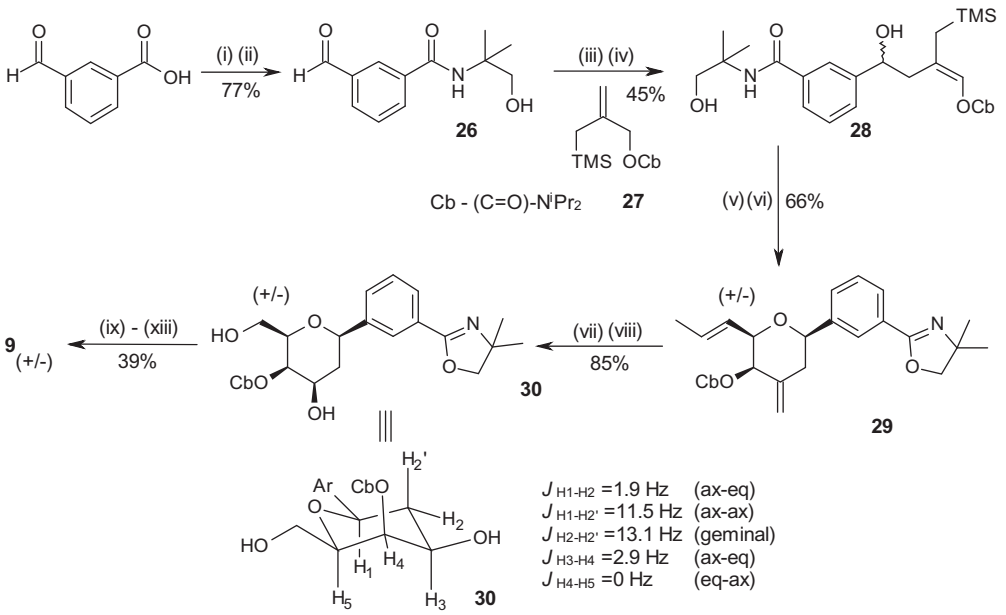
Scheme 2. Attempted synthesis of tiazofurin pyranosyl C-nucleoside **7**.



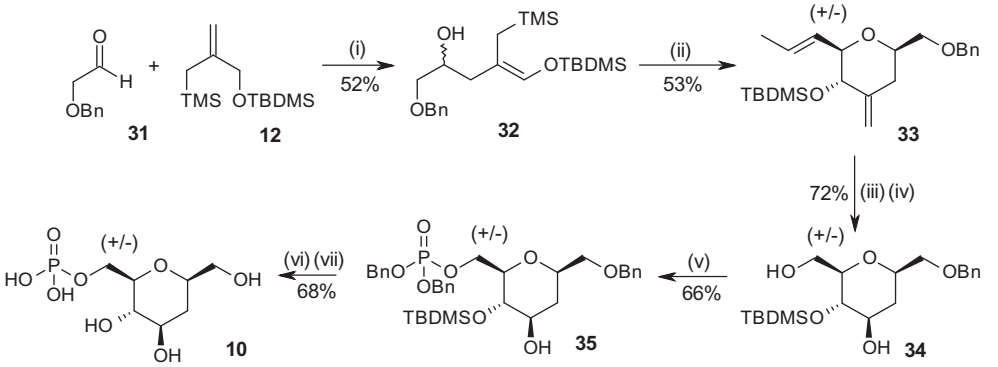
Scheme 3. Synthesis of (D/L)-2-deoxy-β-tiazofurin C-glucoside **7**. Reagents and conditions: (i) Et_2AlCl, CH_2Cl_2; (ii) crotonaldehyde, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (iii) $NH_{3(g)}$, MeOH; (iv) O_3, MeOH/CH_2Cl_2 then Me_2S; (v) $NaBH_4$, MeOH; (vi) Ac_2O, py; (vii) P_2S_5, toluene; (viii) ethyl bromopyruvate, 4 Å MS, Abs EtOH; (ix) TBAF/THF; (x) $NH_{3(g)}$, MeOH.



Scheme 4. Synthesis of (D/L)-2-deoxy-β-phtalan C-glucoside **8**. Reagents and conditions: (i) Et_2AlCl, CH_2Cl_2; (ii) crotonaldehyde **13**, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (iii) K_2CO_3, MeOH; (iv) propargyl ether, $RhCl(PPh_3)_3$, toluene; (v) O_3, MeOH/CH_2Cl_2 then Me_2S; (vi) $NaBH_4$, MeOH; (vii) Ac_2O, py; (viii) TBAF/THF; (ix) $NH_{3(g)}$, MeOH.



Scheme 5. Synthesis of (D/L)-2-deoxy-β-galactopyranosyl-benzoic acid **9**. Reagents and conditions: (i) $SOCl_2$, toluene; (ii) $H_2NC(CH_3)_2CH_2OH$, CH_2Cl_2; (iii) *sec*-BuLi, TMEDA, Et_2O; (iv) $Ti(O^iPr)_4$; (v) crotonaldehyde **13**, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (vi) MsCl, NEt_3, CH_2Cl_2; (vii) O_3, CH_2Cl_2/MeOH then Me_2S; (viii) $NaBH_4$; (ix) $LiAlH_4$, THF; (x) BnBr, TBAI, NaH, 15-crown-5, THF; (xi) MeI, $MeNO_2$; (xii) 20% KOH, MeOH; (xiii) H_2, 10% Pd/C, MeOH.



Scheme 6. Synthesis of (D/L)-β-2,6-anhydro-3-deoxy-*gluco*-heptose-7-phosphate **10**. Reagents and conditions: (i) Et_2AlCl, CH_2Cl_2; (ii) crotonaldehyde **13**, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (iii) O_3, CH_2Cl_2/MeOH then Me_2S; (iv) $NaBH_4$; (v) $ClP(O)(OBn)_2$, Py, CH_2Cl_2; (vi) TBAF/THF; (vii) H_2, 10% Pd/C.

unprotected pyranosyl analogue of tiazofurin, **7**, albeit in low overall yields. It was thought that the low yield was due to the instability of the thiazole group to the unoptimised aminolysis reaction conditions. Yet, it is worth noting that compounds such as **18** and **19** are powerful synthetic intermediates, as they can easily be manipulated to provide structurally diverse derivatives.

2.2. Synthesis of (D/L)-2-deoxy-β-phtalan C-glucoside 8

Kool et al. have shown the usefulness of bicyclic and tricyclic ribosyl-C-nucleosides for analysing the effect of increased DNA base pair sizes on the stability of the double helix.[47–51] From a synthetic perspective, Toshima reported the very efficient aryl C-glycosidation of unprotected 2-deoxy pyranoses using electron-rich aryls in the presence of a TMSOTf-based catalyst.[52] This work followed on from the very efficient aryl-C-glycoside syntheses via an O→C-glycoside rearrangement, reported independently by Kometani[53] and Suzuki.[54] Consequently, we have applied our flexible protocol to access electron-rich bicyclic 2-deoxy-C-pyranosides which could not be prepared via an in situ O→C rearrangement, such as the 2-deoxy-phthalan C-pyranoside **8** (Scheme 4).

Firstly, (*Z*)-homoallylic alcohol **22** was isolated in 55% yield and cyclised with crotonaldehyde **13**. Following this, selective desilylation of the trimethylsilyl alkyne functionality using potassium carbonate was carried out to yield the C-glycoside **23**. It is worth pointing out that this versatile organic synthon may be used for many reactions including click chemistry or cross-coupling reactions.[55–57] The [2+2+2] cyclotrimerisation of **23** with propargyl ether catalysed by Wilkinson's catalyst, $RhCl(PPh_3)_3$, afforded the phthalan *exo*-methylene tetrahydropyran **24**, albeit in 31% isolated yield. The next step was our standard ozonolysis conditions followed by sodium borohydride mediated reduction. To facilitate desired product isolation and purification, acetylation of the free alcohols on C-3 and C-6 was necessary and led to the formation of the fully protected pyranosyl C-nucleoside **25** in moderate yields, with the stereochemistry confirmed by ^1H NMR using the relevant coupling constants. The fully unprotected phthalan pyranosyl C-glucoside **8** was then readily obtained following our standard deprotection protocols.

2.3. Synthesis of (D/L)-2-deoxy-β-galactopyranosyl-benzoic acid 9

We also wanted to demonstrate that the present method was flexible in terms of the introduction of different stereo-centres around the pyranosyl unit, and access mannoside and galactoside type stereochemistry on the glycon unit of C-glycosides of type **9**.[26,28] To access the relative R chirality at the C-4 of the pyranoside a diisopropylcarbamate protected allylsilane must be employed.[28] This type of the protecting group requires the use of $LiAlH_4$ at reflux in THF for its removal. As such, the transmetallation–IMSC sequence (Scheme 5) to access **9** is limited by the type of electron-deficient functionalities which can be introduced on the aryl moiety.[26] Yet, the 4,4-dimethyl-4,5-dihydro-oxazoline group was identified as such stable functionality which could be removed at a later stage in the synthesis to access a 2-(D/L)-deoxy-β-galactoside substituted with a carboxylated aryl.

Using this approach, we synthesised the carboxylic acid phenyl pyranoside **9**, analogue of nicotinic acid riboside,[58] from the *exo*-alkene pyran **29** in seven steps via an intermediate **26**. (Scheme 5). The (*E*)-isomer **28** was exclusively obtained following the lithiation of 2-[(trimethylsilyl)methyl]-2-propen-1-yl-bis(isopropyl) carbamate **27**, using *sec*-BuLi in the presence of TMEDA, then the sequential reactions of transmetallation using titanium tetraisopropoxide and finally γ-allylation with 3-formyl-*N*-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide **27**, in one pot. It must be noted that both the transmetallation and IMSC reactions readily occurred in the presence of an unprotected alcohol group. IMSC condensation of compound **28**, followed by aryl oxazoline formation via mesylation of the free hydroxyl was carried out in 66% yield to provide dialkene **29**. Subsequent ozonolysis and in situ reduction of the carbonyl functionalities with sodium borohydride yielded **30** with complete stereocontrol at the C-3 position of the sugar moiety as evident from the coupling constants, (Scheme 5) and in agreement with the literature.[28]

Subsequently, the removal of the diisopropyl carbamate group was carried out using $LiAlH_4$ in refluxing THF. Tri-benzylation of the resultant three hydroxyls was required in order to increase hydrophobicity, prior to methylation and base-catalysed hydrolysis of the oxazoline moiety. The fully deprotected 2-deoxy-*C*-galactopyranosyl-benzoic acid **9** was obtained following simple hydrogenation over 10% Pd/C in 39% yield over five steps. Therefore, the oxazoline protecting group chemistry proved to be an invaluable approach to galactoside and mannoside type C-nucleosides incorporating functionality analogous to the biologically important benzamide riboside **1**, previously inaccessible using the transmetallation/IMSC methodology.

2.4. Synthesis of (D/L)-β-2,6-anhydro-3-deoxy-*gluco*-heptose-7-phosphate 10

Using the described methodologies, we also examined the possibility of accessing bioisosteres of glucose-6-phosphate (G6P), such as compound **10**, (Scheme 6). β-G6P is a substrate for two key enzymes in metabolism: glucose-6-phosphate dehydrogenase and β-phosphoglucomutase. While these enzymes have been extensively studied, non-reducing sugars possessing the appropriate stereochemistry at the C-1 position can be extremely useful tools when conducting structural investigations.[59] We therefore examined how efficacious the preparation of phosphate 2,6-anhydro-heptoses could be using the ene-IMSC sequence.

The synthesis of the G6P bio-isostere **10** began with the isolation and Sakurai cyclisation of (*Z*)-homoallylic alcohol **32** with crotonaldehyde **13**. Standard double oxidation and reduction of the alkene functionality of **33** provided diol **34** in 72% yield, with the stereochemistry assigned using ^1H NMR as described for the previous series. Subsequently, a selective phosphorylation of the resultant 5′-OH using dibenzyloxychlorophosphate[60] in pyridine provided intermediate **35** in 66% isolated yield. The fully deprotected G6P analogue **10** was easily obtained following desilylation using TBAF in THF and hydrogenolysis was performed directly under continuous flow conditions using an H-Cube reactor and a 10% Pd/C catalyst cartridge in good yields.

3. Conclusion

In summary, we have further exemplified the versatility of the tandem ene/IMSC and transmetallation methodologies towards the synthesis of racemic D/L C-glycosides. While the examples reported here belong to the 2-deoxy series, we have previously demonstrated that the C-4-deoxy series can be as readily obtained, and this by a simple reagent sequence exchange.[26] The routes, presented herein, therefore offer access to a large range of racemic aromatic, heteroaromatic and bicyclic C-glycosides and simple C-glycosides, for which pure forms could be obtained through chiral syntheses using now well established literature precedents.[61,62]

4. Experimental

4.1. General

Chemicals were purchased from Sigma–Aldrich, Lancaster, VWR, Maybridge or ACROS. Solvents for extractions and chromatography were of technical grade. Solvents used in reactions were freshly distilled from appropriate drying agents before use. Flash chromatography was carried out using Merck Silica (40–60 μ) and acid washed sand. Analytical TLC was performed with Merck Silica gel 60 F_{254} plates. ^1H, ^{13}C and 2D (H-COSY, HMQC) NMR spectra were all recorded on Brüker avance DPX 300 and Brüker avance DPX 500. TMS (0 ppm, ^1H NMR) and $CDCl_3$ (77 ppm, ^{13}C NMR) were used as internal references. The chemical shifts (δ) are reported in ppm (parts per million). High-resolution mass spectrometry (HRMS) was recorded on a VG Quattro Triple Quadrupole Mass Spectrometer (ES). Note—all pyran containing products were obtained as a racemate.

4.1.1. Synthesis of 3

4.1.1.1. (*Z*)-Ethyl-5-(*tert*-butyldimethylsilyloxy)-2-hydroxy-4-((trimethylsilyl)methyl)pent-4-enoate (17). *4.1.1.1.1. General ene-reaction procedure.* In a 100 mL RBF flushed with argon, aldehyde (19.0 mmol, 5.0 equiv) and TBS allylsilane **12** (1.0 g, 3.76 mmol, 1.0 equiv) were dissolved in dry CH_2Cl_2 (30 mL). Et_2AlCl (1 M in CH_2Cl_2, 1.5 equiv) was syringed into the solution at −78 °C. The reaction mixture was allowed to warm up to 0 °C and stirred for 3 h. The solution was quenched with satd $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude yellow oil was purified by column chromatography with pet. ether/EtOAc (7:3) as eluent to afford pure ene-product.

General ene-reaction was carried out using compound **12** with ethyl glyoxalate **16**. Clear oil. Yield: 502 mg, 37%. ^1H NMR (300 MHz, $CDCl_3$): δ 6.07 (s, 1H, C=C*H*), 4.63–4.65 (m, 1H, C*H*OH), 4.19 (q, 2H, J = 6.9 Hz, CH_2CH_3), 2.60 (d, 1H, J = 6.0 Hz, O*H*), 2.32 (ABX, 1H, $J_{a,a'}$ = 14.0 Hz, $J_{a,b}$ = 4.5 Hz, CH_2CHOH), 2.14 (ABX, 1H, $J_{a,a'}$ = 14.1 Hz, $J_{a',b}$ = 7.8 Hz, CH_2CHOH) 1.56 (AB, 1H, J = 13.5 Hz, CH_2-TMS), 1.42 (AB, 1H, J = 13.6 Hz, CH_2-TMS), 1.27 (t, 3H, J = 6.8 Hz, CH_2CH_3), 0.89 (s, 9H, (Si—C—(CH_3)$_3$), 0.07 (s, 6H, 2× Si—CH_3), 0.00 (s, 9H, TMS). ^{13}C NMR (75 MHz, $CDCl_3$,): δ 171.8 (C=O), 140.1 (C=CH), 109.8 (*C*=CH), 70.3 (*C*HOH), 62.6 (CH_2CH_3), 40.0 (CH_2CHOH), 30.7 (Si—*C*—(CH_3)$_3$), 25.8 (Si—C—(*C*H$_3$)$_3$), 22.4

(CH_2—TMS), 14.1 (CH_2CH_3), 2.0 (TMS), −2.2 (2× Si—CH_3). MS (ES) *m*/*z*: calculated for $C_{17}H_{36}NaO_4Si_2$ $[M+Na]^+$ 382.1972, found 382.1975.

4.1.1.2. (±) (2*R*,5*S*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-methylene-6-((*E*)-prop-2enyl)tetrahydro-2*H*-pyran-2-carboxamide (18).

4.1.1.2.1. General Sakurai cyclisation procedure. In a 25 mL RBF flushed with argon, enol ether (0.14 mmol, 1.0 equiv) and the aldehyde (0.17 mmol, 1.2 equiv) were dissolved in dry CH_2Cl_2 (20 mL) under argon. The solution was cooled down to −78 °C before the drop-wise addition of distilled $BF_3{\cdot}Et_2O$ (0.16 mmol, 1.1 equiv). The reaction was stirred for 6 h while slowly warming up to 0 °C and was then diluted with CH_2Cl_2 (15 mL) and washed with satd $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography with pet. ether/EtOAc (1:1) as eluent to afford pure cyclised product.

The cyclisation of **17** with crotonaldehyde **13** was carried out using the general Sakurai cyclisation procedure. The purified ester intermediate (0.18 g, 0.53 mmol, 1.0 equiv) was then dissolved in dry MeOH (10 mL) under argon. The solution was then cooled down to −78 °C and ammonia gas was bubbled through the mixture for 10 min. The flask was sealed and the reaction mixture allowed to warm up to rt overnight. The mixture was then concentrated under reduced pressure. The residue was purified by column chromatography with pet. ether/EtOAc (6:4) as eluent to afford amide **18**. Yellow oil. Yield: 143 mg, 31% over two steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.52 (br s, 1H, CONH_2), 5.75 (dq, 1H, *J* = 13.0 Hz, *J* = 6.5 Hz, CH_3CH=CH), 5.47 (ddq, 1H, *J* = 13.1 Hz, *J* = 7.8 Hz, *J* = 1.5 Hz, CH_3CH=C*H* and br s, 1H, CONH_2), 5.13 (s, 1H, C=CH_2), 4.97 (s, 1H, C=CH_2), 3.87 (dd, 1H, *J* = 11.5 Hz, *J* = 2.5 Hz, H-1 (anomeric)), 3.75 (d, 1H, *J* = 8.9 Hz, H-4), 3.56 (dd, 1H, *J* = 8.7 Hz, *J* = 8.0 Hz, H-5), 2.89 (dd, 1H, *J* = 13.5 Hz, *J* = 2.5 Hz, H-2), 2.23 (dd, 1H, *J* = 13.4 Hz, *J* = 11.7 Hz, H-2′), 1.74 (dd, 3H, *J* = 6.5 Hz, *J* = 1.6 Hz, CH_3CH=CH), 0.91 (s, 9H, (Si—C—(CH_3)$_3$), 0.03 (s, 6H, (2× Si—CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3 (C=O), 144.9 (*C*=CH_2), 130.3 (CH_3C H=CH), 129.5 (CH_3CH=*C*H), 108.5 (*C*=CH_2), 84.3 (C-5), 77.4 (C-1), 73.7 (C-4), 38.1 (C-2), 29.5 (Si—*C*—(CH_3)$_3$), 25.7 (Si—C—(*C*H_3)$_3$), 17.9 (*C*H_3CH=CH), −4.5 (2× Si—*C*H_3). MS (ES) *m*/*z*: calculated for $C_{16}H_{29}O_3SiN$ $[M+Na]^+$ 334.1814, found 334.1794.

4.1.1.3. (±) ((2*R*,3*S*,4*R*,6*R*)-4-Acetoxy-3-(*tert*-butyldimethylsilyloxy)-6-carbamoyl-tetrahydro-2*H*-pyran-2-yl)methyl acetate (19).

4.1.1.3.1. General ozonolysis procedure. Pyran (0.7 mmol, 1.0 equiv) was dissolved in MeOH (15 mL) and dry CH_2Cl_2 (15 mL) under argon and the system was cooled to −78 °C. O_3 was bubbled through the solution until a blue colour persisted and then it was stirred for an additional 2–3 min before the stream of O_3 was replaced with argon. After the solution became clear Me_2S (2.8 mmol, 4.0 equiv) was syringed in and stirred for 15 min at −78 °C. Then $NaBH_4$ (2.8 mmol, 4.0 equiv) was added in one portion, warmed to rt and stirred for 24 h. The mixture was concentrated and purified by column chromatography with $CHCl_3$/EtOH (95:5) as eluent to afford pure product.

General ozonolysis procedure was carried out on compound **18**. The crude product was re-dissolved in dry pyridine (10 mL) and acetic anhydride (4 mL) and the solution was stirred for 24 h. The mixture was then concentrated under reduced pressure. The residue was purified by column chromatography with pet. ether/EtOAc (7:3) as eluent to afford pure **19**. Yellow oil. Yield: 80 mg, 64% over three steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.48 (br s, 1H, CONH_2), 5.29 (br s, 1H, CONH_2), 4.84 (ddd, 1H, *J* = 11.6 Hz, *J* = 8.9 Hz, *J* = 4.9 Hz, H-3), 4.51 (ABX, 1H, $J_{a,a'}$ = 12.0 Hz, $J_{a',b}$ = 1.9 Hz, CH_2OAc), 4.19 (ABX, $J_{a,a'}$ = 12.1 Hz, J_{ab} = 5.2 Hz, CH_2OAc), 4.00 (dd, 1H, *J* = 12.1 Hz, *J* = 2.4 Hz, H-1), 3.66 (dd, 1H, *J* = 9.2 Hz, *J* = 8.9 Hz, H-4), 3.50 (ddd, 1H, *J* = 9.2 Hz, *J* = 4.9 Hz, *J* = 1.9 Hz, H-5), 2.67 (ddd, 1H, *J* = 12.9 Hz, *J* = 4.9 Hz, *J* = 2.5 Hz, H-2), 2.12 (s, 3H, OAc), 2.08 (s, 3H, OAc), 1.48 (ddd, 1H, *J* = 12.9 Hz, *J* = 12.3 Hz, *J* = 11.5 Hz, H-2′), 0.86 (s, 9H, (Si—C—(CH_3)$_3$), 0.00 (s, 6H, (2× Si—CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3 (*C*=O—NH_2), 170.8 (2× OAc), 78.9 (C-5), 75.3 (C-3), 74.9 (C-1), 69.7 (C-4), 63.4 (CH_2-OAc), 33.8 (C-2), 31.2 (Si—*C*—(CH_3)$_3$), 26.1 (Si—C—(*C*H_3)$_3$), 21.7 (OAc), 21.3 (OAc), −2.0 (2× Si—*C*H_3). MS (ES) *m*/*z*: calculated for $C_{17}H_{35}N_2O_7Si$ $[M+NH_4]^+$ 407.2214, found 407.2280.

4.1.1.4. (±) Ethyl-2-((2*R*,4*R*,5*S*,6*R*)-4-acetoxy-6-(acetoxymethyl)-5-(*tert*-butyldimethylsilyloxy)tetrahydro-2*H*-pyran-2-yl)thiazole-4-carboxylate (20).

Compound **19** (80 mg, 0.20 mmol, 1.0 equiv) was dissolved in dry toluene (10 mL) and P_2S_5 (50 mg, 0.20 mmol, 1.0 equiv) was added to the solution. The reaction mixture was heated at reflux for 90 min, then cooled down to RT and washed with satd $NaHCO_3$ (5 mL). The organic phase was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography with pet. ether/EtOAc (7:3) as eluent to afford pure product. The thioamide intermediate (40 mg, 0.10 mmol, 1.0 equiv) was dissolved in absolute EtOH (10 mL) and ethyl bromopyruvate (0.012 mL, 0.10 mmol, 1.0 equiv) was added to the solution followed by 4 Å molecular sieves. The reaction mixture was heated to reflux for 2.5 h, cooled down, filtered and concentrated under reduced pressure. The residue was re-dissolved in EtOAc (15 mL) and the organic phase was washed with satd $NaHCO_3$ (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography with pet. ether/EtOAc (7:3) as eluent to afford pure **20**. Yellow oil. Yield: 45 mg, 40% over two steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (s, 1H, C=C*H* —S), 4.92 (ddd, 1H, *J* = 11.3 Hz, *J* = 8.9 Hz, *J* = 4.8 Hz, H-3), 4.88 (dd, 1H, *J* = 11.7 Hz, *J* = 2.1 Hz, H-1), 4.50 (ABX, 1H, $J_{a,a'}$ = 12.0 Hz, $J_{a',b}$ = 1.9 Hz, CH_2OAc), 4.39 (q, 2H, *J* = 7.0 Hz, CH_2CH$_3$), 4.21 (ABX, $J_{a,a'}$ = 12.0 Hz, J_{ab} = 5.0 Hz, CH_2OAc), 3.76 (dd, 1H, *J* = 9.2 Hz, *J* = 9.0 Hz, H-4), 3.64 (ddd, 1H, *J* = 9.4 Hz, *J* = 5.0 Hz, *J* = 1.8 Hz, H-5), 2.87 (ddd, 1H, *J* = 12.8 Hz, *J* = 5.0 Hz, *J* = 2.2 Hz, H-2), 1.66 (ddd, 1H, *J* = 12.7 Hz, *J* = 12.0 Hz, *J* = 11.6 Hz, H-2′), 1.38 (t, 3H, *J* = 7.1 Hz, CH$_2$CH_3), 0.85 (s, 9H, (Si—C—(CH_3)$_3$), 0.05 (s, 6H, (2× Si—CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9 (S—*C*=N), 170.1 (OAc), 161.5 (O=*C*—OEt), 147.2 (*C*=CH—S), 127.9 (C=*C*H—S), 80.7 (C-5), 79.1 (C-1), 75.0 (C-4), 70.2 (C-3), 66.6 (*C*H$_2$OAc), 61.6 (*C*H$_2$CH$_3$), 38.7 (C-2), 29.2 (Si—C—(CH$_3$)$_3$), 25.9 (Si—C—(*C*H$_3$)$_3$), 21.5 (OAc), 21.1 (OAc), 14.5 (CH$_2$*C*H$_3$), −0.5 (2× Si—CH_3). MS (ES) *m*/*z*: calculated for C_{22}-$H_{36}NO_8SSi$ $[M+H]^+$ 502.1931, found 502.1935.

4.1.1.5. (±) 2-((2*R*,4*R*,5*S*,6*R*)-4,5-Dihydroxy-6-(hydroxymethyl) tetrahydro-2*H*-pyran-2-yl)thiazole-4-carboxamide (7).

To a solution of **20** (30 mg, 0.061 mmol, 1.0 equiv) in dry THF (3 mL) was added TBAF (0.073 mL, 0.073 mmol, 1 M in THF, 1.2 equiv). The mixture turned yellow/orange. This solution was stirred for 24 h to ensure full desilylation and was then concentrated under reduced pressure. The crude residue was then re-dissolved in dry MeOH (7 mL) and ammonia gas was bubbled through the solution at −78 °C for 15 min. The flask was sealed and the reaction mixture was allowed to warm up to rt overnight. The solution was then concentrated under reduced pressure. The residue was purified by column chromatography with $CHCl_3$/EtOH (9:1) as eluent to afford carboxamide **7**. Yellow oil. Yield: 1.5 mg, 9%. ^{1}H NMR (500 MHz, CD_3CN): δ 8.15 (s, 1H, C=C*H* —S), 4.77 (dd, 1H, *J* = 11.3 Hz, *J* = 1.9 Hz, H-1), 3.71–3.68 (m, 1H, H-3), 3.63–3.54 (m, 2H, H-6), 3.33 (ddd, 1H, *J* = 9.4 Hz, *J* = 5.6 Hz, *J* = 2.7 Hz, H-5), 3.16 (dd, 1H, *J* = 9.8 Hz, *J* = 8.3 Hz, H-4), 2.36 (ddd, 1H, *J* = 12.7 Hz, *J* = 4.8 Hz, *J* = 2.2 Hz, H-2), 1.65–1.61 (m, 1H, H-2′). ^{13}C NMR

(125 MHz, MeOD): δ 171.7 (S—*C*═N), 163.2 (*C*═O—NH_2), 150.9 (*C*═CH—S), 129.2 (C═*C*H—S), 81.7 (C-5), 75.2 (C-1), 72.3 (C-3), 72.0 (C-4), 62.1 (C-6), 40.2 (C-2).

4.1.2. Synthesis of 8

4.1.2.1. (*Z*)-1-(Trimethylsilyl)propyl-5-(*tert*-butyldimethylsilyloxy)-4-trimethylsilylmethyl-pent-4-en-2-ol (22). General enereaction was carried out using compound **12** with TMS-propynal **21**. Clear oil. Yield: 302 mg, 55%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.97 (s, 1H, C═C*H*), 4.22–4.16 (m, 1H, C*H*OH), 2.10 (ABX, 1H, $J_{a,a'}$ = 11.0 Hz, $J_{a,b}$ = 4.4 Hz, CH_2CHOH), 2.04 ((ABX, 1H, $J_{a,a'}$ = 11.0 Hz, $J_{a',b}$ = 5.2 Hz, CH_2CHOH)), 1.80 (d, 1H, *J* = 4.7 Hz, O*H*), 1.53 (AB, 1H, *J* = 13.2 Hz, CH_2-TMS), 1.24 (AB, 1H, *J* = 13.3 Hz, CH_2-TMS), 0.75 (s, 9H, (Si—C—(CH_3)$_3$), 0.08 (s, 6H, 2× Si—CH_3), 0.0 (s, 18H, 2× TMS). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.6 (C═*C*H), 113.5 (*C*═CH), 107.0 (*C*≡C-TMS), 89.4 (C≡*C*-TMS), 60.6 (*C*HOH), 42.2 (*C*H_2CHOH), 29.9 ((Si—*C*—(CH_3)$_3$), 25.9 (Si—C—(*C*H_3)$_3$), 17.6 (*C*H_2-TMS), 0.05 (TMS), −0.4 (TMS), −2.3 (2× Si—*C*H_3). MS (ES) *m*/*z*: calculated for $C_{19}H_{40}O_2Si_3Na$ [M+Na] 407.2234, found 407.2247.

4.1.2.2. (±) *tert*-Butyldimethyl-((2*R*,3*S*,6*R*)-4-methylene-2-((*E*)-prop-1-enyl)-6-((trimethylsilyl)ethynyl)tetrahydro-2*H*-pyran-3-yloxy)silane (23). The cyclisation of **22** with crotonaldehyde **13** was carried out using the general Sakurai cyclisation procedure. To a solution of TMS-alkyne protected cyclised intermediate (0.13 g, 0.36 mmol, 1.0 equiv) in dry MeOH (5 mL) was added K_2CO_3 (35 mg, 0.25 mmol, 0.7 equiv). The reaction mixture was stirred at rt for 24 h. The solution was then diluted with EtOAc (20 mL) and the organic phase was washed with satd NH_4Cl (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography with pet. ether/EtOAc (8:2) as eluent to afford pure alkyne **23**. Yellow oil. Yield: 96 mg, 42% over two steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (dq, 1H, *J* = 15.3 Hz, *J* = 6.2 Hz, CH_3C*H* ═CH), 5.47 (ddq, 1H, *J* = 15.3 Hz, *J* = 7.9 Hz, *J* = 1.5 Hz, CH_3CH═C*H*), 5.08 (d, 1H, *J* = 1.2 Hz, C═CH_2), 4.87 (d, 1H, *J* = 1.2 Hz, C═CH_2), 4.11 (dd, 1H, *J* = 11.2 Hz, *J* = 2.7 Hz, H-1), 3.80 (d, 1H, *J* = 8.7 Hz, H-4), 3.47 (dd, 1H, *J* = 8.7 Hz, *J* = 8.1 Hz, H-5), 2.62 (dd, 1H, *J* = 13.5 Hz, *J* = 2.7 Hz, H-2), 2.49 (dd, 1H, *J* = 13.3 Hz, *J* = 11.5 Hz, H-2′), 1.71 (dd, 3H, *J* = 6.6 Hz, *J* = 1.8 Hz, CH_3CH═CH), 0.91 (s, 9H, (Si—C—(CH_3)$_3$), 0.16 (s, 6H, 2× Si—CH_3), 0.09 (s, 9H, TMS). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2 (*C*═CH_2), 129.6 (CH_3-CH═*C*H), 129.3 (CH_3*C*H═CH), 114.0 (C═*C*H_2), 108.3 (*C*≡C-TMS), 107.1 (C≡*C*-TMS), 83.7 (C-4), 80.9 (C-1), 67.2 (C-5), 40.9 (C-2), 28.7 (Si—*C*—(CH_3)$_3$), 24.7 (Si—C—(*C*H_3)$_3$), 16.9 (*C*H_3CH═CH), 0.0 (TMS), −5.5 (2× Si—CH_3). MS (EI) *m*/*z*: calculated for $C_{20}H_3O_2Si_2$ $[M]^+$ 364.2254, found 364.2253.

4.1.2.3. (±) *tert*-Butyldimethyl((2*R*,3*S*,6*R*)-6-(1,3-dihydro-iso-benzofuran-5-yl)-4-methylene-2-((*E*)-prop-1-enyl)tetrahydro-2*H*-pyran-3-yloxy)silane (24). To a solution of alkyne **23** (0.10 g, 0.34 mmol, 1.0 equiv) in dry toluene (10 mL) was added Wilkinson's catalyst $RhCl(PPh_3)_3$ (10 mg, 3 mol%) under argon. Propargyl ether (0.05 mL, 0.51 mmol, 1.5 equiv) was then added to the solution drop-wise via a syringe over 1 h. The reaction mixture was stirred at rt for 24 h and was then concentrated under reduced pressure. The residue was purified by column chromatography with petroleum ether (60–80)/EtOAc (4:1) as eluent to afford pure **24**. Yellow oil. Yield: 40 mg, 31%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, 1H, *J* = 8.5 Hz, Ar), 7.24 (s, 1H, Ar), 7.18 (d, 1H, *J* = 8.2 Hz, Ar), 5.78 (dq, 1H, *J* = 15.5 Hz, *J* = 6.5 Hz, CH_3C*H*═CH), 5.55 (ddq, 1H, *J* = 15.1 Hz, *J* = 7.7 Hz, *J* = 1.4 Hz, CH_3CH═C*H*), 5.08 (s, 4H, 2× CH_2O), 5.01 (s, 1H, C═CH_2), 4.92 (s, 1H, C═CH_2), 4.41 (dd, 1H, *J* = 11.5 Hz, *J* = 2.0 Hz, H-1), 3.88 (d, 1H, *J* = 8.5 Hz, H-4), 3.67 (dd, 1H, *J* = 8.2 Hz, *J* = 8.0 Hz, H-5), 2.60 (dd, 1H, *J* = 13.5 Hz, *J* = 2.5 Hz, H-2), 2.39 (dd, 1H, *J* = 13.0 Hz, *J* = 11.5 Hz, H-2′), 1.72 (dd, 3H, *J* = 6.5 Hz, *J* = 1.0 Hz, CH_3CH═CH), 0.93 (s, 9H, (Si—C—(CH_3)$_3$), 0.06 (s, 6H, 2× Si—CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.8 (Ar), 141.3 (C═CH_2), 139.4 (Ar), 138.5 (Ar), 130.1 (CH_3CH═CH), 129.7 (CH_3CH═CH), 125.3, 120.7, 118.5 (Ar), 107.1 (C═CH_2), 84.8 (C-1), 80.3 (C-4), 74.2 (C-5), 73.5 (C—CH_2O), 73.4 (C—CH_2O), 43.8 (C-2), 30.9 (Si—*C*—(CH_3)$_3$), 25.8 (Si—C—(*C*H_3)$_3$), 17.9 (*C*H_3CH═CH), −4.5 (2× Si—*C*H_3). MS (EI) *m*/*z*: calculated for $C_{23}H_{34}O_3Si$ $[M]^+$ 386.2277, found 386.2281.

4.1.2.4. (±) ((2*R*,3*S*,4*R*,6*R*)-4-Acetoxy-3-(*tert*-butyldimethylsilyloxy)-6-(1,3-dihydro-iso-benzofu-ran-5-yl)tetrahydro-2*H*-pyran-2-yl)methyl acetate (25). General ozonolysis procedure was carried out on compound **24**, followed by acetylation as described for compound **19**. Yellow oil. Yield: 51 mg, 21% over 3 steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.28 (m, 3H, Ar), 5.17 (d, 4H, *J* = 2.4 Hz, CH_2O), 4.91 (ddd, 1H, *J* = 11.4 Hz, *J* = 8.9 Hz, *J* = 5.0 Hz, H-3), 4.56 (dd, 1H, *J* = 11.2 Hz, *J* = 1.4 Hz, H-1), 4.47 (ABX, 1H, $J_{a,a'}$ = 11.8 Hz, $J_{a',b}$ = 1.8 Hz, CH_2OAc), 4.20 (ABX, $J_{a,a'}$ = 11.8 Hz, J_{ab} = 4.9 Hz, CH_2OAc), 3.78 (dd, 1H, *J* = 9.2 Hz, *J* = 9.0 Hz, H-4), 3.60 (ddd, 1H, *J* = 9.3 Hz, *J* = 4.9 Hz, *J* = 1.7 Hz, H-5), 2.42 (ddd, 1H, *J* = 13.0 Hz, *J* = 4.9 Hz, *J* = 1.6 Hz, H-2), 2.10 (s, 6H, 2× OAc), 1.91 (dd, 1H, *J* = 13.0 Hz, *J* = 11.5 Hz, H-2′), 0.87 (s, 9H, (Si—C—(CH_3)$_3$), 0.10 (s, 6H, 2× Si—CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4 (2× OAc), 146.4, 138.5, 136.7, 128.3, 127.5, 125.9 (Ar), 83.8 (C-5), 81.3 (C-4), 80.5 (C-1), 73.1 (CH_2O), 72.8 (C-3), 61.8 (CH_2OAc), 35.7 (C-2), 30.9 (Si—*C*—(CH_3)$_3$), 26.2 (Si—C—(*C*H_3)$_3$), 19.8 (2× OAc), −2.4 (2× Si—CH_3). MS (ES) *m*/*z*: calculated for $C_{24}H_{37}O_7Si$ $[M+H]^+$ 465.2309, found 465.2317.

4.1.2.5. (±) (2*R*,3*S*,4*R*,6*R*)-6-(1,3-Dihydro-iso-benzofuran-5-yl)-2-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4-diol (8). See procedure used for the preparation of compound **7**. Clear oil. Yield: 7 mg, 57% over two steps. ^{1}H NMR (500 MHz, D_2O): δ 7.42 (s, 1H, Ar), 7.35 (d, 1H, *J* = 7.9 Hz, Ar), 7.32 (d, 1H, *J* = 8.1 Hz, Ar), 4.68 (s, 2H, CH_2O), 4.67 (s, 2H, CH_2O), 4.61 (dd, 1H, *J* = 11.5 Hz, *J* = 4.9 Hz, H-1), 3.87–3.79 (m, 1H, H-3), 3.80 (ABX, 1H, $J_{a,a'}$ = 12.1 Hz, $J_{a',b}$ = 3.6 Hz, CH_2OH), 3.72 (ABX, $J_{a,a'}$ = 12.1 Hz, J_{ab} = 5.4 Hz, CH_2OH), 3.45 (ddd, 1H, *J* = 9.7 Hz, *J* = 5.4 Hz, *J* = 3.4 Hz, H-5), 3.37 (dd, 1H, *J* = 9.5 Hz, *J* = 9.1 Hz, H-4), 2.21 (ddd, 1H, *J* = 12.9 Hz, *J* = 4.9 Hz, *J* = 1.9 Hz, H-2), 1.72 (ddd, 1H, *J* = 12.9 Hz, *J* = 12.3 Hz, *J* = 11.6 Hz, H-2′). ^{13}C NMR (125 MHz, D_2O): δ 143.1, 141.1, 140.8, 131.8, 129.6, 129.1 (Ar), 82.9 (C-5), 80.2 (C-1), 75.0 (C-3), 73.9 (C-4), 64.0 (CH_2OH), 63.8 (CH_2O), 63.7 (CH_2O), 42.6 (C-2). MS (ES) *m*/*z*: calculated for $C_{14}H_{17}O_5$ $[M-H]^+$ 265.1076, found 265.108.

4.1.3. Synthesis of 9

4.1.3.1. 3-Formyl-*N*-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide (26). Thionyl chloride (4.9 mL, 66.7 mmol, 10.0 equiv) was added to a suspension of 3-formylbenzoic acid (1.0 g, 6.7 mmol, 1.0 equiv) in dry toluene (50 mL) under argon. This was stirred at reflux for 2 h, and it turned from a suspension to a solution and was then allowed to cool to rt. The toluene and excess thionyl chloride was removed under vacuum. This crude mixture was dissolved in dry CH_2Cl_2 (30 mL) and 2-amino-2-methyl-propanol (1.3 mL, 13.3 mmol, 2.0 equiv) was slowly added dropwise at 0 °C. This was stirred for 5 h and then filtered and concentrated to provide a dull yellow oil. This residue was purified by column chromatography with $CHCl_3$/EtOH (98:2) as eluent to afford pure **26**. White solid. Yield: 1.04 g, 77% over two steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.06 (s, 1H, O═C-*H*), 8.20 (t, 1H, *J* = 1.5 Hz, Ar), 8.06 (ddd, 1H, *J* = 7.7 Hz, *J* = 1.8 Hz, *J* = 1.3 Hz, Ar), 8.01 (td, 1H, *J* = 7.6 Hz, 1.4 Hz, Ar), 7.63 (t, 1H, *J* = 7.7 Hz, Ar), 6.37–6.48 (m, 1H, C═O—N*H*), 4.41–4.54 (m, 1H, OH), 3.72 (s, 2H, CH_2), 1.45 (s, 6H, 2× CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.9 (O═*C*-H), 167.3 (*C* ═O—NH), 136.8, 136.3, 133.5, 133.1, 129.9, 127.8 (Ar), 70.8 ((CH_3)$_2$—*C*—CH_2), 57.1 (CH_2), 25.0 (2× *C*H_3). MS (ES) *m*/*s*: $C_{12}H_{14}O_3N$ calculated $[M-H]^+$ −220.0974, actual $[M-H]^+$ −220.0970.

4.1.3.2. (*E*)-4-Hydroxy-4-(3-(1-hydroxy-2-methylpropan-2-yl-carbamoyl)phenyl)-2-((trimethylsilyl)methyl)but-1-enyl diisopropylcarbamate (28). A solution of TMEDA (1.66 mL, 11.1 mmol, 3.0 equiv) in dry Et_2O (20 mL) at −78 °C under argon was prepared. To this solution was added *sec*-BuLi (1.40 M, 7.92 mL, 3.0 equiv). After 15 min, a solution of carbamate **27**[28] (1.0 g, 3.7 mmol, 1.0 equiv) in dry Et_2O (20 mL) was syringed drop wise at −78 °C. The reaction mixture turned yellow and was stirred for 30 min. Neat $Ti(O^iPr)_4$ (5.51 mL, 18.4 mmol, 5.0 equiv) was added at −78 °C and the dark orange mixture was stirred for 30 min. A solution of aldehyde **26** (0.57 mL, 5.54 mmol, 1.5 equiv) in dry Et_2O (20 mL) was syringed into the main reaction mixture which subsequently turned yellow. The reaction was rapidly warmed-up to 0 °C and stirred for 1 h. The mixture was then poured onto cold 1 M HCl (100 mL) and the resulting solution extracted with Et_2O (2 × 50 mL). The organic layers were mixed and washed with satd $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by column chromatography with pet. ether/EtOAc (1:1) as eluent to afford pure **28**. White solid. Yield: 0.79 g, 45% over two steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53–7.60 (m, 2H, Ar), 7.44 (d, 1H, J = 7.7 Hz, Ar), 7.33 (t, 1H, J = 7.6 Hz, Ar), 6.65 (s, 1H, C=C*H*), 6.30–6.37 (m, 1H, C=ON*H*), 4.77–4.85 (m, 1H, C*H*OH), 3.69–3.98 (m, 2H, O=CNC*H*$(CH_3)_2$), 3.62 (d, 2H, J = 5.7 Hz, $(CH_3)_2$—C—*CH*$_2$), 2.60 (ABX, 1H, $J_{a,a'}$ = 13.4 Hz, $J_{a,b}$ = 8.6 Hz, C*H*$_2$—CHOH), 2.24 (ABX, 1H, $J_{a,a'}$ = 13.4 Hz, $J_{a',b}$ = 5.2 Hz, C*H*$_2$—CHOH), 1.30–1.45 (m, 8H, C*H*$_2$-TMS, $(CH_3)_2$—C—CH_2), 1.17 (d, 6H, J = 3.3 Hz, O=CNCH(CH_3)$_2$), 1.15 (d, 6H, J = 3.3 Hz, O=CNCH(CH_3)$_2$), 0.00 (s, 9H, TMS). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9 (*C*=O—NH), 154.5 (O=*C*NCH$(CH_3)_2$, 146.0, 136.3, 133.8, 129.9, 129.7, 127.3, 125.4, 119.4 (Ar, *C*=CH, C=*C*H), 72.6 (*C*HOH), 72.0 ($(CH_3)_2$—*C*—CH_2), 57.7 (*C*H$_2$OH), 47.3–48.0 (2× O=CNC*H*$(CH_3)_2$), 42.2 (*C*H$_2$—CHOH), 25.9 (2× *C*H$_3$), 22.1 (*C*H$_2$-TMS), 21.3–22.7 (2× O=CNCH(*C*H$_3$)$_2$), 0.0 (TMS). MS (ES) *m*/*s*: $C_{26}H_{45}O_5N_2Si$ calculated $[M+H]^+$ −493.3092, actual $[M+H]^+$ −493.3112.

4.1.3.3. (±) (2*R*,3*R*,6*R*)-6-(3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl)-4-methylene-2-((*E*)-prop-1-enyl)tetrahydro-2*H*-pyran-3-yl diisopropylcarbamate (29). The cyclisation of **28** with crotonaldehyde **13** was carried out using the general Sakurai cyclisation procedure. The purified intermediate (40 mg, 0.07 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (10 mL) and dry NEt_3 (2 mL). At 0 °C mesyl chloride (13.5 μL, 0.15 mmol, 2.0 equiv) was syringed into the mixture under argon and was stirred at 0 °C for ~1 h, warmed to rt and stirred for further 24 h. The mixture was concentrated and submitted directly to column chromatography purification with pet. ether/EtOAc (1:1) as eluent to afford pure **29**. Yellow oil. Yield: 30 mg, 66% over two steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H, Ar), 7.78 (d, 1H, J = 7.7 Hz, Ar), 7.51 (d, 1H, J = 7.7 Hz, C=C*H*), 5.76 (dq, 1H, J = 15.4 Hz, J = 6.4 Hz, CH_3C*H* =CH), 5.54 (ddq, 1H J = 15.5 Hz, J = 6.0 Hz, J = 1.5 Hz, CH_3CH=C*H*), 5.18 (s, 1H, C=C*H*$_2$), 5.16 (s, 1H, C=C*H*$_2$), 4.97 (s, 1H, H-4), 4.43 (dd, 1H, J = 11.3 Hz, J = 2.7 Hz, H-1), 4.01–4.21 (m, 4H, O=CNC*H*$(CH_3)_2$, $(CH_3)_2$—*C*—*CH*$_2$, H-5), 3.54–3.77 (m, 1H, O=CNC*H*$(CH_3)_2$), 2.50 (dd, 1H, J = 13.6 Hz, J = 1.3 Hz, H-2), 2.34 (dd, 1H, J = 13.6 Hz, J = 2.7 Hz, H-2′), 1.63 (dd, 3H, J = 6.4 Hz, J = 1.5 Hz, C*H*$_3$), 1.31 (s, 6H, $(CH_3)_2$—C—CH_2), 1.03–1.26 (m, 12H, O=CNCH(CH_3)$_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9 (*C*=N), 154.2 (*C*=O), 141.5, 141.1, 127.8, 127.6, 127.5, 127.1, 126.7, 126.4, 125.1 (arom, C-3, C-6, C-7), 113.1 (C=*C*H$_2$), 80.2 (C-5), 79.2 (C-1), 78.1 ($(CH_3)_2$—C—CH_2), 73.3 (C-4), 66.6 ($(CH_3)_2$—*C*—CH_2), 44.0–46.2 (2× O=C*N*CH$(CH_3)_2$), 38.5 (C-2), 27.4 (2× CH_3), 19.3–21.1 (2× O=CNCH(*C*H$_3$)$_2$), 17.0 (*C*H$_3$—C=C). MS (ES) *m*/*s*: $C_{27}H_{39}O_4N_2$ calculated $[M+H]^+$ −455.2910, actual $[M+H]^+$ −455.2928.

4.1.3.4. (±) (2*R*,3*R*,4*R*,6*R*)-6-(3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl)-2-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4-diol (30). General ozonolysis procedure was carried out on compound **29**. White solid. Yield: 252 mg, 85% over three steps. ^{1}H NMR (300 MHz, $CDCl_3$): 7.85 (s, 1H, arom), 7.80 (d, 1H, J = 7.6 Hz, arom), 7.40 (d, 1H, J = 7.8 Hz, arom), 7.32 (t, 1H, J = 7.8 Hz, arom), 5.15 (d, 1H, J = 2.9 Hz, H-4), 4.47 (dd, 1H, J = 1.9 Hz, 11.5 Hz, H-1), 3.97–4.18 (m, 3H, O=CNC*H*$(CH_3)_2$, C*H*$_2$—C—$(CH_3)_2$), 3.63–3.81 (m, 3H, O=CNC*H*$(CH_3)_2$, H-6, H-6′), 3.49–3.61 (m, 1H, H-5), 3.38–3.47 (m, 1H, H-3), 2.07 (ddd, 1H, J = 13.1 Hz, J = 4.4 Hz, J = 1.8 Hz, H-2), 1.85 (dd, 1H, J = 13.1 Hz, J = 11.5 Hz, H-2′), 1.31 (s, 6H, CH_2—C—(C*H*$_3$)$_2$), 1.31–1.34 (m, 3H, O=CNCH(C*H*$_3$)$_2$), 1.27 (d, 3H, J = 6.8 Hz, O=CNCH(C*H*$_3$)$_2$), 1.17 (d, 6H, J = 6.8 Hz, 2× O=CNCH(C*H*$_3$)$_2$). ^{13}C NMR: δ 162.3 (C=N), 158.2 (C=O), 141.3, 130.2, 128.9, 128.1, 127.1, 126.4 (arom), 19.5, 78.5, 78.2 (C-1, C-5, $(CH_3)_2$—C—*C*H$_2$), 70.3 (C-4), 69.6 (C-3), 67.0 ($(CH_3)_2$—C—*C*H$_2$), 61.2 (C-6), 40.2–44.1 (2× O=C*N*CH$(CH_3)_2$), 38.7 (C-2), 28.8 (CH_2—C—(C*H*$_3$)$_2$), 20.8–21.7 (2× O=CNCH(C*H*$_3$)$_2$). MS (ES) *m*/*s*: $C_{24}H_{37}O_6N_2$ calculated $[M+H]^+$ −449.2652, actual $[M+H]^+$ −449.2658.

4.1.3.5. (±) 3-[(2*R*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]benzoic acid (9). Compound **30** (88 mg, 0.2 mmol, 1.0 equiv) was dissolved in dry THF (10 mL) and at 0 °C $LiAlH_4$ (15 mg, 0.4 mmol, 2.0 equiv) was added in one portion and heated to reflux. After stirring for 2 h a further 3 equiv of $LiAlH_4$ was added to the cooled mixture, and again brought to reflux and stirred for further 18 h. The mixture was cooled to rt and EtOAc was added to consume the excess $LiAlH_4$. The mixture was then filtered through a pad of Celite and washed through with MeOH. The organics were concentrated and purified by column chromatography with pet. ether/EtOAc (1:1) as eluent to afford the pure deprotected intermediate. The pure pyran intermediate (50 mg, 0.16 mmol, 1.0 equiv) was then dissolved in dry THF (10 mL) and to this was added NaH (63 mg, 60% in mineral oil, 1.56 mmol, 10.0 equiv), followed by 15-crown-5 (0.25 mL, 1.25 mmol, 8.0 equiv) and TBAI (20 mg, 0.05 mmol, 0.3 equiv). Benzyl bromide (0.12 mL, 0.95 mmol, 6.0 equiv) was syringed into this suspension at rt and stirred under nitrogen. This was stirred for 24 h or until completion by TLC and then H_2O (10 mL) was added and extracted with CH_2Cl_2 (2 × 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography with pet. ether/EtOAc (7:3) as eluent to afford pure product. The tribenzylated intermediate was dissolved in nitromethane (8 mL) and methyl iodide (1 mL) was added to this solution and heated to reflux under argon. The solution was stirred for 24 h and the mixture was evaporated, and the residue was re-dissolved in MeOH (10 mL) and 20% KOH (3 mL) and refluxed for 44 h. The mixture was reduced to half its volume under reduced pressure, and then neutralised with HCl and extracted with EtOAc (3 × 10 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography with $CHCl_3$/EtOH (95:5) as eluent to afford product. Hydrogenation over a 10% Pd/C catalyst in MeOH followed to cleanly afford pure product after concentration. Clear gum. Yield: 19 mg, 39% over five steps. ^{1}H NMR (500 MHz, MeOD): δ 8.01 (s, 1H, Ar), 7.83 (dt, 1H, J = 7.6 Hz, J = 1.5 Hz, Ar), 7.59 (d, 1H, J = 7.6 Hz, Ar), 7.34 (t, 1H, J = 7.6 Hz, Ar), 4.83 (d, 1H, J = 4.5 Hz, H-1), 4.41–4.44 (m, 1H, H-5), 3.64–3.80 (m, 3H, C*H*$_2$OH, H-3), 3.50 (m, 1H, H-4), 1.78–1.82 (m, 2H, H-2). ^{13}C NMR (125 MHz, MeOD): δ 169.9 (C=O), 144.1, 132.0, 131.9, 129.8, 129.4, 128.6 (Ar), 80.9 (C-5), 78.9 (C-1), 71.1 (C-3), 69.1 (C-4), 63.4 (*C*H$_2$OH), 37.6 (C-2). MS (ES) *m*/*z*: calculated for $C_{13}H_{15}O_6$ $[M-H]^+$ 267.0869, found 267.0882.

4.1.4. Synthesis of 10

4.1.4.1. (*Z*)-1-Benzyloxy-5-[*tert*-butyl(dimethyl)silyl]oxy-4-(trimethylsilylmethyl)pent-4-en-2-ol (32). General ene-reaction was carried out using compound **12** with benzyloxyacetaldehyde[63] **31**. Clear oil. Yield: 6.2 g, 52%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25–7.35 (m, 5H, arom-benzyl), 6.06 (s, 1H C=C*H*), 4.55 (s, 2H, CH_2-benzyl), 3.84–3.89 (m, 1H, C*H*OH), 3.48 (ABX, 1H, $J_{a,a'}$ = 9.6 Hz, $J_{a,b}$ = 6.8 Hz, CH_2—OBn), 3.36 (ABX, 1H, $J_{a,a'}$ = 9.6 Hz, $J_{a',b}$ = 3.2 Hz, CH_2-OBn), 1.95–2.04 (m, 2H, HC=C—CH_2), 1.59 (AB, d, 1H, J = 13.4 Hz, TMS—CH_2), 1.38 (AB, d, 1H, J = 13.4 Hz, TMS—CH_2), 0.90 (s, 9H, Si—C—(CH_3)$_3$), 0.08 (s, 3H, Si—CH_3), 0.07 (s, 3H, Si—CH_3), 0.00 (s, 9H, TMS). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 134.9, 129.1, 128.4, 128.4 (arom and *C*=CH), 115.1 (C=*C*H), 74.8 (*C*H_2-OBn), 74.1 (*C*H_2-Ph), 68.8 (*C*HOH), 38.4 (HC=C—*C*H_2), 26.4 (Si—C—(*C*H_3)$_3$), 18.8 (Si—*C*—(CH$_3$)$_3$), 0.0 (TMS), −4.5 (2× Si—*C*H$_3$). MS (ES) m/s: $C_{22}H_{40}Si_2O_3$: calculated $[M+Na]^+$ −431.2440, actual $[M+Na]^+$ −431.2418.

4.1.4.2. (±) [(2*R*,3*S*,6*R*)-6-(Benzyloxymethyl)-4-methylene-2-[(*E*)-prop-1-enyl]tetrahydropyran-3-yl]oxy-*tert*-butyl(dimethyl)silane (33). The cyclisation of **32** with crotonaldehyde **13** was carried out using the general Sakurai cyclisation procedure. Clear oil. Yield: 509 mg, 53%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25–7.33 (m, 5H, arom-benzyl), 5.72 (dq, 1H, J = 15.3 Hz, J = 6.5 Hz, CH$_3$C*H*=CH), 5.46 (ddq, 1H, J = 15.3 Hz, J = 7.7 Hz, J = 1.6 Hz, CH$_3$CH=C*H*), 5.03 (br s, 1H, C=CH_2), 4.83 (br s, 1H, C=CH_2), 4.55 (s, 2H, CH_2Ph), 3.75 (d, 1H, J = 8.7 Hz, H-4), 3.59–3.54 (m, 1H, H-1), 3.53–3.48 (m, 1H, H-5), 3.52 (ABX, dd, 1H, $J_{a,a'}$ = 9.8 Hz, $J_{a,b}$ = 5.1 Hz, CH_2OBn), 3.44 (ABX, dd, 1H, $J_{a,a'}$ = 9.8 Hz, $J_{a',b}$ = 4.7 Hz, CH_2OBn), 2.40 (dd, 1H, J = 13.3 Hz, J = 2.3 Hz, H-2), 2.18 (dd, 1H, J = 13.3 Hz, J = 11.3 Hz, H-2′), 1.69 (dd, 3H, J = 6.5 Hz, J = 1.5 Hz, C*H*$_3$CH=CH), 0.88 (s, 9H, Si—C—(CH_3)$_3$), 0.01 (s, 3H, Si—CH_3), 0.00 (s, 3H, Si—CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.6 (*C*=CH$_2$), 138.4 (arom), 130.2 (CH$_3$-CH=*C*H), 130.1 (CH$_3$*C*H=CH), 128.5, 127.9, 127.8 (arom), 107.2 (C=*C*H$_2$), 84.8 (C-5), 84.6 (C-1), 74.2 (C-4), 73.6 (*C*H$_2$Ph), 72.7 (*C*H$_2$-OBn), 38.2 (C-2), 25.9 (Si—C—(*C*H$_3$)$_3$), 18.4 (*C*H$_3$CH=CH), 17.8 (Si—*C*—(CH$_3$)$_3$), −3.8 (Si—*C*H$_3$), −4.3 (Si—*C*H$_3$). MS (ES) m/z: calculated for $C_{23}H_{37}O_3Si$ $[M+H]^+$ 389.2512, found 389.2521.

4.1.4.3. (±) (2*R*,3*S*,4*R*,6*R*)-6-(Benzyloxymethyl)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-(hydroxymethyl) tetrahydropyran-4-ol (34). General ozonolysis procedure was carried out on **33**. White solid. Yield: 481 mg, 72% over three steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.26 (m, 5H, arom-benzyl), 4.44 (s, 2H, CH_2Ph), 3.69–3.76 (m, 1H, CH_2OBn), 3.59 (dddd, 1H, J = 11.7 Hz, J = 5.9 Hz, J = 4.1 Hz, J = 2.1 Hz, H-1), 3.47–3.55 (m, 2H, CH_2OBn, H-5), 2.61 (ABX, 1H, $J_{a,a'}$ = 10.2 Hz, $J_{a,b}$ = 6.0 Hz, CH_2OH), 2.52 (ABX, 1H, $J_{a,a'}$ = 10.2 Hz, $J_{a',b}$ = 4.2 Hz, CH_2OH), 3.23 (dd, 1H, J = 9.3 Hz, J = 8.6 Hz, H-4), 3.11 (ddd, 1H, J = 9.3 Hz, J = 5.5 Hz, J = 2.8 Hz, H-3), 1.86 (ddd, 1H, J = 12.8 Hz, J = 5.0 Hz, J = 2.0 Hz, H-2), 1.34 (dt, 1H, J = 12.8 Hz, J = 11.7 Hz, H-2′), 0.78 (s, 9H, Si—C—(CH_3)$_3$), 0.02 (s, 3H, Si—CH_3), 0.00 (s, 3H, Si—CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 128.5, 127.8, 127.7 (arom), 79.9 (C-5), 74.7 (C-1), 73.6 (C-4), 73.4 (C-3), 73.4 (CH_2Ph), 72.6 (*C*H$_2$OBn), 62.3 (*C*H$_2$OH), 34.4 (C-2), 25.9 (Si—C—(*C*H$_3$)$_3$), 18.2 (Si—*C*—(CH$_3$)$_3$), −3.9 (Si—*C*H$_3$), −4.7 (Si—*C*H$_3$). MS (ES) m/z: calculated for $C_{20}H_{34}O_5Si$ $[M+Na]^+$ 405.2021, found 405.2073.

4.1.4.4. (±) Dibenzyl[(2*R*,3*S*,4*R*,6*R*)-6-(benzyloxymethyl)-3-[*tert*-butyl(dimethyl)silyl]oxy-4-hydroxy-tetrahydropyran-2-yl]methyl phosphate (35). Pyran **34** (140 mg, 0.37 mmol, 1.0 equiv) was dissolved in dry pyridine (8 mL) under nitrogen. To this mixture a solution of freshly prepared dibenzylchlorophosphate[60] (163 mg, 0.55 mmol, 1.5 equiv) dissolved in dry CH_2Cl_2 (5 mL) was added dropwise at 0 °C. The solution was allowed to warm to rt and stirred for 24 h. Addition of H_2O (1 mL) was followed by concentration of the mixture under vacuum. The residue was purified by column chromatography with pet. ether/EtOAc (3:2) as eluent to afford pure **35**. Clear oil. Yield: 155 mg, 66%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.29 (m, 15H, arom-benzyl), 4.92–4.98 (m, 4H, 2× CH_2Ph), 4.39 (AB, 1H, J = 12.0 Hz, CH_2Ph), 4.35 (AB, 1H, J = 12.0 Hz, CH_2Ph), 4.22–4.30 (m, 1H, H-4), 4.04 (ddd, 1H, J = 11.2 Hz, J = 6.7 Hz, J = 4.8 Hz, H-5), 3.54 (m, 2H, H-1, H-3), 3.24–3.41 (m, 4H, CH_2OBn, CH_2O-P=O(OBn)$_2$), 1.92 (ddd, 1H, J = 13.0 Hz, J = 5.0 Hz, J = 2.0 Hz, H-2), 1.34 (dt, 1H, J = 13.0 Hz, J = 11.5 Hz, H-2′), 0.80 (s, 9H, Si—C—(CH_3)$_3$), 0.05 (s, 3H, Si—CH_3), 0.00 (s, 3H, Si—CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.5, 128.4, 128.4, 127.9, 127.8, 127.7, 127.6 (benzyl), 78.6 (C-5), 74.8 (C-1), 73.5 (C-3), 73.4 (benzyl), 73.2 (C-4), 72.4 (*C*H$_2$O-P=O(OBn)$_2$, d, J = 5.2 Hz), 69.1 (2× *C*H$_2$Ph, m), 67.0 (*C*H$_2$OBn), 35.7 (C-2), 25.9 (Si—C—(*C*H$_3$)$_3$), 18.2 (Si—*C*—(CH$_3$)$_3$), −3.8 (Si—*C*H$_3$), −4.7 (Si—*C*H$_3$). ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.08 (*P*=O(OBn)$_2$). MS (ES) m/z: calculated for $C_{34}H_{47}O_8SiP$ $[M+Na]^+$ 665.2699, found 665.2676.

4.1.4.5. (±) [(2*R*,3*S*,4*R*,6*R*)-3,4-Dihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]methyl dihydrogen phosphate (10). To a solution of **35** (155 mg, 0.24 mmol, 1.0 equiv) in dry THF (5 mL) was added TBAF (0.29 mL, 0.29 mmol, 1 M in THF, 1.2 equiv). The solution was stirred for 24 h to ensure full desilylation and was then concentrated under reduced pressure. The residue was purified by column chromatography with pet. ether/EtOAc (1:1) as eluent to afford the desilylated intermediate that was then dissolved in MeOH (10 mL). The solution was passed through an H-cube reactor over a Pd/C catalyst cartridge at a rate of 1 mL/min and atmospheric pressure. The collected solution was collected and concentrated to afford pure **10** without the need for further purification. Clear oil. Yield: 42 mg, 68% over two steps. ^{1}H NMR (500 MHz, D_2O): δ 3.96–4.14 (m, 2H, CH_2OH), 3.44–3.66 (m, 4H, CH_2O-P=O(OH)$_2$, H-3, H-1), 3.32–3.39 (m, 1H, H-5), 3.19–3.26 (m, 1H, H-4), 1.85–1.86 (dd, 1H, J = 12.5 Hz, J = 4.3 Hz, H-2), 1.30 (dt, 1H, J = 12.5 Hz, J = 11.5 Hz, H-2′). ^{13}C NMR (125 MHz, D_2O): δ 78.2 (C-5, d, J = 6.6 Hz), 76.2 (C-1), 71.7 (C-3), 70.8 (C-4), 65.3 (*C*H$_2$O-P=O(OH)$_2$, m), 63.8 (*C*H$_2$OH), 34.3 (C-2). ^{31}P NMR (121 MHz, $CDCl_3$): δ 0.81 (*P*=O(OH)$_2$). MS (ES) m/z: calculated for $C_7H_{15}O_8P$ $[M+H]^+$ 259.0586, found 259.0583.

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References

1. Simons, C. *Nucleoside Mimetics Their Chemistry and Biological Properties*; Gordon and Breach Science Publishers: Australia, Canada, 2001.
2. Brito-Arias, M. A. *Synthesis and Characterization of Glycosides*; Springer Science, 2007.
3. Jasamai, M.; Balzarini, J.; Simons, C. *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 56–61.
4. Simons, C.; Wu, Q.; Htar, T. T. *Curr. Top. Med. Chem.* **2005**, *5*, 1191–1203.
5. Kifli, N.; Htar, T. T.; De Clercq, E.; Balzarini, J.; Simons, C. *Bioorg. Med. Chem.* **2004**, *12*, 3247–3257.
6. Rowan, A. S.; Nicely, N. I.; Cochrane, N.; Wlassoff, W. A.; Claiborne, A.; Hamilton, C. J. *Org. Biomol. Chem.* **2009**, *7*, 4029–4036.
7. Wlassoff, W. A.; Finlay, R. M. J.; Hamilton, C. J. *Synth. Commun.* **2007**, *37*, 2927–2934.
8. Peasley, K. *Med. Hypotheses* **2000**, *55*, 408–414.
9. Wu, Q.; Simons, C. *Synthesis* **2004**, *10*, 1533–1553.
10. Daves, G. D. *Acc. Chem. Res.* **1990**, *23*, 201–206.
11. Stambasky, J.; Hocek, M.; Kocovsky, P. *Chem. Rev.* **2009**, *109*, 6729–6764.
12. Navarre, J.; Guianvarch, D.; Giorgio, A. F.; Condom, R.; Benhida, R. *Tetrahedron Lett.* **2003**, *44*, 2199–2202.
13. Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700–717.
14. Townsend, L. B. *Chemistry of Nucleosides and Nucleotides*; Plenum Press: New York, 1994. pp 421–535.
15. Declercq, E.; Balzarini, J.; Madej, D.; Hansske, F.; Robins, M. *J. Med. Chem.* **1987**, *30*, 481–486.

16. Cooney, D. A.; Jayaram, H. N.; Gebeyehu, G.; Betts, C. R.; Kelley, J. A.; Marquez, V. E.; Johns, D. G. *Biochem. Pharmacol.* **1982**, *31*, 2133–2136.
17. Krohn, K.; Heins, H.; Wielckens, K. *J. Med. Chem.* **1992**, *35*, 511–517.
18. Bieganowski, P.; Brenner, C. *Cell* **2004**, *117*, 495–502.
19. Belenky, P.; Bogan, K. L.; Brenner, C. *Trends Biochem. Sci.* **2007**, *32*, 12–19.
20. Belenky, P.; Racette, F. G.; Bogan, K. L.; McClure, J. M.; Smith, J. S.; Brenner, C. *Cell* **2007**, *129*, 473–484.
21. Tempel, W.; Rabeh, W. M.; Bogan, K. L.; Belenky, P.; Wojcik, M.; Seidle, H. F.; Nedyalkova, L.; Yang, T.; Sauve, A. A.; Park, H.-W.; Brenner, C. *PLoS Biol.* **2007**, *5*, e263.
22. Belenky, P. A.; Mogu, T. G.; Brenner, C. *J. Biol. Chem.* **2008**, *283*, 8075–8079.
23. Bogan, K. L.; Brenner, C. *Annu. Rev. Nutr.* **2008**, *28*, 115–130.
24. Belenky, P.; Stebbins, R.; Bogan, K. L.; Evans, C. R.; Brenner, C. *PLoS ONE* **2011**, *6*, e19710.
25. Canto, C.; Houtkooper, R. H.; Pirinen, E.; Youn, D. Y.; Oosterveer, M. H.; Cen, Y.; Fernandez-Marcos, P. J.; Yamamoto, H.; Andreux, P. A.; Cettour-Rose, P.; Gademann, K.; Rinsch, C.; Schoonjans, K.; Sauve, A. A.; Auwerx, J. *Cell Metab.* **2012**, *15*, 838–847.
26. Redpath, P.; Macdonald, S.; Migaud, M. E. *Org. Lett.* **2008**, *10*, 3323–3326.
27. Markó, I. E.; Dumeunier, R.; Leclercq, C.; Leroy, B.; Plancher, J.; Mekhalfia, A.; Bayston, D. J. *Synthesis* **2002**, *7*, 958–972.
28. Markó, I. E.; Leroy, B. *J. Org. Chem.* **2002**, *67*, 8744–8752.
29. Midtkandal, R. R.; Macdonald, S. J. F.; Migaud, M. E. *Chem. Commun.* **2010**, 4538–4540.
30. Midtkandal, R. R.; Redpath, P.; Trammell, S. A. J.; Macdonald, S. J. F.; Brenner, C.; Migaud, M. E. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5204–5207.
31. Merino, P.; Tejero, T.; Marca, E.; Gomollón-Bel, F.; Delso, I.; Matute, R. *Heterocycles* **2012**, *2*, 791–820.
32. Gómez, A. M.; Pedregosa, A.; Casillas, M.; Uriel, C.; López, J. C. *Eur. J. Org. Chem.* **2009**, *21*, 3579–3588.
33. Hocek, M.; Polh, R.; Klepetářová, B. *Eur. J. Org. Chem.* **2005**, *21*, 4525–4528.
34. Larsen, E.; Jorgensen, P. T.; Sofan, M. A.; Pedersen, E. B. *Synthesis* **1994**, *10*, 1037–1038.
35. Migaud, M. E.; Batoux, N.; Paradisis, F.; Engel, P. C. *Tetrahedron* **2004**, *60*, 6609–6617.
36. Whitcombe, N.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449–7476.
37. Singh, I.; Seitz, O. *Org. Lett.* **2006**, *8*, 4319–4322.
38. Bookser, B. C.; Raffaele, N. B. *J. Org. Chem.* **2007**, *72*, 173–179.
39. Vidal, T.; Langlois, Y.; Haudrechy, A. *Tetrahedron Lett.* **1999**, *40*, 5677–5680.
40. Martinez, A.; Hénon, E.; Coiffier, C.; Banchet, A.; Harakat, D.; Nuzillard, J.; Haudrechy, A. *Carbohydr. Res.* **2010**, *345*, 1088–1093.
41. Hu, G. X.; Vasella, A. *Helv. Chim. Acta* **2002**, *85*, 4369–4391.
42. Larrosa, I.; Romea, P.; Urpi, F. *Tetrahedron* **2008**, *64*, 2683–2723.
43. Shaban, M. A. E.; Nasr, A. Z. *Adv. Heterocycl. Chem.* **1997**, *68*, 223–432.
44. Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth. Coll.* **1984**, *62*, 58.
45. Desilylated pyran product also obtained from the $BF_3{\cdot}OEt_2$ cyclization.
46. Qiao, Q.; So, S. S.; Goodnow, R. A. *Org. Lett.* **2001**, *3*, 3655–3658.
47. Lee, A. H. F.; Kool, E. T. *J. Am. Chem. Soc.* **2006**, *128*, 9219–9230.
48. Lee, A. H. F.; Kool, E. T. *J. Am. Chem. Soc.* **2005**, *127*, 3332–3338.
49. Gao, J.; Liu, H.; Kool, E. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3118–3122.
50. Gao, J.; Liu, H.; Kool, E. T. *J. Am. Chem. Soc.* **2004**, *126*, 11826–11831.
51. Liu, H.; Gao, J.; Maynard, L.; Saito, Y. D.; Kool, E. T. *J. Am. Chem. Soc.* **2004**, *126*, 1102–1109.
52. Toshima, K.; Matsuo, G.; Ishizuka, T.; Ushiki, Y.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1998**, *63*, 2307–2313.
53. Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, *12*, 1005–1006.
54. Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K. *J. Am. Chem. Soc.* **1991**, *113*, 6982–6992.
55. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
56. Spiteri, C.; Moses, J. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 31–33.
57. Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.
58. Yang, T.; Chan, N. Y.; Sauve, A. A. *J. Med. Chem.* **2007**, *50*, 6458–6461.
59. Griffin, J. L.; Bowler, M. W.; Baxter, N. J.; Leigh, K. N.; Dannatt, H. R. W.; Hounslow, A. M.; Blackburn, G. M.; Webster, C. E.; Cliff, M. J.; Waltho, J. P. *PNAS* **2012**, *109*, 6910–6915.
60. Pollex, P.; Millet, A.; Müller, J.; Hiersemann, M.; Abraham, L. *J. Org. Chem.* **2005**, *70*, 5579–5591.
61. Innis, L. V.; Plancher, J. M.; Markó, I. E. *Org. Lett.* **2006**, *8*, 6111–6114.
62. Keck, G. E.; Covel, J. A.; Schiff, T.; Yu, T. *Org. Lett.* **2002**, *4*, 1189–1192.
63. Gao, F.; Yan, X.; Sthakya, T.; Baettig, O. M.; Ait-Mohand-Brunet, S.; Berghuis, A. M.; Wright, G. D.; Auclair, K. *J. Med. Chem.* **2006**, *49*, 5273–5281.