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β-Selective One-Pot Synthesis of Acyl-*C*-Glycosides via Corey–Seebach Umpolung Reaction

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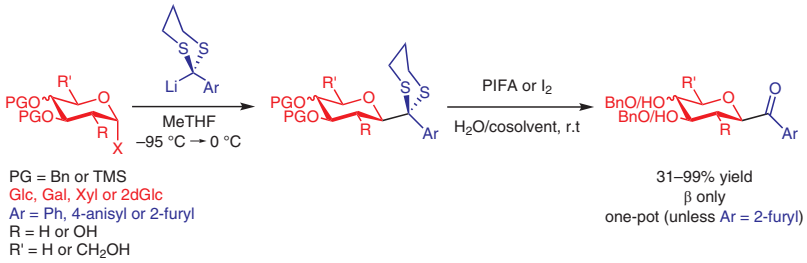
Dedicated to Prof. Armin de Meijere on the occasion of his 80th birthday



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Abstract *C*-Glycosides are commonly used as carbohydrate mimics in drug development due to their stability against enzymatic and chemical hydrolysis. In this *Synpacts* article we elaborate on our fast and efficient β-selective approach towards protected and unprotected acyl glycosides. Application of a Corey–Seebach umpolung reaction enables the exclusive formation of the β-anomer of aromatic acyl-*C*-glycosides in good to excellent yields.

Key words carbohydrates, *C*-glycosylation, umpolung, Corey–Seebach reaction, natural products, scleropentasides

1 Introduction

Scleropentasides are furanoyl-β-*C*-glucosidic compounds that have been obtained from the leaves and twigs of the sandalwoods *Scleropyrum pentadrum*[1] and from the stems of *Dendrotrophe frutescens*.[2]

The structural motif of acyl-*C*-glycosidic was so far unprecedented in plant natural products. The structurally simplest compound is scleropentaside A (**1a**, Figure 1).

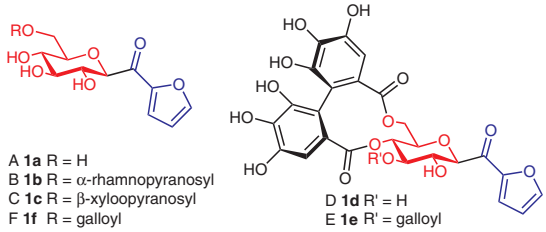
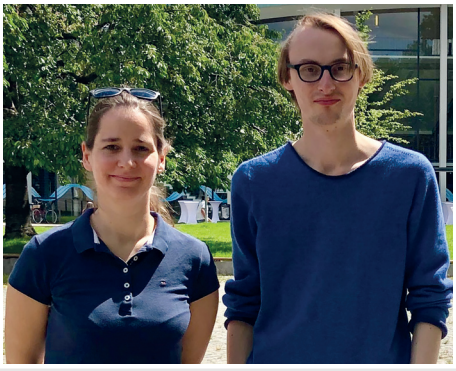


Figure 1 Scleropentasidse A–F **1**



Nina Schützenmeister (left) was born in Reinbek, Germany and received her diploma in 2006 from the Georg-August-University Göttingen after an external diploma thesis in the group of Prof. P. H. Seeberger and her PhD in 2012 from the Georg-August-University Göttingen under guidance of Prof. L. F. Tietze. After a postdoctoral stay at the Max-Planck-Institute for biophysical chemistry in Göttingen in the group of Prof. C. Griesinger (2012–2013) she moved to Bristol (UK) for a postdoctoral stay at the University of Bristol in the group of Prof. V. K. Aggarwal F.R.S. (2013–2015). Since 2015 she is Juniorprofessor at the Institute for Pharmacy at the Universität Hamburg with research interest in the efficient synthesis of natural products and the development of novel anti-infective compounds.
G. Jacob Boehlich (right) was born in Hamburg, Germany and received his BSc (2015) and MSc (2017) under the guidance of Prof. N. Schützenmeister. Since 2018 he is a PhD student working on the synthesis of β-*C*-glycosides and biologically active natural products.

To further investigate the biological activities of these substances we thought a synthetic approach towards these compounds might be useful. Employed methods[3] for the synthesis of *C*-glycosides seemed unsuitable due to the 1,2-difunctionalized anomeric bond requiring an umpolung reaction.[4] Acyl-*C*-glycosides had been synthesized by addition of organometallic compounds to nitrile **2**.[5] A Corey–Seebach umpolung reaction[6] that generated lactol **6**, which had to be reduced subsequently, was also reported.[7] A cross-coupling

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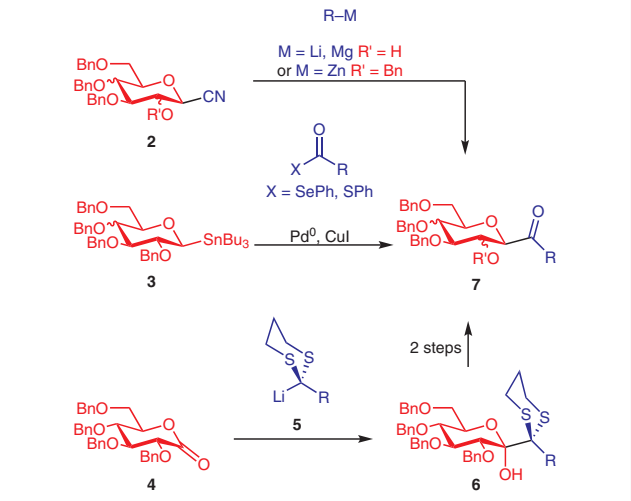
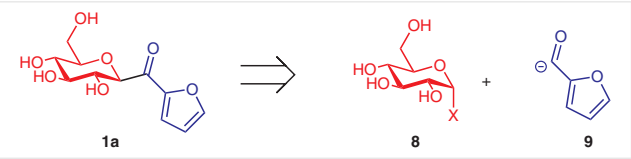
of glycosylstannanes **3** with retention of stereochemistry using large amounts of copper salts was described recently by Walczak et al. (Scheme 1).[8]



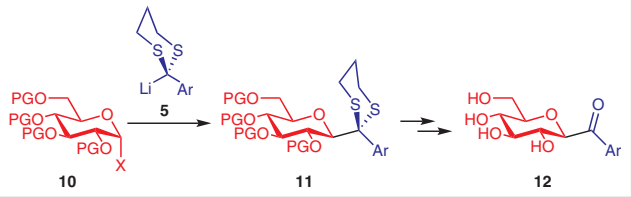
Scheme 1 Previous syntheses of acyl-β-*C*-glycosidic compounds

Most of these methods require multiple steps. Thus, we investigated a more direct S_N2 approach between a suitable glucosyl donor **8** and a carbonyl anion equivalent **9** of furfural (Scheme 2).



Scheme 2 Basic idea behind our approach

We chose the masked carbonyl compound **5** as a carbonyl anion equivalent to react with glycosyl donor **10** in a Corey–Seebach reaction (Scheme 3).[9] The desired β-*C*-glycosidic bond can be generated by a S_N2'-type nucleophilic attack on the α-glycosyl donor **10**, which can be selectively obtained because of the anomeric effect.[10]

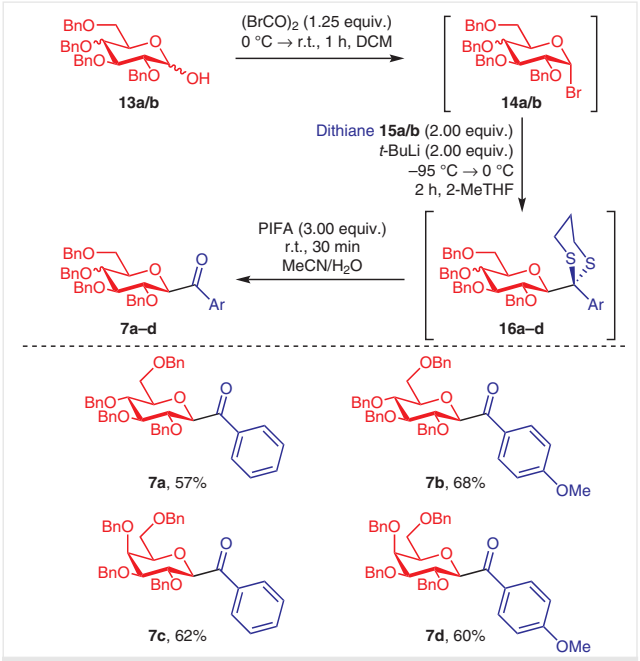


Scheme 3 Approach for the synthesis of acyl-β-*C*-glycosidic compounds

2 *C*-Glycosylation of Benzylated Glycosyl Donors

Because of their widespread use and the high stability of benzyl groups we investigated the use of glycosyl donors **13a**/**b**, which were synthesized according to reported procedures.[11] The donors **14a**/**b** were obtained by anomeric bromination of **13a**/**b** and used after solvent removal without further purification. The aromatic dithianes **15a**/**b** were obtained in one step from benzaldehyde or 4-methoxybenzaldehyde,[12] and lithiated by *t*-BuLi at –95 °C. Reaction of these lithiated dithianes **15a/b** with D-glucosyl or D-galactosyl donors **14a**/**b** provided the β-*C*-glycosides **16a–d**. The reaction failed when the corresponding D-mannosyl or D-allosyl donors were employed. In case of the D-mannosyl donor the crude spectrum after quenching only showed the starting materials dithianes **15a**/**b** and benzylated mannosyl bromide, indicating that no reaction occurred at all. The D-allosyl donor, however, decomposed and gave a complex mixture due to 1,3-diaxial interactions.

After solvent exchange to MeCN/H_2O, the crude perbenzylated dithianes **16a–d** were converted into the ketones **7a–d** under oxidative conditions with (bis(trifluoroacetoxy)iodo) benzene (PIFA)[13] to give the acyl-β-*C*-glycosides **7a–d** in 57–68% yield over three steps (Scheme 4). This three-step one-pot reaction exclusively yielded acyl-β-*C*-glycosides, which was proven by NMR spectroscopic analysis. The major side reaction was elimination of HBr from donor **13a**/**b**, which yielded glycals **17a**/**b** (Figure 2). This side reaction, which is common for reactions of glycosyl halides with organometallics,[14] was partially suppressed by



Scheme 4 β-Selective one-pot syntheses of acyl-glycosides **7a–d**

use of 2-MeTHF instead of THF as solvent. In the synthesis of **7a**, small amounts of the glucal **18** formed, which is probably caused by elimination of benzyl alcohol from the acyl glucoside. Guillarme et al. also observed this product when they reacted Li and Mg organometallics with perbenzylated glycosyl cyanides (Figure 2).[5]

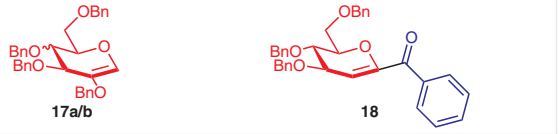
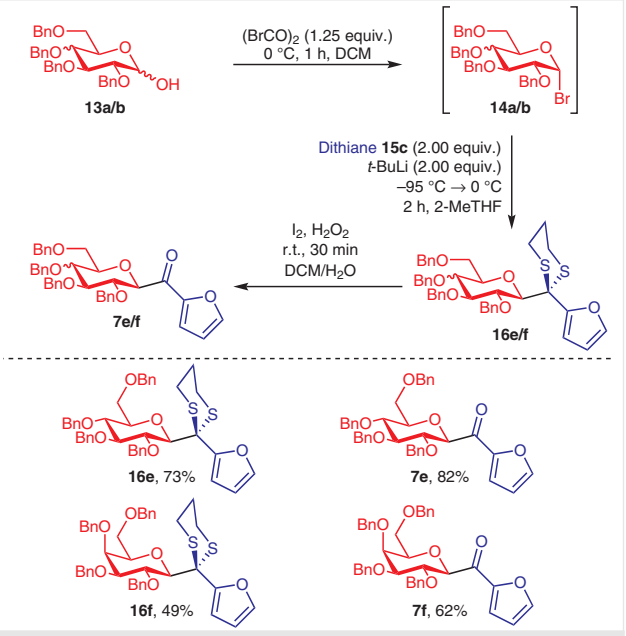


Figure 2 Observed side products in the synthesis of acyl-β-clycosides

The synthesis of scleropentaside A (**1a**) required furyldithiane **15c** as building block, which can be synthesized from furfural in one step.[15] However, the furan substituent was more challenging to introduce. First of all, the lithiated dithiane **5c** is more unstable compared to the lithiated dithianes **5a**/**b** as it readily decomposes even at lower temperatures.[16] Secondly, the resulting glycosyl dithianes **16e**/**f** also proved to be unstable employing the hydrolysis method using PIFA. Thus, the glycosyl dithianes **16e**/**f** had to be purified prior to hydrolysis of the dithiane moiety under milder conditions. While the Corey–Seebach umpolung reaction of D-glucose donor **14a** and dithiane **5c** provided **16e** in an excellent yield of 73%, a significant reduction in yield was observed using the D-galactose derivative **16f** (49%).

As before, in both cases the exclusive formation of β-*C*-glycosidic anomers was achieved. The hydrolyses of the dithianes **16e**/**f** were performed using I_2 and H_2O_2 in DCM/H_2O[17] to yield acyl-β-*C*-glycosides **7e**/**f** in good to excellent yields (Scheme 5).



Scheme 5 β-Selective syntheses of acyl-glycosides **7e**/**f**

Furthermore, the β-configuration of furoyl-*C*-glycoside **7e** was proven beyond doubt by single-crystal X-ray diffraction analysis (Figure 3).[18]

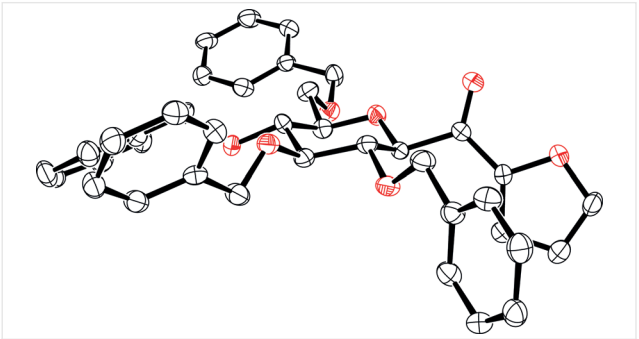
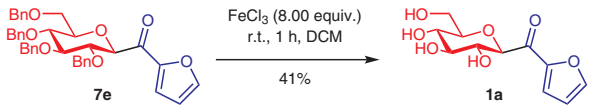


Figure 3 Single crystal X-ray structure of **7e**

Removal of the benzyl groups proved to be difficult. Even though most methods to synthesize acyl-*C*-glycosides use benzyl-protective groups they do not offer an efficient way to remove these. In our case, standard hydrogenation procedures showed no conversion at all. Walzcak et al. reported hydrogenolytic conditions that cleaved the benzyl groups, but also reduced the ketone to the alkane.[8] We had moderate success by using $FeCl_3$ in DCM[19] but the workup was tedious and the yield mediocre (Scheme 6).



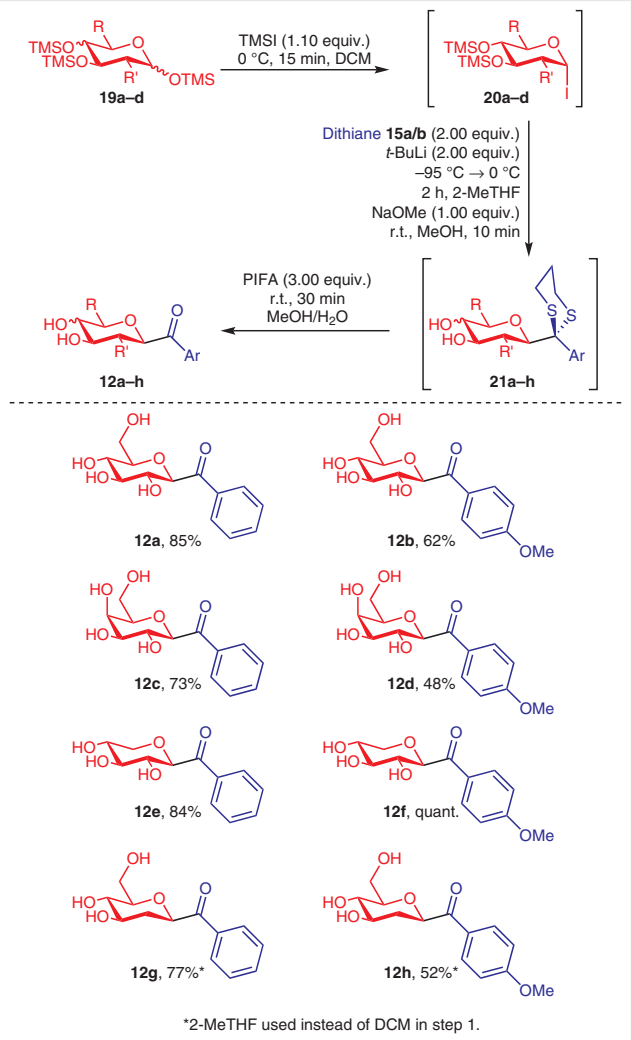
Scheme 6 Deprotection of benzylated β-acyl-glycoside **7e**

3 *C*-Glycosylation of Silylated Glycosyl Donors

To overcome this problem, we investigated the use of TMS as protective group. The easily synthesized persilylated monosaccharides **19a–d** were converted into the corresponding donors **20a–d** by a literature-known procedure.[20] Solvent exchange to 2-MeTHF after donor synthesis and subsequent Corey–Seebach umpolung reaction between the donors **20a–d** and the lithiated species **5a**/**b** of the dithianes **15a**/**b** provided the β-*C*-glycosides **21a–h**.

Again, use of THF instead of 2-MeTHF as the solvent led to a significant reduction in yield. Removal of the TMS groups by NaOMe in MeOH and oxidative hydrolysis of the respective dithianes delivered the ketones **12a–h** in excellent to quantitative yields for the four-step one-pot procedure. Again, in all cases only the acyl-β-*C*-glycosides **12a–h** were formed (Scheme 7).

The 2-deoxyglucosyl iodide **20d** proved to be unstable in DCM. However, unlike other glycosyl iodides it was possible to generate the iodide in 2-MeTHF. Employing this donor in the following key step only generated the desired *C*-glycosides with excellent β-selectivity. This observation

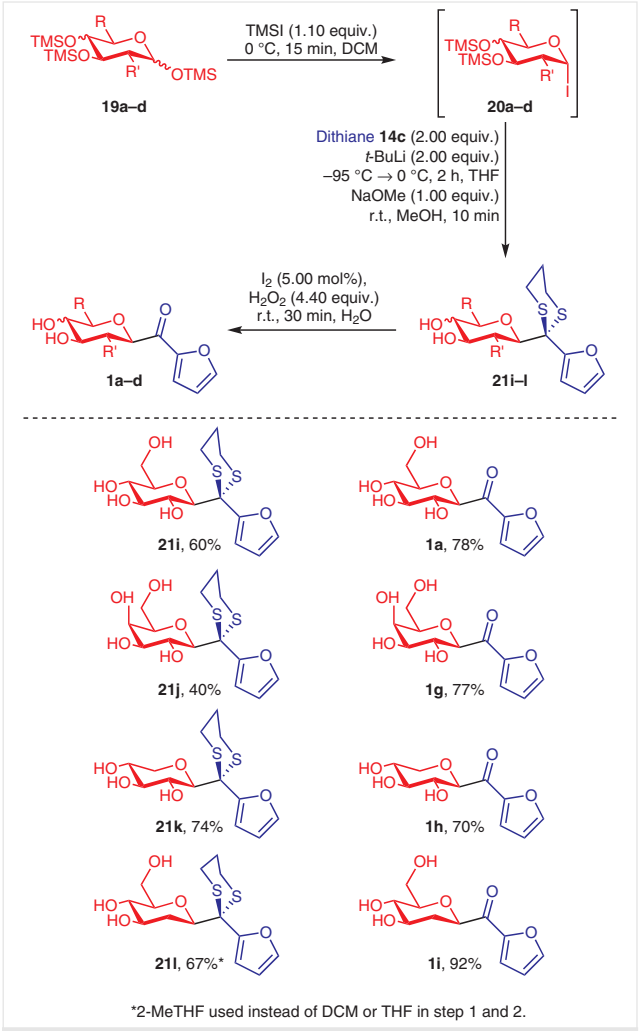


Scheme 7 β-Selective one-pot syntheses of acyl-glycosides **12a–h**[18]

supports the assumption of an S_N2-controlled mechanism during nucleophilic attack at the anomeric center due to a lack of a shielding group in 2-position.

In most cases, decrease in yield was observed when D-galactosyl donors were employed. This is probably caused by the shielding effect of the axial substituent. This assumption is in agreement with the observation that α-mannosyl donors, which have their axial substituent closer to the anomeric center, did not react at all. α-Allosyl donors were too unstable due to 1,3-diaxial interactions and decomposed under the reaction conditions.

Again, the furyl substituent required special treatment to be introduced. When 2-MeTHF was used as solvent, all donors except 2-deoxyglucosyl donor **20d** only yielded traces of product. Solvent exchange to THF after donor synthesis and Corey–Seebach umpolung reaction of donor **20a–d** and the lithiated species **5c** of dithiane **15c** provided exclusively the β-*C*-glycosides **21i–l** after cleavage of the silyl groups by NaOMe in MeOH. Finally, oxidative hydrolysis of dithianes **21i–l** by I_2 and H_2O_2 in H_2O yielded scleropentaside A (**1a**), its D-galactose analogue **1g**, its D-xylose analogue **1h**, and 2-deoxy scleropentaside A (**1i**) in very good yields (Scheme 8).



Scheme 8 β-Selective syntheses of furoyl-glycosides **1**

As before, single-crystal X-ray diffraction analysis confirmed the β-*C*-glycosidic linkage beyond doubt (Figure 4).[21]

4 Conclusion

In conclusion, we have developed a fast and exclusively β-selective approach towards benzylated and unprotected acyl-β-*C* glycosides. The applicability of the method was shown on the dramatically short synthesis of scleropentaside A (**1a**), which was synthesized in only four steps in with an excellent overall yield of 47%. Furthermore, the

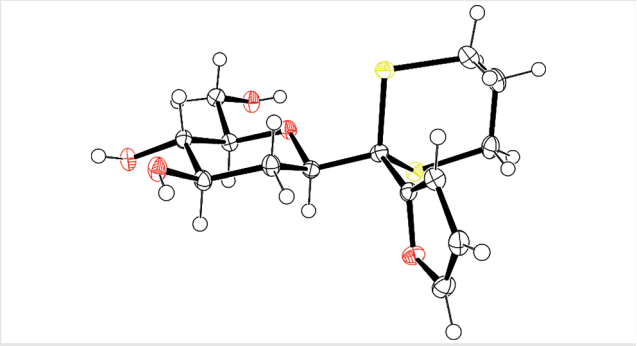


Figure 4 Single-crystal X-ray structure of **21l**[21]

synthesis of differently substituted anomeric acyl-β-*C*-glycosides general efficiency of the protocol showed the general applicability of the synthetic strategy.

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