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Article

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Stereocontrolled nucleophilic addition to five-membered oxocarbenium ions directed by the protecting groups. Application to the total synthesis of (+)-varitriol and of two diastereoisomers thereof

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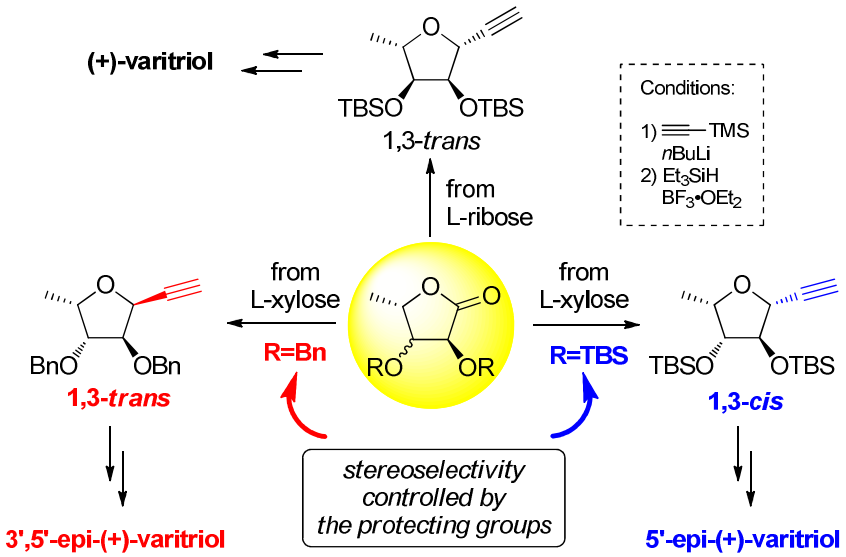
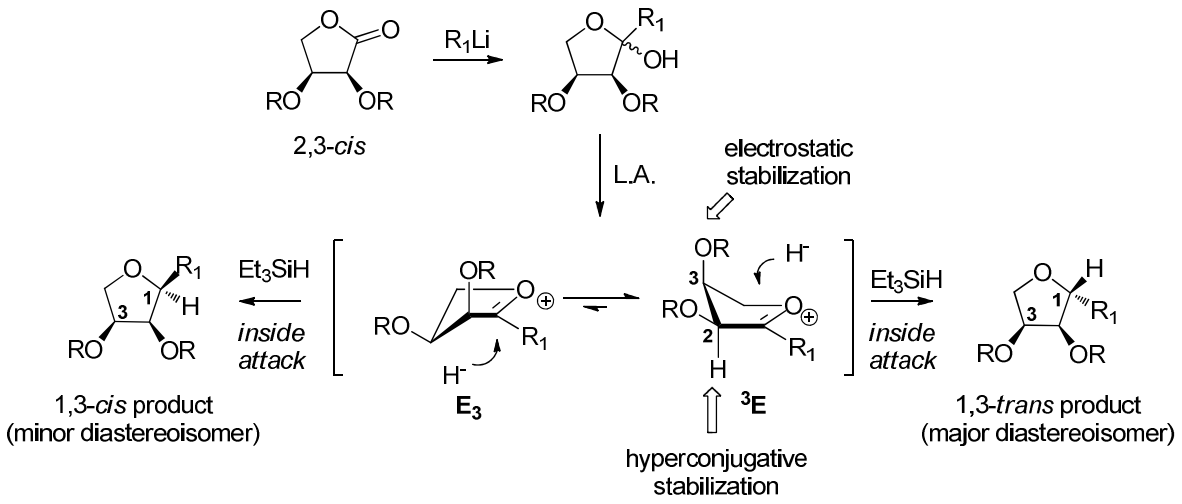


Abstract. A stereodivergent *C*-glycosidation of carbohydrate-derived lactones can be mediated by the protecting groups, and applied to the total synthesis of (+)-varitriol and of two diastereoisomers thereof, which represent an unprecedent use of the protecting groups in the synthesis of a naturally occurring compound. In particular, the stereoselective nucleophile attack for 2,3-*trans* substituted five-membered ring oxocarbenium ions is strongly influenced by the presence of aromatic rings in the protecting groups. According to quantum chemical calculations, the stereoselectvity depends on the π- π interactions between the aromatic ring of the C-2 protecting group with the exocyclic triple bond and the oxocarbenium ion. These interactions account for the stabilization of the conformer in which the C-2 and C-3 substituents adopt pseudoaxial orientations. When protecting groups do not contain an aromatic ring, the sterochemical outcome is dictated by stereoelectronic factors established by the Woerpel's model. Based on these findings, a concise total synthesis of the natural product (+)-varitriol and of two diastereoisomers was acomplished.

Introduction

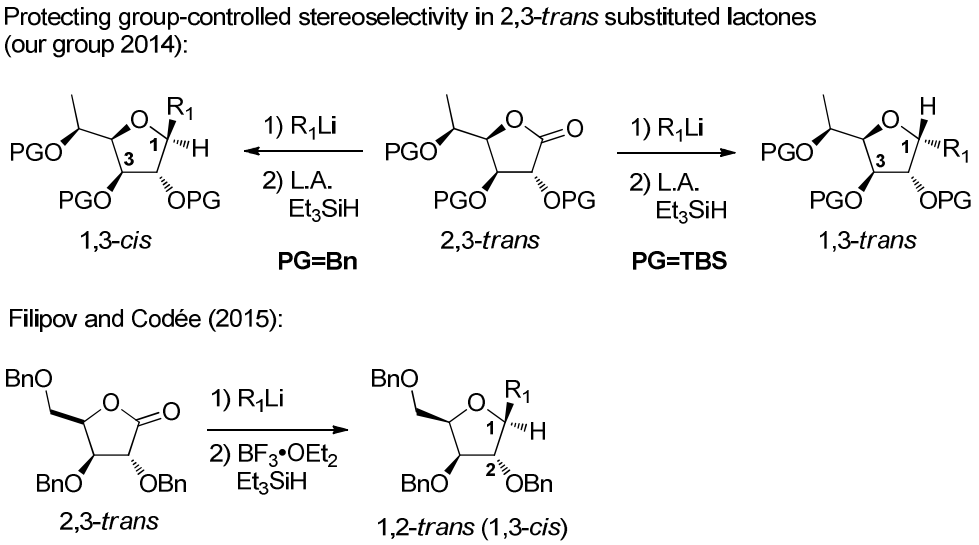
The presence of a *C*-*C* bond at the anomeric position of a carbohydrate derivative makes the *C*-glycosides more resistant to acid and enzymatic hydrolysis, thereby allowing to express more effectively their myriad pharmacological activities.[1]

A convenient method for the construction of *C*-glycosides is the Kishi protocol.[2] This sequence employs a carbohydrate-derived lactol as the nucleophile acceptor, which by treatment with a Lewis acid forms a five-membered ring oxocarbenium ion that is attacked by a nucleophile (usually Et_3SiH) to finally render the desired *C*-glycoside. The stereochemical outcome for the nucleophilic addition step can be explained by the *inside attack model* advanced by Woerpel and coworkers.[3] This model postulates that the five-membered oxocarbenium ion adopts an enveloped conformation, being $\mathbf{E_3}$ and $^{3}\mathbf{E}$ the preferred conformers. When the C-3 substituent bears a partial negative charge (*i.e.* a protected alcohol), the lowest energy conformer is $^{3}\mathbf{E}$, where the C-3 substituent adopts a pseudoaxial orientation and is in closest proximity to the oxocarbenium positive charge, providing an effective electrostatic stabilization.[3,4] Woerpel also demonstrated that for 2,3-*cis* furanose derivatives, an hyperconjugative stabilization from the C-H bond at C-2 contributes to the preference of $^{3}\mathbf{E}$ over $\mathbf{E_3}$, along with the preferential pseudoequatorial positioning of the C-2 substituent. Additionally, the nucleophile attack is favored from the inside face due to the formation of an alternate product,[5] rendering the 1,3-*trans* product as the major diastereoisomer. Thus, a synergic effect of C-2 and C-3 is the responsible for the high selectivity observed in 2,3-*cis* furanose derivatives (Scheme 1).



Scheme 1. Kishi's protocol and Woerpel's model for furanose derivatives.

In contrast, the 2,3-*trans* carbohydrate furanose-derivatives present some discrepancies.[6] For example, our group recently found that the stereochemistry in the *C*-glycosidations using the Kishi's protocol on D-fucose derivatives can be modulated by the protecting groups. Whereas TBS protected lactones produce the α anomer (1,3-*trans*), their benzyl congeners provide the opposite stereoisomer (β, 1,3-*cis*).[7] Soon after, Filippov and Codée[8] reported that the 1,2-*trans* *C*-glycosides are systematically obtained as the major products from either 2,3-*cis* (D-ribo-, D-lyxose) or 2,3-*trans* (D-arabino- and D-xylose) benzyloxy lactones (Scheme 2).

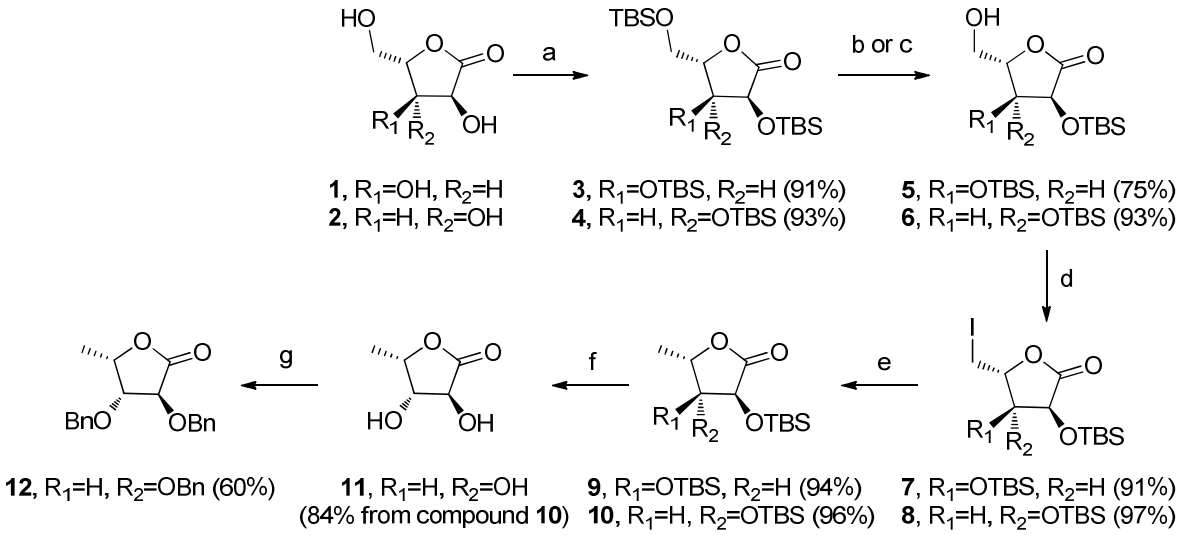


Scheme 2. Stereoselective Kishi's *C*-glycosidation modulated by protecting groups.

Although our preliminary observations demonstrated that the stereochemistry of the nucleophile addition into oxocarbenium ions can be controlled by the protecting groups, the origin of this behavior was unclear. In order to get further insight from this stereoelectronic effect, in this paper we provide further evidence regarding whether the 2,3-*trans* disposition and the electronic nature of the protecting groups in these positions are the responsible for this stereocontrol. Additionally, a synthetic application is highlighted in the total synthesis of (+)-varitriol and of two diastereoisomers.

Results and discussion

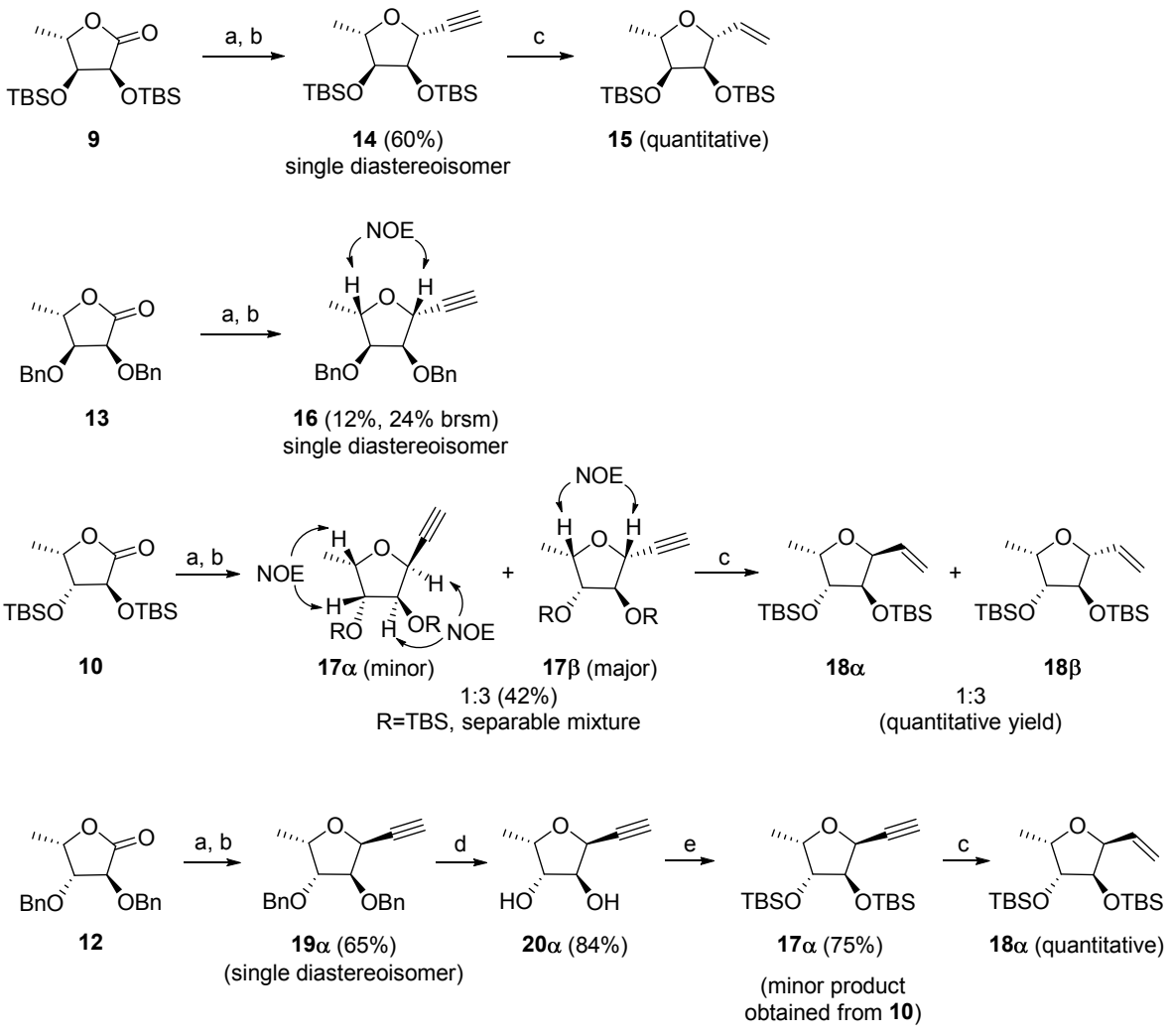
In our previous work, D-fucose derived lactones were used as electrophiles. To discard the participation of the C-5 substituent and to verify that the 2,3-*trans* disposition is indeed guiding the stereochemical outcome, lactones **9**, **10** and **12**, bearing a methyl group at C-4 were prepared. Initial efforts for preparing **9** and **10** were conducted from commercially available L-ribono-1,4-lactone (**1**) and L-xylono-1,4-lactone (**2**), respectively (Scheme 3). For this purpose, attempts for direct halogenation of the primary alcohol by using Garegg-Samuelsson protocol[9] or by treatment with $SOCl_2$ or $SOBr_2$[10] were tested, however, these procedures turned out to be inefficient on our substrates. Thus, a full protection of lactones **1** and **2** to **3**[11] and **4**, respectively, followed by selective mono deprotection of the more reactive primary alcohol was found to be the best choice for obtaining lactones **5** and **6** in good overall yields. Conversion of **5** and **6** to the corresponding iodinated derivatives (**7** and **8**), and subsequent reduction under typical free radical conditions – Bu_3SnH/1,1'-azobis-1-cyclohexanenitrile (ACN) – afforded the desired lactones **9**[12] and **10**. Finally, lactone **12** was prepared by deprotection of **10** and benzylation under neutral conditions.



Scheme 3. Preparation of lactones **9**, **10** and **12**. Reagents and conditions: a) TBSCl, imidazole, CH_2Cl_2, r.t., 4 h; b) for **3**: THF:H_2O:TFA (4:1:1), 0 °C, 1h; c) for **4**: $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, r.t., 2h; d) I_2, imidazole, THF, r.t.; e) Bu_3SnH, ACN, toluene, 100 °C. f) $BF_3{\cdot}OEt_2$, CH_3CN, 0 °C to r.t.; g) BnBr, Ag_2O, CH_2Cl_2, r.t.

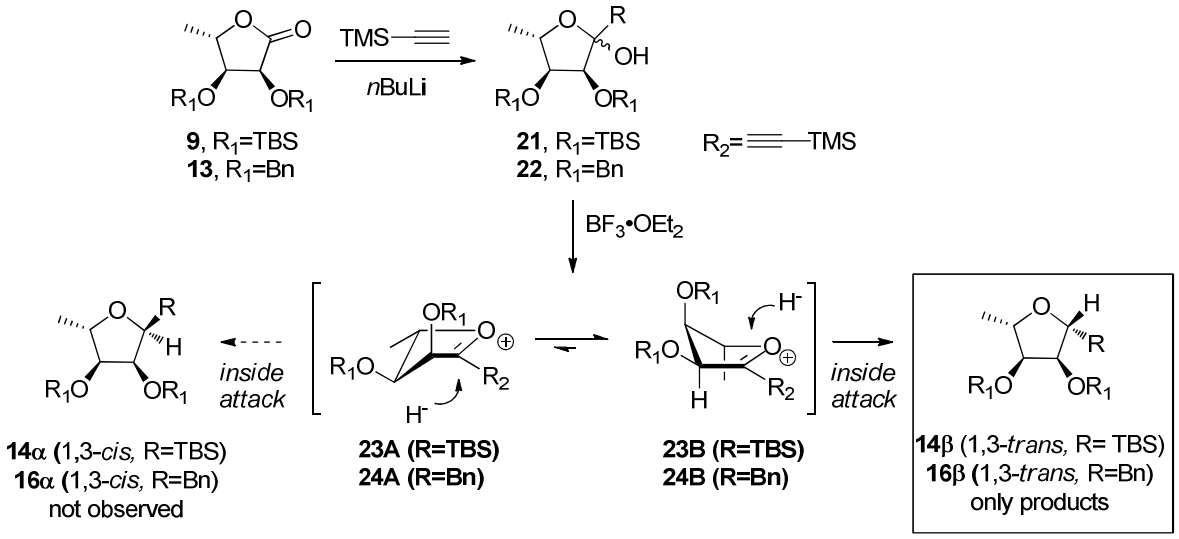
With the carbohydrate moieties in hand, the L-ribose and L-xylose derivatives **9**, **10**, **12** and known per-*O*-benzylated L-ribonolactone **13**[13] were submitted to *C*-glycosidation. When lactones **9**, **10**, **12** and **13** were treated with the freshly prepared lithium(trimethylsilyl)acetylide at –78 °C, the corresponding lactols (not shown) were obtained and directly treated with Et_3SiH and $BF_3{\cdot}OEt_2$ to furnish alkynes **14**, **16**, **18** and **20**, respectively, in 24-65% yield, with the fortuitous TMS group removal. As expected, compounds **14** and **16** were obtained with complete diastereoselectivity (β anomer, 1,3-*trans*), according to the Woerpel's model. Partial hydrogenation of **14** in the presence of Lindlar catalyst proceeded in quantitative yield, rendering terminal alkene **15**. The absolute configuration of **15** was confirmed by comparison of its spectroscopic data with those reported by Ghosh,[14] whereas a H1/H4 NOE interaction was observed for **16**. On the other hand, lactone **10** produced the corresponding alkynes **17** as a 1:3 mixture of diastereoisomers that were easily separated by column chromatography, favouring the β anomer (**17β**). The stereochemistry of **17α** and **17β** was stablished by NOE experiments (H1/H2 and H3/H4 interactions observed for **17α** and a H1/H4 interaction for **17β**). Also,

the absolute configuration of the major product **17β** was confirmed by comparing the partial hydrogenated compound (**18β**) with the data reported by Ghosh.[14] In contrast, reacting lactone **12** with the acetylide anion followed by reduction gave **19α** as the only anomer. Stereochemical configuration was determined by chemical correlation, transforming **19α** into alkyne **17α**, that shown to be identical to the minor product obtained from the *C*-glycosidation of lactone **10**. Finally, partial hydrogenation of alkyne **17α** conducted to **18α** in quantitative yield, and corroborated the stereochemical outcome of the *C*-glycosidation of benzylated lactone **12** (Scheme 4).



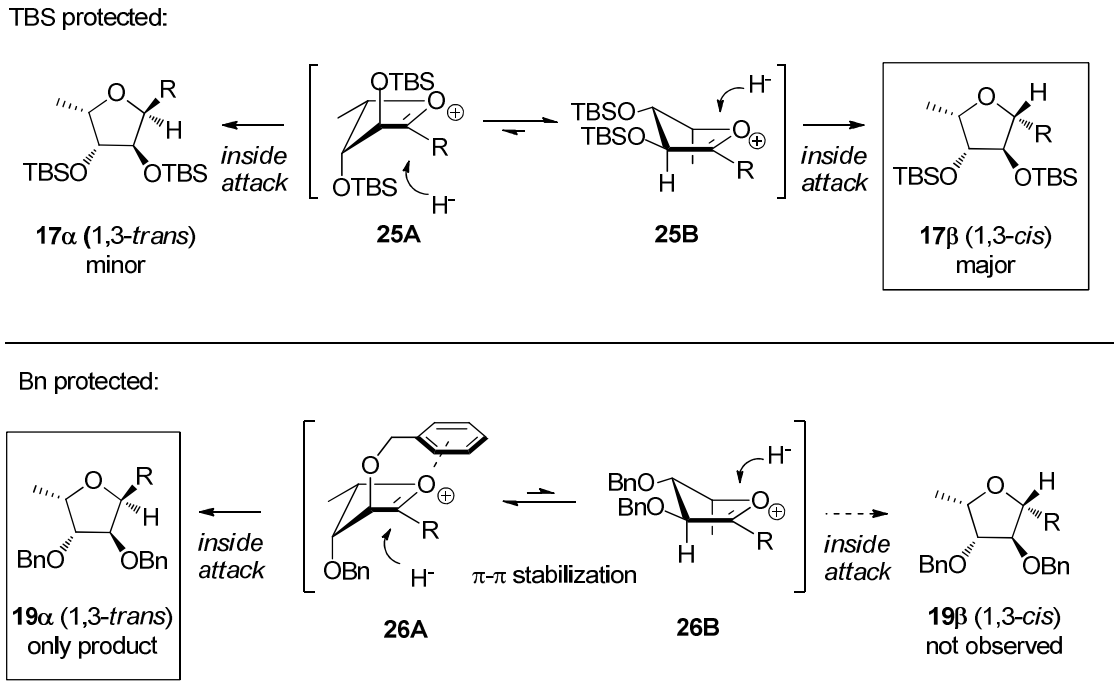
Scheme 4. *C*-glycosidation of lactones **9**, **10**, **12** and **13**. Reagents and conditions: a) TMS-acetylene, *n*BuLi, THF, –78 °C, then **9**, **10**, **12** or **13**; b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –40 °C; c) H_2 (1 atm.), Lindlar catalyst, MeOH, r.t. d) BCl_3, CH_2Cl_2, 0 °C; e) TBSCl, imidazole, CH_3CN, reflux.

The above results demonstrate that carbohydrate derived oxocarbenium ions bearing substituents at C2 and C3 behave differently, depending either on their *cis* or *trans* disposition. For 2,3-*cis* substituted carbohydrates, Woerpel's model is consistent with these substrates and the product can be predicted fairly good. For the case of lactones **9** and **13**, derived from L-ribose, lactols **21** and **22**, respectively, generated from the acetylide addition, undergo oxocarbenium ion formation by the reaction with the Lewis acid, giving rise to two predominant conformers for each compound: **23A** / **24A** and **23B** / **24B** (Scheme 5). According to Woerpel's model, **23B** and **24B** are favoured due to the synergic effect of both C2 (in pseudoequatorial orientation) and C3 (in pseudoaxial orientation), allowing the hydride to attack from the inside face, which results in a complete selectivity for **14β** and **16β** (β anomers, 1,3- *trans*). It is important to note that these stabilizing effects are the same for either TBS or Bn protecting groups.



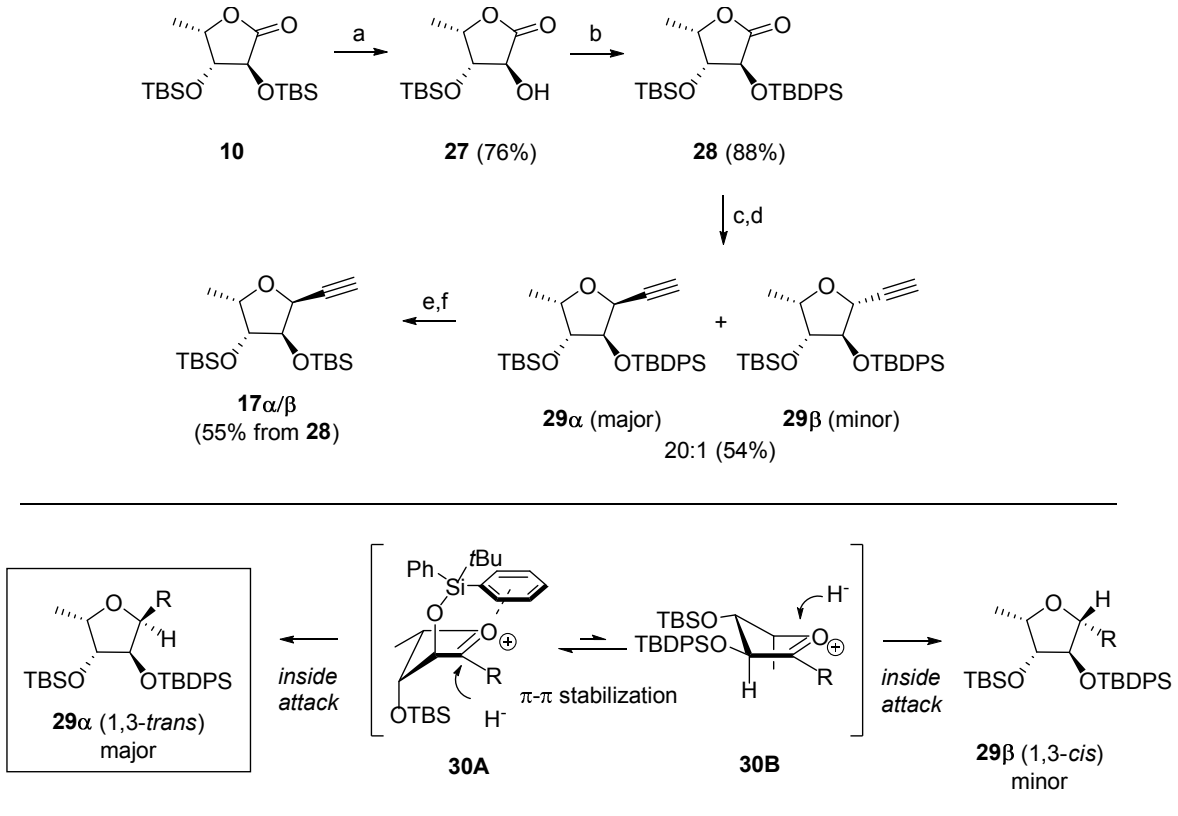
Scheme 5. Explanation for the high stereoselectivity for lactones **9** and **13**.

On the other hand, when substituents are in a 2,3-*trans* disposition, the stereoselectivity can indeed be controlled by the protecting groups. For the *C*-glycosidation of L-xylonolactone **10**, two possible conformations of the reactive oxocarbenium ion with OTBS **25A** and **25B** are formed (Scheme 6). In concordance with Woerpel's observations, the preferred conformation would be **25A**, with the C3 substituent in pseudoaxial orientation. Nevertheless, the C2 substituent is also pseudoaxially positioned and does not contribute to the stabilization of **25A**, allowing the other conformer (**25B**) to be the predominant but with contribution of **25A**, resulting in a modest selectivity in favour of **17β** (1,3-*cis*). For lactone **12**, bearing benzyl groups, similar oxocarbenium ions **26A** and **26B** are the reactive intermediates. Assuming that the hydride delivery takes place from the inside face, then the predominant conformer should be **26A**, giving rise exclusively to **19α** (1,3-*trans*). For explaining these results, we postulate that the higher stabilization of **26A** versus **26B** could be due to a π-π interaction between the oxocarbenium ion and the phenyl group at C2, in addition to the well-known electrostatic stabilization by C3. This double stabilization could be more important than the conformational stabilization provided by C2 and C3 substituents in pseudoequatorial orientation, allowing conformer **26A** to be the predominant one.



Scheme 6. Plausible explanation of the selectivity inversion for lactones **10** and **12**.

To support that the presence of an aromatic group at C2 would influence the stereoselectivity of the reduction step, we carried out the *C*-glycosidation of lactone **28**, which bears differentiated silyl protecting groups (TBS at C3 and a TBDPS at C2). Lactone **28** was thus prepared by careful monodesilylation[15] of compound **10** with 1 equivalent of TBAF at –10 °C (76% yield) and reprotection of **27** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in 88% yield. Because of the presence of phenyl groups in the TBDPS group, we anticipated that the latter functionality would exert a similar stabilization effect as for lactone **12**. Indeed, when the latter compound was submitted to the previously employed conditions for *C*-glycosidation, we observed a complete inversion of the stereochemistry, obtaining a 20:1 mixture of anomers **29α/β** in 54% combined yield, favouring the α (1,3-*trans*) diastereoisomer (Scheme 7). This inversion of stereoselectivity provides evidence that the aromatic ring of C2 makes an important contribution to the stability of one of the oxocarbenium intermediates even if this group is a bulky one like TBDPS, and allows the reaction to be controlled by protecting groups.

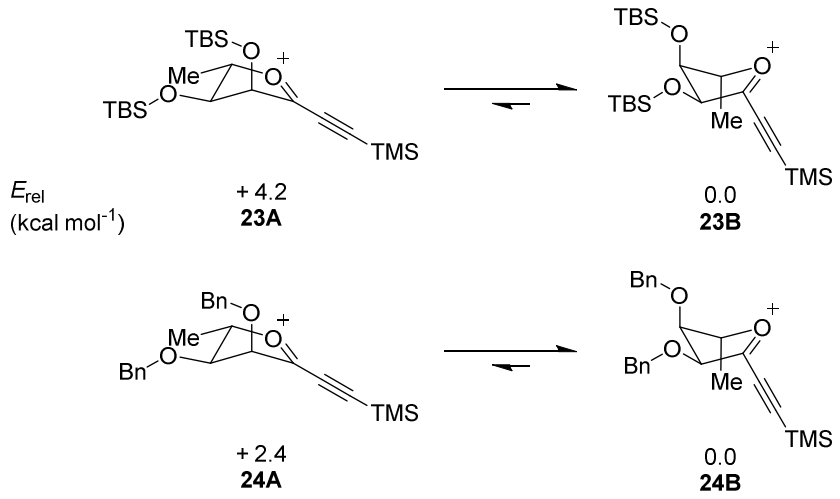


Scheme 7. Stereoselectivity with differentiated silyl protecting groups. Reagents and conditions: a) TBAF, THF, –10 °C; b) TBDPSCl, imidazole, CH_3CN, r.t.; c) TMS-

acetylene, *n*BuLi, THF, –78 °C, then **28**; d) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –40 °C; e) TBAF, THF, r.t.; f) TBSCl, imidazole, CH_2Cl_2, reflux.

To provide further evidence for the reasons of the observed stereoselectivities and to confirm our experimental observations, we carried out quantum chemical calculations. We optimized the two conformations E^3 (**A**) and ^3E (**B**) of oxocarbenium intermediates of TBS-protected L-ribose **23A/B**, Bn-protected L-xylose **24A/B**, TBS-protected L-xylose **25A/B**, Bn-protected **26A/B** and OTBDPS/OTBS-protected **30A/B** with SMD(CH_2Cl_2)-M06-2x/6-31+G(d,p) level of theory.

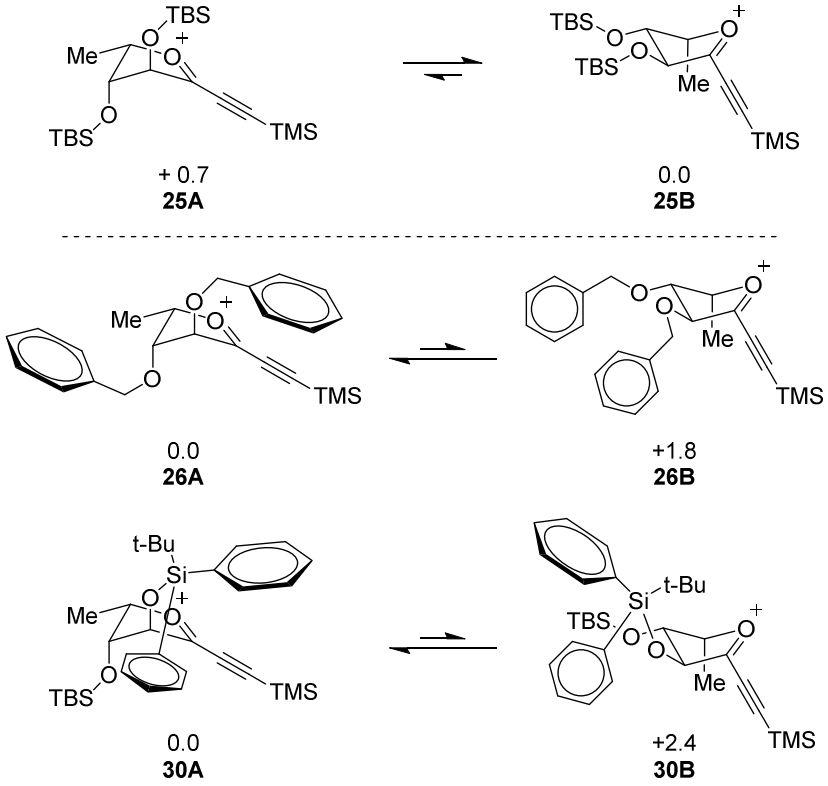
Scheme 8 shows the relative stabilities of the modeled compounds derived from L-ribose. For the TBS-protected intermediates arising from L-ribonolactone derivative **9**, the conformer **23B**, that leads to compound **14β**, is the most stable. A close situation is found for intermediates **24A** and **24B**, arising from lactone **13**, being **24B** the most stable. This is in agreement with Woerpel's[3] experimental results and Codée's[8] theoretical modeling of ribose analogs.



Scheme 8. Relative energies in kcal/mol of oxocarbenium intermediates **23** and **24**.

Similarly, TBS-protected L-xylose lactone **10** generates oxocarbenium ions **25A** and **25B**, for which the same conformation **B** is more stable than **A** but with lower energy preference,

thus predicting a mixture of diastereomers which is in line with the experimental outcome (Scheme 9). Nevertheless, for intermediates **26A/B**, arising from lactone **12** (di-*O*-benzyl xylonolactone), the conformer **A** is now favored, hence forecasting the addition of the nucleophile from the opposite side. Preference for conformer **A** seems to be originated as a consequence of the phenyl group at C2, since conformer **30A** is also more stable than its counterpart **30B** for the oxocarbenium ion originated from lactone **28** (OTBDPS at C2 and OTBS at C3). These calculations sustain the observed reverse selectivity during *C*-glycosidation reactions of xylonolactones **12** and **28** (Schemes 4 and 7).



Scheme 9. Relative energies in kcal/mol of oxocarbenium intermediates **25**, **26** and **30**.

Careful examination of **26A** suggests that a π-π interaction between the phenyl ring of the benzyl group and the conjugated oxocarbenium is responsible for its lower energy. This is reflected in the short distances between the centroid of the phenyl and the carbons of the alkyne and the distance between the ipso carbon and C1 of the sugar (Figure 1). These distances are shorter than the distance between centroids in sandwich dimmer benzene-

benzonitrile at CCSD(T) (3.79 Å)[16] but the different electronic environment should be taken into account.

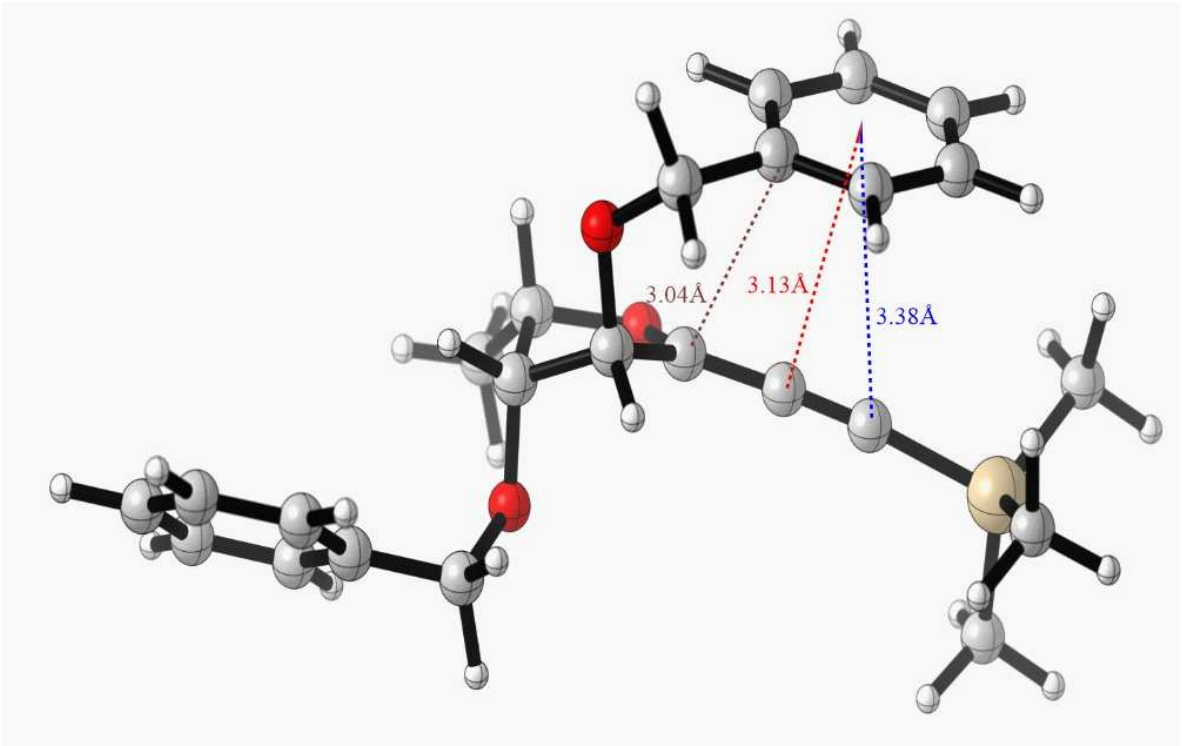
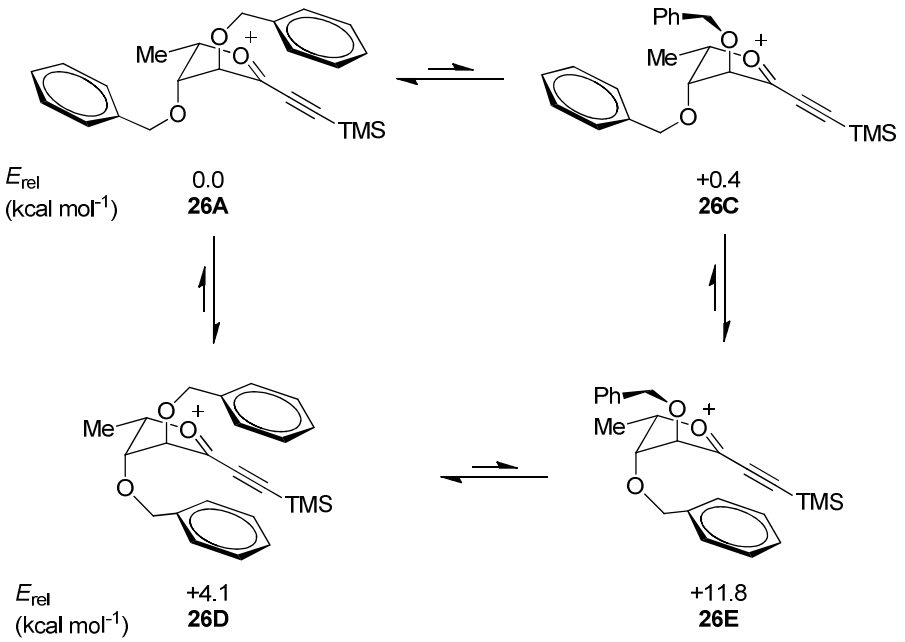


Figure 1. Modelled structure of oxocarbenium **26A** showing representative distances between carbons for the π-π interaction.

To analyze if the putative interaction was responsible for the stabilization of **26A** it was rotated the C_2O-Bn and C_3O-Bn bonds to find other local minima. We find out that the most important π-π interaction occurs between the C_2O-Bn and the conjugated oxocarbenium moiety with little contribution of the conformers with π-π stacking with the participation of C_3O-Bn. (Scheme 10). Therefore, we conclude that in fact the π-π contacts are an important non-covalent effect that changes the conformational preference of the intermediates.

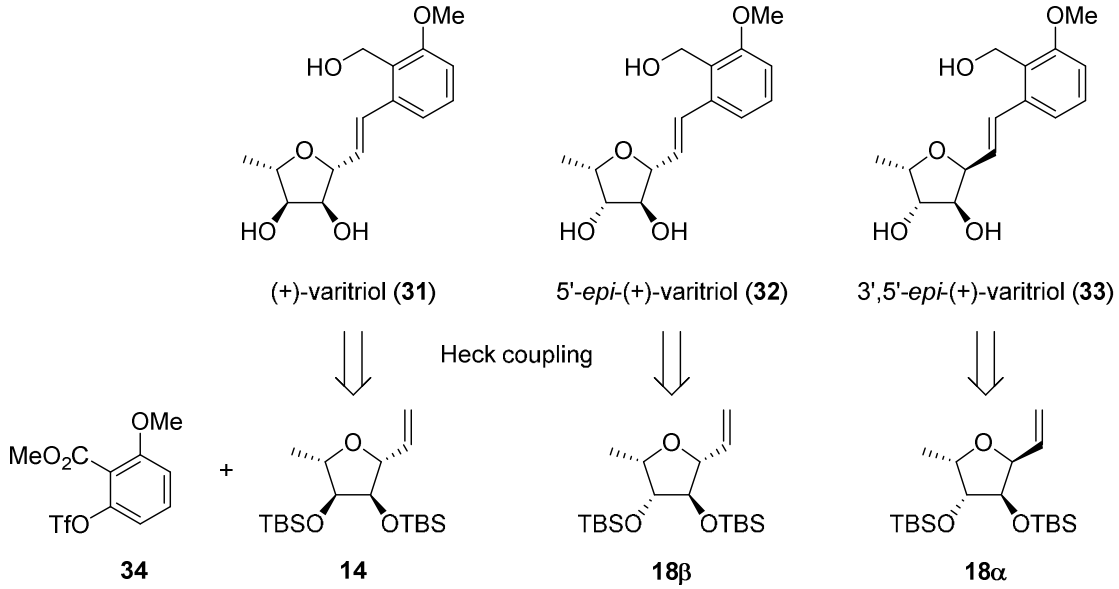


Scheme 10. Rotamers of **26A**.

These results thus provide further evidence that the stereochemical outcome of the nucleophilic addition into five-membered oxocarbenium ions is controlled by the relative disposition of C-2 and C-3 substituents and of the electronic nature of the protecting groups in these positions.

As an application of this modulable and stereoselective *C*-glycosidation, we planned to apply it to the total synthesis of natural product (+)-varitriol (**31**), a low molecular weight *C*-glycoside isolated in 2002 by Barrero *et al.*[17] from the marine fungi *Emericella variecolor*. This compound has shown important cytotoxic activity against renal, central nervous system and breast cancer cell lines.[18] The biological activity shown by **31** has attracted the attention of the synthetic community, and 12 total syntheses have been published so far.[19,20] Also, due to its important biological activity and lack of a complete understanding of the action mode of this natural product, the preparation of diastereoisomers of varitriol has also been a constant subject in recent years.[21] By taking advantage of the stereodiergent *C*-glycosidation of L-xylose drivatives, we envisaged to synthesize 5'-*epi*-(+)-varitriol (**32**) and 3',5'-*epi*-varitriol (**33**), two diastereoisomers of the natural product (Scheme 11). Since alkenes **14**, **18α** and **18β** were already prepared, featuring a Heck coupling reaction between these *C*-glycosides and known aryl triflate **34**[22]

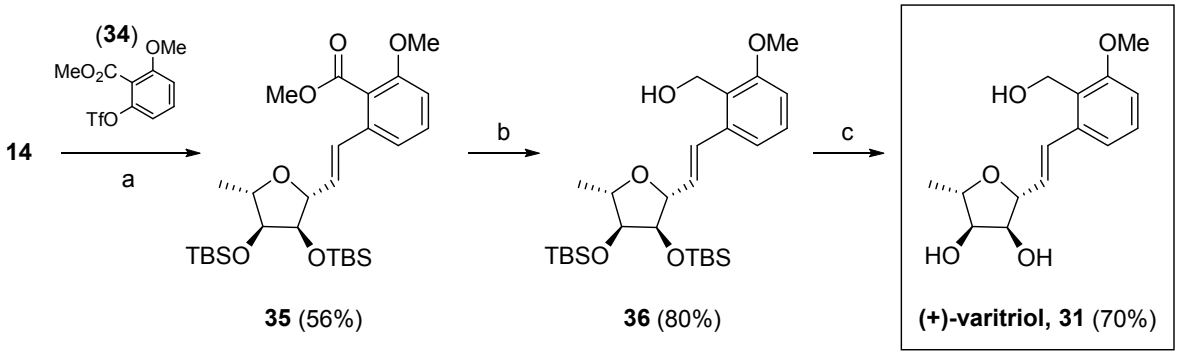
would render the final products. It is important to note that analogues **28** and **29** would arise from a common precursor (L-xilonolactone **2**) that is differentiated by simply changing the protecting groups to perform a stereodivergent *C*-glycosidation (*vide infra*).



Scheme 11. Retrosynthesis for (+)-varitriol (**31**) and epimers at 5' (**32**) and at 3',5 (**33**).

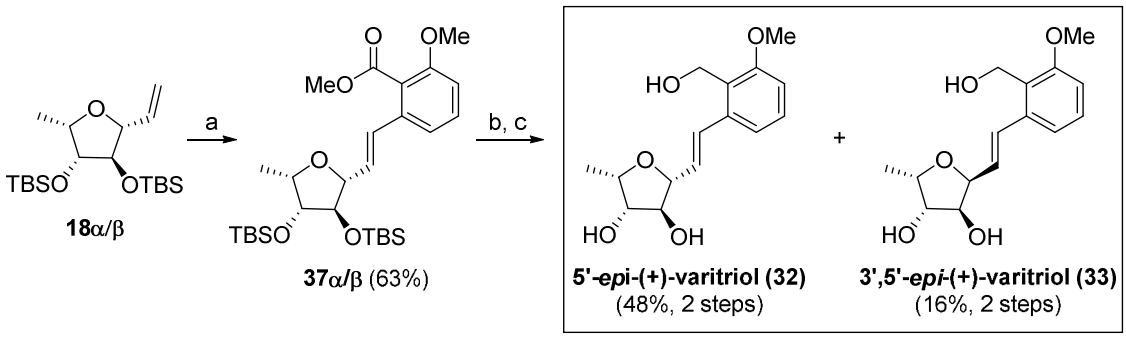
Initial attempts to forge the desired union between fragments **14** and **34** were focused on the Heck coupling reaction. Different reaction conditions were screened. Catalysts such as ($Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $PdCl_2(CH_3CN)_2$) were tested, and phosphine ligands such as (PPh_3, (o-Tol)$_3$P) with either DMF or DMA as solvents within a range of temperatures, however, the desired product was only observed in trace amounts. After examining different reaction conditions such as catalyst and ligand loads, base and temperature, it was found that the reaction proceeded smoothly with 20 mol% of $Pd(OAc)_2$, 40 mol% of caffeine[23,24] and 1 equivalent of Na_2CO_3 in DMF at 100 °C. In this way, the desired *E*-alkene **35** was isolated in 56% yield as a single isomer (no trace of either the regioisomer or the *Z*-stereoisomer was detected). After reduction of the ester group of **35** with DIBAL and removal of the TBS groups, the total synthesis of (+)-varitriol (**31**) was completed in 11% overall yield. Along with Shaw's,[20f] Gracza's[20h] and Liu's[20i] syntheses, the route reported

herein is the shortest one achieved to date (9 steps). The physical and spectroscopic data of **31** fully matched to those reported in the literature[17,20] (Scheme 12).



Scheme 12. Endgame for (+)-varitriol (**31**). Reagents and conditions: a) **34**, $Pd(OAc)_2$, caffeine, Na_2CO_3, DMF, 100 °C; b) DIBAL, CH_2Cl_2, 0 °C to r.t.; c) TBAF, THF, r.t.

The synthesis of varitriol diastereoisomers **32** and **33** was executed as outlined in Scheme 13. Although **18α** and **18β** were separated for characterization purposes when prepared from lactone **10**, this operation was tedious. Therefore, it was considered more convenient to perform the rest of the route with the diastereoisomeric mixture and to separate the products at the end of the synthesis. Applying the same conditions as before for the Heck coupling resulted in poor yields and incomplete reactions. However, switching the palladium source from $Pd(OAc)_2$ to $Pd(PPh_3)_4$ pleasingly provided the coupled compounds **37α/β** (only the β isomer is shown) in 63% yield. Finally, treatment with DIBAL and deprotection of the TBS groups under standard conditions (TBAF in THF) allowed us to isolate, after separation by preparative thin layer chromatography, 5'-*epi*-varitriol (**32**) and 3',5'-*epi*-varitriol (**33**) in 48 and 16% yields, respectively (64% combined yield for two steps). Compound **32** has been already reported in the literature,[14] and its spectroscopic data is in full concordance with those reported, whereas 3',5'-*epi*-varitriol (**33**) is a new varitriol diastereoisomer.



Scheme 13. Total synthesis of 5'-*epi*-varitriol (**32**) and 3',5'-*epi*-varitriol (**33**). Reagents and conditions: a) **34**, $Pd(PPh_3)_4$, caffeine, Na_2CO_3, DMF, 100 °C; b) DIBAL, CH_2Cl_2, 0 °C to r.t.; c) TBAF, THF, r.t.

In summary, we have provided further evidence that for carbohydrate-derived lactones bearing 2,3-*trans* substituents, the stereocontrol of the *C*-glycosidation step is influenced by the presence of aromatic rings in the protecting groups. According to quantum chemical calculations, this reversal in stereoselectvity may be due to π- π interactions between the aromatic ring of the C-2 protecting group with the exocyclic triple bond and the oxocarbenium ion. These interactions account for the stabilization of the conformer in which the C-2 and C-3 substituents adopt pseudoaxial orientations. This modulation of the stereochemistry could be a useful tool for the stereodivergent synthesis of tetrahydrofuran derivatives. Based on these findings, a concise total synthesis of the natural product (+)-varitriol (**31**) and of two diastereoisomers (**32** and **33**) were accomplished, which represent an unprecedent use of the protecting groups in the synthesis of a naturally occurring compound.

EXPERIMENTAL SECTION

Computational part.

The geometric parameters for all reactive intermediates were completely optimized with the SMD(CH_2Cl_2)-M06-2x/6-31+G(d,p) approximation as implemented in the Gaussian 2009 package.[25] The M06-2x was chosen due to the good performance with organic molecules

and implicit correction for dispersion forces.[26] Solvents effects were considered through the SMD model.[27] Each stationary structure was characterized as a local minimum by means of frequency calculations.

General considerations. All operations were carried out under an inert atmosphere of nitrogen or argon gas using standard techniques. Anhydrous THF was obtained by distillation under an inert atmosphere over sodium and benzophenone. Column chromatography was performed using 70-230 mesh silica gel. All reagents and solvents were obtained from commercial suppliers and used without further purification. IR spectra were recorded on a Perkin-Elmer 283B or 1420 spectrophotometer, by means of film and KBr techniques, and all data are expressed in wave numbers (cm^{-1}). Melting points were obtained on a Melt-Temp II apparatus and are uncorrected. NMR spectra were measured with a JEOL Eclipse +300 and a Varian Gemini (200 MHz), using $CDCl_3$ as solvent. Chemical shifts are in ppm (δ), relative to TMS. The MS-FAB^+ and MS-DART spectra were obtained on a JEOL SX 102A and a JEOL DART AccuTOF JMS-T100CC, respectively, the values of the signals are expressed in mass/charge units (*m/z*), followed by the relative intensity with reference to a 100% base peak.

General procedures.

General procedure A (trisilylation of lactones 1 and 2). To a solution of the corresponding lactone **1** or **2** (1.0 mmol) in CH_3CN (5 mL) were added imidazole (6.0 mmol) and *tert*-butyldimethylsilyl chloride (6.0 mmol). The reaction mixture was warmed to room temperature and allowed to react for 4 h. After this time, the reaction mixture was quenched by addition of water (5 mL) and extracted five times with ethyl acetate (30 mL). The organic phase was dried with Na_2SO_4, evaporated under reduced pressure, and the resultant residue was purified by column chromatography.

General procedure B (free radical reduction of iodolactones 7 and 8). To a solution of the corresponding iodinated compound (1 mmol) in dry and degassed toluene (20 mL) at 80 °C was added slowly Bu_3SnH (1.7 mmol) and 0.5 mmol of 1,1′-azobis-cyclohexanecarbonitrile

(ACHN). The reaction mixture was refluxed until complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography.

General procedure C (C-glycosidation). To a solution of TMS-acetylene (3.2 mmol) in dry THF (9.6 mL) at –78 °C under argon atmosphere was added dropwise *n*BuLi (2.8 mmol, 2.5 M solution in THF). The resultant solution was warmed to room temperature and stirred for 1 h at 25 °C. Then, the reaction was chilled to –40 °C, a solution of 1 mmol of the corresponding lactone (**9, 10, 12**, **13**, **28** or **30**) in dry THF (10 mL) was transferred to the reaction flask and the mixture was stirred at –40 °C until complete consumption of the starting lactone (usually 1.5-2 h, monitored by TLC). The reaction was quenched with saturated aqueous NH_4Cl solution and stirred for an additional 1 h. The reaction was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. The crude lactol was directly used for the reduction step without further purification.

To a solution of the crude lactol (1 mmol) in 12 mL of anhydrous CH_2Cl_2 at –78°C was added Et_3SiH (4.0 mmol) followed by $BF_3{\cdot}OEt_2$ (4.0 mmol, added dropwise). The resulting solution was stirred at –78 °C for 2 h, neutralized with a saturated aqueous solution of $NaHCO_3$ (pH ~ 7) and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resultant residue was purified by flash column chromatography.

General procedure D (partial hydrogenation of alkynes). A mixture of the corresponding alkyne (1 mmol) and Lindlar catalyst (20 wt. %) in methanol (4 mL) was hydrogenated at 1 atm at room temperature. When the starting material was completely consumed, the mixture was filtered over neutral alumina and washed with EtOAc. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography.

General procedure E (DIBAL reduction of esters). To a solution of the esters **37** or **39** (1 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C, was added dropwise DIBAL (2.5 mmol, 1M solution in CH_2Cl_2). The reaction mixture was stirred at room temperature until complete consumption of the starting material. The reaction was quenched by the addition of 1 mL of Rochelle´s salt solution and the mixture was stirred for further 10 min. The organic phase

was extracted with ethyl acetate, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography.

General procedure F (deprotection with TBAF). To a solution of alcohols **38** or **39** (1 mmol) in dry THF at 0 °C, was added dropwise TBAF (2.5 mmol, 1M solution in THF). The reaction mixture was stirred at room temperature until disappearance of the starting material (monitored by TLC). Water (1 mL) was added and the organic phase was extracted with ethyl acetate (20 mL). The organic phase was dried over Na_2SO_4, evaporated under reduced pressure, and the resultant residue was purified by column chromatography.

Tri-*O*-(*tert*-butyldimethylsilyl)-L-ribono-γ-lactone (3). The title compound was prepared from L-ribono-1,4-lactone (**1**, 168 mg) according to *general procedure A* to afford, after purification by column chromatography (silica gel, hexane:ethyl acetate, 30:1), compound **3** in 91% yield (537 mg) as a white solid. m.p. = 117-118 °C. $[\alpha]_D^{25}$= –25.3 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (d, *J* = 4.9 Hz, 1H), 4.28-4.26 (m, 2H), 3.88-3.72 (m, 2H), 0.93 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 85.8, 72.1, 70.7, 62.5, 25.9 (6C), 25.8 (3C), 18.6, 18.4, 18.3, –4.4, –4.5, –4.7, –4.9, –5.4, –5.5. IR (ATR) ṽ = 2934 (m), 2871 (m), 1781 (s), 1492 (w), 1450 (m), 1359 (w), 1329 (m), 1099 (s), 1060 (s), 954 (m), 937 (m), 730 (w), 696 (m), 607 (w), 560 (w) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{23}H_{51}O_5Si_3$ $[M+H^+]$: 491.3044 found: 491.3022. The spectroscopic data matched to those reported in the literature[11] for the D-ribose derivative.

Tri-*O*-(*tert*-butyldimethylsilyl)-L-xylono-γ-lactone (4). Following *general procedure A*, this compound was obtained from L-xilono-1,4-lactone **2** (250 mg). Purification by column chromatography (silica gel, hexane:ethyl acetate, 35:1) afforded compound **4** (93% yield, 814 mg) as a clear oil. $[\alpha]_D^{25}$= –60.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (d, *J* = 7.4 Hz, 1H), 4.40 (t, *J* = 7.3 Hz, 1H), 4.31 (ddd, *J* = 7.3, 2.9, 1.8 Hz, 1H), 3.92 (dd, *J* = 11.2, 1.8 Hz, 1H), 3.81 (dd, *J* = 11.1, 2.7 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.17 (s, 3H), 0.11 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 78.8, 76.1, 74.1, 60.4, 25.9 (3C), 25.83 (3C), 25.80 (3C), 18.3, 18.2, 18.0, -4.3, –4.6 (2C), –4.7, –5.4, –5.5. IR (ATR) ṽ = 2940 (m), 2869 (m), 1782 (s), 1499 (w),

1451 (m), 1357 (w), 1326 (m), 1102 (s), 1056 (s), 955 (m), 937 (m), 730 (w), 695 (m), 607 (w), 557 (w) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{23}H_{51}O_5Si_3$ $[M+H^+]$: 491.3044 found: 491.3031.

2,3-Di-*O*-(*tert*-butyldimethylsilyl)-*L*-ribono-γ-lactone (5). To solution of protected lactone **3** (860 mg, 1.75 mmol,) in anhydrous THF (7 mL) at 0 °C was slowly added a 1:1 (v/v) mixture of water:TFA (3.5 mL) and allowed to react for 4 h. After this time the mixture was treated with a saturated aqueous solution of $NaHCO_3$ to adjust pH ~7. Extraction with ethyl acetate (50 mL), followed by drying with Na_2SO_4 and concentrating under reduced pressure, gave a residue that was purified by column chromatography on silica gel (hexane:ethyl acetate, 15:1) to afford 495 mg (75%) of compound **5** as a white solid. mp = 113-114°C. $[\alpha]_D^{25}$ = –45.4 (*c* 1.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (d, *J* = 5.0 Hz, 1H), 4.34 (dd, *J* = 5.4, 2.7 Hz, 1H), 4.30 (dd, *J* = 5.1, 2.1 Hz, 1H), 3.96 (ddd, *J* = 12.6, 5.1, 2.7 Hz, 1H), 3.75 (ddd, *J* = 14.1, 6.0, 2.7 Hz, 1H), 2.44 (brs, 1H), 0.92 (s, 9H), 0.88 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 85.7, 71.5, 70.8, 61.4, 25.9 (3C), 25.8 (3C), 18.5, 18.3, –4.4, –4.5, –4.7, –4.9. IR (ATR) $\tilde{\nu}$ = 2953 (w), 2929 (m), 2888 (w), 2856 (m), 1788 (s), 1466 (s), 1388 (w), 1104 (s), 983 (w), 951 (m), 832 (s), 666 (w), 511 (w) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{17}H_{37}O_5Si_2$ $[M+H^+]$: 377.2180; found: 377.2170.

2,3-Di-*O*-(*tert*-butyldimethylsilyl)-*L*-xylono-γ-lactone (6). To solution of lactone **4** (890 mg, 1.81 mmol) in anhydrous CH_2Cl_2 (72 mL) at 0 °C was added dropwise $BF_3{\cdot}OEt_2$ (7.25 mmol, 0.910 mL). The reaction mixture was allowed to stir for further 2 h at room temperature. After this time, the mixture was treated with a saturated aqueous solution of $NaHCO_3$ to adjust pH ~ 7. Extraction with ethyl acetate (80 mL), followed by drying with Na_2SO_4 and concentrating under reduced pressure gave a residue that was purified by column chromatography on silica gel (hexane:ethyl acetate, 20:1) to afford 835 mg (93%) of compound **6** as a white solid. mp = 82-84 °C. $[\alpha]_D^{25}$ = –50.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55-4.38 (m, 3H), 3.95 (dd, *J* = 12.8, 3.7 Hz, 1H), 3.87 (dd, *J* = 12.9, 2.8 Hz, 1H), 2.01-1.97 (m, 1H), 0.92 (s, 18H), 0.19 (s, 3H), 0.14 (s, 6H), 0.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6, 79.8, 76.1, 74.5, 61.5, 25.8 (3C), 25.7 (3C), 18.3, 18.0,

–4.3, –4.5, –4.6, –4.8. IR (ATR) ṽ = 3421 (w), 2954 (w), 2928 (m), 2894 (w), 2856 (m), 1781 (s), 1465 (m), 1171 (m), 943 (w), 880 (m), 779 (s), 573 (m) cm^{-1}. HRMS (DART) m/z calcd for $C_{17}H_{37}O_5Si_2$ [$M+H^+$]: 377.2180; found: 377.2154.

2,3-Di-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-5-iodo-L-ribono-γ-lactone (7). To a solution of alcohol **5** (495 mg, 1.31 mmol), PPh_3 (514 mg, 1.96 mmol), and imidazole (294 mg, 4.32 mmol) in dry CH_2Cl_2 (25 mL) at room temperature was added I_2 (494 mg, 1.5 mmol). The reaction was stirred for a further hour. After this time, the mixture reaction was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 40:1) to afford 580 mg (91%) of compound **7** as a white solid. mp = 52-53 °C. $[\alpha]_D^{25}$ = –17.8 (*c* 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (ddd, *J* = 7.6, 4.9, 2.6 Hz, 1H), 4.33 (d, *J* = 4.5, 1H), 4.26 (ddd, *J* = 4.7, 2.6, 0.6 Hz, 1H), 3.34 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.25 (dd, *J* = 11.0, 8.1 Hz, 1H), 0.93 (s, 9H), 0.90 (s, 9H), 0.19 (s, 3H), 0.16 (s, 6H), 0.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 83.1, 73.4, 70.4, 25.9 (3C), 25.8 (3C), 18.5, 18.2, 2.1, –4.2, –4.4 –4.5, –4.8. IR (ATR) ṽ = 2954 (w), 2930 (m), 2889 (w), 2856 (m), 1785 (s), 1467 (m), 1385 (w), 1359 (w), 1251 (s), 1164 (s), 1144 (s), 1101 (s), 1067 (m), 1010 (m), 988 (m), 937 (s), 917 (m), 672 (m) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{17}H_{36}IO_4Si_2$ [$M+H^+$]: 487.1197; found: 487.1164.

2,3-Di-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-5-iodo-L-xylono-γ-lactone (8). To a mixture of alcohol **6** (635 mg, 1.68 mmol), PPh_3 (1.76 g, 6.72 mmol), and imidazole (462 mg, 6.72 mmol) in dry CH_2Cl_2 (32 mL) at room temperature was added I_2 (1.06 g, 4.20 mmol). The reaction was stirred for a further hour. After this time, the mixture reaction was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate 40:1) to afford 790 mg (97%) of compound **8** as a yellow oil. $[\alpha]_D^{25}$= –5.2 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.79 (ddd, *J* = 8.1, 6.2, 3.7 Hz, 1H), 4.20 (dd, *J* = 3.9, 2.4 Hz, 1H), 4.10 (d, *J* = 2.4 Hz, 1H), 3.40-3.26 (m, 2H), 0.90 (s, 9H), 0.89 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H),0.13 (s, 3H), 0.12 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 82.4, 75.2, 74.7, 25.7 (3C), 25.6 (3C), 18.1, 17.9, –0.9, –4.3, –4.6, –4.7, –4.9. IR (ATR) ṽ = 3225 (w), 2955 (w), 2931 (w), 2889 (w),

1780 (s), 1467 (m), 1251 (m), 1097 (s), 935 (m), 841 (s), 673 (m), 527 (m), 474 (w) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{17}H_{36}IO_4Si_2$ $[M+H^+]$: 487.1196; found: 487.1188.

2,3-Di-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-γ-L-ribonolactone (9). The title compound was obtained from iodolactone **7** (950 mg) following *general method B*, to afford after purification by column chromatography (silica gel, hexane:ethyl acetate, 40:1), compound **9** in 94% yield (720 mg) as a white solid. mp = 54-55 °C. $[\alpha]_D^{25}$= –34.92 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.43 (qd, *J* = 6.8, 2.3 Hz, 1H), 4.30 (d, *J* = 4.6 Hz, 1H), 3.95 (dd, *J* = 4.6, 2.4 Hz, 1H), 1.36 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 9H), 0.88 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 81.2, 75.3, 70.4, 25.9 (3C), 25.8 (3C), 18.5, 18.3, 18.1, –4.3, –4.4, –4.8, –4.9. IR (ATR) $\tilde{\nu}$ = 2930 (m), 2874 (m), 1775 (s), 1490 (w), 1454 (m), 1366 (w), 1331 (m), 1100 (s), 1070 (s), 938 (m), 736 (w), 693 (m), 611 (w), 560 (w) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{17}H_{37}O_4Si_2$ $[M+H^+]$: 361.2230 found: 361.2210.

2,3-Di-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-γ-L-xilonolactone (10). This compound was prepared from lactone **8** (900 mg) according to *general procedure B*. Purification by column chromatography on silica gel (hexane:ethyl acetate, 40:1) gave compound **10** in 96% yield (640 mg) as a pale yellow oil. $[\alpha]_D^{25}$= –54.2 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.66 (dd, *J* = 6.5, 3.8 Hz, 1H), 4.14-4.10 (m, 2H), 1.33 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 18H), 0.16 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.1, 78.0, 75.9, 74.7, 25.8 (3C), 25.7 (3C), 18.2, 18.1, 14.9, –4.5, –4.6, –4.7, –4.9. IR (ATR) $\tilde{\nu}$ = 2930 (m), 2872 (m), 1778 (s), 1491 (w), 1456 (m), 1364 (w), 1334 (m), 1098 (s), 1073 (s), 940 (m), 732 (w), 699 (m), 610 (w), 556 (w) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{17}H_{37}O_4Si_2$ $[M+H^+]$: 361.2230 found: 361.2221. Except for the optical rotation, the spectroscopic data matched to those reported by Hodgson[12] for the D-xylose derivative, except for the sign of the optical rotation.

5-Deoxy-γ-L-xilonolactone (11). To a solution of lactone **10** (280 mg, 0.77 mmol), in dry CH_3CN (12 mL) at 0°C was added slowly $BF_3{\cdot}OEt_2$ (0.38 mL, 3.10 mmol). The reaction mixture was stirred for 30 min at 25°C. After this time, the reaction was treated with a

saturated aqueous solution of $NaHCO_3$ to adjust pH ~ 7, and extracted with ethyl acetate. The organic phase was dried with Na_2SO_4, evaporated under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 1:2), to give 85 mg (84%) of **11** as a pale yellow oil. $[\alpha]_D^{25}$= –63.1 (*c* 1, acetone); ^{1}H NMR (300 MHz, *acetone d*$_6$) δ: 5.19 (d, *J* = 4.8 Hz, 1H), 4.85 (d, *J* = 4.2 Hz, 1H), 4.69 (ddd, *J* = 12, 6.0, 6.0 Hz, 1H), 4.26 (dq, *J* = 10.3, 5.5 Hz, 2H), 1.33 (d, *J* = 6.7 Hz, 3H).^{13}C NMR (100 MHz, *acetone d*$_6$) δ 175.4, 78.0, 74.8, 74.0, 14.7. IR (ATR) ṽ = 3425 (w), 2955 (w), 2930 (m), 2891 (w), 2853 (m), 1787 (s), 1462 (m), 1177 (m), 944 (w), 880 (m), 775 (s), 573 (m) cm^{-1}. HRMS (DART) *m/z* calcd for $C_5H_9O_4$ [M+H$^+$]: 133.0500; found: 133.0496.

2,3-Di-*O*-benzyl-5-deoxy-5-methyl-γ-L-xilonolactone (12). To a solution of **11** (85 mg, 0.643 mmol) and AgO_2 (372 mg, 1.60 mmol) in dry CH_2Cl_2 (6 mL) was added BnBr (0.764 mL, 6.43 mmol). The reaction mixture was stirred for 2 h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 7:1) to afford 0.170 g (65%) of compound **12** as a yellow oil. $[\alpha]_D^{25}$= –70.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.24 (m, 10 H), 4.99 (d, *J* = 11.6 Hz, 1H), 4.79 – 4.72 (m, 2H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.21-4.13 (m, 2H), 1.38 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 137.2, 136.9, 128.7 (4C), 128.4 (2C), 128.3, 128.2, 127.8 (2C), 79.6, 76.9, 76.8, 72.5, 72.3, 15.2. IR (ATR) ṽ = 3064 (w), 3031 (w), 2983 (w), 2934 (m), 2871 (m), 1779 (s), 1496 (w), 1454 (m), 1365 (w), 1329 (m), 1108 (s), 1060 (s), 954 (m), 938 (m), 736 (w), 696 (m), 607 (w), 565 (w) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{19}H_{21}O_4$ [M+H$^+$]: 313.1439; found: 313.1441.

(2*R*,3*R*,4*S*,5*S*)-2-Ethynyl-5-methyl-3,4-bis-*O*-*tert*-butyldimethylsilyl-tetrahydrofuran (14). The title compound was prepared from lactone **9** (200 mg) and TMS-acetylene as described in the *general method C*. The product was purified by column chromatography (silica gel, hexane:ethyl acetate, 40:1) to give of **14** (60% yield, 120 mg) as a pale yellow oil. $[\alpha]_D^{25}$= +6.2 (*c* 1, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 3.7 2.2 Hz, 1H), 4.08 (dd, *J* = 4.1, 4.1 Hz, 1H), 3.93 (ddd, *J* = 12.6, 12.6, 6.3 Hz, 1H), 3.76 (dd, *J* = 6.0, 4.4 Hz, 1H), 2.53 (d, *J* = 2.0 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.3, 78.8,

78.2, 78.1, 74.8, 73.1, 26.0 (6C), 19.3, 18.2 (2C), –4.10, –4.29, –4.32, –4.5. IR (ATR) $\tilde{\nu}$ = 3732 (w), 3703 (w), 3621 (w), 3598 (m), 3290 (w), 2919 (w), 2870 (w), 2294 (w), 1496 (w), 1450 (m), 1065 (s), 1031 (s), 730 (m), 691 (m), 667 (m) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{19}H_{39}O_3Si_2$ $[M+H^+]$: 371.2437 found: 371.2436.

(2*R*,3*R*,4*S*,5*S*)-2-Methyl-3,4-bis-*O*-*tert*-butyldimethylsilyl-5-vinyl tetrahydrofuran (15). Following *general procedure D* (partial hydrogenation), this compound was obtained from alkyne **14** (155 mg) in 98% yield (148 mg) after purification by column chromatography (silica gel, hexane:ethyl acetate, 50:1) as a pale yellow oil**.** $[\alpha]_D^{25}$= +2.9 (*c* 1, $CHCl_3$). Lit[14] $[\alpha]_D^{25}$= +3.9 (c 1.82 $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.78 (ddd, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.31 (dt, *J* = 17.0, 1.7 Hz, 1H), 5.16 (dt, *J* = 10.4, 1.8 Hz, 1H), 4.25-4.20 (m, 1H), 4.01-3.92 (m, 1H), 3.76 (t, *J* = 4.5 Hz, 1H), 3.59 (dd, *J* = 5.3, 4.5 Hz, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.065 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.5, 116.9, 84.5, 78.6, 77.8, 77.1, 26.0 (6C), 19.5, 18.3, 18.2, –4.1, –4.13, –4.16, –4.4. IR (ATR) $\tilde{\nu}$ = 3020 (w), 2923 (w), 1613 (m), 1511 (w), 1216 (m), 1027 (s), 737 (m), 695 (m), 670 (m) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{19}H_{41}O_3Si_2$ $[M+H^+]$: 373.2594 found: 373.2601.

(2*R*,3*R*,4*S*,5*S*)-2-Ethynyl-5-methyl-3,4-bis-*O*-benzyl-tetrahydrofuran (16). The title compound was prepared from lactone **13** (40 mg) and TMS-acetylene as described in the *general method C*. The product was purified by column chromatography (silica gel, hexane:ethyl acetate, 40:1) to give of **16** (12% yield, 5 mg, 24% brsm) as a pale yellow oil. $[\alpha]_D^{25}$= -15.2 (*c* 0.5, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41-7.29 (m, 10H), 4.73 (d, *J* = 12.3 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 12.3 Hz, 1H), 4.59 (dd, *J* = 4.5, 2.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.09-4.02 (m, 2H), 3.63 (dd, *J* = 6.6, 5.4 Hz, 1H), 2.56 (d, *J* = 2.4 Hz, 1H), 1.30 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.9, 137.6, 128.6 (2C), 128.5 (2C), 128.2 (2C), 128.1, 128.0 (3C), 82.8, 81.9, 77.8, 77.4, 75.0, 72.6, 71.41, 71.43, 19.4. IR (ATR) $\tilde{\nu}$ = 3730 (w), 3702 (w), 3627 (w), 3596 (m), 3284 (w), 2923 (w), 2861 (w), 2295 (w), 1496 (w), 1453 (m), 1064 (s), 1027 (s), 737 (m), 695 (m), 670 (m) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{21}H_{23}O_3$ $[M+H^+]$: 323.1647 found: 323.1662.

Alkynes 17α and 17β. According to *general method C* for the *C*-glycosidation, this compound was prepared from lactone **10** (200 mg) and TMS-acetylene, affording a separable mixture of alkynes **17α** (13% yield, 26 mg, minor) and **17β** (40% yield, 82 mg, major) after purification by column chromatography (silica gel, hexane:ethyl acetate, 40:1).

(((*2S*,*3R*,*4R*,*5S*)-2-Ethynyl-5-methyltetrahydrofuran-3,4-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (17α). Pale yellow oil. $[\alpha]_D^{25}$ = +68.4 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.74 (dd, *J* = 2.8 Hz, 1H), 4.36 (qd, *J* = 6.4, 3.0 Hz, 1H), 4.00 (dd, *J* = 3.2, 1.6 Hz, 1H), 3.84 (dd, *J* = 3.1, 1.6 Hz, 1H), 2.46 (d, *J* = 2.2 Hz, 1H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s. 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 80.6, 80.0, 79.1, 77.1, 75.6, 71.8, 25.9 (3C), 25.8 (3C), 18.2, 18.1, 14.6, –4.3, –4.4, –4.5, –4.7. IR (ATR) ṽ = 2921 (w), 2860 (w), 2293 (w), 1493 (w), 1452 (m), 1066 (s), 1022 (s), 730 (m), 701 (m), 660 (m) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{19}H_{39}O_3Si_2$ [M+H$^+$]: 371.24377 found: 371.24276.

(((*2R*,*3R*,*4R*,*5S*)-2-Ethynyl-5-methyltetrahydrofuran-3,4-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (17β). Pale yellow oil. $[\alpha]_D^{25}$= +71.3 (*c* 1, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.29 (t, *J* = 2.1 Hz, 1H), 4.18 (t, *J* = 1.6 Hz, 1H), 4.12 (qd, *J* = 6.3, 3.0 Hz, 1H), 3.8 (dd, *J* = 3.0, 1.4 Hz, 1H), 2.50 (d, *J* = 2.3 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 6H), 0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 85.0, 82.2, 80.1, 78.4, 75.4, 74.3, 25.9 (3C), 25.8 (3C), 18.2, 17.9, 14.6, –4.4 (2C), –4.6, –4.7. IR (ATR) ṽ = 2920 (w), 2860 (w), 2292 (w), 1499 (w), 1461 (m), 1065 (s), 1028 (s), 736 (m), 700 (m), 655 (m) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{19}H_{39}O_3Si_2$ [M+H$^+$]: 371.24377 found: 371.24381.

(((*2S*,*3R*,*4R*,*5S*)-2-Methyl-5-vinyltetrahydrofuran-3,4-diyl)bis(oxy))bis(*tert*-butyl-dimethylsilane) (18α) and (((*2S*,*3R*,*4R*,*5R*)-2-methyl-5-vinyltetrahydrofuran-3,4-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (18β). Following the *general method D* a diastereoisomeric mixture of **17α/β** (300 mg) was hydrogenated in the presence of Lindlar catalyst, giving an inseparable mixture of compounds **18α** and **18β** in 98% combined yield (290 mg) after column chromatography (the diastereoisomeric mixture is described). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 5.98-5.84 (m, $1H_{\alpha}$, $1H_{\beta}$), 5.29 (ddd, *J* = 17.2, 2.0, 0.8 Hz, $1H_{\alpha}$), 5.21 (ddd *J* = 17.6, 2.0, 1.2 Hz, $1H_{\beta}$), 5.19 (ddd, 10.4, 2.0, 0.8 Hz, $1H_{\alpha}$), 5.08 (ddd, *J* = 10.0, 1.6, 0.8 Hz, $1H_{\beta}$), 4.45 (dd, *J* = 8.0, 2.9 Hz, $1H_{\alpha}$), 4.29 (qd, *J* = 6.3, 2.8 Hz, $1H_{\alpha}$), 4.16 (qd, *J* = 6.4, 2.8 Hz, $1H_{\beta}$), 4.08 (dd *J* = 8.2, 1.1 Hz, $1H_{\beta}$), 3.91 (dd, *J* = 3.0, 1.4 Hz, $1H_{\alpha}$), 3.86 (t, *J* = 1.2 Hz, $1H_{\beta}$), 3.82 (dd, *J* = 2.8, 1.2 Hz, $1H_{\alpha}$), 3.74 (dd, *J* = 2.8, 1.2 Hz, $1H_{\beta}$), 1.24 (d, *J* = 6.4 Hz, $3H_{\beta}$), 1.18 (d, *J* = 6.4 Hz, $3H_{\alpha}$), 0.91 (s, $9H_{\alpha}$), 0.90 (s, $9H_{\beta}$), 0.89 (s, $9H_{\alpha}$, $9H_{\beta}$), 0.09 (s, $3H_{\alpha}$), 0.08-0.06 (m, $12H_{\beta}$, $6H_{\alpha}$), 0.04 (s, $3H_{\alpha}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.5, 118.0, 116.2, 88.7, 84.0, 82.5, 80.7, 80.4, 79.8, 77.6, 25.9, 18.23, 18.20, 18.17, 18.0, 14.9, 14.6, –4.2, –4.3, –4.4, –4.5, –4.6, –4.7, –4.8. HRMS (DART) *m/z* calcd for $C_{19}H_{41}O_3Si_2$ $[M+H^+]$: 373.2594 found: 373.2600.

(2*S*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2-ethynyl-5-methyltetrahydrofuran (19α). The title compound was prepared from lactone **12** (200 mg) and TMS-acetylene according to *general method C*. Purification by flash column chromatography (hexane:ethyl acetate, 8:1) gave **19α** in 65% yield (130 mg) as a pale yellow oil. $[\alpha]_D^{25}$ = –30.2 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.24 (m, 10H), 4.84 (dd, *J* = 4.8, 2.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.39 (qd, *J* = 6.4, 4.4 Hz, 1H), 4.03 (dd, *J* = 4.8, 2.4 Hz, 1H), 3.86 (dd, *J* = 4.4, 2.4 Hz, 1H), 2.57 (d, *J* = 2.4 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.0, 137.7, 128.6 (2C), 128.5 (2C), 128.0, 127.99 (2C), 127.91, 127.6 (2C), 83.4, 83.3, 79.7, 76.2, 76.1, 72.7, 72.1, 70.0, 14.4. IR (ATR) $\tilde{\nu}$ = 3732 (w), 3624 (w), 3601 (m), 3285 (w), 2910 (w), 2878 (w), 2294 (w), 1494 (w), 1457 (m), 1067 (s), 1025 (s), 730 (m), 690 (m), 662 (m) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{21}H_{23}O_3$ $[M+H^+]$: 323.1647; found: 323.1639.

(2*S*,3*R*,4*R*,5*S*)-2-Ethynyl-5-methyltetrahydrofuran-3,4-diol (20α). To a solution of alkyne **19α** (133 mg, 0.412 mmol), in dry CH_2Cl_2 (3.3 mL) at 0°C was added dropwise BCl_3 (1.23 mL, 1.23 mmol, 1M solution in hexane). The reaction mixture was allowed to react for 30 min at 25°C. After this time, the reaction was treated with a saturated aqueous solution of $NaHCO_3$ to adjust pH ~ 7 and extracted with ethyl acetate. The organic phase

was dried with Na_2SO_4, evaporated under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 1:2), to give 48 mg (84%) of alcohol **20α** as a white solid. mp = 93-95 °C. $[\alpha]_D^{25}$ = +26.4 (*c* 0.5, $(CH_3)_2CO$). ^{1}H NMR (300 MHz, Acetone-d_6) δ: 4.74 (dd, *J* = 3.6, 2.4 Hz, 1H), 4. 26 (qd, *J* = 6.4, 3.4 Hz, 1H), 4.18 (brs, 1H), 4.10 (brs, 2H), 3.98 (brs, 1H), 2.91 (d, *J* = 2.0 Hz, 1H), 1.14 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $COCD_6$) δ: 81.1, 79.8, 78.4, 77.2, 76.8, 72.2, 14.4. IR (ATR) $\tilde{\nu}$ = 3420 (w), 2955 (w), 2932 (m), 2899 (w), 2856 (m), 2290 (w), 1499 (w), 1441 (m), 1060 (s), 1032 (s), 731 (m), 688 (m), 655 (m) cm^{-1}. HRMS (DART) *m/z* calcd for $C_7H_{11}O_3$ [M+H$^+$]: 143.0708; found: 143.0710.

3-*O*-*tert*-Butyldimethylsilyl-5-deoxy-γ-L-xilonolactone (27). To a solution of lactone **10** (180 mg, 0.499 mmol), in dry THF (5 mL) at –10°C was slowly added TBAF (1.25 mL, 1.24 mmol, 1M solution in THF) and the reaction mixture stirred for 20 min at –10°C. Then, water was added and the reaction was extracted with ethyl acetate. The organic phase was dried with Na_2SO_4, evaporated under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 2:1), to give 93 mg (76%) of **27** as a pale yellow oil. $[\alpha]_D^{25}$ = –31.0 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (quint, *J* = 6.7 Hz, 1H), 4.37 (t, *J* = 7.2 Hz, 1H), 4.31 (d, *J* = 7.3 Hz, 1H), 2.99 (brs, 1H), 1.36 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 77.6, 75.0, 73.1, 25.8 (3C), 18.2, 15.4, –4.5, –5.0. IR (ATR) $\tilde{\nu}$ = 2911 (m), 2866 (m), 1780 (s), 1496 (w), 1451 (m), 1361 (w), 1333 (m), 1103 (s), 1082 (s), 935 (m), 732 (w), 699 (m), 613 (w), 565 (w) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{11}H_{23}O_4Si$ [M+H$^+$]: 247.13656 found: 247.13559.

3-*O*-*tert*-Butyldimethylsilyl-2-*O*-*tert*-butyldiphenyl-5-deoxy-γ-L-xilonolactone (28). To a solution of lactone **27** (93 mg, 0.377 mmol) in CH_3CN (9 mL) at room temperature were added imidazole (51 mg, 0.754 mmol) and *tert*-butyldiphenylsilyl chloride (0.190 mL, 0.754 mmol). The reaction mixture was stirred for 12 h. After this time, water was added and the reaction extracted with ethyl acetate. The organic phase was dried with Na_2SO_4, evaporated under reduced pressure and resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 15:1), to give 160 mg (88%) of **28** as a

pale yellow oil. $[\alpha]_D^{25}$ = –16.0 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.68 (m, 4H), 7.46-7.38 (m, 6H), 4.89 (qd, *J* = 6.5, 3.4 Hz, 1H), 4.04 (d, *J* = 2.1 Hz, 1H), 3.97 (dd, *J* = 3.4, 2.1 Hz, 1H), 1.35 (d, *J* = 6.5 Hz, 3H), 1.08 (s, 9H), 0.74 (s, 9H), -0.14 (s, 3H), -0.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 136.1 (2C), 135.9 (2C), 133.0, 132.0, 130.3, 130.2, 128.0 (2C), 127.9 (2C), 79.6, 75.8, 75.6, 26.9 (3C), 25.7 (3C), 19.5, 18.0, 14.3, –5.0, –5.1. IR (ATR) ṽ = 3071 (w), 3049 (w), 2953 (w), 2934 (m), 2929 (m), 2887 (w), 2857 (m), 1734 (w), 1462 (m), 1427 (m), 1112 (s), 1081 (s), 1044 (m), 835 (s), 822 (m), 776 (m), 700 (s), 502 (s), 486 (s) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{27}H_{41}O_4Si_2$ $[M+H^+]$: 485.25434; found: 485.25395.

***tert*-Butyl(((*2S*,*3R*,*4R*,*5S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-ethynyl-5-methyltetra-hydrofuran-3-yl)oxy)diphenylsilane (29α).** Alkynyl compounds **29α** and **29β** were prepared from lactone **28** (92 mg) and TMS-acetylene following the *general method C*. Analysis of the ^{1}H NMR spectrum revealed a 20:1 mixture of diastereoisomers, however, after purification by column chromatography, only **29α** (major isomer) could be recovered and fully characterized. Pale yellow oil, 55% yield (50 mg). $[\alpha]_D^{25}$ = +25.5 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78-7.69 (m, 4H), 7.47-7.36 (m, 6H), 4.69-4.68 (m, 1H), 4.47 (qd, *J* = 6.4, 4.4 Hz, 1H), 4.11 (brs, 1H), 3.71 (brs, 1H), 2.48 (d, *J* = 2.1 Hz, 1H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.09 (s, 9H), 0.73 (s, 9H), -0.26 (s, 3H), -0.40 (s, 3H). ^{13}C NMR (75 MHz, $ClCD_3$) δ 136.4 (2C), 136.1 (2C), 133.9, 133.0, 130.1, 130.0, 127.9 (2C), 127.7 (2C), 80.7, 80.3, 78.2, 77.1, 76.2, 71.8, 27.1 (3C), 25.8 (3C), 19.7, 18.0, 14.7, –4.9, –5.3. IR (ATR) ṽ = 3314 (w), 2953 (w), 2929 (m), 2887 (w), 2857 (m), 1472 (m), 1463 (m), 1253 (m), 1106 (m), 1080 (s), 1084 (m), 1006 (w), 874 (m), 832 (s), 814 (w), 774 (s), 669 (m), 654 (m) cm^{-1}. HRMS (DART) *m/z* calcd for $C_{29}H_{46}NO_3Si_2$ $[M+NH_4]^+$: 512.30162 found: 512.29924.

Methyl 2-((*E*)-2-((*2R*,*3R*,*4S*,*5S*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-5-methyltetra-hydrofuran-2-yl)vinyl)-6-methoxybenzoate (35). To a solution of olefinic compound **15** (50 mg, 0.134 mmol) in dry and degassed DMF (0.7 mL) under argon atmosphere were sequentially added Na_2CO_2 (42 mg, 0.402 mmol), caffeine (8 mg, 0.042 mmol), triflate **34** (100 mg, 0.33 mmol) and $Pd(OAc)_2$ (12 mg, 0.042 mmol). The reaction mixture was heated at 100 °C for 5 h and cooled to room temperature. Then, water was added to the mixture

and the reaction was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, hexane:ethyl acetate, 10:1) to afford 40 mg (57%) of **35** as a white solid. mp = 93-95 °C. $[\alpha]_D^{25}$ = +27.6 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.61 (d, *J* = 15.6 Hz, 1H), 6.12 (dd, *J* = 15.8, 6.8 Hz, 1H), 4.4 (ddd, *J* = 6.5, 4.2, 1.2 Hz, 1H), 4.01 (ddd, *J* = 12.3, 12.3, 6.4 Hz, 1H), 3.90 (s, 3H), 3.85-3.82 (m, 1H), 3.83 (s, 3H), 3.63 (dd, *J* = 5.6, 4.4 Hz, 1H), 1.27 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H) 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.4, 156.5, 135.6, 132.2, 130.5, 128.0, 122.9, 117.9, 110.0, 84.2, 78.7, 77.8, 77.4, 56.1, 52.5, 26.0 (6C), 19.5, 18.3, 18.2, –4.10, –4.13, –4.2, –4.5. IR (ATR) ṽ = 3333 (b), 2951 (m), 2924 (s), 2885 (m), 1727 (m), 1597 (w), 1577 (m), 1496 (m), 1458 (m), 1277 (m), 1256 (m), 1158 (w), 1115 (m), 1065 (m), 1031 (w), 854 (w), 836 (m), 557 (w) cm^{-1}. HRMS (DART) *m*/*z* calcd for 537.3067 $[M+H]^+$ $C_{28}H_{49}O_6Si_2$; found: 537.3064.

(2-((*E*)-2-((*2R*,*3R*,*4S*,*5S*)-3,4-Bis((*tert*-butyldimethylsilyl)oxy)-5-methyltetrahydro-furan-2-yl)vinyl)-6-methoxyphenyl)methanol (36). The title compound was obtained by reduction of ester **35** (40 mg) following the *general procedure E*. Purification by flash column chromatography (silica gel, hexane:ethyl acetate, 4:1) gave **36** in 80% yield (30 mg) as a white solid (mp 72 -74 °C). $[\alpha]_D^{25}$ = +42.3 (*c* 1.0, $CHCl_3$), lit[14] $[\alpha]_D^{25}$= +32.46 (*c* 0.95 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 15.6 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.03 (dd, *J* = 15.8, 7.2 Hz, 1H), 4.78 (brs, 2H), 4.42 (dd, *J* = 7.0, 5.2 Hz, 1H), 4.02 (q, *J* = 6.3 Hz, 1H), 3.86 (s, 3H), 3.86-3.84 (m, 2H), 3.67 (t, *J* = 4.8 Hz, 1H), 1.56 (brs, 2H), 1.27 (d, *J* = 6.4 Hz, 1H), 0.92 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.2, 137.6, 132.3, 129.3, 128.9, 126.5, 119.3, 109.7, 84.2, 79.0, 77.9, 77.3, 56.9, 55.7, 26.0 (6C), 19.7, 18.3 (2C), –4.1 (2C), –4.2, –4.4. IR (ATR) ṽ = 3425 (w), 2957 (w), 2960 (m), 2884 (w), 2846 (m), 1181 (m), 949 (w), 877 (m), 790 (s), 570 (m) cm^{-1}. HRMS (DART) *m*/*z* calcd for $C_{27}H_{52}NO_5Si_2$ $[M+NH_4]^+$: 526.3384; found: 526.33747.

(+)-Varitriol (31). Prepared from compound **36** (25 mg) according to *general procedure F*. Purification by column chromatography on silica gel (hexane:ethyl, acetate 4:1) furnished **(+)-varitriol 31** as a white solid (mp = 98-100°C) in 70% yield (11 mg). $[\alpha]_D^{25}$ = +40.8 (*c* 0.6 MeOH); lit.[20a] $[\alpha]_D^{25}$= +19.4 (c 0.16 MeOH); ^{1}H NMR (400 MHz, CD_3CN) δ: 7.24 (t, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 15.7 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.17 (dd, *J* = 15.8, 6.8 Hz, 1H), 4.66 (s, 2H), 4.22 (ddd, *J* = 6.8, 5.4 , 1.2 Hz, 1H), 3.85 (t, *J* = 5.6 Hz, 1H), 3.84-3.77 (m, 1H), 3.82 (s, 3H), 3.65 (t, *J* = 5.6 Hz, 1H), 2.14 (brs, 2H), 1.27 (brs, 1H), 1.26 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 159.1, 138.8, 132.6, 129.8, 129.5, 127.7, 119.5, 111.0, 85.2, 80.3, 77.0, 76.4, 56.4, 55.7, 19.6. HRMS (DART) *m*/*z* calcd. for 298.16545 $[M+NH_4]^+$: $C_{15}H_{24}NO_5$; found: 298.16498. The spectroscopic data fully matched with those reported in the literature.[14,17,20]

Methyl 2-((*E*)-2-((*2S*,*3R*,*4R*,*5S*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-5-methyltetra-hydrofuran-2-yl)vinyl)-6-methoxybenzoate (37α) and methyl 2-((*E*)-2-((*2R*,*3R*,*4R*,*5S*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-5-methyltetra-hydrofuran-2-yl)vinyl)-6-methoxy-benzoate (37β). To a solution of olefinic compound **18α/β** (50 mg, 0.134 mmol) in dry and degassed DMF (0.7 mL) under argon atmosphere were sequentially added Na_2CO_2 (42 mg, 0.402 mmol), caffeine (8 mg, 0.042 mmol), aromatic triflate **34** (100 mg, 0.33 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.042 mmol). The reaction mixture was heated to 100 °C for 5 h and cooled to room temperature. Then, water was added to the mixture and the reaction was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, hexane:ethyl acetate, 10:1), obtaining an inseparable mixture of **37α** and **37β** in 63% combined yield (87 mg) (the diastereoisomeric mixture is described). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.22 (m, $1H_\alpha$, $1H_\beta$), 7.17 (d, *J* = 7.8 Hz, $1H_\alpha$), 7.12 (d, *J* = 8.1 Hz, $1H_\beta$), 6.97-6.93 (m, $1H_\alpha$), 6.77 (d, *J* = 8.2 Hz, $1H_\beta$), 6.50 (d, *J* = 15.9 Hz, $1H_\alpha$), 6.42 (d, *J* = 15.8 Hz, $1H_\beta$), 6.35 (dd, *J* = 15.9, 8.2 Hz, $1H_\alpha$), 6.28 (dd, *J* = 15.8, 8.5 Hz, $1H_\beta$), 4.56 (dd, *J* = 8.2, 3.0 Hz, $1H_\alpha$), 4.35-4.31 (m, $1H_\alpha$), 4.21-4.16 (m, $2H_\beta$), 3.96-3.91 (m, $1H_\alpha$), 3.82 (brs, $1H_\alpha$), 3.89 (s, $3H_\alpha$), 3.88 (s, $3H_\alpha$), 3.89-3.86 (m, $1H_\beta$), 3.86 (s, $3H_\beta$), 3.79 (s, $3H_\beta$), 3.76-3.73 (m, $1H_\beta$), 1.23 (d, *J* = 6.3 Hz, $3H_\beta$), 1.17 (d, *J* = 6.3 Hz,

$3H_\alpha$), 0.90 (s, $9H_\alpha$), 0.89 (s, $9H_\beta$), 0.87 (s, $9H_\beta$), 0.86 (s, $9H_\alpha$), 0.08 (s, $3H_\alpha$), 0.06 (s, $3H_\alpha$), 0.05 (s, $6H_\beta$), 0.04 (s, $3H_\alpha$, $6H_\beta$), 0.03 (s, $3H_\alpha$). ^{13}C NMR (75 MHz, $CDCl_3$) δ:168.4 (2C), 156.5 (2C), 135.6 (2C), 133.0, 130.4 (2C), 130.0, 128.8, 127.3, 117.9, 117.6, 109.9 (2C), 88.3, 84.3, 81.9, 81.0, 80.3, 79.8, 77.8, 77.2, 56.1(2C), 52.4 (2), 25.9(12 C), 18.2, 18.1, 18.00 (2C), 14.9, 14.6, –4.2, –4.3, –4.4, –4.5 (2C), –4.6, –4.6, –4.8. HRMS (DART) *m*/*z* calcd for 537.3067 [M+H$^+$]: $C_{28}H_{49}O_6Si_2$; found: 537.3076.

5'-*epi*-(+)-Varitriol (32) and 3',5'-*epi*-(+)-varitriol (33). The title compound was obtained in two steps. First, reduction of the diastereoisomeric mixture of esters **37α/β** (17 mg) with DIBAL following the *general procedure E*, afforded a residue that was then subjected to the deprotection conditions with TBAF described in *general procedure F*. The crude reaction mixture was purified by preparative thin-layer chromatography (silica gel, hexane:ethyl acetate, 4:1), to afford compounds **32** and **33** in 64% combined yield (5.7 mg).

5'-*epi*-(+)-Varitriol (32). 48% yield (2 steps), white solid (mp = 138-140 °C). $[\alpha]_D^{25}$= +36.85 (*c* 0.35 MeOH), lit[14] $[\alpha]_D^{25}$= +58.75 (*c* 0.08 $CHCl_3$). ^{1}H NMR (400 MHz, CD_3CN) δ: 7.24 (t, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 15.6 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.21 (dd, *J* = 15.8, 7.2 Hz, 1H), 4.66 (brs, 2H), 4.13 (ddd, *J* = 7.2, 4.0, 1.2 Hz, 1H), 4.07 (qd, *J* = 6.4, 2.8 Hz, 1H), 3.89-3.84 (m, 2H), 3.82 (s, 3H), 3.39 (brs, 1H), 2.9 (brs, 1H), 2.8 (brs, 1H), 1.21 (d, *J* = 6.4 Hz, 3H).^{13}C NMR (100 MHz, CD_3CN) δ 158.9, 138.9, 133.0, 129.8, 128.9, 127.7, 119.4, 110.9, 86.7, 84.2, 80.1, 77.9, 56.4, 55.6, 14.6. HRMS (DART) *m*/*z* calcd. for $C_{15}H_{24}NO_5$ [M+NH_4]$^+$: 298.16545; found: 298.16498. The physical and spectroscopic data for this compound agree with those reported by Ghosh.[14]

3',5'-*epi*-(+)-Varitriol (33). 16% yield (2 steps), pale yellow oil. $[\alpha]_D^{25}$= +40.0 (*c* 0.2 MeOH), ^{1}H NMR (400 MHz, CD_3CN) δ 7.24 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.1 Hz, 1H), 7.01 (d, *J* = 16.0 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.19 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.66 (d, *J* = 5.7 Hz, 2H), 4.63 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.26 (qd, *J* = 6.5, 3.4 Hz, 1H), 4.04-4.02 (m, 1H), 3.92-3.91 (m, 1H), 3.8 (s, 3H), 3.08-3.06 (m, 2H), 2.86-2.83 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ: 159.0, 139.1, 130.5, 129.9, 129.7, 127.6, 119.6, 110.9, 82.0, 80.4, 79.2, 77.2, 56.4, 55.6, 14.6. IR (ATR) ν̃ = 3425 (w), 2957 (w), 2955 (m),

2889 (w), 2841 (m), 1173 (m), 955 (w), 886 (m), 778 (s), 571 (m) cm^{-1}. HRMS (DART) *m*/*z* calcd for $C_{15}H_{24}NO_5$ $[M+NH_4]^+$: 298.16545; found: 298.16445.

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Supporting Information

Copies of ^1H and ^{13}C spectra for all new compounds and Cartesian coordinates and energies of computed structures. This material is available free of charge on the ACS Publications website at DOI:

References and notes

1. (a) Postema, M. H. D. *C-Glycoside Synthesis*; CRS Boca Raton, FL, 1995; (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford. 1995. (c) Bokor, E.; Kun, S.; Goyard, D.; Tóth, M.; Praly, J.-P.; Vidal, S.; Somsák, L. *Chem. Rev.* **2017**, *117*, 1687.
2. (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370; (c) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 2814; (d) Boyd, V. A.; Drake, B. E.; Sulikowski, G. A. *J. Org. Chem.* **1993**, *58*, 3191; (e) Terauchi, M.; Abe, H.; Matsuda, A.; Shuto, S. *Org. Lett.* **2004**, *6*, 3751.
3. (a) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208; (b) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149; (c) Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063; (d) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879.
4. Sánchez-Eleuterio, A.; Quintero, L.; Sartillo-Piscil, F. *J. Org. Chem.* **2011**, *76*, 5466.
5. Um, J. M.; Houk, K. N.; Phillips, A. J. *Org. Lett.* **2008**, *10*, 3769.
6. (a) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610. (b) Calzada, E.; Clarke, C. A.; Roussin-Bouchard, C.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 517. (c) Aslam, T.; Fuchs, M. G. G.; Le Formal, A.; Wightman, R. H. *Tetrahedron Lett.* **2005**, *46*, 3249. (d) Hernández-Torres, G.; Carreño, M. C.; Urbano, A.; Colobert, F. *Chem. Eur. J.* **2011**, *17*, 1283.

7. Cortezano-Arellano, O.; Meléndez-Becerra, C. A.; Cortés, F. Sartillo-Piscil, F.; Cordero-Vargas, A. *Carbohydr. Res.* **2014**, *393*, 51.
8. Van Rijssel, E. R.; van Delft, P.; van Marle, D. V.; Bijvoets, S. M.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A.; Filippov, D. V.; Codée, J. D. C. *J. Org. Chem.* **2015**, *80*, 4553.
9. Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978.
10. Bouchez, V. ; Stasik, I.; Beaupère, D.; Uzan, R. *Carbohydr. Res.* **1997**, *300*, 139.
11. Barret, G. M.; Attwood, S. V. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1315.
12. Hodgson, D. A.; Bailey, J. M.; Villalonga-Barber, C.; Drew, M. G. B.; Harrison, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3432.
13. Rodríguez, M. A.; Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 2470.
14. Ghosh, S.; Pradhan, T. K. *J. Org. Chem.* **2010**, *75*, 2107.
15. The regioselectivity of the monodeprotection of compound **10** was stablished by observing a COSY interaction of the OH signal (5.1 ppm) with H-2 (4.08 ppm) in lactone **23**. The COSY spectrum is included in the supporting information.
16. Wheeler, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 10262.
17. Malmstrøm, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. *J. Nat. Prod.* **2002**, *65*, 364.
18. Mayer, A. M. S.; Gustafson, K. R. *Eur. J. Cancer* **2004**, *40*, 2676.
19. For a review on the total synthesis of varitriol, see: Majik, M. S.; Tilvi, S.; Parvatkar, P. T. *Curr. Org. Synth.* **2014**, *11*, 268.
20. (a) Clemens, R. T.; Jennings, M. P. *Chem. Commun.* **2006**, 2720. (b) Nagarapu, L.; Paparaju, V.; Satyender, A.; Bantu, R. *Tetrahedron Lett.* **2011**, *52*, 7075. (c) Kumar, V.; Shaw, A. K. *J. Org. Chem.* **2008**, *73*, 7526. (d) Palík, M.; Karlubíková, O.; Lásiková, A.; Kožíšek, J.; Gracza, T. *Eur. J. Org. Chem.* **2009**, 709. (e) Srinvas, B.; Sridhar, R.; Rao, R. *Tetrahedron* **2010**, *66*, 8527. (f) Ghosal, P.; Sharma, D.; Kumar, B.; Meena, S.; Sinha, S.; Shaw, A. K. *Org. Biomol. Chem.* **2011**, *9*, 7372. (g) Vamshikrishna, V.; Srihari, P. *Tetrahedron* **2012**, *68*, 1540. (h) Karlubíková, O.; Palík, M.; Lásiková, A.; Gracza, T. *Synthesis* **2010**, 3449. (i) Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 42.
21. (a) Sun, T.; Deutsch, C.; Krause, N. *Org. Biomol. Chem.* **2012**, *10*, 5965. (b) Brichacek, M.; Batory, L. A.; McGrath, N. A.; Njardarson, J. T. *Tetrahedron* **2010**, *66*, 4832. (c) Nagarapu, L.; Paparaju, V.; Satyender, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2351.
22. Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087.
23. (a) Conelly-Espinosa, P.; Toscano, R. A.; Morales-Morales, D. *Tetrahedron Lett.* **2014**, *55*, 5841. (b) Landaeta, V. R.; Rodríguez-Lugo, R. E.; Rodríguez-Arias, E. N.; Coll-Gómez, D. S.; González, T. *Transition Met. Chem.* **2010**, *35*, 165. (c) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151. (d) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804.
24. Patrushev, S. S.; Sharikov, M. M.; Shults, E. E. *Chem. Heterocycl. Compd.* **2016**, *52*, 165.
25. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A. Gaussian Inc., Wallingford CT, **2013**.
26. (a) Zhao, Y.; Truhlar, D. *Theor. Chem. Acc.* **2008**, *120*, 215– 241. (b) Schenker, S.; Schneider, C.; Tsogoeva, S. B.; Clark, T. *J. Chem. Theory Comput.* **2011**, *7*, 3586–3595.
27. Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B,* **2009**, *113*, 6378-6396.