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Stereoselective synthesis of 2-*O*-MEM-2,3-unsaturated-β-O-glycosides and elaboration to useful synthetic tools

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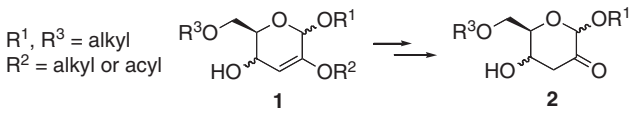
ABSTRACT

The glycosylation of alcohols by the new 2-*O*-MEM-substituted D-galactal-derived allyl epoxide affords the corresponding alkyl 2-*O*-MEM-3-deoxy-β-D-*threo*-hex-2-enopyranosides through a completely 1,4-regio- and a highly to completely *substrate-dependent* stereoselective glycosylation processes. The glycosides obtained can be regioselectively transformed into corresponding 3-deoxy-β-O-glycosides, 3-deoxy-β-D-*threo*-hexopyranosid-2-uloses, and 3,4-dideoxy-β-D-*glycero*-hex-3-enopyranosid-2-uloses, which are useful synthetic tools for further transformations.

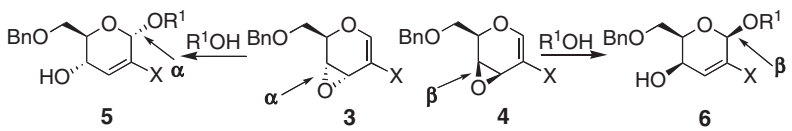
Alkyl 2-O-protected-3-deoxy-hex-2-enopyranosides (**1**) are useful synthetic intermediates,[1] and, starting from 2-acetoxy-3,4,6-tri-*O*-acetyl-D-glucal as the chiral precursor, have been prepared and used in the synthesis of natural products such as tetrodotoxin and okadaic acid, valuable antitumor agents,[1a,b] and Melillo's lactone.[1c] Moreover, compounds **1** can reasonably be transformed into corresponding alkyl 3-deoxy-hexopyranosid-2-uloses (**2**), which are useful for further functionalizations (Scheme 1).



Scheme 1. Alkyl 2-O-protected-3-deoxy-hex-2-enopyranosides (**1**) and corresponding alkyl 3-deoxy-hexopyranosid-2-uloses (**2**).

We recently found a new O-glycosylation protocol consisting of the addition of *O*-nucleophiles (alcohols and partially protected monosaccharides) to D-allal- (**3**, X = H) and D-galactal-derived allyl epoxide (**4**, X = H): corresponding alkyl 2,3-dideoxy-α- (**5**, X = H) and -β-hex-2-enopyranosides (**6**, X = H) were obtained, respectively, in a completely 1,4-regio- and stereoselective fashion (Scheme 2).[2] In this connection, the possibility of an interesting application of this original protocol to the regio- and stereoselective synthesis of the title compounds was envisaged: if the corresponding 2-O-protected-epoxides **3** and **4** (X = OR^2) showed a behavior similar to **3** and **4** (X = H), in the addition reaction of alcohols, a stereoselective synthesis of alkyl 2-O-protected-3-deoxy-hex-2-enopyranosides **5** and **6** (X = OR^2) could be obtained (Scheme 2).

Considering that among the different possibilities attempted,[3] the 2-*O*-methoxyethoxymethyl (2-*O*-MEM) functionality turned out to be the best protective group for our purposes, the experimental



X, = H, OR^2; R^1 = Me, Et, *i*-Pr, *t*-Bu; R^2 = Me, Bn, Ac

Scheme 2. Glycosylation of alcohols by allyl epoxides **3** and **4**.

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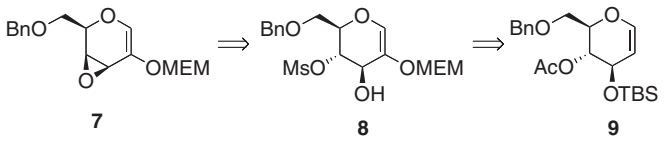


Scheme 3. Retrosynthetic analysis for epoxide **7**.

feasibility of the above described O-glycosylation process was checked by means of the 2-*O*-MEM-substituted-D-galactal-derived allyl epoxide **7**, taken as an appropriate model (Scheme 3).

A retrosynthetic analysis indicated that epoxide **7** could be obtained by cyclization under basic conditions of the *trans*-hydroxy mesylate **8**, and could be prepared on its own from the appropriately O-protected-D-glucal **9** (Scheme 3). Our intention was to introduce the 2-*O*-MEM-1,2-unsaturated moiety present in **7** and **8** by a glycosylation reaction of **9** with an appropriate nucleophile, followed by elimination.

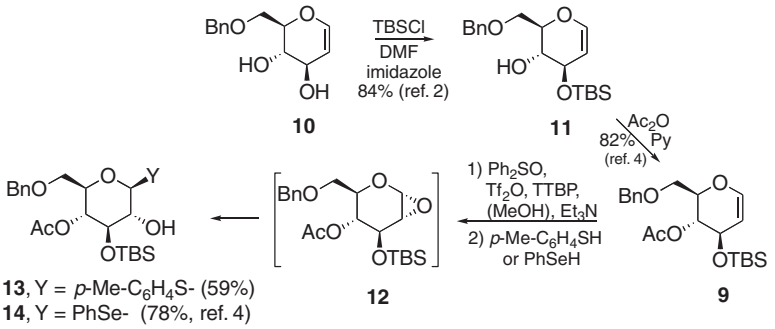
Fully protected D-glucal **9**[4] was prepared by acetylation of the residual OH-functionality of the known mono-*O*-TBS derivative **11** of 6-*O*-(benzyl)-D-glucal (**10**)[2b] (Scheme 4).

At this point, the synthetic protocol required a glycosylation process which is able to introduce contemporaneously, in an anti-stereoselective fashion, a hydroxy group on C(2) and a glycosyl acceptor on C(1), based on an element, such as S or Se, capable to subsequently give, through the corresponding oxide (sulfoxide or selenoxide), a β-*syn*-elimination.[5]

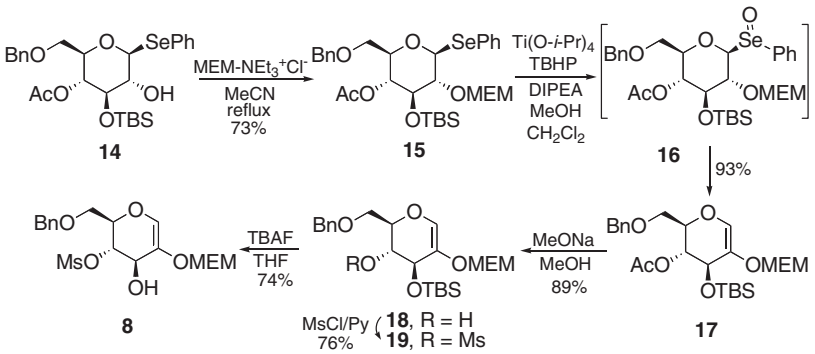
Gin's direct oxidative glycosylation of alcohols by glycals is known as a very effective protocol for the regio- and stereoselective synthesis, through the formation of an intermediate glycal α-epoxide, of corresponding *trans*-2-hydroxy-β-O-glycosides.[6] We thought that the replacement of the alcohol-nucleophile, as described in the original procedure, by an *S*- or *Se*-nucleophile might lead to what we needed. Actually, the application of the direct oxidative glycosylation to *p*-thiocresol and PhSeH by the use of our glycal **9** afforded, through the intermediate formation of glucal α-epoxide **12**, *p*-tolyl *trans*-2-hydroxy-β-thioglycoside **13** and phenyl *trans*-2-hydroxy-β-selenoglycoside **14**,[4] respectively, in a completely stereoselective fashion, as desired (Scheme 4). It is interesting to note that the complete anti-β-stereoselectivity found in the glycosylation of PhSeH, under these conditions,[4] is opposite to the complete syn-α-stereoselectivity found by Danishefsky, with the same nucleophile, in the glycosylation of tri-*O*-benzyl-D-glucal under his original reaction conditions, which similarly proceed through a corresponding glucal α-epoxide.[7]

The decidedly simpler protocol related to the synthesis of the *O*-MEM selenoxide **16** and subsequent *syn*-elimination process (one-pot reaction, 0 °C to room temperature, 93% yield, Scheme 5) compared with the alternative protocol by means of the corresponding sulfoxide [two-step reaction, including a scantily reliable and low yielding thermal elimination (90 °C), 23% yield] (see Supplementary data) determined the preference of β-phenylselenoglycoside **14** for the pursuit of the synthetic route to epoxide **7**.

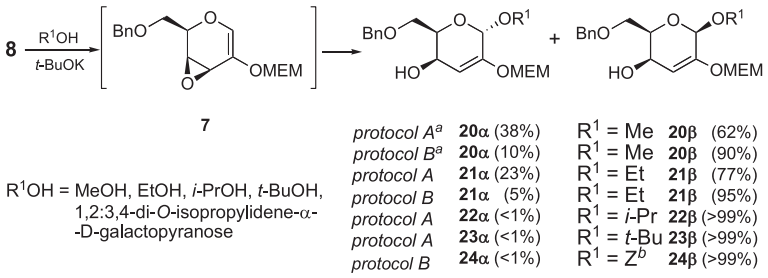
By refluxing with MEM-$NEt_3^+Cl^-$ in THF, β-phenylselenoglycoside **14** was transformed into the corresponding 2-*O*-MEM derivative **15**.[8] Following a previously described protocol [$Ti(O\text{-}i\text{-}Pr)_4$/TBHP in CH_2Cl_2 in the presence of DIPEA, 0 °C to room temperature],[9] 2-*O*-MEM-β-phenylselenoglycoside **15** underwent a Sharpless-type oxidation with the intermediate formation of selenoxide **16** which was followed by spontaneous selenoxide β-syn-elimination with the vicinal H(2) giving the 2-*O*-MEM-substituted glucal **17**. Saponification (MeONa/MeOH) of glucal **17** afforded secondary alcohol **18** which was transformed (MsCl/Py) into the corresponding mesylate **19**. Deprotection of **19** by the TBAF/THF protocol at 0 °C led to trans hydroxy mesylate **8**, the stable ultimate precursor of allyl epoxide **7** (Schemes 5 and 6).



Scheme 4. Synthesis of β-thioglycoside **13** and β-selenoglycoside **14**.



Scheme 5. Synthesis of *trans*-hydroxy mesylate **8**.



[a] *Protocol A*: a solution of *trans* hydroxy mesylate **8** in the glycosyl acceptor (alcohol) is treated with *t*-BuOK (1 equiv); *Protocol B*: a solution of *trans* hydroxy mesylate **8** in anhydrous MeCN is treated with *t*-BuOK (1 equiv). After 15 min stirring, the glycosyl acceptor (3 equiv) is added.
[b] Z = 6-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl).

Scheme 6. Regio- and stereoselectivity of the glycosylation of alcohols and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose by epoxide **7** under *protocol A* and/or *B*.

In the examination of the regio- and stereochemical behavior of the new 2-*O*-MEM-substituted-D-galactal-derived allyl epoxide **7** with *O*-nucleophiles, the addition reactions with simple, low-boiling alcohols, such as MeOH, EtOH, *i*-PrOH, and *t*-BuOH were examined under *protocol A* reaction conditions (Scheme 6). The reactions turned out to be completely 1,4-regioselective, with the exclusive nucleophilic attack on the C(1) carbon of the allyl system. No traces of the corresponding 1,2-addition products were ever observed.

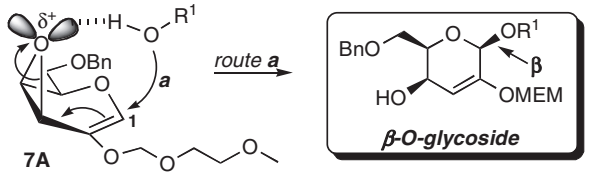
As for the stereoselectivity, the reactions with the less nucleophilic and more sterically hindered *i*-PrOH and *t*-BuOH, in spite of the presence of a large amount of nucleophilic molecules (alcohol as the solvent) are completely β-stereoselective with the exclusive formation of the corresponding alkyl β-O-glycosides **22β** and **23β**, respectively, with the same configuration (β) as the starting epoxide. On the contrary, the reactions with the more nucleophilic MeOH and EtOH are not stereoselective, and mixtures of the corresponding anomeric methyl O-glycosides **20α** and **20β** (38:62) and ethyl O-glycosides **21α** and **21β** (23:77) are obtained, respectively. Even if not completely stereoselective, it is worth noting that, in each mixture, the corresponding β-anomer **20β** (62%) and **21β** (77%) with the same configuration as the starting epoxide is the main product. However, in both cases, when the reactions are repeated under *protocol B* reaction conditions (Scheme 6), a decided increase is observed in the β-stereoselectivity (90% with MeOH and 95% with EtOH), even if a completely β-stereoselective result is not obtained, as it is with the structurally related allyl epoxide **4** (X = H) (Scheme 2).[2b]

Protocol B reaction conditions were used also for the reaction with a partially protected monosaccharide such as 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, for which *protocol A* reaction conditions were not clearly possible. A complete β-stereoselective result was obtained with the exclusive formation of the β-linked disaccharide **24β** (Scheme 6).

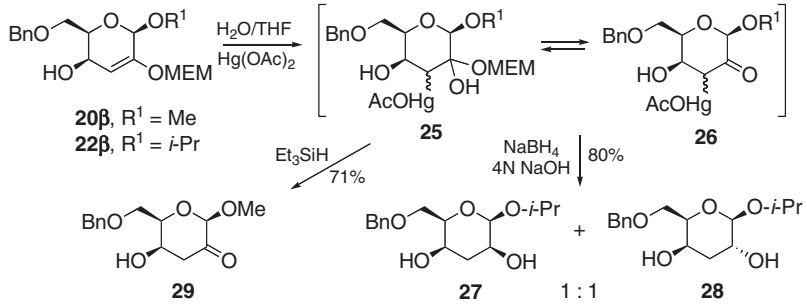
Analogously to the same reaction with the related epoxides **3** and **4** (X = H), the glycosylation of alcohols by epoxide **7** was rationalized by a coordination (hydrogen bond) between the oxirane oxygen and the *O*-nucleophile. In this way, the nucleophile (alcohol) is guided to the β-face of **7**, reacting through conformer **7A**,[10] which is suitably arranged for an entropically favored attack on the C(1) carbon from the same side as the oxirane ring (*route* ***a***, Scheme 7). The corresponding 2-*O*-MEM-2,3-unsaturated-β-O-glycosides **20**–**24β**, with the same configuration as the starting epoxide, are consequently obtained in a directly *substrate-dependent* stereoselective process.[11]

Procedures were tried in order to deprotect the 2-*O*-MEM functionality and transform β-O-glycosides **20**–**24β** into the corresponding 3-deoxy-β-hexopyranosid-2-uloses: methyl (**20β**) and *i*-propyl β-O-glycoside **22β** were taken as suitable models for checking the possibility of this transformation.

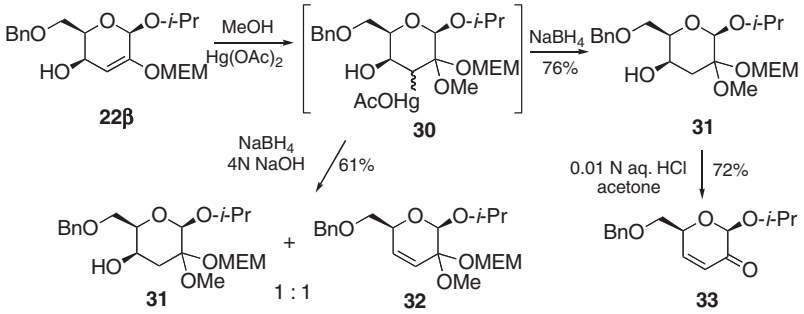
After observing that the usual deprotection protocol for the *O*-MEM protective group ($ZnCl_2$ in Et_2O for 12 h at room temperature) led to an extensive decomposition of the pseudoglycal system of **22β**, a completely different approach was tried (Scheme 8).



Scheme 7. Rationalization of the *substrate-dependent* stereoselectivity in the glycosylation of *O*-nucleophiles by allyl epoxide **7**.



Scheme 8. Deprotection of 2-*O*-MEM functionality of **20β** and **22β** and synthesis of hydroxy ketone **29** and 3-deoxy-O-glycosides **27** and **28**.



Scheme 9. Deprotection of 2-*O*-MEM functionality of **22β** and synthesis of enone **33**.

The oxymercuration of *i*-propyl O-glycoside **22β** (an enol ether) with $Hg(OAc)_2$ in THF/H_2O indicated a very fast consumption of the starting material (TLC), and the possible formation of 3-acetoxymercuryl hemiacetal **25** (R^1 = *i*-Pr) in a reasonable equilibrium with the corresponding 3-acetoxymercuryl ketone **26** (R^1 = *i*-Pr). Actually, the subsequent addition of $NaBH_4$ and aqueous 4 N NaOH determined the formation of an almost 1:1 mixture of the diastereoisomeric 3-deoxy-β-D-*lyxo*- (**27**)[12] and -β-D-*xylo*-hexopyranosides (**28**),[13] as the contemporary demercuration and reduction product of the intermediate ketone **26** (R^1 = *i*-Pr).

In this way, the clean deprotection of glycoside **22β** was achieved, but the carbonyl function at C(2) was lost. To our delight, the replacement of $NaBH_4$–4 N NaOH protocol with Et_3SiH as the demercuration agent turned out to be effective for our purposes and, starting from methyl O-glycoside **20β**, the desired hydroxy ketone **29** was obtained as the only reaction product (Scheme 8).[14,15]

In a further attempt to affect the deprotection of **22β** (or **20β**), a methoxymercuration–demercuration approach was tried (Scheme 9). In this way, the reaction of enol ether **22β** with MeOH/$Hg(OAc)_2$ followed by demercuration ($NaBH_4$/aqueous 4 N NaOH) of the intermediate 3-acetoxymercuryl acetal **30** led to an almost 1:1 mixture of 4-hydroxy acetal **31** and the corresponding α,β-unsaturated derivative **32**.[16] In order to avoid the elimination process, no aqueous 4 N NaOH was added in the demercuration step of intermediate **30**, and only $NaBH_4$ was used. Under these modified conditions, 4-hydroxy acetal **31** turned out to be the only reaction product. However, once again, the elimination process could not be completely eliminated. Actually, the subsequent hydrolysis of the acetal functionality of **31**, necessarily carried out under acid conditions (0.01 N aqueous HCl/acetone), afforded the desired deprotection which was, also in this case, accompanied by a simultaneous elimination reaction, with the formation of enone **33**,[17] as the only final product (Scheme 9).[18]

In conclusion, we have demonstrated the possibility of synthesizing stereoselectively 2-*O*-MEM-3-deoxy-β-D-*threo*-hex-2-enopyranosides, such as **20**–**24β**, by the application of the directly *substrate-dependent* glycosylation process to the new 2-*O*-MEM-D-galactal-derived allyl epoxide **7**. The 2-*O*-MEM-β-O-glycosides obtained can be successfully transformed into corresponding **27**- and **28**-type 3-deoxy-β-O-glycosides, **29**-type 3-deoxy-β-hexopyranosid-2-uloses, and **33**-type 3,4-dideoxy-β-hex-3-enopyranosid-2-uloses, which are useful synthetic intermediates for further transformations, for which a synthetic procedure, starting from a common precursor, is not presently available. A new mild protocol for the deprotection of the vinyl-*O*-MEM functionality and the formation of the corresponding ketone is also described.

Acknowledgments

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Supplementary data

Supplementary data (experimental details for all reaction products and theoretical conformational analysis for epoxide **7-OMe**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.061.

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3. The -*O*-MEM protection was preferred to –OAc, –OMe and –OBn protective groups in view of the easier introduction, absence of any interference with the synthetic sequence to epoxide **7** and easy removable protocol.
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10. A theoretical conformational analysis carried out on an appropriate, simplified model (epoxide **7-OMe**) indicated that epoxide **7** exists as the only corresponding conformer **7A**, with the $–CH_2OBn$ group equatorial (see Supplementary data).
11. The non-completely β-stereoselective glycosylation process observed with MeOH and EtOH under *protocol A* and *B* reaction conditions could be simply ascribed to their more nucleophilic character compared to the other alcohols tried. Accordingly, the β-selectivity increases when less nucleophile is used (*protocol B*).
12. For compounds structurally related to **27**, see: (L-series) (a) Lei, P.-S.; Duchaussoy, P.; Sizun, P.; Mallet, J.-M.; Petitou, M.; Sinay, P. *Bioorg. Med. Chem.* **1998**, *6*, 1337–1346; (b) Huber, H.; Reichstein, T. *Helv. Chim. Acta* **1948**, *31*, 1645–1655.
13. For compounds structurally related to **28**, see: (a) Kovac, P.; Edgar, K. E. *Carbohydr. Res.* **1990**, *201*, 79–93; (b) Chiu, T. M. K.; Watanabe, K. A.; Fox, J. J. *Carbohydr. Res.* **1974**, *32*, 211–216; (c) Zinner, H.; Wulf, G. *J. Prakt. Chem.* **1970**, *312*, 635–640; (d) Antonakis, K. *Bull. Soc. Chim. Fr.* **1969**, 122–126.
14. Although new in the present application, the use of the oxymercuration–demercuration protocol for the hydrolysis of a vinyl-*O*-MEM ether stems from a previously described original result: Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279–3285. To the best of our knowledge, the use of Et_3SiH in the demercuration step is original.
15. For compounds structurally related to **29**, see Ref. 13d and Zunszain, P.; Varela, O. *Tetrahedron: Asymmetry* **1998**, *9*, 1269–1276.

16. The axial position of C(4)–OH group and the slight acidity of axial C(3)–Hα to the acetal group can reasonably be the cause of the elimination process of **31** to **32** under basic conditions.
17. For compounds structurally related to **33**, see Ref. 15 and: (a) Köll, P.; Klenke, K.; Eisermann, D. *J. Carbohydr. Chem.* **1984**, *3*, 403–415; (b) Brimacombe, J. S.; Hunedy, F.; Mather, A. M.; Tucker, L. C. N. *Carbohydr. Res.* **1979**, *68*, 231–238; (c) Holden, N. L.; Fraser-Reid, B. *Can. J. Chem.* **1973**, *51*, 3357–3365; (d) Bock, K.; Pedersen, C. *Tetrahedron Lett.* **1969**, *10*, 2983–2986.
18. The use of more diluted aqueous HCl/acetone solution (10^{-5}–10^{-3} N) in the acetal hydrolysis step was not effective, and the starting acetal **31** was recovered completely unreacted.