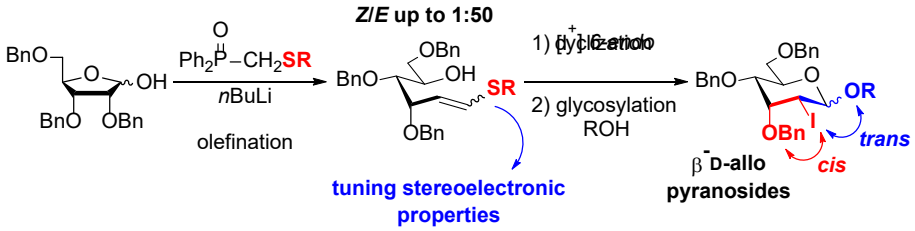
Tuning the Stereoelectronic Properties of 1-Sulfanyl-hex-1-enitols for the Sequential Stereoselective Synthesis of 2-Deoxy-2-iodo-*β*-D-allopyranosides

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

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/ Marcel·lí Domingo s/n, 43007 Tarragona, Spain.

**E-mail(s): omar.boutureira@urv.cat, yolanda.diaz@urv.cat*

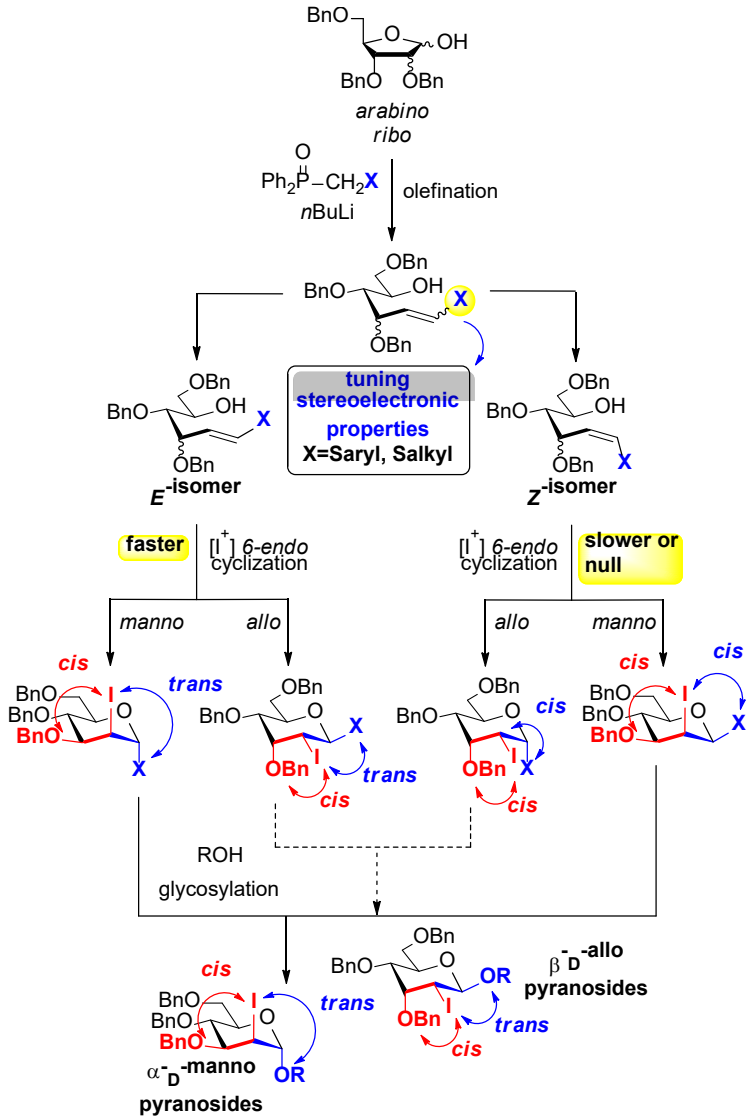


ABSTRACT: The preparation of challenging 2-deoxy-2-iodo-*β*-D-*allo* precursors of 2-deoxy-*β*-D-*ribo*-hexopyranosyl units and other analogs is reported using a robust olefination-cyclization-glycosylation sequence. Here, we particularly focus on tuning the stereoelectronic properties of the alkenyl sulfides intermediates in order to improve the diastereoselectivity of the cyclization step, hence the efficiency of the overall transformation. Phosphine oxides with general formula $Ph_2P(O)CH_2SR$ (R=*t*Bu, Cy, *p*MeOPh, 2,6-di-ClPh, and 2,6-di-MePh) were easily synthesized and subsequently used in the olefination reaction with 2,3,5-tri-*O*-benzyl-D-ribose and D-arabinose. The corresponding sugar-derived alkenyl sulfides were submitted to a *6-endo* $[I^+]$-induced cyclization and the resulting 2-deoxy-2-iodohexopyranosyl-1-thioglycosides used as glycosyl donors for the stereoselective synthesis of 2-deoxy-2-iodohexopyranosyl glycosides. Among the different *S*-groups studied, *t*Bu derivative was the best performer for the synthesis of cholesteryl 2-deoxy-2-iodo-mannopyranosides whereas for the synthesis of 2-deoxy-2-iodo-allopyranosides none of the derivatives here studied proved superior to the phenyl analog previously described. Glycosylation of cholesterol with different D-*allo* and D-*manno* derivatives produced 2-deoxy-2-iodoglycosides with stereoselectivities in the same order in each case, reinforcing the involvement of an oxocarbenium ion as the common intermediate of this crucial glycosylation step.

INTRODUCTION

2-Deoxy and 2,6-dideoxy-*β*-D-*ribo*-hexopyranosyl units are structural motifs present in many natural products of plant origin.[1] They are recurrent in cardiac glycosides,[2] appetite suppressants,[3] and synthetic, biologically active nucleosides and nucleotides.[4] Despite recent advances in the preparation of 2-deoxy and 2,6-dideoxyglycosides,[5] those with all-*cis* C2-C3-C4 *β*-D-*ribo* configuration (directly accessed from 2-deoxy-2-iodo-*β*-D-*allo*)[6] remain challenging structures. Methods typically employed for their preparation involve the use of D-allal derivatives with $Ph_3P{\cdot}HBr$[7] or Re(V)[8] catalysts, 2-deoxy[9] and other specialized 2,6-anhydro-2,6-dideoxy-2,6-dithio glycosyl donors,[10] and *de novo* metal-mediated protocols.[11] In this context, our group developed a general two-step procedure for synthesizing 2-deoxy-2-iodo-1-thioglycosides from furanoses which were used as glycosyl donors for the synthesis of 2-deoxyglycosides, being particularly efficient for those with *β*-D-*allo* and *xylo* configurations[12] (Scheme 1). The first step is an olefination of furanoses to obtain a *Z/E* mixture of sulfanyl alkene derivatives, which undergo a NIS–induced cyclization reaction in a second step to give 2-deoxy-2-iodo-1-thioglycosides in a regio- and stereoselective manner. This methodology was further refined to develop a *one-pot* procedure[13] directly from the corresponding alkenes and it was also applied to the synthesis of pyranoid glycals of restricted availability[14] (*e.g.* D-allal, D-gulal), 2-iodoglycals[15] to access unnatural 2-*C*-sugar mimetics[16] and futher extended to other electrophiles (*e.g.* $PhSe^+$) leading to 2-deoxy-2-phenylselenenylglycosides.[17] Alternative methods for fine-tuning the reactivity of such vinyl chalcogenides by replacing the sulfur atom with a selenium to alter the stereochemical properties of this moiety towards the electrophile-induced cyclization were also explored.[18] This would ultimately promote the mild activation of the anomeric leaving group at lower temperatures, which has proven to be a key issue to afford better selectivities in the glycosylation step. In all these studies we observed that during the iodonium-induced cyclization of alkenes, the *Z*-alkene cyclizes much more slowly than the *E*-isomer or does not cyclize at all, limiting the efficiency of the cyclization step. Attempts to improve this *E*-selectivity by using metal-mediated cross-metathesis protocols were recently explored in our group but resulted unsuccessful in terms of selectivity (1:1 *Z*/*E* mixtures were typically obtained).[19] Various reagents had been utilized in the olefination of furanoses, including Wittig,[12,20] Wittig–Horner[12] (WH), Horner–Wadsworth–Emmons[12] (HWE)

and Peterson olefination.[12] The best results in terms of chemoselectivity and yield of alkene were obtained under WH conditions, that is, using phosphine oxide carbanions formed by Li–bases, although, as expected for semistabilized carbanions, the alkene product was always obtained as a *Z*/*E* mixture, which resulted inseparable (Scheme 1).

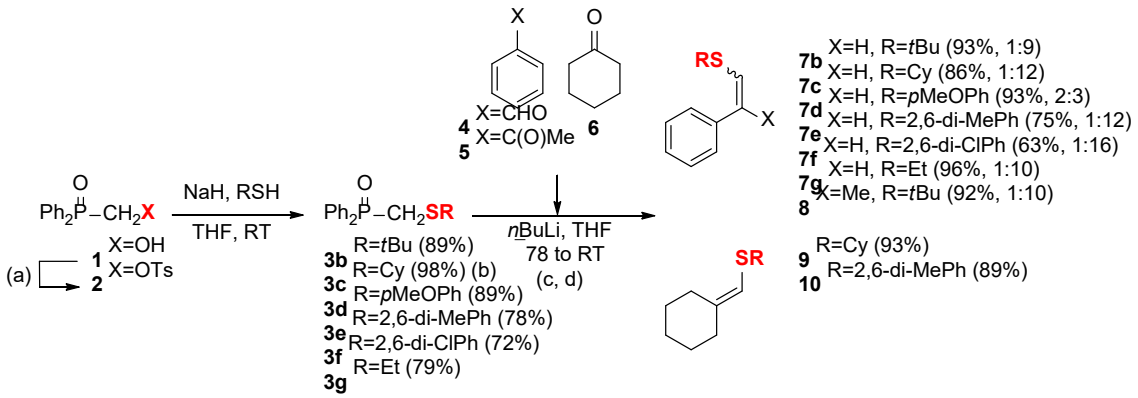


Scheme 1. General strategy for the preparation of representative (C-3eq/ax) 2-deoxy-2-iodo-D-manno and allopyranosyl glycosides after fine tuning the stereoelectronic properties of key 1-sulfanyl-hex-1-enitol intermediates.

To increase the *E* stereoselectivity of the olefination and the efficiency of the cyclization, and eventually the overall 2-deoxyglycoside synthesis, we decided to study the influence of substituents at sulfur on the stereoselectivity of the olefination using a phenyl, substituted phenyl, *tert*-butyl, cyclohexyl, etc.

RESULTS AND DISCUSSION

Synthesis and reactivity of phosphine oxides with model carbonyl compounds. For this study to be done, we first needed to have in our hands a series of (sulfanylmethyl)diphenylphosphine oxides. The most common procedure for preparing phosphine oxide derivatives is the Michaelis–Arbuzov reaction,[21] which consists of reacting an *O*-ethyl-diphenylphosphinite with an electrophilic reagent, typically an alkyl halide. (Sulfanylmethyl)diphenylphosphine oxides[22] have been prepared by Arbuzov reaction with available chloromethyl thioethers[23] (*e.g.* phenylsulfanyl **3a** with R=Ph) although these halides are usually unstable and difficult to prepare. An alternative procedure for synthesizing these phosphine oxides involves reacting methyldiphenylphosphine oxide with *n*BuLi in the presence of an electrophilic heteroatomic reagent. These reagents, however, are rarely available and must be specifically prepared.[24] (Sulfanylmethyl)diphenylphosphine oxides can also be accessed from (tosyloxymethyl)diphenylphosphine oxide **2**[25] (directly obtained from **1**) by a substitution reaction with sulfur nucleophiles[22] (Scheme 2).



Scheme 2. Synthesis of (sulfanylmethyl)diphenylphosphine oxides **3b**–**g** and their reactivity towards model carbonyl compounds **4**–**6**. *Reagents and conditions:* (a) TsCl, DMAP, CH_2Cl_2, reflux, 4 h, 95% (see ref. 25); (b) LDA was used as a base; (c) Isolated yield; (d) *Z*/*E* ratio.

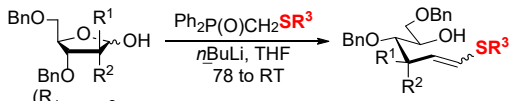
This method was considered the procedure of choice for the preparation of a variety of (sulfanylmethyl)diphenylphosphine oxides since the most common thiolates can be easily prepared *in situ* by deprotonation of readily available thiols. Thus, starting from (tosyloxymethyl)diphenylphosphine oxide **2**, phosphine oxides **3b**–**g** were prepared in excellent yields (up to 98%). We first explored the olefination of benzaldehyde **4** using phosphine oxides **3b**–**g** to give sulfanyl alkenes **7b**–**g**. Highly hindered sulfanyl alkenes **7b,c** and **7e,f** were obtained with good to

excellent yields (up to 93%). High stereoselectivities (*Z*/*E* ≥ 1:9) were obtained when aliphatic alkyl groups and 2,6-disubstituted aryl substituents were used. Only the *p*-methoxyphenylsulfanyl derivative **3d** furnished alkene product **7d** with low stereoselectivity. The formation of *α*-hydroxyphosphine oxide intermediates was not observed in these syntheses. Phosphine oxide **3b**, which bears a *tert*-butylsulfanyl group, was made to react with acetophenone **5** to give sulfanyl alkene **8** with excellent yield (92%) and stereoselectivity (*Z*/*E* 1:10). The configurational assignment of **8** was carried out by comparison with the experimental ^{1}H NMR data reported, where the chemical shift for the vinyl proton geminal to the sulfur moiety in the *E* alkene is unshielded related to that of the *Z* alkene.[26] Phosphine oxides **3c** and **3e** were also treated with cyclohexanone **6** in the presence of *n*BuLi to give sulfanyl alkenes **9** and **10** in excellent 93% and 89% yields, respectively.

Olefination of furanoses. With these results in hand, we turned our attention to the olefination of furanoses. First, 2,3,5-tri-*O*-benzyl-D-ribose **11** was allowed to react with (sulfanylmethyl)diphenylphosphine oxides **3a**–**c** and **3e,f** in the presence of *n*BuLi or LDA at –78 ºC (Table 1). The yields and stereoselectivities obtained were compared to those observed for the reference reaction with phenylsulfanyl-substituted derivative **3a** (Table 1, entry 1). WH olefination of **11** with *tert*-butylsulfanyl derivative **3b** produced sulfanyl alkene **12b** with a 65% yield and an excellent *Z*/*E* ratio of 1:25 (Table 1, entry 2). Cyclohexyl derivative **3c** furnished the desired sulfanyl alkene **12c** with a 47% yield and a moderate-to-good stereoselectivity (Table 1, entry 3). Better yield (83%) and stereoselectivity (*Z*/*E* 1:50) was obtained from 2,6-dimethyl derivative **3e** to give sulfanyl alkene **12e** (Table 1, entry 4). WH reaction with 2,6-dichlorophenyl derivative **3f** generated the corresponding product in low yield and selectivity (Table 1, entry 5). Thus, compared to the phenylsulfanylmethyl)diphenylphosphine oxide **3a** (Table 3, entry 1), increased stereoselectivities were obtained in almost all WH reactions with phosphine oxides **3b,c** and **3e,f**. Particularly relevant are the *Z*/*E* ratios ranging from 1:25 up to 1:50 obtained with phosphine oxides **3b** and **3e** (Table 1, entries 2 and 4). Olefination of 2,3,5-tri-*O*-benzyl-D-arabinofuranose **13** with (sulfanylmethyl)diphenylphosphine oxides **3a,b** and **3d**–**f** was further explored (Table 1, entries 6–10). Obtaining a high *E*-stereoselectivity in the olefination reaction of *arabino* derivatives is especially important as in the cyclization step of the *Z*/*E*-alkene of such a configuration, only the *E*-alkene cyclizes, thus limiting the

efficiency of the entire process.[12] WH olefination of **13** with *tert*-butyl derivative **3b** afforded compound **14b** in excellent yield (93%) and with an improved *E*-selectivity (Table 1, entry 7) compared to those obtained with phenyl derivative **3a** (Table 1, entry 6). WH reaction with *p*-methoxy derivative **3d** produced sulfanyl alkene **14d** with poor yield and stereoselectivity (Table 1, entry 8). In this case, the best stereoselectivity (*Z*/*E* = 1:12) was obtained with 2,6-dimethylphenyl derivative **3e**, although the isolated yield of **14e** was comparably lower than that for **14b** (Table 1, entries 7 *vs.* 9). WH olefination with dichlorophenyl derivative **3f** furnished sulfanyl alkene **14f** with a practical 78% yield and stereoselectivity (Table 1, entry 10). Thus, all sulfanylmethyl phosphine oxides led to the corresponding alkenes with improved *E*-stereoselectivity related to that of the reference phenylsulfanyl-substituted olefinating agent **3a** (Table 1, entry 6). Among the different derivatives, *tert*-butyl derivative **3b** seems to combine better yield and stereoselectivy followed by the 2,6-dimethylphenyl derivative **3e**.

Table 1. Olefination of furanoses **11**, **13** to **12**, **14**[a]



11 (R_1=H, R^2=OBn)
13 (R_1=OBn, R^2=H)

12, **14**

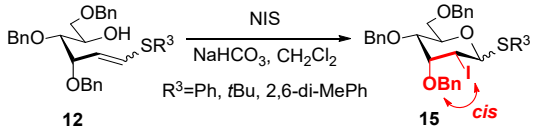
Entry	Furanose	Phosphine oxide (R^3)	Product	Yield (%)	*Z*/*E* ratio[b]
1[c]	**11**	**3a** (Ph)	**12a**	72	1:4
2	**11**	**3b** (*t*Bu)	**12b**	65	1:25
3[d]	**11**	**3c** (Cy)	**12c**	47	1:7
4	**11**	**3e** (2,6-di-MePh)	**12e**	83	1:50
5	**11**	**3f** (2,6-di-ClPh)	**12f**	17(62)[e]	1:2
6[c]	**13**	**3a** (Ph)	**14a**	100	2:3
7	**13**	**3b** (*t*Bu)	**14b**	93	1:8
8	**13**	**3d** (*p*MeOPh)	**14d**	32(50)[e]	1:3
9	**13**	**3e** (2,6-di-MePh)	**14e**	64(93)[e]	1:12
10	**13**	**3f** (2,6-di-ClPh)	**14f**	78	1:6

[a]*General conditions*: phosphine oxide (2 equiv.), *n*BuLi (3.5 equiv.) and furanose (1 equiv.) in dry THF unless otherwise indicated. [b]Determined by integration of the olefinic proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [c]See ref. 12. [d]LDA (3.5 equiv.) was used as a base. [e]Yield in round brackets is based on recovered starting material. Cy=cyclohexyl, LDA=Lithium diisopropylamide.

Cyclization reaction. The sulfanyl-hex-1-enitols prepared were tested in electrophile–induced cyclization reactions to study whether the presence of the different *S*-alkyl or *S*-aryl groups influence the yield and the selectivity of the 6-

endo cyclization reaction. To this end, we selected *S*-2,6-dimethylphenyl- and *S*-*tert*-butyl-substituted *ribo*-hex-1-enitols **12b** and **12e**, which were obtained with the best *Z/E* ratio in the previous olefination experiments. The cyclization reactions were performed under standard conditions, with NIS in the presence of sodium bicarbonate in dichloromethane, starting at –60 ºC, and allowing the temperature to increase until the cyclization reactions started. Results are summarized in Table 2.

Table 2. Iodonium-induced cyclization of **12** to **15**[a]



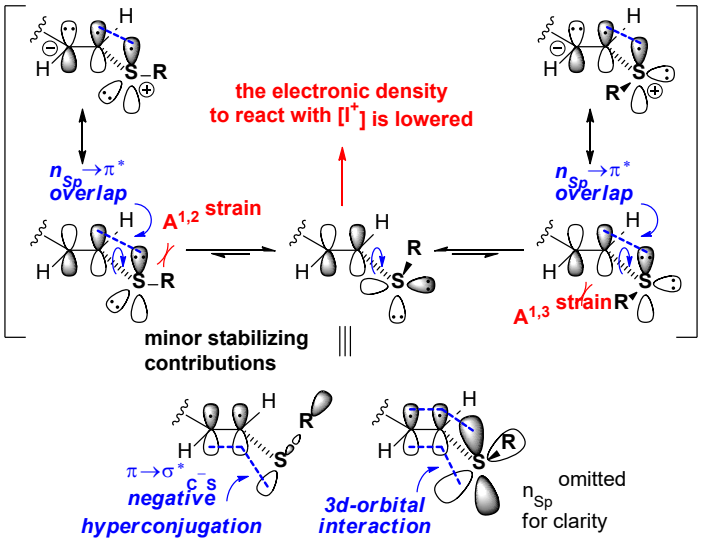
12 **15**

Entry	Hex-1-enitol (*Z*/*E* ratio[b])	*T* (ºC)	*t* (h)	Product	Yield (%)	*α*/*β* ratio[b]
1[c]	**12a** (1:2)	–30 to RT	15	**15a**	77	1:9
2	**12b** (1:8)	–78 to –10	18	**15b**	57	1:13
3	**12e** (1:50)	–78 to –10	18	**15e**	49	1:25

[a]*General conditions*: hex-1-enitol (1 equiv.), NIS (1.5 equiv.) and $NaHCO_3$ (1.5 equiv.) in dry CH_2Cl_2 unless otherwise indicated. [b]Determined by integration of the olefinic and anomeric proton signals in the ^1H NMR spectrum of the crude reaction mixture, respectively. [c]See ref. 12; reaction performed in dry CH_3CN as a solvent.

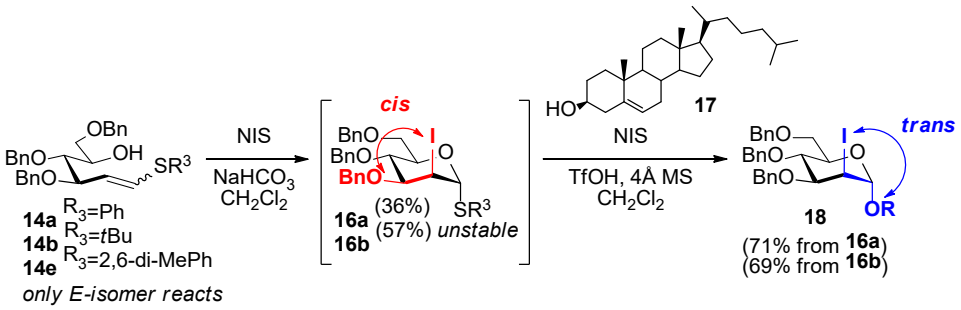
Starting from **12b**, reaction with NIS/$NaHCO_3$ led to *6-endo* cyclization product 2-deoxy-2-iodo-1-thio-allopyranoside **15b** in 57% yield as an anomeric *α*/*β* mixture of 1:13 (Table 2, entry 2). The reaction was comparatively slower than the reference reaction from **12a** (Table 2, entry 1), and required slightly lower temperatures. The moderate yield of **15b** might be a consequence of partial decomposition of the cyclized product under the forced reaction conditions. The steric bulk of the *t*BuS group might be responsible for the low reactivity of alkene **12b** towards cyclization, probably increasing the hindrance of the complex alkene-I^+ system towards intramolecular attack of the hydroxyl group. The reductance to cyclization could also be associated to a stereoelectronic issue; the coplanarity of the alkene system with the sulfur atom ($n_{S(3pz)} \rightarrow \pi^*$ conjugation) in the most reactive conformation for cyclization may be disrupted due to 1,2- and 1,3-allylic ($A^{1,2}$ and $A^{1,3}$) strain between the *t*Bu and the olefinic protons, lowering the electronic density of the double bond and consequently slowing down the electrophilic cyclization (Scheme 3). Additional features that may also account for this reduced electronic density include the inductive and polarizability effects of the SR group together with

hyperconjugative effects such as 3d-orbital interactions and negative hyperconjugation ($\pi \rightarrow \sigma^*_{C-S}$) that may play a minor role if any.[27] A similar result was obtained in the cyclization of **12e** to give 1-thioglycoside **15e** (Table 2, entry 1), although yields were even lower in this case, probably suggesting the presence of even more serious $A^{1,2}$ and $A^{1,3}$ strains with the flat arylsulfanyl framework.



Scheme 3. Stabilizing and destabilizing effects in substituted vinyl sulfides (R=2,6-di-MePh, *t*Bu).

We then studied the cyclization reactions of *arabino*-hex-1-enitols **14b** and **14e**, which had produced the best results in the olefination reaction (Scheme 4). When compound **14b** was submitted to cyclization conditions, 2-deoxy-2-iodo-thio-*manno*-pyranoside **16b** was obtained in 57% yield altogether with 3,4,6-tri-*O*-benzyl-D-glucal byproduct (25%). A similar elimination reaction had been observed previously in our group during the preparation of 2-deoxy-2-iodo[15,28] and 2-deoxy-2-phenylselenenyl-1-thiohexopyranoses.[17] Subsequent glycosylation of cholesterol **17** starting from *tert*-butyl thio-mannopyranoside **16b** rendered **18** as a 37:1 *α/β* mixture in 69% yield, which is in line with the results obtained starting from phenyl derivative **16a** (71%, 37:1 *α/β*).[12] Cyclization of **14e** did not proceed**,** even at room temperature after several days of reaction.



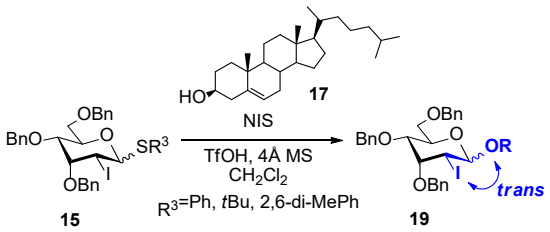
Scheme 4. Cyclization-glycosylation sequence for **14a** (see ref. 12), **14b** and **14e**.

The results obtained from the cyclization of the different *S*-substituted sulfanyl alkenes are in agreement with those previously reported by our group[12–19] and may be summarized as follows: (a) the cyclization reaction is completely regioselective towards 6-*endo* cyclization products, (b) the relative stereochemistry of sulfany group at C-1 and the C-2 iodo group in the thioglycosides obtained is conditioned by the *Z*/*E* composition of the starting alkenes and their relative reactivity, (c) the formation of the cyclized products with a *cis* arrangement between the C-2 iodo group and the alkoxy group at C-3 is of general application to alkenols with an allylic alkoxy group. It is a consequence of a stereoelectronic effect that dictates the more reactive conformation of the alkene, known as *inside-alkoxy effect*,[29] and (d) relative energy difference between the preferred conformation and the most reactive one dictates the relative reactivities between the *E*- and the *Z*-alkenes isomers, so that, for the *arabino* derivatives **14a,b** only the *E*-alkenes cyclize to give the corresponding thioglycosides as a single α-anomer, whereas for the *ribo* derivatives **12a,b** and **12e** both the *E* and *Z* alkenes cyclize, although at different rates, to give an anomeric mixture of thioglycosides. This fact also accounts for the lower reactivity of the *arabino* alkenes towards cyclization compared to those of the *ribo* alkenes.[30]

Glycosylation reaction. Glycosylation reactions of cholesterol **17** using derivatives **15a,b** and **15e** were carried out under typical glycosylation conditions for thioglycosides using NIS and TfOH as a promoter system (Table 3). The reaction was started at –78 ºC and then left to warm until glycosylation was finished (*ca.* –40 ºC). When *tert*-butyl 1-thio-glycoside **15b** was used as a glycosyl donor, glycosylation proceeded readily at low temperature (–60 ºC) to give compound **19** in an excellent 95% yield (Table 3, entry 2). The β-stereoselectivity, though, was of the same order than that obtained when starting from the phenyl 1-thio-glycoside **15a**

(Table 3, entry 1). Similar results were obtained in the glycosylation of cholesterol **17** with glycosyl donor **15e** but in this case the yield was slightly lower (Table 3, entry 3).

Table 3. Glycosylation of **17** to **19**[a]



Entry	1-Thioglycoside (α/β ratio[b])	T (ºC)	t (h)	Product	Yield (%)	α/β ratio[b]
1[c]	**15a** (1:9)	–40	2.5	**19**	81	1:9
2	**15b** (1:13)	–78 to –40	4	**19**	95	1:7
3	**15e** (1:25)	–78 to –40	4	**19**	60	1:10

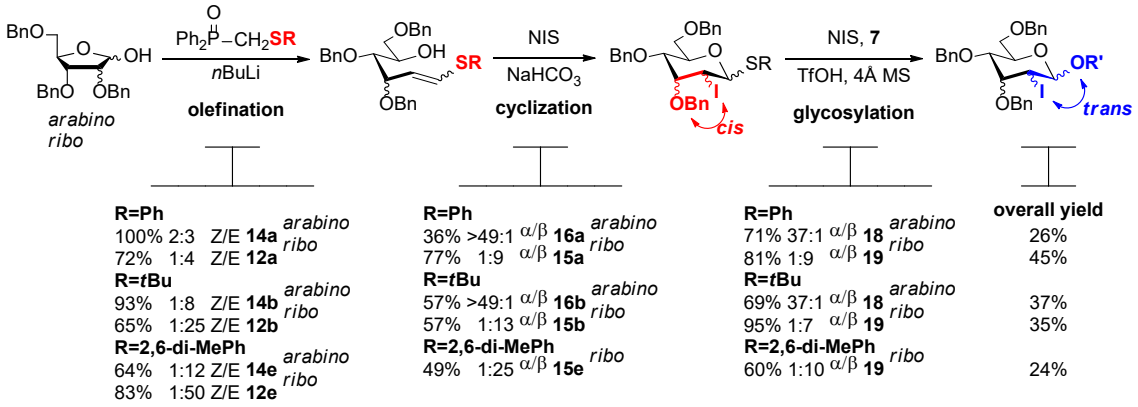
[a]*General conditions*: 1-thioglycoside (1 equiv.), Cholesterol **17** (2 equiv.), NIS (2.2 equiv.), TfOH (20 mol %) and 4Å MS in dry CH_2Cl_2 unless otherwise indicated. [b]Determined by integration of the anomeric proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [c]See ref. 12.

As already described in previous studies, glycosylations from 2-deoxy-2-iodo-1-thiopyranosides seem to proceed via formation of an oxocarbenium ion intermediate and subsequent nucleophilic attack of the glycosyl acceptor. The stereoselectivity of this attack is determined by the reactivity/conformational profile of the oxocarbenium ion intermediate.[31] Hence, glycosylations starting from glycosyl donors of the same configuration (*allo*) but differing only in the anomeric sulfanyl substituent (**15a,b** and **15e**), are supposed to proceed through the same oxocarbenium intermediate, and therefore should all render glycoside **19** with virtually the same stereoselectivty, as it happens to be. Differences in the yield might derive from their activation profiles due to the electronic/steric properties of the substituent at the anomeric sulfanyl moiety. The same interpretation can be inferred for the synthesis of *manno* glycoside **18** from glycosyl donors **16a,b**.

CONCLUSION

A concise synthetic strategy has been developed for the preparation of 2-deoxy-2-iodo-β-allopyranosides precursors of 2-deoxy-β-D-*ribo*-hexopyranosyl units commonly found in antibiotics and natural products. We have explored the synthesis

of 2-deoxy-2-iodoglycosides from furanoses in three steps: Wittig-Horner olefination of furanoses with (sufanylmethyl)diphenyl-phosphine oxides to give sulfanylalkenes, electrophilic iodine–induced cyclization, and glycosylation. In particular, we have gained insight into the stereoelectronic effect of substitutions on sulfur in terms of yield and stereoselectivity of olefination, cyclization and glycosylation reactions compared to previous results obtained with SPh derivatives. The use of phosphine oxide derivatives $Ph_2P(O)CH_2X$ (X=*t*Bu, 2,6-di-Me-Ph) provided good yields and excellent *E* selectivities in the WH olefination reaction of both ribo- and arabinofuranoses. The presence of bulky *S*-substituents generally decreases the rate and yield of cyclization reactions starting from *ribo*-hex-1-enitols and seems to slightly increase the cyclization yield of the *tert*-butyl *arabino*-hex-1-enitol derivative. However, no cyclization product was obtained starting from the 2,6-dimethylphenyl *arabino*-hex-1-enitol derivative. Glycosylation reactions were studied starting from 2-deoxy-2-iodo-1-thio-*allo*-glycosides **15b** and **15e**, which have *t*Bu and 2,6-di-Me-Ph groups at sulfur and from unstable 2-deoxy-2-iodo-1-thio-*manno*-glycoside **16b** and their results were compared with the reference compounds **15a** and **16a** (SPh). Moreover, no aglycon transfer of any of the leaving groups (Ph, *t*Bu, etc.) was noticed under the conditions tested.[32] The stereoselectivity of the glycosylation is independent of the anomeric sulfanyl group present in the glycosyl donor, which is in agreement with the intermediacy of an oxocarbenium ion and only moderate changes in the glycosylation yields were observed. Scheme 5 summarizes the performance of the different sulfanyl derivatives in the synthetic route towards 2-deoxy-2-iodo-pyranosides that involves olefination, cyclization and glycosylation. The use of *t*BuS group does not appear advantageous over the PhS group for the *ribo* series especially because the yield for cyclization step is considerably lower than for PhS, probably due to the high steric hindrance on sulfur. Contrarily, the *tert*-butyl derivative was superior to the phenyl analog for the *arabino* series. In this case, an increase in the *E* stereoselectivity of the olefination step was crucial for obtaining a moderately good yield of thio-*manno*-pyranoside product and eventually of the final glycoside, since the *Z* alkene is completely resistant to cyclization.



Scheme 5. Summary of the results for the olefination-cyclization-glycosylation sequence of vinyl sulfides **12a,b,e** and **14a,b,e** with R=Ph (see ref. 12), *t*Bu and 2,6-di-MePh.

EXPERIMENTAL SECTION

General remarks. Proton (^{1}H NMR), carbon (^{13}C NMR) and phosphorus (^{31}P NMR) nuclear magnetic resonance spectra were recorded on a (400 MHz for ^{1}H), (100.6 MHz for ^{13}C) and (162 MHz for ^{31}P) spectrometer. Spectra were fully assigned using COSY, HSQC, HMBC and NOESY. All chemical shifts are quoted on the δ scale in ppm using either Me_4Si (^{1}H NMR: $CDCl_3$ = 0.00) or the residual solvent as internal standard (^{1}H NMR: $CDCl_3$ = 7.26 and ^{13}C NMR: $CDCl_3$ = 77.23) and 85% H_3PO_4 as external standard (^{31}P NMR: $CDCl_3$ = 0.00). 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. Melting points were determined on a melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a FTIR-ATR spectrophotometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Elemental analyses (C, H, N, and S) were performed with the corresponding analyzer. Thin layer chromatography (TLC) was carried out using commercial aluminium backed sheets coated with 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 (230–400 mesh). Radial chromatography was performed on 1, 2, or 4 mm plates of silica gel, depending on the amount of product. Mobile phases are reported in relative composition (*e.g.* 1:1 EtOAc/hexane v/v). HPLC grade dichloromethene (DCM), tetrahydrofuran (THF) and dimethylformamide (DMF) were dried using a solvent purification system. All reagents were used as received from commercial suppliers. All reactions using anhydrous conditions were performed using flame-dried apparatus under an

atmosphere of argon.

General procedure for the synthesis of diphenylphosphine oxides. Thiol (1.1 mmol) was added to a suspension of sodium hydride (60% in mineral oil, 1.1 mmol) in anhydrous THF (4 mL) at 0 ºC under argon atmosphere. The reaction mixture was warmed up to room temperature and stirred for an hour. A solution of **2**[25] (1 mmol) in anhydrous THF (2 mL) was added at 0 ºC. The reaction mixture was warmed up to room temperature and stirred for 2 hours. After quenching with a saturated solution of aqueous NH_4Cl the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The white solid typically obtained was purified by recrystallization from ethyl acetate and hexane solvent mixtures.

(*tert*-Butylsulfanylmethyl)diphenylphosphine oxide[22] **(3b).** White crystalline solid; yield: 1.08 g (89%); mp: 155.5–157 ºC; FTIR (ATR, ν_{max}): 1436.7, 1183.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81–7.46 (m, 10H), 3.31 (d, $^2J_{HP}$ = 12.4 Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 143.1, 132.3, 131.3, 128.8, 128.4, 34.4 (d, $^1J_{CP}$ = 67.2 Hz), 30.4, 21.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ 30.12. Anal. Calcd for $C_{17}H_{21}OPS$: C, 67.08; H, 6.95; S, 10.53. Found: C, 67.37; H, 7.01; S, 10.35 S.

(Cyclohexylsulfanylmethyl)diphenylphosphine oxide[22] **(3c).** White crystalline solid; yield: 3.25 g (98%); mp: 100–101 ºC; FTIR (ATR, ν_{max}): 1436.7, 1183.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.49 (m, 10H), 3.29 (d, $^2J_{HP}$ = 9.6 Hz, 2H), 2.69 (m, 1H), 1.91–1.57 (m, 5H), 1.20 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 132.2, 131.6, 131.4, 128.8, 128.7, 45.6, 33.2, 28.5 (d, $^1J_{CP}$ = 94.5 Hz), 26.1, 25.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.87; Anal. Calcd for $C_{19}H_{23}OPS$: C, 69.06; H, 7.02; S, 9.70. Found: C, 68.95; H, 7.11; S, 9.73.

(4-Methoxyphenylsulfanylmethyl)diphenylphosphine oxide[33] **(3d).** White crystalline solid; yield: 3.16 g (89%); mp: 71–72 ºC; FTIR (ATR, ν_{max}): 1436.8, 1185; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.43 (m, 10H), 7.27 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 3.63 (d, $^2J_{HP}$ = 9.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.6, 134.1, 132.2, 131.5, 131.4, 128.8, 128.7, 114.8, 55.5, 35.9 (d, $^1J_{CP}$ = 67.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.74; Anal. Calcd for $C_{20}H_{19}O_2PS$: C, 67.78; H, 5.40; S, 9.05. Found: C, 67.44; H, 5.24; S, 8.93.

(2,6-Dimethylphenylsulfanylmethyl)diphenylphosphine oxide (3e). White crystalline solid; yield: 2.74 g (78%); mp: 119–120 ºC; FTIR (ATR, ν_{max}): 1436.7, 1189.9; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–6.96 (m, 13H), 3.44 (d, $^2J_{HP}$ = 9.6 Hz,

2H), 2.35 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 142.7, 132.2–128.1, 34.1 (d, $^1J_{CP}$ = 67.9 Hz), 21.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.89; Anal. Calcd for $C_{21}H_{21}OPS$: C, 71.57; H, 6.01; S, 9.10. Found: C, 71.93; H, 5.96; S, 9.73.

(2,6-Dichlorophenylsulfanylmethyl)diphenylphosphine oxide (3f). White crystalline solid; yield: 2.84 g (72%); mp: 181.5–183 ºC; FTIR (ATR, ν_{max}): 1436.7, 1188.9; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.12 (m, 13H), 3.74 (d, $^2J_{HP}$ = 9.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 141.0, 132.3–128.6, 33.3 (d, $^1J_{CP}$ = 67.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.55; Anal. Calcd for $C_{19}H_{15}Cl_2OPS$: C, 58.03; H, 3.84; S, 8.15. Found: C, 57.92; H, 3.57; S, 8.06.

(Ethylsulfanylmethyl)diphenylphosphine oxide[34] **(3g).** White crystalline solid; yield: 2.18 g (79%); mp: 88–89 ºC; FTIR (ATR, ν_{max}): 1436.7, 1178.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.46 (m, 10H), 3.26 (d, $^2J_{HP}$ = 9.6 Hz, 2H), 2.64 (q, J = 7.6 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 141.0, 132.3–128.8, 31.1, 29.9 (d, $^1J_{CP}$ = 70.9 Hz), 14.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ 30.05; Anal. Calcd for $C_{15}H_{17}OPS$: C, 65.20; H, 6.20; S, 11.60. Found: C, 65.4; H, 5.94; S, 11.36.

General procedure for Wittig–Horner olefination. *n*BuLi (3.5 mmol, 1.6 M in hexanes) was slowly added to a cold (–78 ºC) solution of (alkylsulfanyl- or arylsulfanylmethyl)diphenylphosphine oxide (2 mmol) in anhydrous THF (13 mL) under argon atmosphere and the mixture stirred at the same temperature for 30 minutes. A solution of the corresponding aldehyde (1.0 mmol) in anhydrous THF (5 mL) was subsequently added via cannula and warmed up to room temperature. The reaction progress was monitored by TLC. After 24 h, the reaction mixture was quenched with a saturated solution of aqueous NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatographic techniques. A second fraction was obtained during the olefination of pyranoses when a mixture of the corresponding β-hydroxyphosphine oxide intermediate and unreacted (alkylsulfanyl- or arylsulfanylmethyl)diphenylphosphine oxide, obtained after purification, was dissolved in anhydrous THF and treated with either KH or *t*BuOK at 40 ºC for 30 minutes.

(*Z*/*E*)-*tert*-Butyl(styryl)sulfane[35] **(7b).** Colourless oil; yield: 179 mg (93%) as an inseparable 1:9 *Z*/*E* mixture; R_f (1:8 EtOAc/hexane): 0.53; Anal. Calcd for $C_{12}H_{16}S$:

C, 74.94; H, 8.39; S, 16.67. Found: C, 74.75; H, 8.33; S, 16.53. Data for *Z*-**7b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (m, 2H), 7.52 (m, 1H), 7.23 (m, 2H), 6.45 (d, J = 11.2 Hz, 1H), 6.36 (d, J = 11.2 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 135.3, 131.2, 129.7, 128.5, 127.9, 124.2, 43.2, 31.0. Data for *E*-**7b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (m, 2H), 7.52 (m, 1H), 7.23 (m, 2H), 6.87 (d, J = 15.6 Hz, 1H), 6.72 (d, J = 15.6 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 135.6, 131.5, 129.7, 128.5, 127.9, 122.0, 44.3, 31.1.

(*Z*/*E*)-Cyclohexyl(styryl)sulfane[35] (7c). LDA (3.5 mmol) was used as a base; colourless oil; yield: 188 mg (86%) as an inseparable 1:12 *Z*/*E* mixture; R_f (1:6 EtOAc/hexane): 0.83; Anal. Calcd for $C_{14}H_{18}S$: C, 77.01; H, 8.31; S, 14.68. Found: C, 76.95; H, 8.35; S, 14.54. Data for *Z*-**7c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.17 (m, 5H), 6.42 (d, J = 11.2 Hz, 1H), 6.32 (d, J = 11.2 Hz, 1H), 2.89 (m, 1H), 2.02 (m, 2H), 1.79 (m, 2H), 1.63 (m, 1H), 1.55–1.27 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 137.4, 128.8, 127.9, 125.8, 128.4, 125.2, 48.0, 34.0, 33.9, 26.0, 25.9. Data for *E*-**7c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 4H), 7.17 (m, 1H), 6.76 (d, J = 15.6 Hz, 1H), 6.56 (d, J = 15.6 Hz, 1H), 2.97 (m, 1H), 2.02 (m, 2H), 1.79 (m, 2H), 1.63 (m, 1H), 1.45–1.27 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 137.4, 128.8, 127.9, 125.8, 124.3, 45.5, 33.9, 26.3, 25.9.

(*Z*/*E*)-4-Methoxyphenyl(styryl)sulfane[35] (7d). Yellow oil; yield: 225 mg (93%) as an inseparable 2:3 *Z*/*E* mixture; R_f (1:6 EtOAc/hexane): 0.83; Anal. Calcd for $C_{15}H_{14}OS$: C, 74.34; H, 5.82; S, 13.23. Found: C, 74.04; H, 5.94; S, 13.36. Data for *Z*-**7d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–6.42 (m, 7H), 6.90 (d, J = 10.8 Hz, 2H), 6.43 (d, J = 10.8 Hz, 1H), 6.33 (d, J = 10.8 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.5, 136.1, 132.9, 128.7, 128.4, 127.6, 125.7, 114.7, 55.2. Data for *E*-**7d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.22 (m, 7H), 6.76 (d, J = 15.6 Hz, 1H), 6.56 (d, J = 15.6 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.5, 136.1, 133.9, 131.7, 128.7, 128.4, 127.6, 125.7, 124.3, 114.6, 55.2.

(*Z*/*E*)-2,6-Dimethylphenyl(styryl)sulfane[36] (7e). Colourless oil; yield: 180 mg (75%) as an inseparable 1:12 *Z*/*E* mixture; R_f (1:6 EtOAc/hexane): 0.80; Anal. Calcd for $C_{16}H_{16}S$: C, 79.95; H, 6.71; S, 13.34. Found: C, 80.02; H, 6.94; S, 13.35. Selected data for *Z*-**7e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.00 (m, 8H), 6.61 (d, J = 11.2 Hz, 1H), 6.43 (d, J = 11.2 Hz, 1H), 2.47 (s, 6H). Data for *E*-**7e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.00 (m, 8H), 6.65 (d, J = 15.2 Hz, 1H), 5.96 (d, J = 15.2 Hz, 1H), 2.49 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 143.6, 143.5, 137.2, 134.9,

128.6, 128.4, 128.5, 128.1, 127.3, 125.3, 124.7, 21.9.

(***Z*/*E*)-2,6-Dichlorophenyl(styryl)sulfane (7f).** White solid; yield: 177 mg (63%) as an inseparable 1:16 *Z*/*E* mixture; R_f (1:6 EtOAc/hexane): 0.83; Anal. Calcd for $C_{14}H_{10}Cl_2S$: C, 59.80; H, 3.58; S, 11.40. Found: C, 59.75; H, 3.55; S, 11.45. Selected data for *Z*-**7f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.21 (m, 8H), 6.57 (d, J = 11.2 Hz, 1H), 6.00 (d, J = 11.2 Hz, 1H). Data for *E*-**7f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.21 (m, 8H), 6.67 (d, J = 15.2 Hz, 1H), 6.40 (d, J = 15.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 141.1, 136.6, 131.3–125.6, 122.5.

(***Z*/*E*)-Ethyl(styryl)sulfane**[37] **(7g).** Colourless oil; yield: 184 mg (96%) as an inseparable 1:10 *Z*/*E* mixture; R_f (1:8 EtOAc/hexane): 0.63; Anal. Calcd for $C_{10}H_{12}S$: C, 73.12; H, 7.36; S, 19.52. Found: C, 72.95; H, 7.33; S, 19.53. Selected data for *Z*-**7g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.35 (m, 5H), 6.45 (d, J = 10.8 Hz, 1H), 6.26 (d, J = 10.8 Hz, 1H), 2.80 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). Data for *E*-**7g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.35 (m, 5H), 6.73 (d, J = 15.2 Hz, 1H), 6.46 (d, J = 15.2 Hz, 1H), 2.82 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 137.2, 131.6, 128.6, 128.5, 128.2, 125.0, 26.7, 14.7.

(***Z*/*E*)-(*tert*-Butyl-2-phenylprop-1-enyl)sulfane (8).** Colourless oil; yield: 189 mg (92%) as an inseparable 1:10 *Z*/*E* mixture; R_f (1:10 EtOAc/hexane): 0.70; Anal. Calcd for $C_{13}H_{18}S$: C, 75.67; H, 8.79; S, 15.54. Found: C, 75.75; H, 8.83; S, 15.53. Selected data for *Z*-**8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.12 (m, 5H), 6.11 (s, 1H), 2.10 (s, 3H), 1.28 (s, 9H). Data for *E*-**8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.12 (m, 5H), 6.42 (s, 1H), 2.06 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 142.7, 135.1, 128.5–125.4, 120.0, 44.3, 31.3, 17.9.

Cyclohexyl(cyclohexylidenemethyl)sulfane[38] **(9).** Colourless oil; yield: 202 mg (93%); R_f (1:6 EtOAc/hexane): 0.75; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.60 (s, 1H), 2.69–2.63 (m, 1H), 2.23 (m, 2H), 2.10 (m, 2H), 1.95–1.89 (m, 2H), 1.73–1.71 (m, 2H), 1.57–1.20 (m, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 143.0, 113.1, 45.7, 37.4, 33.7, 30.4, 28.4, 27.2, 26.5, 26.1, 25.8; Anal. Calcd for $C_{13}H_{22}S$: C, 74.22; H, 10.54; S, 15.24. Found: C, 74.34; H, 10.47; S, 15.33.

Cyclohexylidenemethyl-2-6-dimethylphenylsulfane (10). Yellowish oil; yield: 207 mg (89%); R_f (1:9 EtOAc/hexane): 0.90; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–6.99 (m, 3H), 5.36 (s, 1H), 2.49 (s, 6H), 2.23–2.10 (m, 4H), 1.58–1.25 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 143.6, 142.7, 142.3, 129.5, 128.5, 115.2, 36.4, 30.3,

28.5, 27.4, 26.7, 22.3, 21.9; Anal. Calcd for $C_{15}H_{20}S$: C, 77.53; H, 8.67; S, 13.80. Found: C, 77.45; H, 8.53; S, 13.59.

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-*tert*-butylsulfanyl-D-*ribo*-hex-1-enitol (12b). Colourless syrup; yield: 288 mg (65%) as an inseparable 1:25 *Z*/*E* mixture; R_f (1:3 EtOAc/hexane): 0.60; Anal. Calcd for $C_{31}H_{38}O_4S$: C, 73.48; H, 7.56; S, 6.33. Found: C, 73.37; H, 7.43; S, 6.27. Data for *E*-**12b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.21 (m, 15H), 6.44 (d, J = 15.2 Hz, 1H), 5.90 (dd, J = 15.2, 8.4 Hz, 1H), 4.76 (d, J = 11.2 Hz, 1H), 4.65 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.48 (d, J = 11.2 Hz, 1H), 4.36 (d, J = 11.2 Hz, 1H), 4.17 (dd, J = 8.4, 4.2 Hz, 1H), 3.81 (m, 1H), 3.68 (dd, J = 8.4, 4.2 Hz, 1H), 3.61 (m, 2H), 2.89 (bs, 1H), 1.35 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.5, 138.4, 138.1, 129.0, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.82, 127.75, 127.7, 81.7, 81.0, 74.3, 73.4, 71.1, 71.0, 70.3, 43.8, 31.0.

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-cyclohexylsulfanyl-D-*ribo*-hex-1-enitol (12c). LDA (3.5 mmol) was used as a base; yellowish syrup; yield: 253 mg (47%) as an inseparable 1:7 *Z*/*E* mixture; R_f (1:3 EtOAc/hexane): 0.63; Anal. Calcd for $C_{33}H_{40}O_4S$: C, 74.40; H, 7.57; S, 6.02. Found: C, 74.03; H, 7.52; S, 6.07. Data for *E*-**12c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.13 (m, 15H), 6.23 (d, J = 15.2 Hz, 1H), 5.61 (dd, J = 15.2, 8.4 Hz, 1H), 4.67 (d, J = 11.2 Hz, 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.48 (d, J = 11.2 Hz, 1H), 4.41 (d, J = 11.2 Hz, 2H), 4.27 (d, J = 11.2 Hz, 1H), 4.10 (dd, J = 8.4, 4.4 Hz, 1H), 3.72 (m, 1H), 3.49–3.66 (m, 2H), 2.77 (m, 1H), 2.70 (d, J = 4.8 Hz, 1H), 1.89 (m, 2H), 1.66 (m, 2H), 1.53 (m, 1H), 1.33–1.13 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.6, 138.5, 138.1, 129.5, 128.6, 128.5, 128.42, 128.36, 128.3, 128.03, 127.98, 127.9, 127.83, 127.79, 127.74, 127.66, 125.0, 82.1, 81.1, 74.4, 73.5, 71.1, 70.3, 44.8, 33.64, 33.58, 26.1, 25.8.

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-(2,6-dimethylphenyl)sulfanyl-D-*ribo*-hex-1-enitol (12e). Yellowish syrup; yield: 403 mg (83%) as an inseparable 1:50 *Z*/*E* mixture; R_f (1:3 EtOAc/hexane): 0.65; Anal. Calcd for $C_{35}H_{38}O_4S$: C, 75.78; H, 6.90; S, 5.78. Found: C, 75.63; H, 6.85; S, 5.67. Data for *E*-**12e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.10 (m, 18H), 6.23 (d, J = 15.2 Hz, 1H), 5.17 (dd, J = 15.2, 8.8 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.46 (d, J = 11.6 Hz, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.29 (d, J = 11.6 Hz, 1H), 4.10 (dd, J = 8.8, 4.4 Hz, 1H), 3.76 (m, 1H), 3.59–3.55 (m, 3H), 2.82 (d, J = 3.6 Hz, 1H), 2.45 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 143.2, 138.6, 138.3, 138.1, 129.8,

129.4, 129.3, 128.50, 128.47, 128.3, 127.9, 127.9, 127.8, 127.7, 127.62, 127.56, 122.3, 81.4, 81.1, 74.0, 73.4, 71.10, 71.07, 70.2, 21.8.

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-(2,6-dichlorophenyl)sulfanyl-D-*ribo*-hex-1-enitol (12f). Yellowish syrup; yield: 103 mg (17%, 62% based on recovered starting material) as an inseparable 1:2 *Z*/*E* mixture; R_f (1:3 EtOAc/hexane): 0.65; Anal. Calcd for $C_{33}H_{32}Cl_2O_4S$: C, 66.55; H, 5.42; S, 5.38. Found: C, 66.48; H, 5.32; S, 5.30. Data for *Z*-**12f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.15 (m, 18H), 6.22 (d, J = 10.4 Hz, 1H), 5.90 (appt, J = 10.4, 10.4 Hz, 1H), 4.82 (d, J = 11.2 Hz, 1H), 4.74 (d, J = 11.2 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 11.2 Hz, 1H), 4.35 (d, J = 11.2 Hz, 1H), 4.06 (dd, J = 10.4, 4.4 Hz, 1H), 3.95 (m, 1H), 3.69–3.53 (m, 3H), 2.89 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 140.6, 138.5, 138.21, 138.15, 130.54, 130.48, 129.9, 129.8, 120.0, 128.6, 128.4, 128.2, 128.02, 127.98, 127.9, 127.7, 127.3, 81.4, 81.1, 77.42, 74.38, 71.35, 71.3, 71.2. Data for *E*-**12f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.15 (m, 18H), 6.25 (d, J = 15.2 Hz, 1H), 5.50 (dd, J = 15.2, 8.4 Hz, 1H), 4.82 (d, J = 11.2 Hz, 1H), 4.74 (d, J = 11.2 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 11.2 Hz, 1H), 4.35 (d, J = 11.2 Hz, 1H), 4.14 (dd, J = 8.4, 4.4 Hz, 1H), 3.82 (m, 1H), 3.69–3.53 (m, 3H), 2.78 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 141.2, 138.5, 138.2, 138.1, 130.9, 129.1, 128.60, 128.58, 128.53, 128.46, 128.1, 128.0, 127.93, 127.90, 127.78, 127.77, 125.7, 81.4, 81.0, 74.3, 73.6, 71.2, 71.1, 70.5.

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-*tert*-butylsulfanyl-D-*arabino*-hex-1-enitol (14b). Yellowish syrup; yield: 472 mg (93%) as an inseparable 1:8 *Z*/*E* mixture; R_f (1:3 EtOAc/hexane): 0.60; Anal. Calcd for $C_{31}H_{38}O_4S$: C, 73.48; H, 7.56; S, 6.33. Found: C, 73.39; H, 7.32; S, 6.27. Selected data for *Z*-**14b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.23 (m, 15H), 6.49 (d, J = 9.6 Hz, 1H), 5.83 (appt, J = 9.6, 9.6 Hz, 1H), 4.66 (dd, J = 9.6, 4.0 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 4.61 (d, J = 11.2 Hz, 1H), 4.52 (d, J = 11.2 Hz, 1H), 4.47 (s, 1H), 4.36 (d, J = 11.2 Hz, 1H), 4.00 (m, 1H), 3.63–3.55 (m, 2H), 2.96 (d, J = 5.2 Hz, 1H), 1.34 (s, 9H). Data for *E*-**14b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.23 (m, 15H), 6.39 (d, J = 15.2 Hz, 1H), 5.89 (dd, J = 15.2, 7.6 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 4.61 (d, J = 11.2 Hz, 1H), 4.61 (d, J = 11.2 Hz, 1H), 4.52 (d, J = 11.2 Hz, 1H), 4.47 (s, 1H), 4.14 (dd, J = 7.6, 4.0 Hz, 1H), 4.00 (m, 1H), 3.63–3.55 (m, 3H), 2.79 (d, J = 5.2 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.24, 138.17, 138.0, 129.0, 128.53, 128.49,

128.4, 128.31, 128.25, 128.2, 128.0, 127.9, 127.8, 126.6, 80.9, 79.6, 74.4, 73.5, 71.1, 70.9, 70.7, 44.0, 31.1.

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-(4-methoxyphenyl)sulfanyl-D-*arabino*-hex-1-enitol (14d). Yellowish syrup; yield: 176 mg (32%, 50% based on recovered starting material) as an inseparable 1:3 *Z*/*E* mixture; R_f (1:3 EtOAc/hexane): 0.53; Anal. Calcd for $C_{34}H_{36}O_5S$: C, 73.35; H, 6.52; S, 5.76. Found: C, 73.19; H, 6.35; S, 5.56. Selected data for *Z*-**14d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.19 (m, 17H), 6.88 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 9.2 Hz, 1H), 5.85 (appt, J = 9.2, 9.2 Hz, 1H), 4.92–4.44 (m, 6H), 4.28 (dd, J = 9.2, 4.8 Hz, 1H), 3.96 (m, 1H), 3.81 (s, 3H), 3.71–3.58 (m, 3H), 3.00 (d, J = 4.4 Hz, 1H). Data for *E*-**14d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.19 (m, 17H), 6.87 (d, J = 8.8 Hz, 2H), 6.38 (d, J = 15.2 Hz, 1H), 5.60 (dd, J = 15.2, 8.0 Hz, 1H), 4.92–4.44 (m, 5H), 4.38 (d, J = 11.2 Hz, 1H), 4.13 (dd, J = 8.0, 4.0 Hz, 1H), 3.98 (m, 1H), 3.80 (s, 3H), 3.63–3.49 (m, 3H), 2.75 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.8, 138.18, 138.15, 138.1, 137.4, 134.1, 130.2, 128.5–127.7, 125.3, 115.1, 80.9, 79.4, 74.4, 73.5, 71.9, 71.0, 70.7, 55.5.

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-(2,6-dimethylphenyl)sulfanyl-D-*arabino*-hex-1-enitol (14e). Yellowish syrup; yield: 357 mg (64%, 93% based on recovered starting material) as an inseparable 1:12 *Z*/*E* mixture; R_f (1:3 EtOAc/hexane): 0.65; Anal. Calcd for $C_{35}H_{38}O_4S$: C, 75.78; H, 6.90; S, 5.78. Found: C, 75.62; H, 6.87; S, 5.72. Selected data for *Z*-**14e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.10 (m, 18H), 6.03 (d, J = 10.0 Hz, 1H), 5.78 (dd, J = 10.0, 8.8 Hz, 1H), 4.72 (dd, J = 8.8, 6.8 Hz, 1H), 4.58 (d, J = 11.6 Hz, 1H), 4.47 (d, J = 11.6 Hz, 1H), 4.42 (s, 2H), 4.41 (d, J = 11.6 Hz, 1H), 4.30 (d, J = 11.6 Hz, 1H), 3.91 (m, 1H), 3.74 (dd, J = 6.8, 3.6 Hz, 1H), 3.65 (d, J = 4.0 Hz, 2H), 3.02 (d, J = 5.6 Hz, 1H), 2.46 (s, 6H). Data for *E*-**14e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.10 (m, 18H), 6.20 (d, J = 15.2 Hz, 1H), 5.12 (dd, J = 15.2, 8.8 Hz, 1H), 4.58 (d, J = 11.6 Hz, 1H), 4.47 (d, J = 11.6 Hz, 1H), 4.42 (s, 2H), 4.41 (d, J = 11.6 Hz, 1H), 4.30 (d, J = 11.6 Hz, 1H), 4.06 (dd, J = 8.8, 3.6 Hz, 1H), 3.91 (m, 1H), 3.52 (d, J = 4.4 Hz, 2H), 3.47 (dd, J = 7.2, 3.6 Hz, 1H), 2.66 (d, J = 5.6 Hz, 1H), 2.47 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 143.4, 138.21, 138.17, 138.0, 129.6, 129.0, 128.7, 128.59, 128.57, 128.4, 128.3, 128.2, 128.1, 127.93, 127.89, 127.8, 121.7, 81.4, 79.6, 74.5, 73.5, 71.0, 70.32, 70.31, 21.8.

(*Z*/*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-(2,6-dichlorophenyl)sulfanyl-D-*arabino*-hex-1-enitol (14f). Yellowish syrup; yield: 464 mg (78%) as an inseparable

1:6 *Z*/*E* mixture; R_f (1:3 EtOAc/hexane): 0.45; Anal. Calcd for $C_{33}H_{32}Cl_2O_4S$: C, 66.55; H, 5.42; S, 5.38. Found: C, 66.61; H, 5.32; S, 5.27. Data for *E*-**14f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.17 (m, 18H), 6.21 (d, J = 15.2 Hz, 1H), 5.40 (dd, J = 15.2, 8.4 Hz, 1H), 4.62 (d, J = 11.2 Hz, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.45 (d, J = 11.2 Hz, 1H), 4.46 (s, 2H), 4.34 (d, J = 11.6 Hz, 1H), 4.11 (dd, J = 8.4, 7.2 Hz, 1H), 3.97 (m, 1H), 3.54–3.52 (m, 2H), 3.51 (dd, J = 7.2, 3.6 Hz, 1H), 2.62 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 141.3, 138.2, 138.1, 137.8, 131.0, 130.0, 129.2, 129.0, 128.9, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.84, 127.8, 127.76, 126.4, 125.0, 81.2, 79.1, 74.4, 73.4, 71.3, 70.7, 70.1.

General procedure for iodonium-induced cyclization. $NaHCO_3$ (1.5 mmol) was added to a cold (–78 ºC) solution of alkenyl sulfide (1 mmol) in anhydrous CH_2Cl_2 (2 mL) under argon atmosphere and the mixture stirred at the same temperature for 5 minutes. NIS (1.5 mmol) was then added and the reaction temperature was left to increase depending on the reactivity of the substrate. The reaction progress was monitored by TLC. 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 under reduced pressure. The residue was purified by chromatographic techniques.

***tert*-Butyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-*α*/*β*-D-allopyranoside (15b).** Yellowish syrup; yield: 181 mg (57%) as an inseparable 1:13 *α*/*β* mixture; R_f (1:3 EtOAc/hexane): 0.45; Anal. Calcd for $C_{31}H_{37}IO_4S$: C, 58.86; H, 5.90; S, 5.07. Found: C, 59.02; H, 5.72; S, 5.03. Data for *β*-**15b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.23 (m, 15H), 5.05 (d, J = 10.8 Hz, 1H), 4.92 (d, J = 11.2 Hz, 1H), 4.78 (d, J = 11.2 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 4.58 (d, J = 11.2 Hz, 1H), 4.52 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 11.2 Hz, 1H), 4.19 (dd, J = 3.4, 2.8 Hz, 1H), 4.16 (ddd, J = 10.0, 9.6, 6.4 Hz, 1H), 3.69 (m, 2H), 2.89 (dd, J = 10.0, 3.4 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.5, 138.4, 137.7, 134.2, 129.7, 128.7, 128.5, 128.3, 128.20, 128.16, 128.0, 127.8, 127.9, 127.3, 81.8, 78.8, 76.8, 75.9, 75.7, 73.6, 72.3, 69.8, 44.8, 32.3, 31.6.

2,6-Dimethylphenyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-*α*/*β*-D-allopyranoside (15e). Yellowish syrup; yield: 123 mg (49%) as an inseparable 1:25 *α*/*β* mixture; R_f (1:3 EtOAc/hexane): 0.45; Anal. Calcd for $C_{35}H_{37}IO_4S$: C, 61.76; H, 5.48; S, 4.71. Found: C, 62.03; H, 5.32; S, 4.66. Data for *β*-**15e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.04 (m, 18H), 4.90 (d, J = 11.2 Hz, 1H), 4.89 (ddd, J = 10.0, 9.6,

6.4 Hz, 1H), 4.88 (d, J = 10.8 Hz, 1H), 4.77 (d, J = 11.2 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.47 (d, J = 11.2 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 4.27 (dd, J = 10.8, 2.0 Hz, 1H), 4.17 (dd, J = 2.0, 1.6 Hz, 1H), 3.76 (dd, J = 10.0, 1.6 Hz, 1H), 3.57 (m, 2H), 2.58 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 144.7, 138.48, 138.46, 137.8, 131.6, 129.1, 128.7, 128.5, 128.31, 128.26, 128.14, 128.08, 128.0, 127.9, 127.8, 127.7, 86.6, 79.0, 76.5, 75.9, 75.8, 73.7, 72.4, 69.6, 31.4, 23.0.

***tert*-Butyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-thio-*α*/*β*-D-mannopyranoside (16b).** The isolated product decomposed in solution and was therefore quickly subjected to the next reaction without further characterization. Yellowish syrup; yield: 179 mg (57%) as an inseparable >49:1 α/β mixture; R_f (1:3 EtOAc/hexane): 0.46; Anal. Calcd for $C_{31}H_{37}IO_4S$: C, 58.86; H, 5.90; S, 5.07. Found: C, 58.67; H, 5.89; S, 4.99. Selected data for α-**16b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.16 (m, 15H), 5.73 (s, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.81 (d, J = 3.9 Hz, 1H), 4.77 (d, J = 12.1 Hz, 1H), 4.69 (d, J = 11.4 Hz, 1H), 4.48 (m, 3H), 4.30 (ddd, J = 9.0, 3.9, 1.6 Hz, 1H), 4.01 (dd, J = 9.0, 8.6 Hz, 1H), 3.87 (dd, J = 11.0, 3.9 Hz, 1H), 3.68 (dd, J = 11.0, 1.6 Hz, 1H), 3.04 (dd, J = 8.6, 3.9 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.3–127.7, 89.9, 77.8, 76.8, 75.6, 73.6, 73.6, 71.3, 68.9, 44.7, 35.0, 31.6.

General procedure for glycosylation. A solution of the glycosyl donor (1 mmol) and cholesterol **17** (2 mmol) in anhydrous CH_2Cl_2 (4 mL) was stirred with 4Å molecular sieves (1 g) at –78 ºC for 2 h. NIS (2.2 mmol) and TfOH (0.2 mmol) were then added and the reaction temperature was left to increase depending on the reactivity of the substrate. The reaction progress was monitored by TLC. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatographic techniques.

Cholesteryl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-*α*/*β*-D-mannopyranoside[12] **(18).** Yellowish foam; yield: 174 mg (69%) as an inseparable 37:1 α/β mixture; R_f (1:3 EtOAc/hexane): 0.63; Anal. Calcd for $C_{54}H_{73}IO_5$: C, 69.81; H, 7.92. Found: C, 69.79; H, 7.92. Data for α-**18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.15 (m, 15H), 5.38 (s, 1H), 5.28 (d, J = 5.2 Hz, 1H), 4.85 (d, J = 10.8 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 11.6 Hz, 1H), 4.53–4.46 (m, 4H), 3.96–3.87 (m, 2H), 4.81 (dd,

J = 10.8, 4.4 Hz, 1H), 3.71 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.48 (m, 1H), 3.36 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.40–0.67 (m, 43H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 140.6, 138.6–138.0, 129.1–127.1, 122.2, 99.6, 77.6, 77.2, 76.1, 75.6, 73.4, 72.2, 71.0, 69.0, 56.3–12.0, 34.6.

Cholesteryl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-*α*/*β*-D-allopyranoside[12] **(19).** Yellowish foam; yield from **15b**: 202 mg (95%) as an inseparable 1:7 *α*/*β* mixture; yield from **15e**: 81 mg (60%) as an inseparable 1:10 *α*/*β* mixture; R_f (1:3 EtOAc/hexane): 0.62; Anal. Calcd for $C_{54}H_{73}IO_5$: C, 69.81; H, 7.92. Found: C, 69.87; H, 7.89. Data for *β*-**19**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.06 (m, 15H), 5.35 (d, *J* = 5.2 Hz, 1H), 4.87 (d, *J* = 10.4 Hz, 1H), 4.86 (d, *J* = 9.0 Hz, 1H), 4.77 (d, *J* = 10.4 Hz, 1H), 4.66–4.50 (m, 4H), 4.18–4.01 (m, 3H), 3.73–3.64 (m, 3H), 3.48 (m, 1H), 2.39–0.67 (m, 43H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 143.6–127.7, 122.0, 99.3, 79.9, 78.6, 76.9, 75.8, 73.5, 73.2, 72.4, 69.6, 57.0, 56.3, 50.3, 42.5, 40.0, 39.7, 38.7, 37.4, 36.9, 36.4, 36.0, 33.4, 32.2, 32.0, 29.7, 28.4, 28.2, 24.5, 24.0, 23.0, 22.8, 21.2, 19.6, 18.9, 12.05.

ASSOCIATED CONTENT

Supporting Information. ^{1}H, ^{13}C, and ^{31}P NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author(s)

*E-mail: omar.boutureira@urv.cat, yolanda.diaz@urv.cat

Notes

The authors declare no competing financial interest.

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