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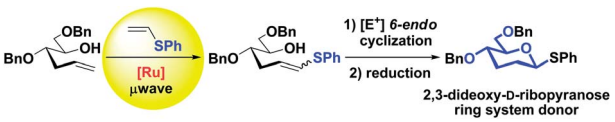
Ruthenium-catalyzed cross-metathesis with electron-rich phenyl vinyl sulfide enables access to 2,3-dideoxy-D-ribopyranose ring system donors

Omar Boutureira,* M. Isabel Matheu, Yolanda Díaz and Sergio Castillón

Microwave irradiation effectively accelerates the cross-metathesis reaction of 2-deoxy-D-ribose hydroxyalkene and derivatives with electron-rich phenyl vinyl sulfide using commercially available ruthenium-based catalysts, thus providing a flexible metal-mediated route to 2,3-dideoxy-D-ribopyranose ring system donors.



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Ruthenium-catalyzed cross-metathesis with electron-rich phenyl vinyl sulfide enables access to 2,3-dideoxy-D-ribopyranose ring system donors†

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2,3-Dideoxy-D-ribopyranose units are important ring systems found in nature. Herein, we develop a metal-mediated strategy to form this important scaffold featuring a cross-metathesis reaction of the corresponding sugar-derived hydroxyalkene with electron-rich phenyl vinyl sulfide using commercially available ruthenium-catalysts under microwave irradiation as a key step. The final 2,3-dideoxyhexopyranose ring is generated in a single step upon 6-*endo* electrophilic cyclization.

Introduction

2,3-Dideoxy- and 2,3,6-trideoxyhexoses are carbohydrate ring systems found in a variety of natural products.[1] These structures are primary constituents of the oligosaccharide side chains of various antibiotics such as kigamicins,[2] landomycins,[3] urdamycins[3,4] and amicetin,[5] among others. Moreover, synthetic 2,3-dideoxy-D-ribopyranosyl nucleoside antibiotics have shown promising antitumor and antiviral activities and also constitute the repeating unit of unnatural hexopyranosyl-(6′ → 4′)-oligonucleotide systems[6] (Fig. 1).

Previous strategies for the preparation of such structures are mainly limited to classical carbohydrate methods (from D-glucal), which typically suffer from long linear and operationally tedious sequences.[1,7] Metal-mediated protocols have recently emerged as attractive alternatives because they enable straightforward access to key sugar intermediates and rare building blocks using a reduced number of steps.[8] As such, olefin cross-metathesis (CM) represents a versatile, powerful metal-mediated C–C bond forming process for the construction of complex carbohydrate-based products.[9] A number of novel applications have become possible due to major advances in catalyst design that led to high yielding transformations, under mild conditions and remarkably, in the presence of a variety of functional groups that were originally detrimental for a productive reaction.[10] For example, by using allyl chalcogens[11] as "forbidden"-atom-containing reactive handles, new and exciting applications such as chemical protein modifications are now accessible,[12] hence representing the renaissance of such groups in catalysis. However, despite all this progress, CM reactions with electron-rich vinyl olefins[13] remains an underrepresented area of olefin metathesis when compared to other twin systems such as ring-opening cross-metathesis (ROCM),[14] ring-closing metathesis (RCM)[15] and enyne cross-metathesis (EYCM).[16] To the best of our knowledge, only a few examples of Ru-CM reactions involving electron-rich vinyl sulfides with model vinyl chlorides[17] and silanes[18] have been described to date, yet the use of such procedures for the preparation of more advanced, synthetically challenging systems remains largely unexplored. This reduced and sometimes non-existent reactivity has been attributed to the formation of relatively unreactive Fischer carbenes, which either rapidly decompose or fail to react further.[19] These findings encouraged us to demonstrate that this particularly challenging transformation can be applied to the construction of an important 2,3-dideoxyhexopyranosyl ring system. Thus, a flexible strategy was envisaged starting from 2-deoxy-D-ribofuranose and featuring a CM reaction of the corresponding sugar-derived hydroxyalkene with electron-rich

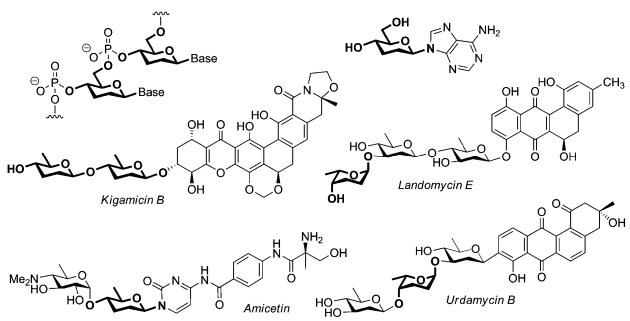

Fig. 1 Representative examples of compounds containing 2,3-dideoxy- and 2,3,6-trideoxyhexose ring systems.

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† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **3**, **6**, **9c** and **11**. See DOI: 10.1039/c4ra01668h

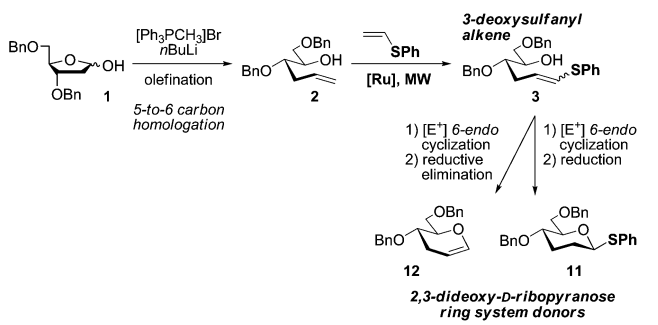
phenyl vinyl sulfide using commercially available Ru-catalysts under microwave (MW) irradiation as a key step (Scheme 1).

Indeed, this transformation will enable the concise synthesis of key 3-deoxysulfanyl alkene intermediate **3** from readily available starting materials that will be further elaborated to the expected 2,3-dideoxy ring system donors **11** (a ready-to-use 1-thioglycosyl donor) and **12** in very few steps.

Results and discussion

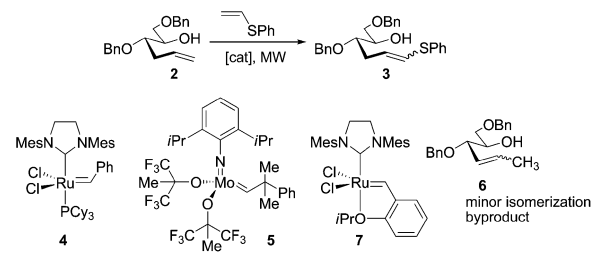
The first step of the proposed route involves a five-to-six carbon homologation of 2-deoxy-D-ribofuranose **1** to afford **2** using a reported Wittig olefination.[20] We next focused on the synthesis of 3-deoxysulfanyl alkene intermediate **3** using the aforementioned CM of 2-deoxysugar hydroxyalkene **2** and phenyl vinyl sulfide as a key step (Table 1).

To select the most suitable catalyst and reaction conditions, initial investigations were carried out under thermal heating using catalysts **4** and **5** (entries 1–3). Reactions in refluxing CH_2Cl_2 with **4** or toluene with **5** failed to generate any CM product (entries 1 and 2). Fortunately, even though the reaction did not reach complete conversion after 20 h in refluxing toluene, the coupled product was obtained in 37% yield and 1 : 1 *Z*–*E* ratio (entry 3) using **4**. With the above results in hand, we carried out additional experiments under MW irradiation to shorten the prolonged reaction time and elevated temperature necessary for these CM reactions, which usually leads to thermal degradation of the ruthenium catalysts.[21] Despite its widespread application in catalytic reactions, microwave-assisted metathesis reactions have only recently gained increasing popularity.[22] In particular, recent reports of dramatic improvements in reaction rates and yields in challenging CM reactions provided by MW irradiation[23] prompted us to explore this avenue (entries 4–11). MW irradiation with readily available Ru-catalyst **4** improved the yield (up to 50%) while impressively reducing the reaction time from 20 to 1 h. Since prolonged reaction times did not increased the conversion, we found that the crude can be purified and subjected to another round of metathesis to finally increase the isolated yield up to 80% (entry 4). Indeed, results from entries 4–6 suggest that the reaction temperature (110–150 °C) reached in the reaction vessel is the more determinant factor in microwave-assisted CM reactions between **2** and phenyl vinyl sulfide.[24] Because no decomposition of starting material was observed in any case, the formation of **3** seems to be only dependent on the catalytically active ruthenium species, which is also reflected in the correlation of yield with the relative amount of the employed ruthenium complex **4** (entries 6 and 7). However, it is worth noting that a reaction temperature higher than 150 °C did not always lead to a higher conversion. Thus, raising the temperature to 175 °C resulted in a decreased yield (37%), most likely due to catalyst decomposition as well as to the formation of 10% of isomerized byproduct **6**. In addition, no significant improvement in the conversion was observed when catalyst **4** was added in two portions separated by a 1 h period (entry 8). We next investigated the reactivity of Hoveyda–Grubbs catalyst **7**. The reaction in toluene afforded 18% conversion to CM product **3** and 10% to isomerized **6** (entry 9). Interestingly, by changing the solvent from toluene to 1,2-dichlorobenzene (DCB) and increasing the temperature from 150 to 200 °C, the conversion increased from 18 to 30%. Furthermore, this change in the solvent properties



Scheme 1 Proposed strategy for the preparation of 2,3-dideoxy-D-ribopyranose ring system donors **11** and **12** using a CM reaction with electron-rich phenyl vinyl sulfide as a key step.

Table 1 Optimization of the microwave-assisted CM reaction conditions of **2** with electron-rich phenyl vinyl sulfide[a]



Entry	Catalyst (mol%)	Solvent	*T* (°C)	*t* (h)	Distribution[b] (%) 2	3	*Z*–*E* ratio[b] of **3**
1[c]	**4** (20)	CH_2Cl_2	40	20	100	—	—
2[c]	**5** (20)	$PhCH_3$	110	17	100	—	—
3[c]	**4** (20)	$PhCH_3$	110	20	63	37	1 : 1
4[d]	**4** (20)	$PhCH_3$	150	1	50	50(80)[e]	1 : 1
5	**4** (20)	$PhCH_3$	110	4	93	7	1 : 1
6	**4** (20)	$PhCH_3$	120	2	80	20	1 : 1
7	**4** (10)	$PhCH_3$	120	1	90	10	1 : 1
8	**4** (20)[f]	$PhCH_3$	175	2	53[g]	37	1 : 1
9	**7** (20)	$PhCH_3$	150	1	54[g]	18	1 : 1
10	**7** (20)	DCB	200	1	60[g]	30	1 : 1
11[h]	**7** (20)	DCB	200	2	20	5	1 : 2

[a] *General conditions*: a solution of phenyl vinyl sulfide (5 equiv.), catalyst (20 mol%) and **2** (1 equiv.) in dry and degassed solvent (0.5 M) was microwave irradiated in a sealed tube using a CEM-Discover™ single-mode synthesizer (temperature control using an external surface sensor, fixed hold time off, normal absorption mode) unless otherwise indicated. [b] Determined by ^{1}H NMR. [c] Thermal heating under open vessel reflux conditions. [d] Prolonged reaction times did not increased the conversion. [e] Isolated yield after two consecutive reaction cycles (see Experimental section for details). [f] Added in two portions. [g] Variable amounts of isomerization byproduct **6** (10–28% and 1 : 5 *Z*–*E* ratio) were also detected. [h] 2,6-Dichloro-1,4-benzoquinone (10 mol %) was added as an additive. DCB = 1,2-dichlorobenzene.

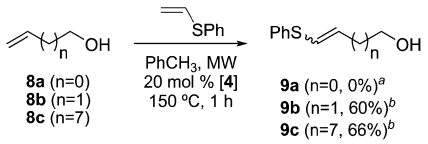
resulted in a reduction of **6** from 28 to 10% (entry 10). Repeating the reaction using 2,6-dichloro-1,4-benzoquinone (10 mol%) as an additive to prevent olefin isomerization[25,26] led only to the CM product in 5% conversion and 1 : 2 *Z*–*E* ratio, although this may be a reflection of incompatibility of either **2** or phenyl vinyl sulfide with the additive (entry 11).

Collectively, the above observations suggest that the formation of Fischer-type carbenes during the Ru-catalyzed CM reactions between electron-rich phenyl vinyl sulfide and terminal 2-deoxysugar hydroxyalkene **2** decreases productive CM drastically, although good conversions (up to 80%) are still achieved using a 40 mol% of catalyst loading. The higher concentration of reactive phenyl vinyl sulfide olefin causes less interaction between the catalyst and the hydroxyalkene, reducing the formation of active vinylalkylidene species and necessitating higher temperatures in order to achieve significant conversion. Importantly, this elevated concentrations are otherwise required since the stepwise addition of increasing amounts of phenyl vinyl sulfide showed the incipient detection of small amounts of undesired dimerization byproducts.

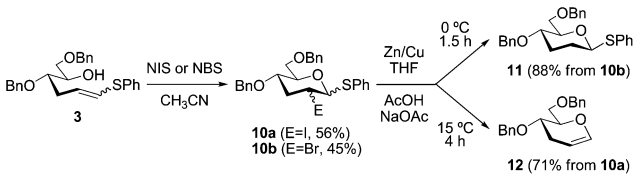
The substrate scope was expanded next using alkenols **8a–c** with phenyl vinyl sulfide as electron-rich olefin partner under optimized reaction conditions (Scheme 2). Despite the expected negative outcome observed with allyl alcohol, due to the known isomerization process previously shown in this type of compounds and their ether counterparts with both first and second Grubbs catalysts,[27] cross-metathesis products **9b,c** where pleasingly obtained in good yields (up to 66% after three reaction cycles) and 1 : 1 *Z*–*E* ratio.

Additional experiments with phenyl vinyl selenide as electron-rich olefin partner to afford selanyl alkenes[28] with the ultimate goal of developing the corresponding selenoglycosyl donors proved unsuccessful.

Having established a flexible method for accessing workable amounts of acyclic hexosulfanyl alkene **3**, we next demonstrated that this intermediate is able to generate a hexopyranose ring system, in a single step, upon 6-*endo* electrophilic cyclization[29] (Scheme 3). Thus, NIS- or NBS-induced 6-*endo* cyclization afforded intermediates **10a,b** in moderate yields (up to 56%) and 1 : 1 epimeric mixtures at both C-1 and C-2 (for **10a**) that were subsequently transformed into 1-thioglycosyl donor **11** (88% from **10b**) and 3-deoxyglycal **12** (71% from **10a**) after C–halogen reduction.[30] These results reinforce the strategic character of **3** since these privileged D-hexopyranose building blocks are obtained from a single precursor and, for example, they can be used for the stereoselective synthesis of naturally occurring 2,3,6-trideoxy (D-amicetose)-containing oligosaccharides[1,7] and other challenging structures such as marine ladder toxins.[31]



Scheme 2 Reaction scope. [a] The starting material decomposed. [b] Isolated yield after three consecutive reaction cycles (60 mol% of catalyst loading in total) and 1 : 1 *Z*–*E* ratio.



Scheme 3 Electrophilic cyclizations of **3** and synthesis of representative glycosyl donors **11** and **12**.

Conclusions

In summary, we have demonstrated that the particularly challenging CM of a 2-deoxysugar hydroxyl alkene with electron-rich phenyl vinyl sulfide using readily available Ru-catalysts as a key step can be applied to the construction of 2,3-dideoxy-D-ribo-pyranose ring system donors and analogs. MW irradiation allows the required high reaction temperature to be reached quickly and homogeneously, thereby providing enough energy for a successful metathesis reaction.

Experimental section

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a (400 MHz for ^{1}H) and (100.6 MHz for ^{13}C) spectrometer. Spectra were fully assigned using COSY, HSQC, HMBC and NOESY. All chemical shifts are quoted on the δ scale in ppm using residual solvent as the internal standard (^{1}H NMR: $CDCl_3$ = 7.26, CD_3OD = 4.87; and ^{13}C NMR: $CDCl_3$ = 77.23; CD_3OD = 49.0). Coupling constants (J) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet and app = apparent. Infrared (IR) spectra were recorded on a Jasco FT/IR-600 Plus ATR Specac Golden Gate spectrophotometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Elemental analyses (C, H, N, and S) were performed with a Carlo Erba EA 1108 Analyzer in the Servei de Recursos Científics (URV). Optical rotations were recorded on a Perkin-Elmer 241 MC polarimeter in a 1 dm cell at 20 °C. Concentrations (c) are given in g per 100 mL. Gas chromatography-mass spectrometry (GC-MS) was measured on an Agilent 9575C MSD apparatus with electronic impact ionization (EI, 70 eV). High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier liquid chromatograph coupled time-of-flight mass spectrometer (HPLC-MS-TOF) with either electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) by the ICIQ MS unit. Nominal and exact m/z values are reported in Daltons. Thin layer chromatography (TLC) was carried out using commercial aluminium backed sheets coated with 60F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λ_{max} = 254 nm) and/or 6% H_2SO_4 in EtOH and/or 2% $PdCl_2$ and 15% H_2SO_4 in water. Flash column chromatography was carried out using silica gel 60 (40–63 μm). Radial chromatography was performed on 1, 2, or 4 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. Mobile phases are reported in relative composition (*e.g.* 1 : 1 EtOAc–hexane v/v). All other reagents and anhydrous

solvents (Analytical or HPLC grade) were used as received from commercial suppliers. All reactions using anhydrous conditions were performed using flame-dried apparatus under an atmosphere of argon.

(*Z*–*E*)-4,6-Di-*O*-benzyl-1,2,3-trideoxy-1-phenylsulfanyl-D-*erythro*-hex-1-enitol (3)

A solution of **2** (ref. 20) (40 mg, 0.13 mmol), phenyl vinyl sulfide (86 μL, 0.64 mmol) and catalyst **4** (22 mg, 20 mol%) in dry and degassed toluene (256 μL) was microwave irradiated in a sealed tube at 150 °C for 1 h (temperature control using an external surface sensor, fixed hold time off, normal absorption mode) using a CEM-Discover™ single-mode synthesizer. The residue was filtered through a short path of silica (1 : 1 EtOAc–petrol) and the solvent evaporated. The crude was subsequently subjected to a second round of the initial reaction conditions (two reaction cycles in total). The solvent was then evaporated and the crude product was purified by radial chromatography (from hexane to 1 : 3 EtOAc–hexane) to afford **3** (32 mg, 80%) as an inseparable 1 : 1 *Z*–*E* mixture as a colourless syrup. R_f (1 : 4 EtOAc–hexane): 0.28. Data for **3***E*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 15H), 6.24 (d, J = 15.0 Hz, 1H), 6.00 (ddd, J = 15.0, 7.5 and 7.5 Hz, 1H), 4.67–4.49 (m, 4H), 3.87–3.84 (m, 1H), 3.70–3.53 (m, 3H), 2.66–2.64 (m, 1H), 2.54–2.43 (m, 1H), 2.44 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.4–124.5, 128.6, 125.4, 79.0, 73.6, 72.3, 71.5, 71.2, 34.1. Data for **3***Z*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 15H), 6.31 (d, J = 11.0 Hz, 1H), 5.94 (ddd, J = 11.0, 7.2 and 7.2 Hz, 1H), 4.67–4.49 (m, 4H), 3.89–3.86 (m, 1H), 3.70–3.53 (m, 3H), 2.66–2.64 (m, 1H), 2.54–2.43 (m, 1H), 2.49 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.3–124.2, 128.5, 125.4, 78.8, 73.6, 72.5, 71.7, 71.1, 30.0. Spectroscopic data are consistent with those reported.[29]

(*Z*–*E*)-4-Phenylsulfanyl-3-buten-1-ol (9b)

A solution of 3-buten-1-ol **8b** (17 mg, 0.23 mmol), phenyl vinyl sulfide (156 μL, 1.15 mmol) and catalyst **4** (39 mg, 20 mol%) in dry and degassed toluene (462 μL) was microwave irradiated in a sealed tube at 150 °C for 1 h (temperature control using an external surface sensor, fixed hold time off, normal absorption mode) using a CEM-Discover™ single-mode synthesizer. The residue was filtered through a short path of silica (1 : 1 EtOAc–petrol) and the solvent evaporated. The crude was subsequently subjected to a second round of the initial reaction conditions (this protocol was repeated up to three reaction cycles in total). The solvent was then evaporated and the crude product was purified by column chromatography (1 : 3 EtOAc–hexane) to afford **9b** (25 mg, 60%) as an inseparable 1 : 1 *Z*–*E* mixture as a brownish syrup. R_f (1 : 3 EtOAc–hexane): 0.17; IR (ATR) ν_{max}/cm^{-1} 3345, 3259, 3056, 2923, 2853, 1749, 1583, 1479, 1439, 1240, 1047, 741; MS (EI, 70 eV) m/z (%) 180.1 (52) $[M]^+$, 149.1 (100), 134.1 (35), 116.1 (61), 109.1 (13), 103.1 (3), 91.1 (4), 85.0 (4), 77.1 (12), 71.0 (6), 65.1 (9), 51.0 (10); HRMS (APCI) m/z calcd for $C_{10}H_{13}OS$ $[M + H]^+$ 181.0682, found 181.0683. Data for **9b***E*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.17 (m, 5H), 6.29 (dd, J = 15.2 and 1.6 Hz, 1H), 5.92 (dt, J = 15.2 and 7.4 Hz, 1H), 3.72 (bt, J = 6.2 Hz, 2H), 2.44 (ddd, J = 13.6, 6.2 and 1.6 Hz, 2H), 1.46 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.1–126.7, 125.0, 62.0, 32.9. Data for **9b***Z*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.17 (m, 5H), 6.37 (dd, J = 9.3 and 1.6 Hz, 1H), 5.86 (dt, J = 9.3 and 7.4, 1H), 3.77 (bt, J = 6.2 Hz, 2H), 2.55 (ddd, J = 14.0, 6.2 and 1.6 Hz, 2H), 1.46 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.1–126.7, 126.3, 62.1, 36.6. Spectroscopic data are consistent with those reported.[32]

(*Z*–*E*)-10-Phenylsulfanyl-9-decen-1-ol (9c)

A solution of 9-decen-1-ol **9c** (37.2 mg, 0.23 mmol), phenyl vinyl sulfide (156 μL, 1.15 mmol) and catalyst **4** (39 mg, 20 mol%) in dry and degassed toluene (462 μL) was microwave irradiated in a sealed tube at 150 °C for 1 h (temperature control using an external surface sensor, fixed hold time off, normal absorption mode) using a CEM-Discover™ single-mode synthesizer. The residue was filtered through a short path of silica (1 : 1 EtOAc–petrol) and the solvent evaporated. The crude was subsequently subjected to a second round of the initial reaction conditions (this protocol was repeated up to three reaction cycles in total). The solvent was then evaporated and the crude product was purified by column chromatography (1 : 3 EtOAc–hexane) to afford **9c** (40.2 mg, 66%) as an inseparable 1 : 1 *Z*–*E* mixture as a brownish syrup. R_f (1 : 3 EtOAc–hexane): 0.28; IR (ATR) ν_{max}/cm^{-1} 3364, 3074, 2925, 2853, 1709, 1584, 1479, 1439, 1361, 1220, 1054, 949, 909, 737; HRMS (ESI) m/z calcd for $C_{16}H_{24}NaOS$ $[M + Na]^+$ 287.1414, found 287.1435. Data for **9c***E*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.17 (m, 5H), 6.14 (dd, J = 14.8 and 1.2 Hz, 1H), 6.01 (dt, J = 14.8 and 7.0 Hz, 1H), 3.69–3.62 (m, 2H), 2.17 (ddd, J = 14.4, 7.0 and 1.2 Hz, 2H), 1.60–1.23 (m, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.9–126.2, 120.9, 63.3, 33.3–25.9. Data for **9c***Z*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.17 (m, 5H), 6.20 (dd, J = 9.3 and 1.6 Hz, 1H), 5.83 (dt, J = 9.3 and 7.4, 1H), 3.69–3.62 (m, 2H), 2.26 (ddd, J = 14.4, 7.4 and 1.6 Hz, 2H), 1.60–1.23 (m, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.8–126.2, 122.8, 63.3, 33.3–25.9.

Phenyl 4,6-di-*O*-benzyl-2,3-dideoxy-2-iodo-1-thio-α–β-D-*arabino*/*ribo*-hexopyranoside (10a)

NIS (164.1 mg, 0.67 mmol) was added to a solution of **3** (1 : 1 *Z*–*E*) (180 mg, 0.43 mmol) in dry CH_3CN (3.5 mL) at −30 °C and stirred for 0.5 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $Na_2S_2O_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by radial chromatography (from hexane to 1 : 3 EtOAc–hexane) to afford **10a** (130 mg, 56%) as a 1 : 1 α–β mixture and 1 : 1 ax/eq. mixture at C-2 (*arabino*/*ribo*) as a yellowish syrup. Selected data for *ribo*-**10a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.19 (m, 15H), 4.83 (dd, J = 9.9 and 5.1 Hz, 1H), 4.82 (dd, J = 10.0 and 4.4 Hz, 1H), 4.22 (m, 1H), 3.86 (ddd, J = 13.0, 9.5 and 4.4 Hz, 1H), 3.69 (m, 2H), 3.66 (m, 2H), 3.49 (dt, J = 10.8 and 4.8 Hz, 1H), 3.45 (ddd, J = 10.4, 9.5 and 4.4 Hz, 1H), 2.85 (dt, J = 12.8 and 4.4 Hz, 1H), 2.60 (dt, J = 12.2 and 4.7 Hz, 1H), 2.45 (dt, J = 13.2 and 9.8 Hz, 1H), 2.10 (ddd, J = 13.0, 12.8 and 10 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.4–124.2, 99.2, 92.1, 79.0–53.6, 41.7, 35.9, 25.7, 22.6. Selected data for *arabino*-**10a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.18 (m, 15H),

4.43 (s, 1H), 4.27 (s, 1H), 4.16 (m, 1H), 3.90 (m, 1H), 3.80 (m, 2H), 3.73 (m, 2H), 3.67 (m, 2H), 2.60 (ddd, J = 14.5, 4.2 and 3.7 Hz, 1H), 2.30–2.17 (m, 2H), 2.05 (ddd, J = 14.5, 10.2 and 3.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.3–127.7, 93.4, 84.6, 79.2–69.5, 37.0, 33.1, 29.6, 26.8.

Phenyl 4,6-di-*O*-benzyl-2,3-dideoxy-1-thio-α-D-*erythro*-hexopyranoside (11)

NBS (63.5 mg, 0.36 mmol) was added to a solution of **3** (1 : 1 *Z*–*E*) (100 mg, 0.23 mmol) in dry CH_3CN (3.4 mL) at −30 °C and stirred for 2.5 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $Na_2S_2O_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was filtered through a short silica plug (from hexane to 1 : 3 EtOAc–hexane) and the solvent evaporated to afford phenyl 4,6-di-*O*-benzyl-2,3-dideoxy-2-bromo-1-thio-α-D-*arabino*/*ribo*-hexopyranoside **10b** (53 mg, 45%) as a brownish syrup. The isolated product decomposed on standing and was therefore quickly subjected to the next reaction. A mixture of **10b** (40 mg, 0.08 mmol) and NaOAc (9.6 mg, 0.12 mmol) were dissolved in THF (0.5 mL) and acetic acid (7 μL) at 0 °C. Zn/Cu couple (53 mg) was then added and the reaction was left to stir at the same temperature for 1.5 h. The mixture was then diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by radial chromatography (from hexane to 1 : 5 EtOAc–hexane) to afford **11** (31 mg, 88%) as a colourless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.22 (m, 15H), 4.71 (d, J = 10.4 Hz, 1H), 4.61–4.40 (m, 4H), 3.80–3.68 (m, 4H), 3.58 (ddd, J = 9.6, 4.8 and 2.0 Hz, 1H), 3.47 (ddd, J = 9.6, 10.4 and 4.4 Hz, 1H), 2.88 (ddd, J = 12.4, 4.8 and 4.4 Hz, 1H), 2.03 (ddd, J = 12.4, 11.2 and 10.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 133.4–127.8, 89.5, 82.0, 73.6, 72.7, 71.7, 69.3, 45.7, 41.9. Spectroscopic data are consistent with those reported.[30]

1,5-Anhydro-4,6-di-*O*-benzyl-D-*erythro*-hex-1-enitol (12)

A mixture of **10a** (130 mg, 0.24 mmol) and NaOAc (27 mg, 0.33 mmol) were dissolved in THF (0.5 mL) and acetic acid (20 μL) at 0 °C. Zn/Cu couple (160 mg) was then added and the reaction mixture was warmed to 15 °C and stirred for 4 h. The mixture was then diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by radial chromatography (from hexane to 1 : 4 EtOAc–hexane) to afford **12** (50 mg, 71%) as a colourless syrup. R_f (1 : 3 EtOAc–hexane): 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.21 (m, 10H), 6.36 (ddd, J = 6.4, 2.4 and 1.6 Hz, 1H), 4.63 (ddd, J = 6.4, 5.2 and 2.6 Hz, 1H), 4.62–4.50 (m, 4H), 3.90 (dd, J = 8.0 and 4.0 Hz, 1H), 3.79 (m, 3H), 2.38 (dddd, J = 16.4, 6.0, 5.2 and 1.6 Hz, 1H), 2.08 (dddd, J = 16.4, 8.4, 2.6 and 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.3, 138.4–127.8, 97.8, 76.9, 73.7, 71.3, 70.7, 69.2, 26.7. Spectroscopic data are consistent with those reported.[30]

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