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Alkynyl-2-deoxy-D-riboses, a *cornucopia* for the generation of families of C-nucleosides

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ABSTRACT

This study focuses on the preparation of some 1-alkynyl-2-deoxy-D-riboses and their application to the generation of C-nucleosides analogues. Examples are provided in which the alkyne functionality took part in alkylation or cycloaddition reactions. A discussion of the protecting group used is provided.

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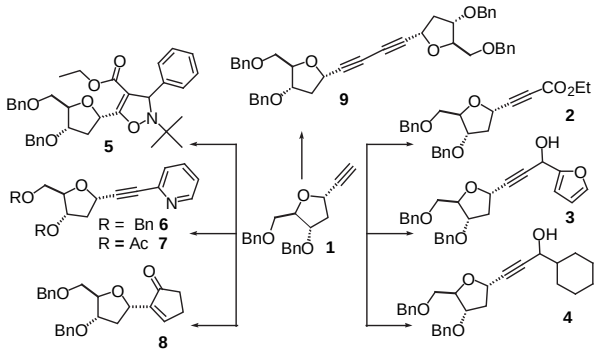
1. Introduction

The emergence of antibiotic resistance and the occurrence of novel virus epidemics justify research into novel anti microbial agents. Nature has provided several nucleoside analogues that possess pertinent biological activities: bredinine[1] (Mizoribine) is an imidazole nucleoside antibiotic clinically used as an immunosuppressant;[2] toyocamycin,[3] mycalisin A[4] and thiosangivamycin[3] are three naturally occurring nucleosides capable of potent antiviral and antitumour activity; pseudouridine,[5] showdomycin,[6] pyrazofurin[7] and tiazofurin[8] have potent activity against bacteria, virus and certain cancer lines. C-Nucleosides are a peculiar class of analogues in which the C–*N* bond linking the heterocycle and the sugar is substituted by a C–C bond. This modification renders the nucleoside stable towards bacterial hydrolases and enables these molecules to interfere with DNA and RNA synthases.[9,10] Several synthetic strategies have been reported for the preparation of 2-deoxy-D-ribose and D-ribose C-nucleosides,[11,12] the most prominent being (i) Heck reaction of 3,5-dihydroxy dihydrofurans and aryl halides, (ii) addition of an aryl lithium to 2′-deoxyribonolactones followed by reduction of the resulting hemiketal, (iii) nucleophilic substitution on a protected 1′-Cl-2′-deoxyribose (Hoffer's chlorosugar), (iv) elaboration of 1′-CN-2′-deoxyribose. Our group[13] and others[14] have recently shown the synthetic potential of 1′-alkynyl deoxyriboses **1**, which were employed to generate several classes of unnatural C-nucleosides. Central to the design of compound **1** was the synthetic versatility of the alkyne functionality (Scheme 1). Lately, interest has increased on the medicinal chemistry of alkynyl substituted nucleosides.[15,16] For example, Matzuda described the preparation and bioactivity of 3′-alkynyl cytosine and 3′-alkynyl uridine.[15] The presence of an additional electrophilic element (alkyne) imparted to these molecules a high antitumour activity. 4′-Alkynyl nucleosides have been prepared and found to be remarkably active against HIV.[16] The high activity displayed by 3′- and 4′-alkynyl nucleosides poses questions about the activity of other alkynyl nucleosides including 1-alkynylnucleosides analogues. With this in mind, we set out to develop a synthetic route to prepare families of C-nucleosides starting from compound **1**.



Scheme 1. Preparation of C-nucleosides analogues **2**–**9**.

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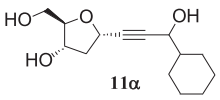
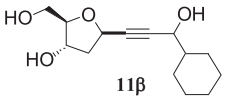
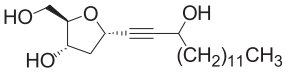
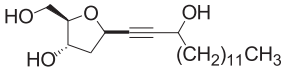
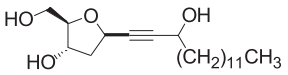
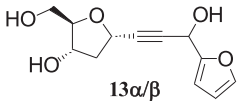
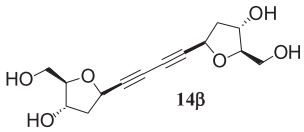
In this context, we have also revisited the synthesis of scaffolds **1**, identifying an improved methodology to access selectively **1α** and **1β**.[13] Compounds **1α** and **1β** were subsequently used to generate C-nucleosides **2**–**9** in both their α and β anomeric series. For simplicity, Scheme 1 shows only the less popular α anomer.

We like now to give a full account of this study including the preparation of additional types of C-nucleosides from **1α** and **1β** and optimal conditions identified for the deprotection of desired C-nucleosides.

2. Results and discussion

With C-nucleosides **2**–**9** in hand,[13] we have submitted these compounds to a few debenzylation procedures. This step is indeed essential as unprotected compounds are required for biological evaluation. The choice of suitable conditions for debenzylating compounds **2**–**9** was unobvious considering the presence of different functionalities in these compounds. In first instance, we focussed on procedures employing BCl_3, as this reagent was used in the deprotection of related benzyl protected 2-deoxy-C-nucleosides.[15] Propargylic alcohols **3**, **4** and **10**[16] were then reacted with BCl_3 (Table 1). Compounds **4** and **10** (Table 1) reacted promptly and the desired **11α**, **11β**, **12α** and **12β** were obtained in good isolated yields. Conversely, compounds **3α** and **3β** containing a furyl aromatic group furnished a complex mixture of products that could not be isolated. A possible explanation lies in the reactivity of furan with oxidizing Lewis acids such as BCl_3. Possibly, the oxygen of furan reacted with boron starting a cascade of reactions that ultimately lead to several unwanted products. We have also attempted this reaction in the presence of suitable radical scavengers, but no improvement was noted. Debenzylation of nucleosides **3α** and **3β** was attempted by other reported methodologies including iodotrimethylsilane,[17] Pd^0 and formic acid,[18] $Pd(OH)_2$ and ammonium formate[19] or $LiAlH_4$,[20] but in all cases gave several undesired products. Similarly, reaction of C-nucleosides **5** and **8** and BCl_3 led to extensive decomposition of starting material without furnishing the desired diols.

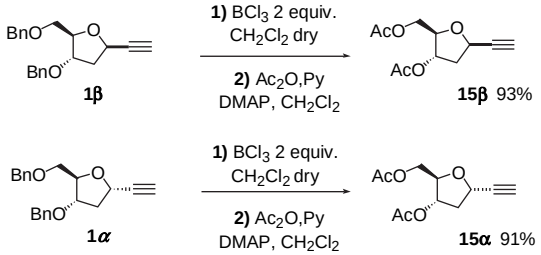
Table 1
Isolated yields of deprotected 1-alkynyl-polyols **11**, **12** and **14**

Entry	Substrate	Product	Yields[a] (%)
1	**4α**	 **11α**	60
2	**4β**	 **11β**	54
3	**10α**	 **12α**	50
4	**10β**	 **12β**	58
5	**3α/3β**	 **12β**	—
6	**9α**	 **13α/β**	98
7	**9β**	 **14β**	98

[a] Isolated yields after column chromatography.

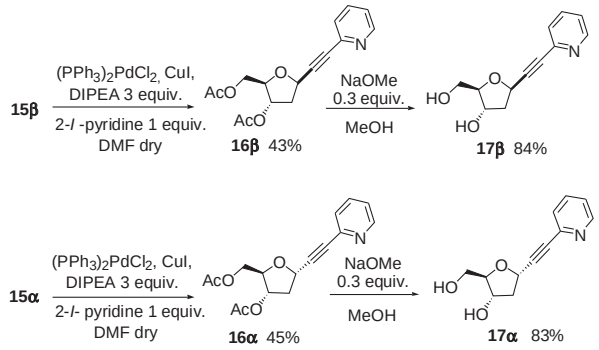
Delightfully, dialkynes **9α** and **9β**, obtained by homocoupling of parents **1α** and **1β**, reacted with BCl_3 to give **14α** and **14β** in excellent isolated yields. This indicated the benzyl group to be an un-optimal protecting group. In order to enlarge the number of compounds obtainable, we have explored alternative protecting groups for 1-alkynyl-2-deoxy-D-riboses. After some experimentation, the acetyl group was selected as a useful replacement.

Hence, benzyl alkynyl nucleosides **1α** and **1β** were independently treated with BCl_3 and the resulting diol reacted in situ with excess acetic anhydride. Delightfully, this procedure gave the desired compounds **15α** and **15β** in excellent isolated yields (Scheme 2).[13] Compounds **15α** and **15β** showed a higher synthetic versatility compared to parents **1α** and **1β** allowing the preparation of a wider range of derivatives. The use of compounds **15α** and **15β** as starting material for (i) Sonogashira coupling, (ii) 1,3-dipolar cycloaddition, (iii) [2+2+2] cycloaddition and (iv) Pauson–Khand reaction is discussed below. Importantly these are modular processes, which would allow expansion of these examples in families of C-nucleosides by variation of one reagent at the time.



Scheme 2. Preparation of acetyl-protected 1-alkynyl-2′-deoxy-D-riboses **15α** and **15β**.

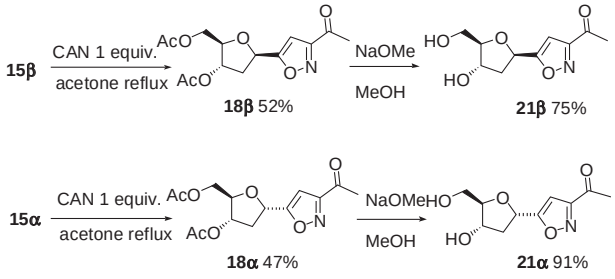
We reported the Sonogashira coupling of compounds **1α** and **1β** give only low yields of the desired cross-coupling products **1α** and **1β**.[13] This reaction gave compounds **9α** and **9β** as the major products, which arose from homocoupling of the starting material. A survey of the literature revealed that copper acetylides undergo homocoupling when exposed to air. Hay reported that the Cu(I) salt in the presence of amine solvents promoted homocoupling of terminal ethynes at room temperatures and in the presence of O_2.[21] Others reported the use of Pd(II) complexes to obtain butadiynes as the major product.[22] Acetylene homocoupling is sometimes observed under Sonogashira conditions. In this context, it was recently reported that a reducing atmosphere (H_2) could reduce the extent of homocoupling therefore improving the yield of the desired cross-coupling compound.[23] We reacted **1α** or **1β** with 2-chloropyridine under a reducing atmosphere. Nevertheless, this reaction gave **6α** or **6β** in similar low yields, with the cross-coupling product **9α** or **9β**, being the main product. We identified the problem in the steric properties of starting materials **1α** and **1β**, in particular of their protecting group. It has been shown that steric properties of protecting groups at 3′ and 5′ have an influence on the reactivity of 2-deoxy-D-riboses.[24] With this in mind, we reasoned that Sonogashira coupling of compounds **15α** and **15β** bearing a less sterically demanding acetyl group may proceed more efficiently. Reaction of acetylated 1-alkynylsugars **15α** and **15β** and 2-chloro or 2-iodo pyridine gave the desired **16α** and **16β** in improved yields and shorter reaction times (Scheme 3). Interestingly in these experiments, compounds **9α** and **9β** were not obtained.[25] Acetylated



Scheme 3. Preparation of 1-alkynylnucleosides **17α** and **17β**.

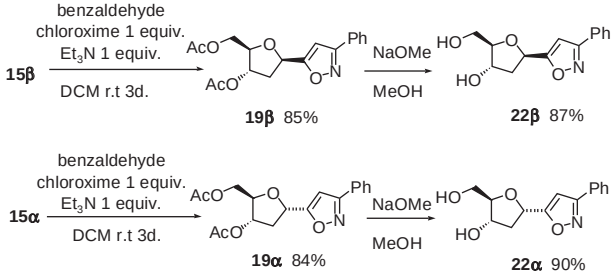
C-nucleosides **16α** and **16β** were subsequently reacted with NaOMe/MeOH, a standard procedure to remove the acetoxy groups. This reaction furnished C-nucleosides **17α** and **17β** in high isolated yields. Importantly, it was verified by ^{1}H NMR that no epimerization occurred in the latter step for both the α and β anomer (Scheme 3).

The alkyne functionality is often employed as a dipolarophile in 1,3-dipolar cycloadditions. Similarly, 1-alkynyl-2-deoxy-D-riboses **15α** and **15β** reacted with several 1,3-dipolar species. For example, compounds **15α** and **15β** reacted with acetone in the presence of cerium(IV) ammonium nitrate to give isoxazoles **18α** and **18β** (Scheme 4). Treatment of acetone with CAN at reflux is a common method to generate nitrile oxides in situ.[26]



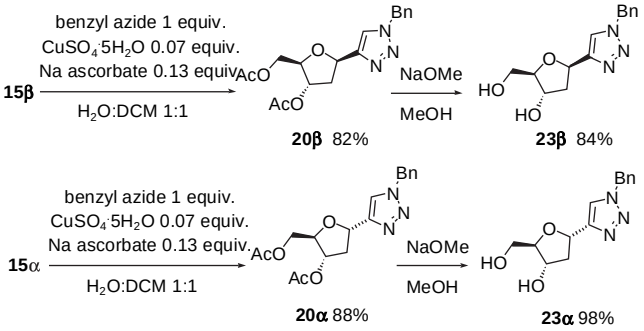
Scheme 4. Preparation of 1-alkynylnucleosides **21α** and **21β**.

Reaction of **15α** and **15β** with the in situ generated nitrile oxide furnished the expected isoxazoles **18α** and **18β** as a single regioisomer. Importantly in this reaction no epimerization of the anomeric centre was observed. Compounds **18α** and **18β** contain multiple H-bond acceptors and may find use in the preparation of artificial DNAs containing unnatural nucleobases.[14] Additionally, the preparation of the isoxazole core in **18α** and **18β** is modular and several analogues could be prepared by variation of the ketone employed. Similarly, alkynyl sugars **15α** and **15β** reacted with benzaldehyde chloroxime to give the corresponding isoxazoles **19α** and **19β** in high yields (Scheme 5). The use of chloroximes is a common method for the in situ preparation of nitrile oxides especially of the aromatic series.



Scheme 5. Preparation of 1-alkynylnucleosides **22α** and **22β**.

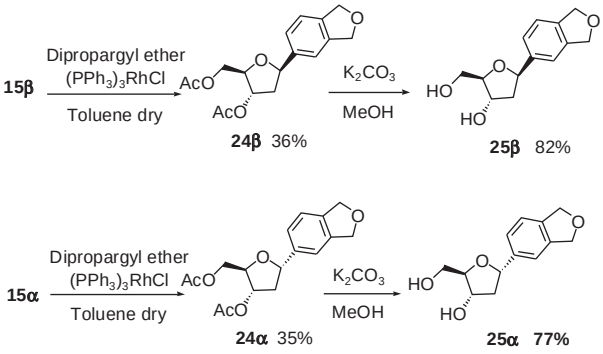
The reaction of terminal alkynes and azides has become a prominent reaction in organic synthesis since click chemistry concept was introduced by Sharpless.[27] We reacted compounds **15α** and **15β** with benzylazide under Cu(I) catalysis in a mixture water/dichloromethane as the organic co-solvent (Scheme 6).



Scheme 6. Preparation of 1-alkynylnucleosides **23α** and **23β**.

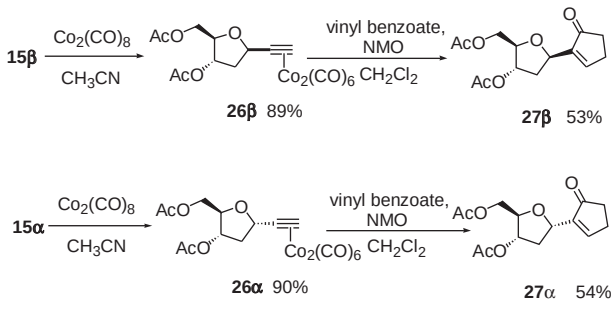
Delightfully, C-nucleosides **20α** and **20β** were obtained in high yields and in short reaction times (2–4 h). As expected based on published literature,[28,29] only one regioisomer was obtained whose structure was confirmed by NOE experiment. The new acetylated C-nucleosides **18**–**20** (Schemes 3–5) were successfully deprotected by treatment with NaOMe/MeOH to give the corresponding free C-nucleosides **21**–**23** in high isolated yields and as pure α or β anomers.

The transition-metal-catalyzed cyclotrimerization of alkynes is an alternative method to build up C-nucleosides starting from alkynyl sugars **15α** and **15β**.[30] In order to obtain useful unprotected C-nucleosides **25α** and **25β**, we have submitted **15α** and **15β** to the conditions reported by Hocek, obtaining acetylated C-nucleosides **24α** and **24β** (Scheme 7). Compounds **24α** and **24β** were then treated with catalytic potassium carbonate to give C-nucleosides **25α** and **25β**.



Scheme 7. Preparation of 1-alkynylnucleosides **23α** and **24β**.

The Pauson–Khand reaction is a formal [2+2+1] cycloaddition in which an alkyne reacts with an alkene in the presence of dicobaltoctacarbonyl to yield a cyclopentenone.[31] Recently, it has been shown that reaction of the preformed dicobalthexacarbonyl–alkyne complex such as **26α** and **26β** (Scheme 8) in the presence of an excess of vinyl ethers or vinyl esters avoids the use of ethylene.[32] We have reacted alkynes **15α** and **15β** with dicobaltoctacarbonyl and have obtained complexes **26α** and **26β** in high isolated yields. Complexes **26α** and **26β** were subsequently reacted with an excess of vinyl benzoate and *N*-methylmorpholine *N*-oxide (NMO) to give cyclopentenones **27α** and **27β** in high isolated yields. It must be noted that the Pauson–Khand reaction of 1-alkynyl-2-deoxy-D-riboses was unaffected by the nature of the protecting group present on the starting material: acetylated and benzylated substrates[13]



Scheme 8. Preparation of acetyl-protected 1-alkynylnucleosides **27α** and **27β**.

gave the correspondent enone in comparable yields. Unfortunately, the deacetylation of **27α** and **27β** was unsuccessful despite the several attempts made using either basic or acidic conditions.

3. Conclusion

In conclusion, we have developed a practical synthesis of acetylated 1-alkynyl-2-deoxy-D-riboses **15α** and **15β**. A wide range of transformations was identified, which could be employed for the generation of novel C-nucleosides. The reactions described herein are modular in nature and will allow the generation of families of compounds by the variation of one reagent. Therefore this study provides a synthetic platform to those involved in the generation of families of bioactive compounds and their screening.

4. Experimental section

4.1. General experimental

Melting points were determined using a Stuart scientific melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded as KBr discs using a Bruker Tensor27 FT-IR instrument. Absorption maximum (ν_{max}) was reported in wave numbers (cm^{-1}) and only selected peaks are reported. NMR experiments were performed on a Bruker Avance 400 instrument and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) in DMSO-d_6 (referenced to 2.52 and 3.35 ppm for ^1H and 40.0 ppm for ^{13}C), in CD_3CN (referenced to 1.96 ppm for ^1H and 118.26 ppm for ^{13}C) and D_2O (referenced to 4.79 ppm for ^1H). Coupling constants (J) are in hertz. Multiplicities are reported as follows: s, singlet, d, doublet, dd, doublets of doublets, t, triplet, q, quartet, m, multiplet, c, complex and br, broad. High resolution mass spectra were obtained on a Waters Micro mass LCT and low resolution mass spectra were recorded on Waters Micro mass Quattro LCMS spectrometers at 70 eV. Tetrahydrofuran and toluene were freshly distilled over sodium benzophenone prior to use according to standard procedure. All other reagents and solvents were used as purchased from Aldrich. Reactions were checked for completion by TLC (EM Science, silica gel 60 F_{254}). Flash chromatography was performed using *silica gel 60* (0.040–0.063 mm, 230–400 mesh). Compounds **2**–**10** were synthesized by the reported procedure.[13]

4.2. 5*R*-(3-Cyclohexyl-3-hydroxy-prop-1-ynyl)-2*R*-hydroxymethyl-tetrahydrofuran-3*S*-ol (11β)

To a stirred solution of **4β** (1.11 g, 2.6 mmol) in dry DCM (72 mL) was added BCl_3 (1 M in DCM, 10.2 mL, 10.2 mmol, 2.0 equiv) by syringe pump over a 20 min period at −78 °C and the reaction mixture was allowed to stir at −78 °C for 90 min. The reaction mixture was then quenched with methanol (5 mL) and allowed to stir at room temperature for 15 h. The reaction mixture was washed with water (3×5 mL) and the water layer was then concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate to give the title compound **11β** as a red oil (354.8 mg, 54% yield); R_f=0.16 (ethyl acetate); $[\alpha]_D^{25}$ −46.05 (*c* 0.15, CH_3CN); ν_{max} (KBr)/cm^{-1} 3388 (br), 2932, 2851, 2357, 2338, 1450, 1350, 1084, 1041; δ_H (CD_3CN, 400 MHz) 4.74–4.69 (m, 1H), 4.23–4.21 (m, 1H), 4.11 (t, J=6, 1H), 3.71–3.69 (m, 1H), 3.53 (t, J=5, 2H), 3.17–3.15 (m, 2H), 2.74 (t, J=6, 1H), 1.85–0.89 (m, 12H); δ_C (100.6 MHz, CD_3CN) 88.3, 86.5, 84.9, 73.3, 68.0, 67.0, 63.5, 45.0, 43.3, 29.3, 28.9, 27.1, 26.60; HRMS found: [M+Na^+] 277.1422, $C_{14}H_{22}NaO_4$ requires 277.1416; *m*/*z*: 254 (100%, M^+).

4.3. 5*S*-(3-Cyclohexyl-3-hydroxy-prop-1-ynyl)-2*R*-hydroxymethyl-tetrahydrofuran-3*S*-ol (11α)

To a stirred solution of **4α** (1.48 g, 3.4 mmol) in dry DCM (96 mL) was added BCl_3 (1 M in DCM, 13.5 mL, 13.5 mmol, 2.0 equiv) by syringe pump over a 20 min period at −78 °C and the reaction mixture was allowed to stir at −78 °C for 90 min. The reaction mixture was then quenched with methanol (5 mL) and allowed to stir at room temperature for 16 h. The reaction mixture was washed with water (3×5 mL) and the water layer was then concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate to give the title compound **11α** as a green oil (516.7 mg, 60% yield); R_f=0.17 (ethyl acetate); $[\alpha]_D^{25}$ −50.10 (*c* 0.51, CH_3CN); ν_{max} (KBr)/cm^{-1} 3388 (br), 2929, 2857, 2244 (br), 1645, 1452, 1336, 1085, 1022, 583; δ_H (CD_3CN, 400 MHz) 4.72 (ddd, J_1=2, J_2=6, J_3=8, 1H), 4.14 (dt, J_1=5, J_2=7, 1H), 4.10 (dt, J_1=2, J_2=6, 1H), 3.80 (dd, J_1=5, J_2=9, 1H), 3.58 (ddd, J_1=1, J_2=4, J_3=12, 1H), 3.50 (ddd, J_1=1, J_2=5, J_3=12, 1H), 1.92–1.06 (m, 15H); δ_C (100.6 MHz, CD_3CN) 86.6, 86.4, 85.8, 72.7, 67.8, 67.0, 62.8, 45.1, 43.0, 29.3, 28.9, 27.1, 26.6; HRMS found: [M+Na^+] 277.1418, $C_{14}H_{22}NaO_4$ requires 277.1416; *m*/*z*: 254 (100%, M^+).

4.4. Preparation of (−)-2*R*-hydroxymethyl-5*R*-(3-hydroxy-pentadec-1-ynyl)-tetrahydrofuran-3*S*-ol (12β)

To a stirred solution of **10β** (1.56 g, 3.00 mmol) in dry DCM (84 mL) was added BCl_3 (1 M in DCM, 12.0 mL, 12.0 mmol, 2.0 equiv) by syringe pump over a 20 min period at −78 °C and the reaction mixture was allowed to stir at −78 °C for 1.5 h. The reaction mixture was then quenched with methanol (6 mL) and allowed to stir at room temperature for 13 h. The reaction mixture was washed with water (3×5 mL) and the organic layer was then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with chloroform/methanol 10:1 to give the title compound **12β** as a pale yellow wax (596.0 mg, 58% yield); R_f=0.30 (chloroform/methanol 10:1); $[\alpha]_D^{25}$ −62.13 (*c* 0.17, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3385 (b), 2925, 2843, 2362, 2343, 1471, 1361, 1092, 1052; δ_H ($CDCl_3$, 400 MHz) 4.85–4.81 (m, 1H), 4.45 (br s, 1H), 4.39 (br s, 1H), 3.89–3.86 (m, 1H), 3.78–3.75 (m, 1H), 3.69–3.66 (m, 1H), 2.38 (br s, 2H), 2.23–2.18 (m, 3H), 1.70–1.69 (m, 2H), 1.25 (br s, 20H), 0.88 (t, J=6, 3H); δ_C (100.6 MHz, $CDCl_3$) 86.9, 83.3, 72.9, 67.7, 62.6, 62.4, 62.3, 42.8, 37.6, 37.5, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.2, 22.7, 14.1; HRMS found: [M+Na^+] 363.2517, $C_{20}H_{36}NaO_4$ requires 363.2512; *m*/*z*: 340 (100%, M^+).

4.5. Preparation of (−)-2*R*-hydroxymethyl-5*S*-(3-hydroxy-pentadec-1-ynyl)-tetrahydrofuran-3*S*-ol (12α)

To a stirred solution of **10α** (1.78 g, 3.42 mmol) in dry DCM (96 mL) was added BCl_3 (1 M in DCM, 14.0 mL, 14.0 mmol, 2.0 equiv) by syringe pump over a 20 min period at −78 °C and the reaction mixture was allowed to stir at −78 °C for 1.5 h. The reaction mixture was then quenched with methanol (7 mL) and allowed to stir at room temperature for 15 h. The reaction mixture was washed with

water (3×5 mL) and the organic layer was then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with chloroform/methanol 10:1 to give the title compound **12α** as a pale yellow wax (579.7 mg, 50% yield); R_f=0.38 (chloroform/methanol 10:1); $[\alpha]_D^{25}$ −65.41 (*c* 0.16, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3390 (br), 2933, 2868, 2373, 2350, 1482, 1331, 1071, 1035; δ_H ($CDCl_3$, 400 MHz) 4.86–4.83 (m, 1H), 4.38–4.32 (m, 2H), 4.19–4.17 (m, 1H), 4.12–4.06 (m, 2H), 3.76–3.68 (m, 2H), 3.35–3.34 (m, 1H), 2.51–2.44 (m, 1H), 2.15–2.06 (m, 1H), 1.73–1.62 (m, 2H), 1.28 (br s, 20H), 0.90 (t, *J*=7, 3H); δ_C (100.6 MHz, $CDCl_3$) 87.4, 85.9, 84.1, 72.8, 67.7, 62.4, 62.1, 42.0, 37.6, 37.4, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 22.8, 14.2; HRMS found: [M+Na^+] 363.2515, $C_{20}H_{36}NaO_4$ requires 363.2512; *m*/*z*: 340 (100%, M^+).

4.6. 2*R*-Hydroxymethyl-5*R*-[4-[(2*R*,3*S*,5*R*)-2-hydroxymethyl-3-hydroxy-tetrahydrofuran-5-yl]-buta-1,3-diynyl]-tetrahydrofuran-3*S*-ol (14β)

To a stirred solution of **9β** (408.9 mg, 0.64 mmol) in dry DCM (18.5 mL) was added BCl_3 (1 M in DCM, 5.3 mL, 5.3 mmol, 2.1 equiv) by syringe pump over a 20 min period at −78 °C and the reaction mixture was allowed to stir at −78 °C for 1.5 h. The reaction mixture was then quenched with methanol (4 mL) and allowed to stir at room temperature for 20 h. The reaction mixture was washed with water (3×5 mL) and the water layer was then concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with chloroform/methanol 4:1 to give the title compound **14β** as a pale yellow wax (176.7 mg, 98% yield); R_f=0.19 (methanol/chloroform 1:4); $[\alpha]_D^{25}$ +24.57 (*c* 1.38, CH_3OH); ν_{max} (KBr)/cm^{-1} 3407 (br), 2950, 2873, 2349, 2338; δ_H (D_2O, 400 MHz) 4.85 (t, *J*=8, 2H), 4.34–4.31 (m, 2H), 3.90–3.86 (m, 2H), 3.63 (dd, J_1=4, J_2=12, 2H), 3.57 (dd, J_1=6, J_2=12, 2H), 2.21 (dd, J_1=4, J_2=8, 4H); δ_C (100.6 MHz, D_2O) 86.8, 72.1, 67.7, 61.6, 40.7; HRMS found: [M+Na^+] 305.1009, $C_{14}H_{18}NaO_6$ requires 305.1001; *m*/*z*: 282 (100%, M^+).

4.7. 2*R*-Hydroxymethyl-5*S*-[4-[(2*R*,3*S*,5*S*)-2-hydroxymethyl-3-hydroxy-tetrahydrofuran-5-yl]-buta-1,3-diynyl]-tetrahydrofuran-3*S*-ol (14α)

To a stirred solution of **9α** (340.0 mg, 0.53 mmol) in dry DCM (15.4 mL) was added BCl_3 (1 M in DCM, 4.4 mL, 4.4 mmol, 2.1 equiv) by syringe pump over a 20 min period at −78 °C and the reaction mixture was allowed to stir at −78 °C for 1.5 h. The reaction mixture was then quenched with methanol (4 mL) and allowed to stir at room temperature for 20 h. The reaction mixture was washed with water (3×5 mL) and the water layer was then concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with chloroform/methanol 4:1 to give the title compound **14α** as a pale yellow wax (147.0 mg, 98% yield); R_f=0.28 (methanol/chloroform 1:4); $[\alpha]_D^{25}$ −25.64 (*c* 1.13, CH_3OH); ν_{max} (KBr)/cm^{-1} 3429 (br), 2944, 2867, 2355, 2333; δ_H (D_2O, 400 MHz) 4.91 (q, *J*=4, 2H), 4.26 (q, *J*=4, 2H), 4.02–3.99 (m, 2H), 3.63 (dd, J_1=4, J_2=12, 2H), 3.53 (dd, J_1=6, J_2=12, 2H), 2.53–2.46 (m, 2H), 2.05 (dt, J_1=4, J_2=14, 2H); δ_C (100.6 MHz, D_2O) 86.0, 71.5, 67.7, 61.0, 40.5; HRMS found: [M+Na^+] 305.1005, $C_{14}H_{18}NaO_6$ requires 305.1001; *m*/*z*: 282 (100%, M^+).

4.8. Preparation of (2*R*,3*S*,5*R*)-acetic acid 3-acetoxy-5-ethynyl-tetrahydrofuran-2-ylmethyl ester (15β)

*Part A: Preparation of (2R,3S,5R)-5-ethynyl-2-hydroxymethyl-tetrahydrofuran-3-ol (**A**).* To a stirred solution of **1β** (1.66 g, 5.2 mmol) in dry DCM (145 mL) was added BCl_3 (1 M in DCM, 21.0 mL, 21.0 mmol, 2.0 equiv) by a syringe pump over a 20 min period at −78 °C. The reaction mixture was then stirred at −78 °C for 1.5 h, then quenched with methanol (10 mL), washed with water (3×5 mL) and the water layer was then concentrated in vacuo. The crude oil so obtained was purified by flash chromatography eluting with chloroform/methanol 4:1 to give the title compound **A** as a green oil (729 mg, 99% yield); R_f=0.63 methanol/chloroform 1:4; $[\alpha]_D^{25}$ +52.00 (*c* 0.50, CH_3CN); ν_{max} (KBr)/cm^{-1} 3385, 3291, 2955, 2878, 1341, 1082, 1038, 658; δ_H (CD_3CN, 400 MHz) 4.70–4.65 (m, 1H), 4.22 (q, *J*=3, 1H), 3.71 (td, J_1=3, J_2=5, 1H), 3.51 (t, *J*=5, 2H), 2.76 (d, *J*=2, 1H), 2.13–2.02 (m, 2H); δ_C (100.6 MHz, $CDCl_3$) 88.5, 84.2, 74.4, 73.3, 67.7, 63.4, 43.0; HRMS found: [M+H^+] 143.0708, $C_7H_{11}O_3$ requires 143.0708; *m*/*z*: 142 (100%, M^+). *Part B: Preparation of (2R,3S,5R)-acetic acid 3-acetoxy-5-ethynyl-tetrahydrofuran-2-ylmethyl ester (**15β**).* To a stirred solution of **A** (682 mg, 4.80 mmol) in DCM (9.8 mL) were sequentially added acetic anhydride (9.8 mL), pyridine (4.8 mL) and a catalytic amount of *N*,*N*-dimethylaminopyridine (40 mg). The reaction mixture was stirred at room temperature for 40 min, then diluted with DCM, washed with HCl 10% (2×50 mL) and with $NaHCO_3$ satd solution in water (2×50 mL). The organic layer was dried over Na_2SO_4, concentrated in vacuo, treated with toluene to evaporate the residual acetic acid and purified by flash chromatography eluting with petroleum spirits/ethyl acetate 1:1 to give the title compound **15β** as a yellow oil (1.02 g, 94% yield); R_f=0.33 ethyl acetate/petroleum spirits 1:4; $[\alpha]_D^{25}$ +58.30 (*c* 0.67, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3269, 2966, 1743, 1385, 1248, 1049; δ_H ($CDCl_3$, 400 MHz) 5.19–5.16 (m, 1H), 4.75–4.70 (m, 1H), 4.29 (dd, J_1=4, J_2=11, 1H, H-5), 4.17–4.10 (m, 2H), 2.52 (d, *J*=2, 1H), 2.31–2.28 (m, 2H), 2.09 (s, 3H, CH_3), 2.07 (s, 3H, CH_3); δ_C (100.6 MHz, $CDCl_3$) 170.7, 170.4, 82.4, 81.6, 75.7, 74.1, 67.8, 64.0, 39.5, 20.9, 20.8; HRMS found: [M+H^+] 227.0919, $C_{11}H_{15}O_5$ requires 227.0912; *m*/*z*: 226 (100%, M^+).

4.9. Preparation of (2*R*,3*S*,5*S*)-acetic acid 3-acetoxy-5-ethynyl-tetrahydrofuran-2-ylmethyl ester (15α)

Part A: Preparation of (2R,3S,5S)-5-ethynyl-2-hydroxymethyl-tetrahydrofuran-3-ol (B). To a stirred solution of **1α** (3.15 g, 9.8 mmol) in dry DCM (275 mL) was added BCl_3 (1 M in DCM, 40.0 mL, 40.0 mmol, 2.0 equiv) by a syringe pump over a 20 min period at −78 °C. The reaction mixture was stirred at −78 °C for 1.5 h, then quenched with methanol (16 mL), stirred at room temperature for 14 h, washed with water (3×5 mL) and the water layer was then concentrated in vacuo. The residue was purified by flash chromatography eluting with chloroform/methanol 4:1 to give the title compound **C** as a green oil (1.36 g, 98% yield); R_f=0.42 chloroform/methanol 4:1; $[\alpha]_D^{25}$ −9.89 (*c* 0.46, CH_3CN); ν_{max} (KBr)/cm^{-1} 3379, 3291, 2939, 1633, 1088; δ_H (CD_3CN, 400 MHz) 4.73–4.69 (m, 1H), 4.16 (dt, J_1=5, J_2=7, 1H), 3.82 (dd, J_1=5, J_2=9, 1H), 3.58 (dd, J_1=4, J_2=12, 1H, H-5), 3.50 (dd, J_1=5, J_2=11, 1H, H-5′), 2.88 (br s, 2H, 2-OH), 2.76 (d, *J*=2, 1H), 2.47 (dt, J_1=7, J_2=13, 1H, H-2), 1.93–1.90 (m, 1H, H-2′); δ_C (100.6 MHz, $CDCl_3$) 86.8, 85.1, 74.2, 72.7, 67.6, 62.7, 42.8; HRMS found: [M+H^+] 143.0709, $C_7H_{11}O_3$ requires 143.0708; *m*/*z*: 142 (100%, M^+). *Part B: Preparation of (2R,3S,5S)-acetic acid 3-acetoxy-5-ethynyl-tetrahydrofuran-2-ylmethyl ester (**15α**).* To a stirred solution of **B** (1.14 g, 8.00 mmol) in DCM (12.6 mL) were sequentially added acetic anhydride (12.6 mL), pyridine (6.3 mL) and *N*,*N*-dimethylaminopyridine (40 mg). The reaction mixture was stirred at room temperature for 35 min and then diluted with DCM (50 mL), washed with HCl 10% (2×25 mL) and finally with $NaHCO_3$ satd (2×25 mL). The organic layer was dried over Na_2SO_4, concentrated in vacuo, treated with toluene to evaporate the residual acetic acid and purified by flash chromatography eluting with petroleum spirits/ethyl acetate 1:1 to give the title compound **15α** as a yellow oil (1.72 g, 95% yield); R_f=0.19 ethyl acetate/petroleum spirits 1:4; $[\alpha]_D^{25}$ +35.69 (*c* 1.26, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3273, 2954, 1744, 1368, 1234, 1060; δ_H ($CDCl_3$, 400 MHz) 5.08 (ddd, J_1=3, J_2=4, J_3=7, 1H), 4.85 (ddd, J_1=2, J_2=4, J_3=8, 1H), 4.33 (dt, J_1=4, J_2=5, 1H), 4.26 (dd, J_1=4, J_2=11, 1H, H-5), 4.14 (dd, J_1=5, J_2=11, 1H, H-

5), 2.57 (dt, J_1=8, J_2=14, 1H, H-2), 2.52 (d, J=2, 1H), 2.18 (ddd, J_1=3, J_2=4, J_3=14, 1H, H-2), 2.09 (s, 3H, CH_3), 2.08 (s, 3H, CH_3); δ_C (100.6 MHz, $CDCl_3$) 170.7, 170.7, 82.5, 81.3, 74.9, 73.8, 67.7, 63.7, 39.2, 21.0, 20.8; HRMS found: [M+H$^+$] 227.0918, $C_{11}H_{15}O_5$ requires 227.0912; m/z: 226 (100%, M$^+$).

4.10. Preparation of acetic acid 3(*S*)-acetoxy-5(*R*)-pyridin-2-ylethynyl-tetrahydrofuran-2(*R*)-ylmethyl ester (16β)

To a stirred solution of 2-I-pyridine (240 μl, 2.3 mmol, 1.2 equiv) in dry DMF (16.0 mL) kept under a hydrogen atmosphere were sequentially added dichlorobis(triphenylphosphine)-palladium(II) (28.6 mg, 0.04 mmol, 0.02 equiv), copper(I) iodide (5.4 mg, 0.03 mmol, 0.02 equiv) and *N*,*N*-diisopropylethylamine (970 μL, 5.57 mmol, 3.0 equiv) and a solution of **15β** (417 mg, 1.8 mmol) in dry DMF (9.0 mL). The reaction mixture was stirred at room temperature for 10 days, then quenched with water and extracted with ethyl acetate (3×50 mL). The organic layer was dried over Na_2SO_4, concentrated in vacuo and treated with heptane to evaporate the residual DMF. The crude compound obtained was purified by flash chromatography eluting with petroleum spirits/ethyl acetate 1:1 to give **16β** as a brown oil (239 mg, 43%); R_f=0.19 ethyl acetate/petroleum spirits 1:1; ν_{max} (KBr)/cm^{-1} 3055, 2940, 1739, 1238; δ_H ($CDCl_3$, 400 MHz) 8.58–8.57 (m, 1H), 7.65 (td, J_1=2, J_2=8, 1H), 7.45 (dt, J_1=1, J_2=8, 1H), 7.25–7.23 (m, 1H), 5.23–5.21 (m, 1H), 5.00–4.96 (m, 1H), 4.33 (dd, J_1=3, J_2=11, 1H), 4.21–4.14 (m, 2H), 2.46–2.36 (m, 2H), 2.10 (s, 3H), 2.09 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 170.7, 170.4, 150.0, 142.5, 136.2, 127.3, 123.2, 86.6, 84.9, 82.6, 75.7, 68.4, 64.0, 39.4, 21.0, 20.9; HRMS found: [M+H$^+$] 304.1174, $C_{16}H_{18}NO_5$ requires 304.1185; m/z: 304 (100%, M+H$^+$).

4.11. Preparation of acetic acid 3(*S*)-acetoxy-5(*S*)-pyridin-2-ylethynyl-tetrahydrofuran-2(*R*)-ylmethyl ester (16α)

To a stirred solution of 2-I-pyridine (320 μl, 3.0 mmol, 1.2 equiv), in dry DMF (21.2 mL) kept under a hydrogen atmosphere were sequentially added dichlorobis(triphenylphosphine)-palladium(II) (37.5 mg, 0.05 mmol, 0.02 equiv), copper(I) iodide (5.2 mg, 0.03 mmol, 0.01 equiv), *N*,*N*-diisopropylethylamine (1.29 mL, 7.41 mmol, 3.0 equiv) and a solution of **15α** (557.8 mg, 2.5 mmol) in dry DMF (12.0 mL) and the reaction mixture was stirred at room temperature for 14 days. The reaction mixture was then diluted with water and extracted with ethyl acetate (3×50 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo and treated with heptane to evaporate the residual DMF. The residue was purified by flash chromatography eluting with petroleum spirits/ethyl acetate 1:1 to give the title compound **16α** as a brown oil (335 mg, 45%); R_f=0.25 ethyl acetate/petroleum spirits 1:1; $[\alpha]_D^{25}$ +60.95 (*c* 0.53, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3720 (br), 3037 (br), 1801, 1744, 1242, 1057; δ_H ($CDCl_3$, 400 MHz) 8.58 (ddd, J_1=1, J_2=2, J_3=5, 1H, Ar), 7.66 (td, J_1=2, J_2=8, 1H, Ar), 7.44–7.42 (m, 1H, Ar), 7.25–7.23 (m, 1H, Ar), 5.15–5.09 (m, 2H), 4.40 (dt, J_1=4, J_2=5, 1H), 4.30 (dd, J_1=4, J_2=12, 1H, H-5), 4.19 (dd, J_1=6, J_2=12, 1H, H-5′), 2.68 (dt, J_1=8, J_2=14, 1H, H-2), 2.33 (dt, J_1=4, J_2=14, 1H, H-2′), 2.10 (s, 3H, CH_3), 2.09 (s, 3H, CH_3); δ_C (100.6 MHz, $CDCl_3$) 170.8, 170.7, 150.0, 142.7, 136.1, 127.1, 123.1, 87.7, 84.9, 81.3, 74.8, 68.2, 63.7, 39.2, 21.0, 20.8; HRMS found: [M+H$^+$] 304.1173, $C_{16}H_{18}NO_5$ requires 304.1185; m/z: 303 (100%, M$^+$).

4.12. Preparation of (2*R*,3*S*,5*R*)-2-(hydroxymethyl)-5-(pyridin-2-ylethynyl)-tetrahydrofuran-3-ol (17β)

To a stirred solution of **16β** (225.1 mg, 0.74 mmol) in methanol (9.0 mL) was added, at 0 °C, a solution of sodium methoxide in methanol 1 M (370 μL, 0.37 mmol, 0.25 equiv) and the reaction mixture was stirred at room temperature for 40 min. The reaction was then quenched with HCl/MeOH 10% until pH=7, concentrated in vacuo and purified by flash chromatography eluting with chloroform/methanol 4:1 to give the title compound **17β** as a brown oil (137.3 mg, 84%); R_f=0.68 (methanol/chloroform 1:4); ν_{max} (KBr)/cm^{-1} 3383 (br), 2930, 2838, 1582, 1450, 1054, 761; δ_H ($CDCl_3$, 400 MHz) 8.52–8.51 (d, J=4, 1H), 7.67–7.63 (td, J_1=2, J_2=8, 1H), 7.44–7.42 (d, J=8, 1H), 7.25–7.22 (m, 1H), 5.05–5.01 (at, J=8, 1H), 4.51–4.49 (m, 1H), 4.29 (br s, 1H), 3.95 (d, J=3, 1H), 3.77–3.69 (m, 3H), 2.34–2.31 (m, 2H); δ_C (100.6 MHz, $CDCl_3$) 149.6, 142.3, 136.6, 127.3, 123.3, 88.8, 87.4, 84.3, 72.7, 67.8, 62.7, 42.4; HRMS found: [M+H$^+$] 220.0964, $C_{12}H_{14}NO_3$ requires 220.0974; m/z: 219 (100%, M$^+$).

4.13. Preparation of (2*R*,3*S*,5*S*)-2-(hydroxymethyl)-5-(pyridin-2-ylethynyl)-tetrahydrofuran-3-ol (17α)

To a stirred solution of **16α** (331.1 mg, 1.1 mmol) in methanol (13.0 mL) was added, at 0 °C, a solution of sodium methoxide in methanol 1 M (540 μL, 0.54 mmol, 0.25 equiv) and the reaction mixture was stirred at room temperature for 40 min. The reaction was then quenched with HCl/MeOH 10% until pH=7, concentrated in vacuo and purified by flash chromatography eluting with chloroform/methanol 4:1 to give the title compound **17α** as a brown solid (199.3 mg, 83%); mp 92–94 °C; R_f=0.35 (methanol/chloroform 1:4); $[\alpha]_D^{25}$ −16.95 (*c* 0.30, CH_3OH); ν_{max} (KBr)/cm^{-1} 3337 (br), 2963, 2920, 2361, 2342, 2219; δ_H (CD_3CN, 400 MHz): 8.56–8.55 (m, 1H, Ar), 7.75 (td, J_1=2, J_2=8, 1H, Ar), 7.48–7.43 (m, 1H, Ar), 7.32 (ddd, J_1=1, J_2=5, J_3=8, 1H, Ar), 4.96 (dd, J_1=8, J_2=5, 1H), 4.22 (dt, J_1=5, J_2=7, 1H), 3.90 (dd, J_1=5, J_2=9, 1H), 3.57 (dd, J_1=4, J_2=12, 1H, H-5), 3.53 (dd, J_1=5, J_2=12, 1H, H-5′), 3.24 (s, 1H, OH), 2.82 (s, 1H, OH′), 2.56 (dt, J_1=8, J_2=13, 1H, H-2), 2.08–2.02 (m, 1H, H-2′); δ_C (100.6 MHz, CD_3CN) 150.9, 137.4, 128.0, 124.2, 90.1, 87.1, 84.8, 72.7, 68.1, 62.8, 42.6; HRMS found: [M+H$^+$] 220.0970, $C_{12}H_{14}NO_3$ requires 220.0974; m/z: 219 (100%, M$^+$).

4.14. Preparation of 1-(5-(4(*S*)-acetoxy-5(*R*)-(acetoxymethyl)-tetrahydrofuran-2(*R*)-yl)isoxazol-3-yl)ethanone (18β)

To a stirred solution of **15β** (522.8 mg, 2.3 mmol) in acetone (14.0 mL) was added cerium(IV) ammonium nitrate (1.29 g, 2.4 mmol, 1.0 equiv), and the reaction mixture was allowed to stir at reflux for 12 h and at room temperature for another 12 h. The reaction mixture was then concentrated in vacuo and purified by flash chromatography eluting with petroleum spirits/ethyl acetate 3:1 to give the title compound **18β** as a yellow oil (372.4 mg, 52% yield); R_f=0.52 (ethyl acetate/petroleum spirits 1:1); $[\alpha]_D^{25}$ +17.48 (*c* 0.80, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3148, 2955, 1743, 1710, 1242; δ_H ($CDCl_3$, 400 MHz) 6.62 (d, J=1, 1H, H-isox.), 5.30–5.27 (m, 2H), 4.32 (dd, J_1=4, J_2=12, 1H, H-5), 4.27 (td, J_1=2, J_2=6, 1H), 4.16 (dd, J_1=4, J_2=12, 1H, H-5′), 2.65 (s, 3H, CH_3C=O), 2.48–2.35 (m, 2H, H-2+H-2′), 2.12 (s, 3H, CH_3Ac), 2.09 (s, 3H, CH_3Ac′); δ_C (100.6 MHz, $CDCl_3$) 191.8, 172.6, 170.6, 170.4, 161.9, 100.4, 83.1, 75.8, 72.5, 63.7, 37.6, 27.3, 21.0, 20.8; HRMS found: [M+H$^+$] 312.1095, $C_{14}H_{18}NO_7$ requires 312.1083; m/z: 311 (100%, M$^+$).

4.15. Preparation of 1-(5-(4(*S*)-acetoxy-5(*R*)-(acetoxymethyl)-tetrahydrofuran-2(*S*)-yl)isoxazol-3-yl)ethanone (18α)

To a stirred solution of **15α** (760.0 mg, 3.4 mmol) in acetone (20.5 mL) was added cerium(IV) ammonium nitrate (1.86 g, 3.4 mmol, 1.0 equiv), and the reaction mixture was allowed to stir at reflux for 12 h and at room temperature for another 12 h. The reaction mixture was then concentrated in vacuo and purified by flash chromatography eluting with petroleum spirits/ethyl acetate 2:1 to give the title compound **18α** as a yellow oil (487.7 mg, 47% yield); R_f=0.23 (ethyl acetate/petroleum spirits 1:1); $[\alpha]_D^{25}$ +55.18 (*c* 1.03, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3566 (br), 3137, 2966, 1743, 1704,

1457, 1363, 1236, 1054,; δ_H ($CDCl_3$, 400 MHz) 6.62 (s, 1H, H-isox.), 5.36 (dd, J_1=4, J_2=8, 1H), 5.21–5.18 (m, 1H), 4.37–4.34 (m, 1H), 4.26 (dd, J_1=4.0, J_2=12, 1H, H-5), 4.19 (dd, J_1=5, J_2=12, 1H, H-5′), 2.81–2.71 (m, 1H, H-2), 2.65 (s, 3H, CH_3C=O), 2.40–2.35 (m, 1H, H-2′), 2.10 (s, 3H, CH_3Ac), 1.98 (s, 3H, CH_3Ac′); δ_C (100.6 MHz, $CDCl_3$) 191.9, 174.1, 170.6, 170.4, 161.9, 100.0, 82.3, 75.0, 72.9, 63.7, 37.0, 27.3, 20.8; HRMS found: [M+H$^+$] 312.1090, $C_{14}H_{18}NO_7$ requires 312.1083; *m/z*: 311 (100%, M$^+$).

4.16. Preparation of (2*R*,3*S*,5*R*)-3-(acetoxy)-2-(acetoxymethyl)-5-(3-phenylisoxazol-5-yl)-tetrahydrofuran (19β)

To a stirred solution of benzaldehyde chloroxime (147.1 mg, 0.95 mmol, 1.0 equiv) in DCM (10.4 mL) was added, at 0 °C, triethylamine (150 μL, 1.1 mmol, 1.2 equiv) and, after 10 min, a solution of **15β** (204.4 mg, 0.9 mmol) in DCM (10.4 mL). The solution was allowed to stir at room temperature for 3 days and then the mixture was concentrated in vacuo and purified by flash chromatography eluting with petroleum spirits/ethyl acetate 2:1 to give the title compound **19β** as a yellow solid (264.9 mg, 85% yield); mp 112–113 °C; R_f=0.23 (ethyl acetate/petroleum spirits 1:2); $[\alpha]_D^{25}$ −23.53 (*c* 0.60, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3136, 2927, 2360, 1748, 1225; δ_H ($CDCl_3$, 400 MHz) 7.81–7.78 (m, 2H, Ph), 7.47–7.44 (m, 3H, Ph), 6.56 (s, 1H, H-isox.), 5.32–5.28 (m, 2H), 4.38 (dd, J_1=4, J_2=12, 1H, H-5), 4.29 (td, J_1=2, J_2=4, 1H), 4.19 (dd, J_1=4, J_2=12, 1H, H-5′), 2.51–2.39 (m, 2H, H-2+H-2′), 2.13 (s, 3H, CH_3), 2.08(s, 3H, CH_3′); δ_C (100.6 MHz, $CDCl_3$) 171.4, 170.6, 170.4, 130.1, 128.9, 126.8, 99.8, 83.0, 76.0, 73.0, 63.9, 37.6, 21.0, 20.8; HRMS found: [M+H$^+$] 346.1278, $C_{18}H_{20}NO_6$ requires 346.1291; *m/z*: 345 (100%, M$^+$).

4.17. Preparation of (2*R*,3*S*,5*S*)-3-(acetoxy)-2-(acetoxymethyl)-5-(3-phenylisoxazol-5-yl)-tetrahydrofuran (19α)

To a stirred solution of benzaldehyde chloroxime (200.6 mg, 1.3 mmol, 1.1 equiv) in DCM (14.0 mL) was added, at 0 °C, triethylamine (210 μL, 1.5 mmol, 1.2 equiv) and, after 10 min, a solution of **15α** (277.1 mg, 1.2 mmol) in DCM (10.4 mL). The solution was allowed to stir at room temperature for 3 days and then the mixture was concentrated in vacuo and purified by flash chromatography eluting with petroleum spirits/ethyl acetate 2:1 to give the title compound **19α** as a yellow oil (356.4 mg, 84% yield); R_f=0.36 (ethyl acetate/petroleum spirits 1:2); $[\alpha]_D^{25}$ +59.65 (*c* 0.29, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3445 (br), 2972, 1749, 1440, 1374, 1237, 1033 [1]; δ_H ($CDCl_3$, 400 MHz) 7.81–7.79 (m, 2H, Ph), 7.48–7.45 (m, 3H, Ph), 6.58 (d, *J*=1, 1H, H-isox.), 5.39 (dd, J_1=4, J_2=8, 1H), 5.23–5.20 (m, 1H), 4.43–4.40 (m, 1H), 4.3 (dd, J_1=4, J_2=12, 1H, H-5), 4.22 (dd, J_1=5, J_2=12, 1H, H-5′), 2.81–2.74 (m, 1H, H-2), 2.49–2.44 (m, 1H, H-2′), 2.12 (s, 3H, CH_3), 1.98 (s, 3H, CH_3′); δ_C (100.6 MHz, $CDCl_3$) 172.7, 170.5, 170.4, 162.2, 130.0, 128.8, 128.7, 126.6, 99.4, 82.0, 75.0, 73.1, 63.7, 36.8, 20.8, 20.7; HRMS found: [M+H$^+$] 346.1289, $C_{18}H_{20}NO_6$ requires 346.1291; *m/z*: 345 (100%, M$^+$).

4.18. Preparation of (2*R*,3*S*,5*R*)-5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-(acetoxymethyl)-3-(acetoxy)-tetrahydrofuran (20β)

A solution of **15β** (199.4 mg, 0.9 mmol), benzylazide (140.3 mg, 1,1 mmol, 1.2 equiv), $CuSO_4 \cdot 5H_2O$ (15.7 mg, 0.06 mmol, 0.07 equiv) and sodium ascorbate (26.2 mg, 0.13 mmol, 0.15 equiv) in H_2O/DCM 1:1 (1.64 mL) was stirred at room temperature for 4 h. The solution was then concentrated in vacuo and purified by flash chromatography eluting with petroleum spirits to eliminate the excess of azide and then with ethyl acetate to give compound **20β** as a white solid (260.8 mg, 82%); mp 110–111 °C; R_f=0.60 (ethyl acetate); $[\alpha]_D^{25}$ −8.98 (*c* 0.67, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3142, 2961, 2889, 1743, 1231, 1055; δ_H ($CDCl_3$, 400 MHz) 7.42 (s, 1H, H-triazole), 7.41–7.36 (m, 3H, Ph), 7.30–7.27 (m, 2H, Ph), 5.51 (s, 2H, CH_2Ph), 5.30–5.26 (m, 1H), 5.23–5.22 (m, 1H), 4.31 (dd, J_1=4, J_2=11, 1H, H-5), 4.20–4.12 (m, 2H), 2.43 (ddd, J_1=2, J_2=6, J_3=14, 1H, H-2), 2.39–2.31 (m, 1H, H-2′), 2.10 (s, 3H, CH_3), 1.98 (s, 3H, CH_3′); δ_C (100.6 MHz, $CDCl_3$) 170.7, 170.5, 148.1, 134.4, 129.1, 128.8, 128.2, 121.1, 82.6, 76.3, 73.7, 64.1, 54.2, 38.6, 21.0, 20.7; HRMS found: [M+H$^+$] 360.1575, $C_{18}H_{22}N_3O_5$ requires 360.1559; *m/z*: 359 (100%, M$^+$).

4.19. Preparation of (2*R*,3*S*,5*S*)-5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-(acetoxymethyl)-3-(acetoxy)-tetrahydrofuran (20α)

A solution of **15α** (210.5 mg, 0.9 mmol), benzylazide (160.0 mg, 1,2 mmol, 1.3 equiv), $CuSO_4 \cdot 5H_2O$ (17.0 mg, 0.07 mmol, 0.07 equiv) and sodium ascorbate (27.9 mg, 0.14 mmol, 0.15 equiv) in H_2O/DCM 1:1 (1.74 mL) was stirred at room temperature for 2 h. The solution was then concentrated in vacuo and purified by flash chromatography eluting with petroleum spirits to eliminate the excess of azide and then with ethyl acetate to give compound **20α** as a white solid (292.9 mg, 88%); mp 76–77 °C; R_f=0.57 (ethyl acetate); $[\alpha]_D^{25}$ +34.34 (*c* 0.50, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3142, 2955, 2360, 1738, 1231; δ_H ($CDCl_3$, 400 MHz) 7.43 (s, 1H, H-triazole), 7.38–7.34 (m, 3H, Ph), 7.28–7.27 (m, 2H, Ph), 5.52 (d, *J*=15, 1H, CH_2Ph), 5.48 (d, *J*=15, 1H, CH_2Ph), 5.35 (dd, J_1=6, J_2=8, 1H), 5.19–5.16 (m, 1H), 4.28 (dt, J_1=4, J_2=6, 1H), 4.23 (dd, J_1=4, J_2=12, 1H, H-5), 4.15 (dd, J_1=6, J_2=12, 1H, H-5′), 2.79–2.72 (m, 1H, H-2), 2.43 (ddd, J_1=4, J_2=6, J_3=14, 1H, H-2′), 2.07 (s, 3H, CH_3), 1.88 (s, 3H, CH_3′); δ_C (100.6 MHz, $CDCl_3$) 170.7, 170.5, 149.4, 134.5, 129.1, 128.8, 128.1, 121.1, 81.3, 75.5, 73.5, 64.0, 54.2, 37.8, 20.8, 20.8; HRMS found: [M+H$^+$] 360.1542, $C_{18}H_{22}N_3O_5$ requires 360.1559; *m/z*: 359 (100%, M$^+$).

4.20. Preparation of 1-(5-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl)isoxazol-3-yl) ethanone (21β)

To a stirred solution of **18β** (356.4 mg, 1.1 mmol) in methanol (15.0 mL) was added, at 0 °C, a solution of sodium methoxide in methanol (1 M, 600 μL, 0.6 mmol, 0.27 equiv) and the reaction mixture was stirred at room temperature for 40 min. The reaction was then quenched with HCl/MeOH 10% until pH=7, concentrated in vacuo and purified by flash chromatography eluting with chloroform/methanol 4:1 to give the title compound **21β** as a yellow oil (194.1 mg, 75%); R_f=0.61 (methanol/chloroform 1:4); $[\alpha]_D^{25}$ +29.70 (*c* 0.40, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3385 (br), 2922, 2360, 1710; δ_H ($CDCl_3$, 400 MHz) 6.62 (d, *J*=1, 1H, H-isox.), 5.32 (dd, J_1=7, J_2=9, 1H), 4.51–4.48 (m, 1H), 4.04–4.01 (m, 1H), 3.75 (dd, J_1=4, J_2=12, 1H, H-5), 3.69 (dd, J_1=4, J_2=12, 1H, H-5′), 2.63 (s, 3H, CH_3), 2.34–2.30 (m, 2H, H-2+H-2′); δ_C (100.6 MHz, $CDCl_3$) 192.1, 173.4, 161.8, 100.2, 87.5, 72.9, 71.9, 62.8, 40.4, 27.3; HRMS found: [M+H$^+$] 228.0866, $C_{10}H_{14}NO_5$ requires 228.0872; *m/z*: 227 (100%, M$^+$).

4.21. Preparation of 1-(5-((2*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl)isoxazol-3-yl) ethanone (21α)

To a stirred solution of **18α** (444.6 mg, 1.4 mmol) in methanol (18.5 mL) was added, at 0 °C, a solution of sodium methoxide in methanol (1 M, 750 μL, 0.75 mmol, 0.27 equiv) and the reaction mixture was stirred at room temperature for 40 min. The reaction was then quenched with HCl/MeOH 10% until pH=7, concentrated in vacuo and purified by flash chromatography eluting with ethyl acetate to give the title compound **21α** as a yellow oil (295.8 mg, 91%); R_f=0.48 (ethyl acetate); $[\alpha]_D^{25}$ +49.28 (*c* 0.35, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3401 (br), 2928, 2360, 2338, 1705, 1446, 1347, 1088; δ_H ($CDCl_3$, 400 MHz): 6.67 (d, *J*=1, 1H, H-isox.), 5.32–5.29 (m, 1H), 4.52–4.48 (m, 1H), 4.07 (dd, J_1=4, J_2=8, 1H), 3.82 (dd, J_1=4, J_2=12, 1H, H-5), 3.73 (dd, J_1=4, J_2=12, 1H, H-5′), 2.74–2.67 (m, 1H, H-2), 2.65 (s, 3H, CH_3), 2.29 (dt, J_1=5, J_2=13, 1H, H-2′), 1.89 (s, 1H, OH), 1.78

(s, 1H, OH′); δ_C (100.6 MHz, $CDCl_3$) 192.2, 174.6, 161.8, 100.05, 86.1, 72.3, 72.0, 62.2, 39.5, 27.3; HRMS found: [M+H$^+$] 228.0880, $C_{10}H_{14}NO_5$ requires 228.0872; *m*/*z*: 227 (100%, M$^+$).

4.22. Preparation of (2*R*,3*S*,5*R*)-2-(hydroxymethyl)-5-(3-phenylisoxazol-5-yl)-tetrahydrofuran-3-ol (22β)

To a stirred solution of **19β** (240.0 mg, 0.69 mmol) in methanol/DCM 2:1 (13.5 mL) was added, at 0 °C, a solution of sodium methoxide in methanol (1 M, 720 μL, 0.72 mmol, 0.52 equiv) and the reaction mixture was stirred at room temperature for 50 min. The reaction was then quenched with HCl/MeOH 10% until pH=7, concentrated in vacuo and purified by flash chromatography eluting with ethyl acetate to give the title compound **22β** as a yellow solid (158.8 mg, 87%); mp 122–124 °C; R_f=0.48 (ethyl acetate); $[\alpha]_D^{25}$ +9.58 (*c* 0.73, CH_3OH); ν_{max} (KBr)/cm^{-1} 3385 (br), 3137, 2933, 2355, 1617; δ_H ($CDCl_3$, 400 MHz) 7.81–7.78 (m, 2H, Ph), 7.47–7.45 (m, 3H, Ph), 6.57 (d, *J*=1, 1H, H-isox.), 5.37 (dd, J_1=6, J_2=9, 1H), 4.59–4.55 (m, 1H), 4.10–4.07 (m, 1H), 3.84 (ddd, J_1=4, J_2=5, J_3=12, 1H), 3.78–3.73 (m, 1H), 2.47–2.33 (m, 2H, H-2+H-2′), 1.94–1.90 (m, 2H); δ_C (100.6 MHz, $CDCl_3$) 171.8, 130.1, 128.9, 128.7, 126.8, 100.0, 87.5, 73.4, 72.3, 63.1, 40.7, 29.7; HRMS found: [M+H$^+$] 262.1067, $C_{14}H_{16}NO_4$ requires 262.1079; *m*/*z*: 261 (100%, M$^+$).

4.23. Preparation of (2*R*,3*S*,5*S*)-2-(hydroxymethyl)-5-(3-phenylisoxazol-5-yl)-tetrahydrofuran-3-ol (22α)

To a stirred solution of **19α** (141.0 mg, 0.41 mmol) in methanol (4.8 mL) was added, at 0 °C, a solution of sodium methoxide in methanol (1 M, 200 μL, 0.20 mmol, 0.24 equiv) and the reaction mixture was stirred at room temperature for 1 h. The reaction was then quenched with HCl/MeOH 10% until pH=7, concentrated in vacuo and purified by flash chromatography eluting with ethyl acetate to give the title compound **22α** as a yellow solid (96.0 mg, 90%); mp 80–82 °C; R_f=0.50 (ethyl acetate); $[\alpha]_D^{25}$ −27.96 (*c* 0.61, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3421 (br), 2962, 2927, 2364; δ_H ($CDCl_3$, 400 MHz): 7.82–7.78 (m, 2H, Ph), 7.49–7.44 (m, 3H, Ph), 6.61 (s, 1H, H-isox.), 5.32 (dd, J_1=5, J_2=8, 1H), 4.51–4.47 (m, 1H), 4.15–4.12 (m, 1H), 3.87–3.82 (m, 1H), 3.77–3.72 (m, 1H), 2.77–2.70 (m, 1H, H-2), 2.35 (dt, J_1=5, J_2=13, 1H, H-2′), 1.97 (d, *J*=6, 1H, OH), 1.80 (t, *J*=6, 1H, OH′); δ_C (100.6 MHz, $CDCl_3$) 173.2, 162.4, 130.1, 128.9, 128.7, 126.8, 99.7, 86.1, 72.6, 72.3, 62,5, 39.8, 29.7; HRMS found: [M+H$^+$] 262.1070, $C_{14}H_{16}NO_4$ requires 262.1079; *m*/*z*: 261 (100%, M$^+$).

4.24. Preparation of (2*R*,3*S*,5*R*)-5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-(hydroxymethyl)-tetrahydrofuran-3-ol (23β)

To a stirred solution of **20β** (247.4 mg, 0.69 mmol) in methanol (9.0 mL) was added, at 0 °C, a solution of sodium methoxide in methanol (1 M, 360 μL, 0.36 mmol, 0.26 equiv) and the reaction mixture was stirred at room temperature for 40 min. The reaction was then quenched with HCl/MeOH 10% until pH=7, concentrated in vacuo and purified by flash chromatography eluting with chloroform/methanol 4:1 to give the title compound **23β** as a yellow solid (159.4 mg, 84%); mp 77–78 °C; R_f=0.50 (methanol/chloroform 1:4); $[\alpha]_D^{25}$ −15.17 (*c* 0.73, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3271 (br), 3117, 2924, 2362, 1051; δ_H ($CDCl_3$, 400 MHz) 7.44 (s, 1H, H-triazole), 7.39–7.37 (m, 3H, Ph), 7.29–7.27 (m, 2H, Ph), 5.50 (s, 2H), 5.30 (dd, J_1=6, J_2=10, 1H), 4.56–4.54 (m, 1H), 4.04 (d, *J*=2, 1H), 3.81 (dd, J_1=3, J_2=12, 1H, H-5), 3.69 (dd, J_1=4, J_2=12, 1H, H-5′), 2.41 (ddd, J_1=6, J_2=9, J_3=13, 1H, H-2), 2.28 (ddd, J_1=2, J_2=6, J_3=13, 1H, H-2′); δ_C (100.6 MHz, $CDCl_3$) 148.8, 134.3, 129.1, 128.8, 128.2, 121.5, 87.9, 73.5, 72.3, 63.2, 54.2, 42.2; HRMS found: [M+H$^+$] 276.1335, $C_{14}H_{18}N_3O_3$ requires 276.1348; *m*/*z*: 275 (100%, M$^+$).

4.25. Preparation of (2*R*,3*S*,5*S*)-5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-(hydroxymethyl)-tetrahydrofuran-3-ol (23α)

To a stirred solution of **20α** (272.1 mg, 0.76 mmol) in methanol (10.0 mL) was added, at 0 °C, a solution of sodium methoxide in methanol (1 M, 400 μL, 0.40 mmol, 0.26 equiv) and the reaction mixture was stirred at room temperature for 40 min. The reaction was then quenched with HCl/MeOH 10% until pH=7, concentrated in vacuo and purified by flash chromatography eluting with chloroform/methanol 4:1 to give the title compound **23α** as a yellow solid (203.5 mg, 98%); mp 106–109 °C; R_f=0.50 (methanol/chloroform 1:4); $[\alpha]_D^{25}$ +65.45 (*c* 1.15, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3386 (br), 3110, 3061, 2923; δ_H ($CDCl_3$, 400 MHz) 7.46 (s, 1H, H-triazole), 7.42–7.35 (m, 3H, Ph), 7.30–7.27 (m, 2H, Ph), 5.55–5.43 (m, 3H), 5.29 (dd, J_1=2, J_2=9, 1H), 4.39–4.34 (m, 1H), 4.16–4.12 (m, 1H), 3.77–3.72 (m, 1H), 3.67–3.61 (m, 1H), 2.56 (ddd, J_1=7, J_2=8, J_3=16, 1H), 2.31 (dt, J_1=2, J_2=14, 1H), 1.91 (t, *J*=6, 1H); δ_C (100.6 MHz, $CDCl_3$) 129.2, 129.0, 128.3, 121.8, 88.2, 73.6, 72.3, 63.3, 54.3, 40.0; HRMS found: [M+H$^+$] 276.1341, $C_{14}H_{18}N_3O_3$ requires 276.1348; *m*/*z*: 275 (100%, M$^+$).

4.26. Preparation of acetic acid 3(*S*)-acetoxy-5(*R*)-(1,3-dihydro-isobenzofuran-5-yl)tetrahydrofuran-2(*R*)-ylmethyl ester (24β)

To a stirred solution of compound **15β** (490.1 mg 2.17 mmol) in dry toluene (32 mL) was added chlorotris(triphenylphosphine) rhodium(I) (212.0 mg, 0.23, mmol, 0.1 equiv) and dipropargyl ether (800 μL, 7.77 mmol, 3.6 equiv) and the mixture was allowed to stir at room temperature for 44 h. The mixture was then concentrated in vacuo and purified by flash chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:4) to give the title compound **24β** as a brown oil (249.5 mg 36%); R_f=0.41 (ethyl acetate/petroleum ether 1:1); ν_{max} (KBr)/cm^{-1} 3392, 2970, 2856, 1754, 1267; δ_H ($CDCl_3$, 400 MHz) 7.25–7.20 (m, 3H), 5.22 (d, *J*=6, 1H), 5.15–5.10 (m, 5H), 4.41–4.36 (m, 1H), 4.28–4.23 (m, 2H), 2.37–2.32 (m, 1H), 2.13 (s, 3H), 2.10–2.01 (m, 4H); δ_C (100.6 MHz, $CDCl_3$) 170.7, 140.0, 139.6, 138.9, 125.1, 121.0, 118.3, 82.6, 80.5, 73.4, 73.3, 64.4, 41.4, 21.1, 20.9; HRMS found: [M+H$^+$] 321.1342, $C_{17}H_{21}O_6$ requires 321.1338; *m*/*z*: 320 (100%, M$^+$).

4.27. Preparation of acetic acid 3(*S*)-acetoxy-5(*S*)-(1,3-dihydro-isobenzofuran-5-yl)tetrahydrofuran-2(*R*)-ylmethyl ester (24α)

To a stirred solution of compound **15α** (1.36 g, 6.01 mmol) in dry toluene (90 mL) was added chlorotris(triphenylphosphine) rhodium(I) (555 mg, 0.60 mmol, 0.1 equiv) and dipropargyl ether (2.2 mL, 21.37 mmol, 3.6 equiv) and the mixture was allowed to stir at room temperature for 48 h. The mixture was then concentrated in vacuo and purified by flash chromatography on silica gel eluting with ethyl acetate/petroleum ether 1:4 to give the title compound **24α** as a yellow oil (671.5 mg 35%); R_f=0.10 (ethyl acetate/petroleum ether 1:4); ν_{max} (KBr)/cm^{-1} 3390, 2967, 2853, 1753, 1260; δ_H ($CDCl_3$, 400 MHz) 7.30–7.22 (m, 3H), 5.26–5.17 (m, 2H), 5.12 (br s, 4H), 4.45–4.42 (m, 1H), 4.31–4.25 (m, 2H), 2.88–2.81 (m, 1H), 2.14–2.04 (m, 7H); δ_C (100.6 MHz, $CDCl_3$); 170.8, 141.2, 138.7, 125.1, 120.9, 118.4, 81.4, 79.9, 75.6, 73.5, 73.4, 64.0, 40.6, 21.0, 20.9; HRMS found: [M+H$^+$] 321.1348, $C_{17}H_{21}O_6$ requires 321.1338; *m*/*z*: 320 (100%, M$^+$).

4.28. Preparation of 5(*R*)-(1,3-dihydro-isobenzofuran-5-yl)-2(*R*)-hydroxymethyl-tetrahydrofuran-3(*S*)-ol (25β)

To a stirred solution of **15β** (241.6 mg, 0.75 mmol) in methanol (11 mL), was added a catalytic amount of potassium carbonate and the solution was allowed to stir at room temperature for 30 min. The mixture was then concentrated in vacuo and purified by flash chromatography on silica gel eluting with chloroform/methanol 8:1 to give the title compound **25β** as a green oil (145.5 mg, 82%);

R_f=0.38 (chloroform/methanol 8:1); ν_{max} (KBr)/cm^{-1} 3398, 2920, 2852, 1043; δ_H ($CDCl_3$, 400 MHz) 7.24–7.20 (m, 3H), 5.20 (dd, J_1=6, J_2=10, 1H), 5.10 (s, 4H), 4.47–4.44 (m, 1H), 4.04–4.01 (m, 1H), 3.85 (dd, J_1=4, J_2=12, 1H), 3.76 (dd, J_1=5, J_2=12, 1H), 2.27 (ddd, J_1=2, J_2=6, J_3=13, 1H), 2.08–2.00 (m, 1H), 1.92 (br s, 2H); δ_C (100.6 MHz, $CDCl_3$); 140.5, 139.6, 138.8, 125.3, 121.0, 118.5, 87.3, 80.0, 73.8, 73.4, 73.3, 63.4, 44.3; HRMS found: [M+H$^+$] 237.1120, $C_{13}H_{17}O_4$ requires 237.1127; *m*/*z*: 236 (100%, M$^+$).

4.29. Preparation of 5(*S*)-(1,3-dihydro-isobenzofuran-5-yl)-2(*R*)-hydroxymethyl-tetrahydrofuran-3(*S*)-ol (25α)

To a stirred solution of **15α** (671.5 mg, 2.10 mmol) in methanol (30 mL), was added a catalytic amount of potassium carbonate and the solution was allowed to stir at room temperature for 30 min. The mixture was then concentrated in vacuo and purified by flash chromatography on silica gel eluting with chloroform/methanol 8:1 to give the title compound **25α** as a green oil (379.2 mg 77%); R_f=0.34 (chloroform/methanol 8:1); $[\alpha]_D^{25}$ −20.74 (*c* 2.17, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3395, 2918, 2848, 1038; δ_H ($CDCl_3$, 400 MHz) 7.32–7.23 (m, 3H), 5.16–5.12 (m, 5H), 4.49 (dd, J_1=7, J_2=13, 1H), 4.11 (dd, J_1=5, J_2=9, 1H), 3.85 (dd, J_1=4, J_2=12, 1H), 3.76 (dd, J_1=5, J_2=12, 1H), 2.74–2.68 (m, 1H), 2.11–1.99 (m, 3H); δ_C (100.6 MHz, $CDCl_3$); 142.1, 139.6, 138.6, 125.0, 121.0, 118.2, 85.4, 79.5, 73.5, 73.4, 73.1, 62.6, 43.8; HRMS found: [M+H$^+$] 237.1127, $C_{13}H_{17}O_4$ requires 237.1127; *m*/*z*: 236 (100%, M$^+$).

4.30. Preparation of hexacarbonyl [(2*R*,3*S*,5*R*)-3-acetoxy-2-acetoxymethyl-5-[μ-[(1,2-η:1,2-η)-ethynyl]]-tetrahydrofuran] dicobalt-(Co–Co) (26β)

To a stirred solution of **15β** (97.8 mg, 0.43 mmol) in acetonitrile (1.8 mL) was added cobalt carbonyl (182.5 mg, 0.53 mmol, 1.2 equiv) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then concentrated in vacuo and purified by flash chromatography on silica gel eluting with petroleum spirits/ethyl acetate 9:1 to give the title compound **26β** as a red oil (196.6 mg, 89% yield); R_f=0.15 (ethyl acetate/petroleum spirits 1:9); ν_{max} (KBr)/cm^{-1} 2932, 2106, 2067, 2018, 1746, 1236; δ_H ($CDCl_3$, 400 MHz) 6.08 (s, 1H), 5.21 (s, 2H), 4.20 (s, 4H), 2.35 (s, 1H), 1.25 (s, 6H); δ_C (100.6 MHz, $CDCl_3$) 199.3, 82.5, 78.6, 76.5, 72.1, 64.3, 41.0, 29.7, 21.1, 20.7.

4.31. Preparation of hexacarbonyl [(2*R*,3*S*,5*S*)-3-acetoxy-2-acetoxymethyl-5-[μ-[(1,2-η:1,2-η)-ethynyl]]-tetrahydrofuran] dicobalt-(Co–Co) (26α)

To a stirred solution of **15α** (504.5 mg, 2.2 mmol) in acetonitrile (9.4 mL) was added cobalt carbonyl (920 mg, 2.7 mmol, 1.2 equiv) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then concentrated in vacuo and purified by flash chromatography on silica gel eluting with petroleum spirits/ethyl acetate 9:1 to give the title compound **26α** as a red oil (1.03 g, 90% yield); R_f=0.28 (ethyl acetate/petroleum spirits 1:9); ν_{max} (KBr)/cm^{-1} 2096, 2052, 2019, 1743, 1242, 520; δ_H ($CDCl_3$, 400 MHz) 6.08 (s, 1H), 5.34 (s, 1H), 5.20 (s, 1H), 4.29–4.23 (m, 3H), 2.88–2.85 (m, 1H), 2.09 (s, 6H, 2×CH_3), 1.95 (d, J=14, 1H); δ_C (100.6 MHz, $CDCl_3$) 199.4, 170.6, 170.5, 95.5, 81.4, 79.1, 75.3, 72.7, 63.9, 39.9, 20.9, 20.8.

4.32. Preparation of 2-[(2*R*,4*S*,5*R*)-4-acetoxy-5-acetoxymethyl-tetrahydrofuran-2-yl]-cyclopent-2-enone (27β)

To a stirred solution of **26β** (196.6 mg, 0.38 mmol) in vinyl benzoate (1.1 mL, 7.9 mmol, 20.9 equiv) was added, by syringe pump over a 3 h period, a solution of *N*-methylmorpholine *N*-oxide recrystallized from moist acetone (567.9 mg, 4.9 mmol, 12.8 equiv) in DCM (11.6 mL) and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was then concentrated in vacuo and purified by flash chromatography eluting firstly with ethyl acetate to eliminate cobalt salts, and then with petroleum spirits/ethyl acetate 1:1 to give the title compound **27β** as a pale brown oil (57.4 mg, 53% yield); R_f=0.30 (ethyl acetate/petroleum spirits 1:1); $[\alpha]_D^{25}$ +22.99 (*c* 0.26, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 2961 2917, 2867, 1738, 1705, 1231; δ_H ($CDCl_3$, 400 MHz) 7.59–7.57 (m, 1H, H-6), 5.17 (d, J=6, 1H), 4.83–4.79 (m, 1H), 4.33–4.28 (m, 1H), 4.18–4.12 (m, 2H), 2.62–2.60 (m, 2H), 2.46–2.43 (m, 2H), 2.38 (ddd, J_1=1, J_2=5, J_3=14, 1H, H-2), 2.08 (s, 3H, CH_3), 2.07 (s, 3H, CH_3'), 1.88–1.80 (m, 1H, H-2′); δ_C (100.6 MHz, $CDCl_3$) 207.9, 170.7, 170.6, 158.6, 145.9, 82.1, 76.3, 74.1, 64.1, 37.9, 35.2, 26.8, 21.0, 20.8; HRMS found: [M+H$^+$] 283.1192, $C_{14}H_{19}O_6$ requires 283.1182; *m*/*z*: 282 (100%, M$^+$).

4.33. Preparation of 2-[(2*S*,4*S*,5*R*)-4-acetoxy-5-acetoxymethyl-tetrahydrofuran-2-yl]-cyclopent-2-enone (27α)

To a stirred solution of **26α** (848.1 mg, 1.7 mmol) in vinyl benzoate (4.7 mL, 33.9 mmol, 20.4 equiv) was added, by syringe pump over a 3 h period, a solution of *N*-methylmorpholine *N*-oxide recrystallized from moist acetone (2.44 g, 20.8 mmol, 12.6 equiv) in DCM (50.0 mL) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated in vacuo and purified by flash chromatography eluting firstly with ethyl acetate to eliminate cobalt salts, and then with petroleum spirits/ethyl acetate 1:1 to give the title compound **27α** as a pale brown oil (250.7 mg, 54% yield); R_f=0.28 (ethyl acetate/petroleum spirits 1:1); $[\alpha]_D^{25}$ +21.99 (*c* 0.86, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 2923, 1741, 1696, 1236; δ_H ($CDCl_3$, 400 MHz) 7.60 (dd, J_1=3, J_2=4, 1H, H-6), 5.17–5.14 (m, 1H), 4.90–4.86 (m, 1H), 4.29 (dt, J_1=4, J_2=6, 1H), 4.25 (dd, J_1=4, J_2=12, 1H, H-5), 4.15 (dd, J_1=6, J_2=12, 1H, H-5′), 2.72–2.67 (m, 1H, H-2), 2.65–2.60 (m, 2H), 2.46–2.44 (m, 2H), 2.09 (s, 3H, CH_3), 2.02 (s, 3H, CH_3'), 2.00–1.97 (m, 1H, H-2′); δ_C (100 MHz, $CDCl_3$) 208.0, 170.8, 170.4, 158.3, 146.6, 81.3, 75.6, 74.1, 64.1, 37.0, 35.3, 26.6, 20.9, 20.9; HRMS found: [M+H$^+$] 283.1169, $C_{14}H_{19}O_6$ requires 283.1182; *m*/*z*: 282 (100%, M$^+$).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.046.

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