Title	Lewis acid induced anomerization of se-glycosides. Application to synthesis of alpha-Se-GalCer
Author(s)	McDonagh, Anthony W.; Mahon, Mary F.; Murphy, Paul V.
Publication Date	2016-01-22
Publication Information	McDonagh, Anthony W., Mahon, Mary F., & Murphy, Paul V. (2016). Lewis Acid Induced Anomerization of Se-Glycosides. Application to Synthesis of -Se-GalCer. Organic Letters, 18(3), 552-555. doi: 10.1021/acs.orglett.5b03591
Publisher	American Chemical Society
Link to publisher's version	http:/dx.doi.org/10.1021/acs.orglett.5b03591
Item record	http://hdl.handle.net/10379/5940
DOI	http://dx.doi.org/10.1021/acs.orglett.5b03591

Lewis Acid Induced Anomerisation of *Se*-Glycosides. Application to Synthesis of α-*Se*-GalCer

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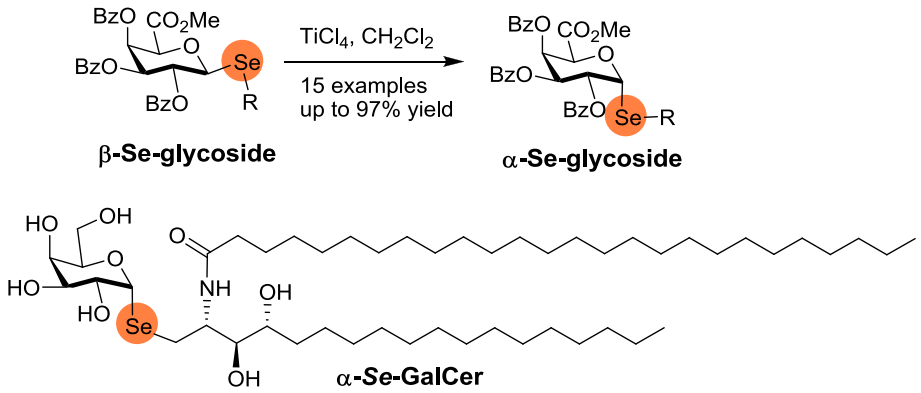
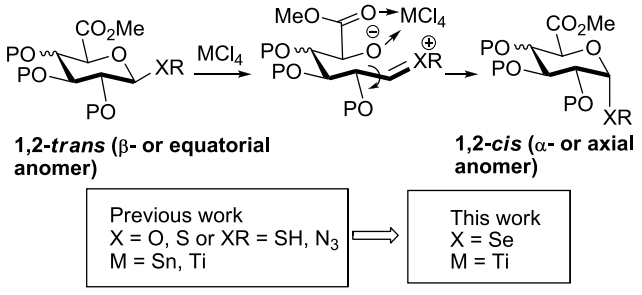
Supporting Information Placeholder



ABSTRACT: The $TiCl_4$ induced anomerisation of selenium glycosides of galacturonic acid derivatives is reported. The reaction was successful for galacturonic acid when various alkyl, alkenyl, alkynyl, saccharide, steroid and lipid groups were attached to the anomeric Se atom. An increased amount of $TiCl_4$ and/or higher temperature were needed to ensure completion of the reaction in some cases. Yields were higher for reactions carried out at higher dilution. The reaction was applied to the synthesis of Se based mimics of the potent immunostimulant α-GalCer (KRN7000).

Carbohydrates play important roles in many biological processes[1] and the configuration of their glycosides influence their properties. The Lewis acid promoted anomerisation of equatorial glycosides generally give rise to axially oriented glycosides, which can be favoured due to the anomeric effect.[2] Lewis acids $TiCl_4$ and $SnCl_4$ have proven effective for the anomerisation of various *O*-, N_3- and *S*-glycosides derived from uronic acids, giving good outcomes in terms of anomeric selectivity and product yield. The presence of the carbonyl group at C-6 of the uronic acid leads to significant increase, through chelation (Scheme 1), in the rate of anomerisation compared to the corresponding reduced pyranoside.[3,4]

Scheme 1. Lewis acid induced anomerisation of glycosides via endocyclic cleavage

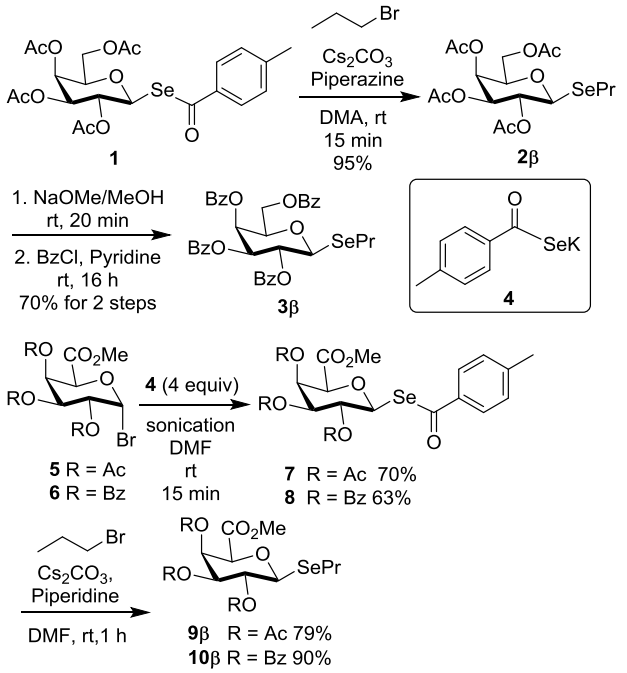


The substitution of the oxygen atom in glycosidic bonds for other elements such as carbon or sulfur has proven attractive as a strategy to obtain glycomimetics for study of their properties.[5] Glycomimetics could be more stable than native glycosides or be useful in vaccine development. In recent years, the synthesis of *S*-glycosidic analogues of oligosaccharide, glycolipids and glycomimetics has been studied.[6] Substitution of oxygen for selenium and tellurium has been less explored in carbohydrate chemistry. Selenoglycosides have been investigated as glycosyl donors in glycoside formation[7] as well as having application in X-ray crystallography.[8] There have been various procedures for the synthesis of β-Se-glycosides (or equatorial glycosides)[9] and relatively few reported for α-Se-glycosides (or axial glycosides), which included the *in situ* production of an axial selenolate anion.[10] Herein is disclosed the results of our recent investigation into the Lewis acid promoted formation of axial glycosyl selenides from the corresponding equatorial anomer. The methodology has been applied to various Se-glycosides, including the α-selenoglycoside analogue of the potent immunostimulant KRN7000 (α-GalCer).

The investigation commenced with the synthesis of propyl β-*Se*-glycosides, which were based on both galactopyranose and the corresponding galacturonic acid **2β, 3β, 9β** and **10β** (Scheme 2). Ishihara and co-workers have reported synthesis

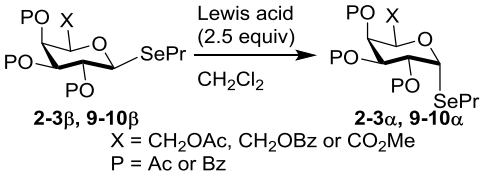
of peracetylated galactose and glucose β-selenides from a β-glycosyl *p*-methylbenzoselenoate, which is a selenolate anion precursor.[11] Hence, the benzoselenoate **1** was treated with piperazine, and this was followed by addition of 1-bromopropane to give β-selenide **2β**. Protecting group exchange provided **3β**. Attempts to form benzoselenoate **7** and **8** from α-glycosyl bromides **5** and **6** with Ishihara conditions gave the desired products in low yields. However, ultrasonication of **4** in the presence of **5** or **6** for 15 min in DMF led to improved yields (63-70%). Subsequently reaction of **7** and **8** with propyl bromide provided **9β** and **10β**.

Scheme 2. Synthesis of equatorial selenoglycosides



Attention next turned to the anomerisation reaction. Previous study with *O*- and *S*-glycosides have shown that use of 2.5 equivalents of Lewis acid in CH_2Cl_2 to be effective and these conditions were chosen as the starting point for the investigation. Compounds **2β** and **3β** were treated with both $SnCl_4$ or $TiCl_4$ at various temperatures but no α-selenoglycoside could be observed or isolated, with the reactions carried out at room temperature providing the corresponding glycosyl chloride; reactions at lower temperature led only to the recovery of **2β** and **3β**. Galacturonates **9β** and **10β** were then studied and it was found that carrying out the reaction at -20 °C in the presence of $TiCl_4$ led to successful formation of **9α** and **10α** in moderate yield. Higher temperatures with $TiCl_4$ led to glycosyl chlorides in these cases. Reactions with $SnCl_4$ did not give α-anomer with only the glycosyl chloride being obtained. There is evidence that α-selenocarbenium ions are generated from O,Se acetals/ketals in the presence of $TiCl_4$ and that this is not the case for $SnCl_4$, where oxocarbenium ions have instead been preferred, due to Sn(IV)'s affinity for Se.[12] The results herein are thus consistent with $TiCl_4$ promoting endocyclic cleavage to give α-selenocarbenium ions and anomerisation whereas reaction with $SnCl_4$ may proceed by breaking the anomeric C to Se bond leading only to glycosyl chloride formation. On lowering the concentration of all reactants, it was observed that the yields increased for both **9α** and **10α**, up to 94% (Table 1). The stereochemistry of the α-selenide was confirmed by ^{1}H NMR ($J_{1,2}$ = 4-5 Hz) and by determination of the single X-ray crystal structure of **10α** (Figure 1). The C-Se bond length (1.98 Å), the C-Se-C angle (97 °) and the C-Se-C distance (2.97 Å) were in agreement with predicted values.[13] These values can be compared to typical C-O, C-S bond lengths (1.4, 1.8 Å), C-O-C, C-S-C bond angles (115 °, 95 °) and C-O-C, C-S-C distances (2.4, 2.9 Å).

Table 1. Investigation of reagents and conditions



entry	β-Se-glycoside	Lewis acid	*t* (°C)	Concentration (μM)	outcome (isolated yield)
1	**2β or 3β**	$TiCl_4$	-15	100	no **2α/3α**
2	**2β or 3β**	$TiCl_4$	rt	100	no **2α/3α**
3	**3β**	$SnCl_4$	rt	100	no **3α**
4	**9β**	$SnCl_4$	rt	90	no **9α**
5	**9β**	$SnCl_4$	0	90	no **9α**
6	**9β**	$SnCl_4$	-20	90	no **9α**
7	**9β**	$TiCl_4$	rt	90	no **9α**
8	**9β**	$TiCl_4$	4	90	**9α** (58%)
9	**9β**	$TiCl_4$	-20	7	**9α** (94%)
10	**10β**	$TiCl_4$	0	80	**10α** (46%)
11	**10β**	$TiCl_4$	-40	70	**10α** (68%)
12	**10β**	$TiCl_4$	-20	15	**10α** (86%)
13	**10β**	$TiCl_4$	-20	7	**10α** (94%)

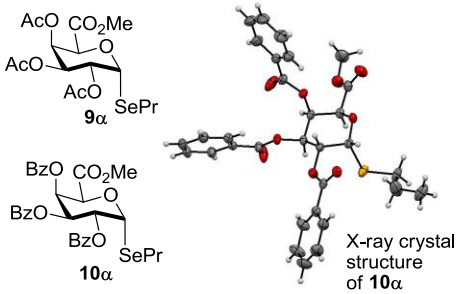


Figure 1. Structures of 9α/10α

A series of benzoylated β-selenides **11-22β** were next prepared to examine the wider scope of the anomerisation reaction (Scheme 3). Benzoylated derivatives were selected for study, given they have been found generally superior to corresponding acetylated saccharides, in particular for the anomerisation of disaccharides or glycolipids.[3g,3i] Thus, reaction of various equatorial Se-glycosides **11β-15β** and **22β** gave the corresponding axial glycosides **11α-15α** and **22α** in good to excellent yield and selectivity. Allyl glycoside **16β** was found to require extra $TiCl_4$ at -20 °C, while anomerisation of the propargyl glycoside **17β** required both increased $TiCl_4$ and higher temperature (0 °C). The same trend was observed for glycolipid **18β**, requiring the reaction to be carried out at room

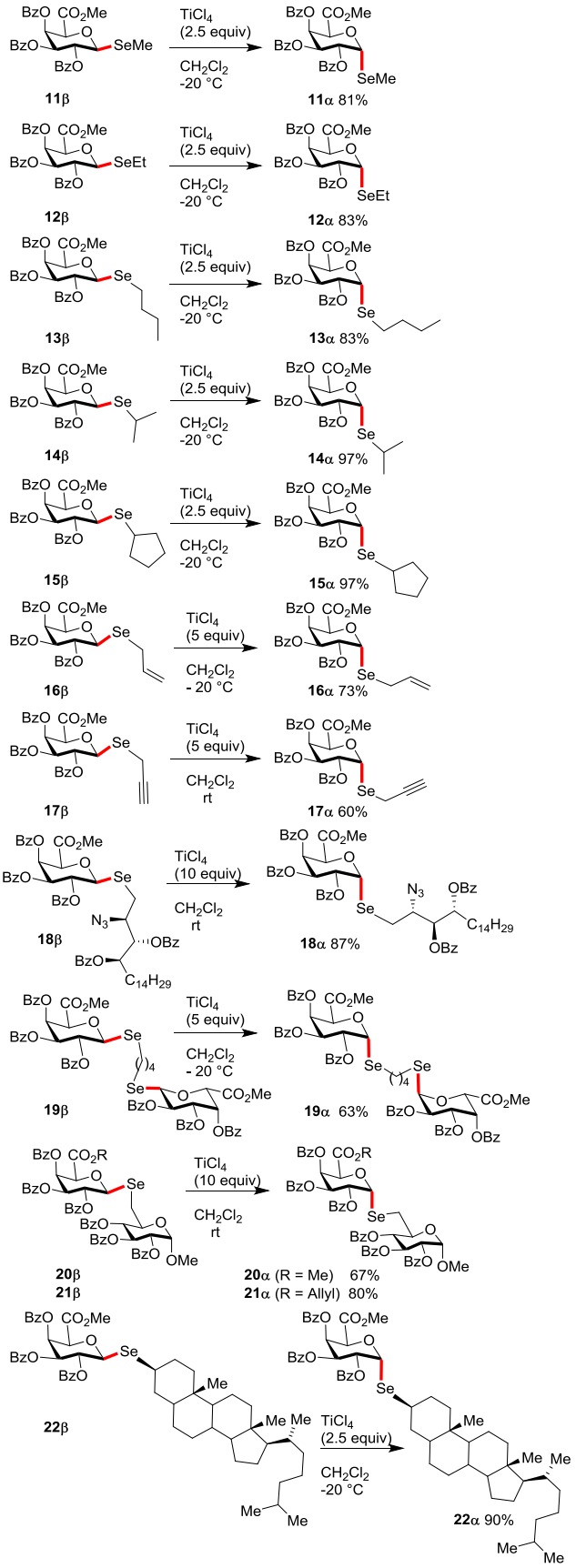
temperature. The double anomerisation reaction of bivalent saccharide **19β** proceeded smoothly at -20 °C to give **19α** with again a higher quantity of promoter being needed. Anomerisation of disaccharides **20β** and **21β** also required additional $TiCl_4$ and temperature to maximize yield of the axial anomer. A higher yield was obtained for the allyl ester **21β** compared to the methyl ester **20β** in line with a faster rate noted previously for an allyl ester of *O*-glycoside of a glucuronic acid derivative when compared to the corresponding methyl ester.[4] The requirement for higher temperature and more Lewis acid can be rationalised on the basis of increasing electron withdrawing properties of the aglycon and an increase in number of sites that can coordinate to the Lewis acid.

To further demonstrate an application of the reaction, we investigated its suitability for preparation of the Se-glycoside mimic of the immunostimulant α-GalCer (KRN7000).[14] One important feature of α-GalCer is the axial orientation of the substituent on the anomeric carbon. The parent *O*-glycolipid has been shown to stimulate high production of T helper 1 (IFN-γ) and T helper 2 (IL-4) cytokines via recognition of the bound glycolipid to the CD1d protein on antigen-presenting cells by the T cell receptor (TCR) on natural killer T (NKT) cells. The production of IFN-γ cytokines can assist in anti-tumor, antiviral and antibacterial infections while IL-4 cytokines assists in alleviating the effects of autoimmune diseases. However despite this high cytokine production IFN-γ and IL-4 antagonise each other's biological functions. It has therefore been an attractive approach to synthesise various analogues of KRN7000 to try to identify compounds what would promote a bias in cytokine production.[15] Analogues prepared previously include *C*-[16] and *S*-glycosides,[17] both of which show interesting properties.

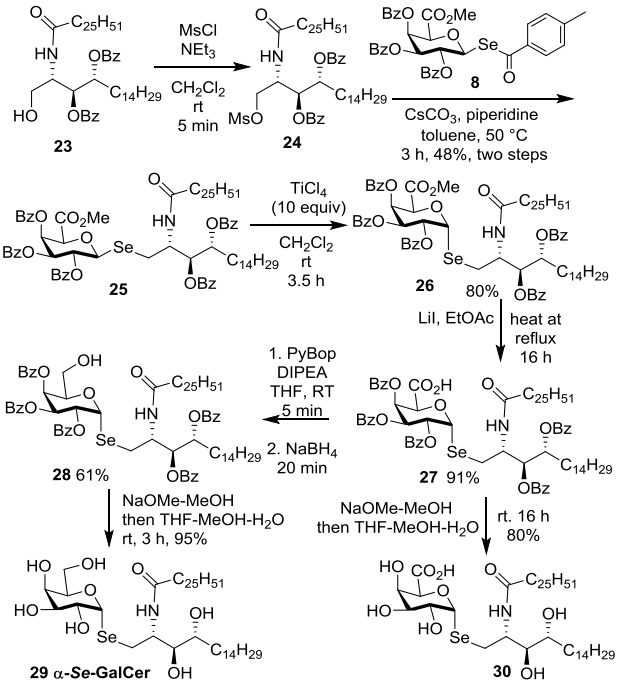
The synthesis of α-Se-GalCer commenced from phytosphingosine **23** (Scheme 4).[18] Reaction of the primary alcohol of **23** with methane sulfonyl chloride provided **24** and this was immediately coupled with **8** to give β-glycolipid **25** in moderate yield. The introduction of other leaving groups (OTf, I, Br, Cl) at the primary alcohol **23** led to a facile formation of an oxazoline by-product, the rate of formation of which was reduced for the mesylate, enabling Se-alkylation to take place. Anomerisation of **25** with $TiCl_4$, in the presence of a large amount of the promoter provided **26** in excellent yield. Next the selective cleavage of the methyl ester on **26** with LiI in EtOAc provided **27**.[19] Removal of all benzoate esters from **27** with NaOMe-MeOH gave the galacturonic acid analogue of α-GalCer **30**.[20] On the other hand, chemoselective activation of the carboxylic acid of **27** with PyBOP followed by one pot reduction of the resulting hydroxybenzotriazoyl ester with $NaBH_4$ furnished primary alcohol **28**.[21] Removal of benzoyl groups from **28** completed the synthesis of α-*Se*-GalCer **29**.

In summary, we have disclosed a convenient chelation-induced anomerisation reaction for the generation of axial or α-Se-glycosides from corresponding equatorial or β-anomers. The methodology has been shown to have wide scope and can accommodate a variety of functionality on the glycoside. The increasing complexity of the aglycon led to the requirement to increase the amount of Lewis acid. Nevertheless in the examples described a high degree of conversion was achieved and the reactions were highly stereoselective. The methodology was further demonstrated by completing the synthesis of Se-glycosides of the potent immunostimmulant KRN7000 which is now available to contribute to structure activity relationships. In addition other α-Se-glycosides will be accessible by this approach.

Scheme 3. Anomerisation of various Se-galacturonides



Scheme 4. Synthesis of *Se*-KRN7000 and acid analogue.



ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

NMR Spectra (PDF)
Experimental Section (PDF)
Crystallographic data for **10α** can be obtained from the Cambridge Crystallographic Data Centre, CCDC 1446829

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ACKNOWLEDGMENT

The research was supported by the Irish Research Council (PhD Scholarship to AMcD) and NUI Galway (College of Science PhD scholarship to AMcD). This publication has also emanated in part from research supported by Science Foundation Ireland (SFI, grant number 12/IA/1398) and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2710.

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