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# Efficient synthesis of a galectin inhibitor clinical candidate (TD139) using a Payne rearrangement/azidation reaction cascade†

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Selective galectin inhibitors are valuable research tools and could also be used as drug candidates. In that context, TD139, a thiodigalactoside galectin-3 inhibitor, is currently being evaluated clinically for the treatment of idiopathic pulmonary fibrosis. Herein, we describe a new strategy for the preparation of TD139. Starting from inexpensive levoglucosan, we used a rarely employed reaction cascade: Payne rearrangement/azidation process leading to 3-azido-galactopyranose. The latter intermediate was efficiently converted into TD139 in a few simple and practical steps.



## Introduction

Galectins are proteins that bind to galactoside residues and their natural ligands are any glycoconjugates with a non-reducing galactopyranoside terminus.[1] Galectins have the ability to regulate numerous biological processes, including neoplastic transformation, tumor cell survival processes, angiogenesis, tumor metastasis, and cell homeostasis.[2] Among the 15 mammalian members, galectins contain a conserved carbohydrate recognition domain (CRD) of about 135 amino acids. Sharing a consensus amino acid sequence for the CRD makes it difficult to prepare selective galectin inhibitors for biological investigations. Over the years, the scientific community has directed efforts in the synthesis of potent and optimized galectin inhibitors. These works have been summarized in reviews by the groups of Pieters,[3] Kiss,[4] Nilsson,[5] Mayo[6] and ours.[7] Small molecular weight glycomimetics are rationally designed to bind the CRD and inhibit the galectin target. As such, TD139 **1**[8] (Fig. 1) is a ditriazolylthiodigalactoside that was designed as one of the most potent antagonist of galectin-3.[9] Compound **1** showed a $K_d$ of 14 nM to galectin-3, as determined using a competitive fluorescence anisotropy assay.[10] Developed by Galecto Inc., TD139 passed a Ib/IIa phase clinical trial in idiopathic pulmonary fibrosis patients (IPF) and is currently in a randomized, double-blind, placebo-controlled phase IIb trial in subjects with IPF investigating its efficacy and safety (see http://www.clinicaltrials.gov).[11] A particular feature of thiodigalactoside analogues is their resistance to glycosidase *in vivo*. Combined with the long and difficult synthetic route to access bis-(3-azido-3-deoxy-β-D-galactopyranosyl)-sulfane core,[12] there is a major need for a fast and efficient synthesis of TD139.

Fig. 1 shows, in retrosynthetic format, the known synthetic strategy leading to TD139 **1**, a 3,3′-bis-(4-aryltriazol-1-yl) thiodigalactoside. The $C_2$ symmetry of **1** allowed for a general two-directional strategy to install triazole moieties through click chemistry. Then, bis-(2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-β-D-galactopyranosyl)-sulfane **2** is accessible from dimerization of 3-azido-3-deoxy-galactopyranoside bromide **3**. Currently, two distinct approaches were reported for the synthesis of 3-azido-3-deoxy-galactose. The first one was initially reported by Lemieux[13] and involved a nucleophilic displacement of a gulofuranose triflate derivative **4**. This approach began with expensive gulofuranose, but the latter compound can be accessed from inexpensive glucose diacetonide **5** in a five-step protocol.[14] The second approach was described more recently by the group of Nilsson and involved the introduction of the 3-azido-functionality *via* nucleophilic azidation at C-3 of a gulopyranoside triflate intermediate **6**.[15] This compound arises from C-3 inversion and functionalization of galactose **7**. Because of the instability of triflate intermediates, this method was later on improved by using more stable imidazylate and tosylate intermediates.[16] Nevertheless, a more convenient preparation of 3-azido-3-deoxy-galactose is much needed for enabling large scale synthesis of thiodigalactoside galectin inhibitors and for a rapid access to active pharmaceutical ingredients. We aimed to develop a new synthetic route to 1,2,4,6-tetra-*O*-acetyl-3-azido-3-deoxy-D-galactopyranose that could operate on large scale and be initiated from inexpensive starting material. The intended synthetic pathway was designed to develop a practical

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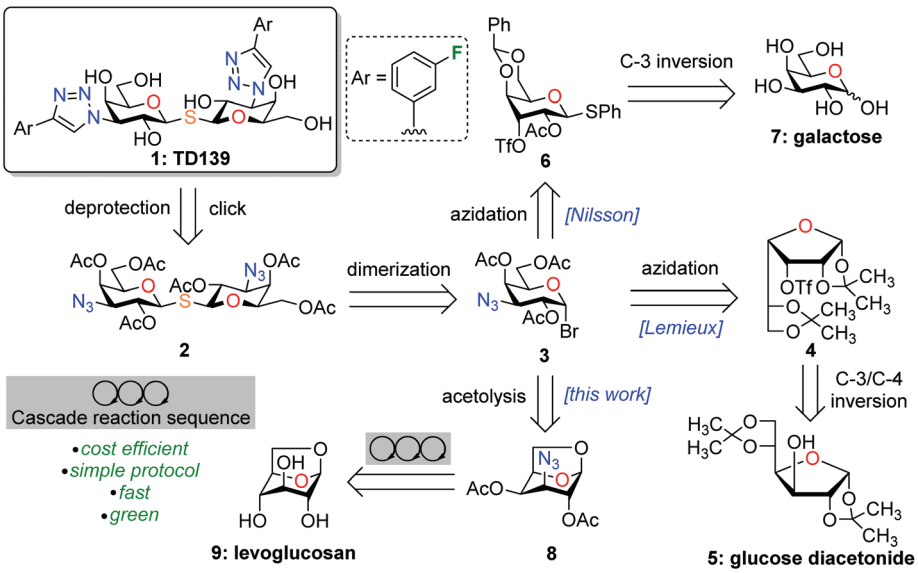



**Fig. 1** Retrosynthetic analysis of TD139 **1**.

alternative to known reported methods.[13,15,16] We explored the possibility of generating crucial intermediate **3** *via* cleavage of the 1,6-anhydro core from 1,6-anhydro-3-azido-3-deoxy-galactopyranose derivative **8**. The requisite azide moiety was introduced using a rarely employed reaction cascade: Payne rearrangement/azidation process.[17] Levoglucosan **9** is an ideal starting material since the 1,6-anhydro core avoided the preliminary protection of O-6 and anomeric positions, and can easily lead to scalable 3-azido-3-deoxy-galactose derivatives *via* simple experimental protocols.

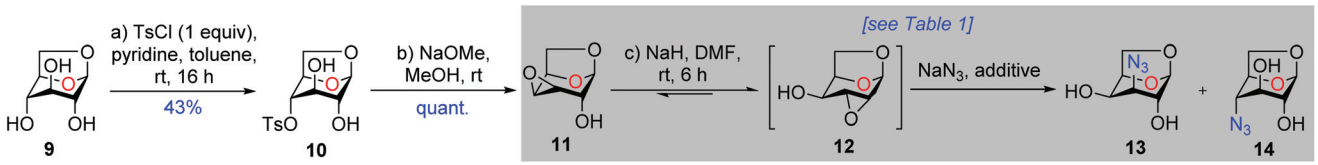
Cascade processes generate *in situ* a series of reactive intermediates that undergo consecutive transformations. They can offer cost saving in terms of reagents and solvents, as well as time and effort. Cascade processes can drastically shorten a synthetic route and thus reducing the number of manipulations. Because of their many advantages, these reactions have found applications in the synthesis of useful pharmaceuticals and other fine chemicals.[18]

Finally, this novel synthetic process could provide a rapid access to 3-azido-3-deoxy-galactose analogues, crucial component to probe the active site of glycosyltransferases,[19] as inhibitors of bacterial adhesins,[20] and to generate novel aminoglycoside antibiotics.[21]

## Results and discussion

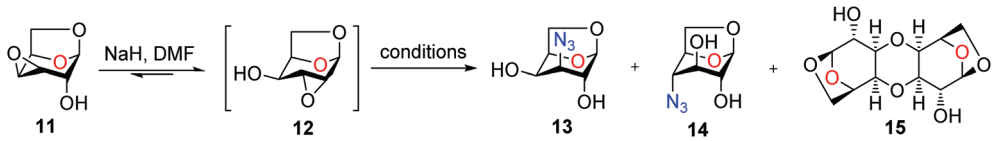
The synthesis of 1,6-anhydro-3-azido-3-deoxy-β-D-galactopyranose **13** from levoglucosan **9** is summarized in Scheme 1. Monotoluenesulfonylation of levoglucosan **9** afforded known 1,6-anhydro-4-*O*-*p*-tolylsulfonyl-β-D-glucopyranose **10**[22] and the latter compound was treated under basic condition to generate 1,6:3,4-dianhydro-β-D-galactopyranose **11** in quantitative yield.[23] An epoxide migration (known as Payne rearrangement)[24] of compound **11** lead to the requisite 1,6:2,3-dianhydro-β-D-gulopyranose **12**, an ideal precursor for azidation reactions. Efforts towards this end are presented in Table 1. Accordingly, compound **11** was treated with sodium hydride in *N*,*N*-dimethylformamide and allowed to come to equilibrium for 6 h prior addition of sodium azide followed by heating at 120 °C for 24 h (entry 1). As propose by the group of Fraser-Reid, in an aprotic solvent, the gulose form should predominate because of a possible chelation between a sodium cation, the O-3 alkoxide, the endocyclic oxygen, and the 1,6-anhydro bridge.[25] The $^1$H NMR of the crude reaction mixture after treatment with sodium hydride revealed formation of compound **12** as major isomer (**11**/**12** ≈ 1 : 9). Unexpectedly, we only isolated an unprecedented dimeric by-product **15** in 72% yield. In order to improve the azidation step, we added 5 equivalents of ammonium chloride (entry 2) and compound **13** was isolated in 65% yield, along with 7% of compound **14**. According to the Fürst–Plattner rule, nucleophilic attack occurs on the C-3 oxirane carbon of compound **12** (leading to **13**) and on the C-4 carbon of compound **11** (leading to **14**).[26] The obtained selectivity can be explain using steric and electronic reasons. Hence, an incoming nucleophile suffered from 1,3-diaxial interaction with the C-2 hydroxyl group for compound **11** and the partial positive charge at C-3 of the oxirane carbon was stabilized by nearby acetal for compound **12**.[27] Further optimisation using other additives ($Na_2SO_4$: entry 3; $Na_2HPO_4$: entry 4; $NH_4Br$: entry 5) failed, but lowering the temperature to 100 °C for 66 hours (entry 6) provided the desired 1,6-anhydro-3-azido-3-deoxy-β-D-galactopyranose **13** in 81% yield, along with 9% of compound **14** as inseparable mixture using standard flash column chromatography. Finally, the latter reaction was even perform on gram scale with no apparent formation of by-product **15**.

A proposed mechanism for the formation compound **15** is shown in Fig. 2 and presumably involves an intermolecular epoxide opening followed by an intramolecular attack from the




**Scheme 1** Synthesis of 1,6-anhydro-3-azido-3-deoxy-β-D-galactopyranose **13** from levoglucosan **9**.

**Table 1** Synthesis of 1,6-anhydro-3-azido-3-deoxy-β-D-galactopyranose **13** from 1,6:3,4-dianhydro-β-D-galactopyranose **11**




| | | Yield[a] (%) | | |
|---|---|---|---|---|
| Entry | Conditions | **13** | **14** | **15** |
| 1 | $NaN_3$, DMF, 120 °C, 24 h | — | — | 72 |
| 2 | $NaN_3$, $NH_4Cl$, DMF, 120 °C, 24 h | 65 | 7 | — |
| 3 | $NaN_3$, $Na_2SO_4$, DMF, 120 °C, 24 h | — | — | 50 |
| 4 | $NaN_3$, $Na_2HPO_4$, DMF, 120 °C, 24 h | 44 | 11 | 30 |
| 5 | $NaN_3$, $NH_4Br$, DMF, 120 °C, 24 h | 51 | 13 | — |
| 6[b] | $NaN_3$, $NH_4Cl$, DMF, 100 °C, 66 h | 81 | 9 | — |

[a] Yields refer to isolated pure products after flash column chromatography. [b] The reaction was perform on gram scale.

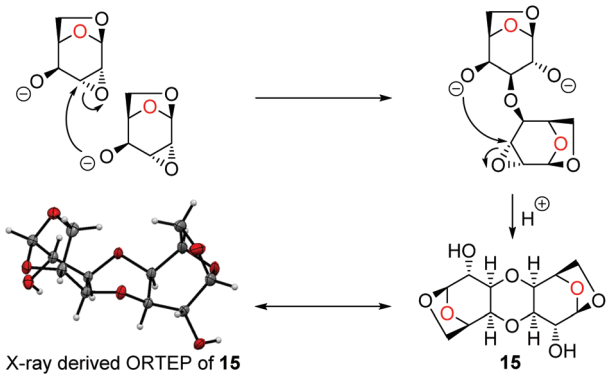
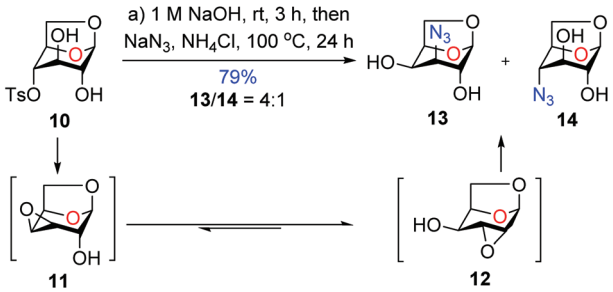



**Fig. 2** Proposed mechanism for the formation of dimeric by-product **15** and X-ray derived ORTEP of compound **15** showing 50% thermal ellipsoid probability, carbon (gray), oxygen (red), hydrogen (white).

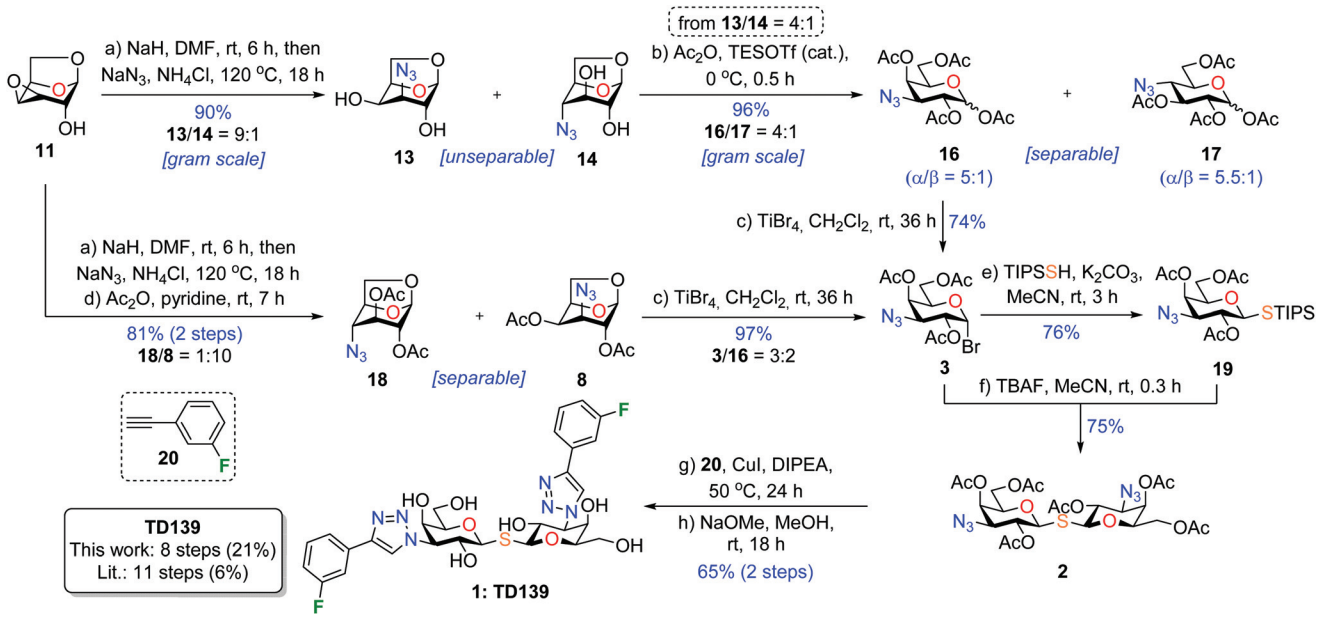



**Scheme 2** Development of a green reaction sequence: epoxide formation/Payne rearrangement/azidation, leading to 1,6-anhydro-3-azido-3-deoxy-β-D-galactopyranose **13**.

*cis*-vicinal alkoxide. Also, an X-ray crystallographic analysis of **15** confirmed its dimeric nature unambiguously (see X-ray derived ORTEP in Fig. 2).[28]

With the ongoing objective of shortening the number of steps to prepare valuable 3-azido-3-deoxy-galactose, we performed our key step starting from mono-tosylate **10** using aqueous sodium hydroxide as base (Scheme 2).[29] To our delight, compound **13** and **14** were isolated in 79% yield (**13**/**14** = 4 : 1, ~93% per step). Presumably, this green process avoided organic solvent and involved the formation of the 3,4-anhydro analogue followed by Payne rearrangement and azidation. To the best of our knowledge, this is the first example of an epoxide formation/Payne rearrangement/azidation reaction sequence.

Encouraged by the successful synthesis of 3-azido-3-deoxy-β-D-galactopyranose derivative from levoglucosan, we maintained our efforts towards the preparation of TD139 **1** (Scheme 3). Thus, triethylsilyl triflate-catalyzed acetolysis of a mixture of **13** and **14** furnished a separable mixture of 3-azido-galactose **16** (77%) and 4-azido-glucose **17** (19%). Then, the galactosyl bromide **3** was slowly generated in 74% yield using $TiBr_4$ from intermediate **16**. Alternatively, intermediate **3** was generated from compound **11**. Accordingly, acetylation of the crude reaction mixture of the key step allowed the preparation of a separable mixture of **18** and **8** (1 : 10) in 81% yield over 2 steps. With compound **8** in hand, a direct bromolysis with $TiBr_4$ afforded in 97% yield a mixture of galactosyl bromide **3**




**Scheme 3** Rapid synthesis of TD139 **1** from 1,6:3,4-dianhydro-β-D-galactopyranose **11**.

and 3-azido-galactose **16** (**3**/**16** = 3 : 2). Subsequently, we used a similar strategy to the group of Nilsson for the preparation of compound **1**.[30] Briefly, a base promoted $S_N2$ substitution of galactosyl bromide **3** with triisopropylsilanethiol afforded triisopropylsilyl β-thio-galactoside **19** in 76% yield.[31] The dimeric nature of the thiodigalactoside core was achieved by treating compounds **3** and **19** under tetrabutylammonium fluoride to generate bis-(2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-β-D-galactopyranosyl)-sulfane **2** in 75% yield. Finally, triazole installation with known alkyne **20** preceded global deprotection, allowing the preparation of TD139 **1** in 65% over 2 steps. The synthesis of compound **1** was described by the group of Nilsson in 11 steps (6% global yield) starting from known intermediate phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside.[9,12] Using the present strategy, compound **1** was prepared in only 8 steps and 21% yield from known tosylate **10**. It is also important to point out that our strategy avoided the use of triflate intermediates,[9,12] unsuitable in large scale synthesis of active pharmaceutical ingredients.

## Conclusions

TD139 is a galectin-3 inhibitor and is currently being evaluated clinically for the treatment of idiopathic pulmonary fibrosis. An efficient synthesis of TD139 **1** from levoglucosan was described. To the best of our knowledge, this is the shortest route to 3-azido-3-deoxy-galactose, a crucial intermediate for the preparation of bis-(2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-β-D-galactopyranosyl)-sulfane. In that manner, we used a rarely employed reaction cascade: Payne rearrangement/azidation, leading to 1,6-anhydro-3-azido-3-deoxy-β-D-galactopyranose. In the course of this study, we also isolated an unprecedented dimeric by-product **15**. We are currently exploring the chemistry and biology of this novel $C_2$-symmetrical compound. Finally, the strategy described herein allowed the preparation of galactose derivatives functionalized at C-3 that could provide useful options for the synthesis of other galectin inhibitors.

## Conflicts of interest

A related provisional patent has been filed with the title "Synthesis of 3-azido-3-deoxy-D-galactopyranose" by Jacob St-Gelais, Vincent Denavit and Denis Giguère (USPTO 62/861,476).

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