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Synthesis of *C*-acyl furanosides *via* the cross-coupling of glycosyl esters with carboxylic acids†

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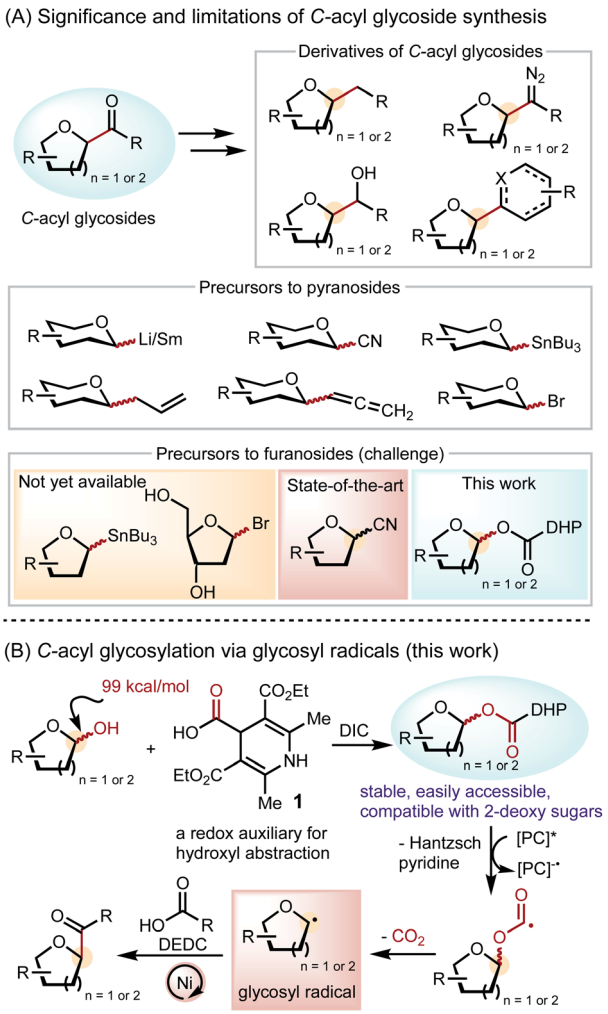
C-Acyl furanosides are versatile synthetic precursors to a variety of natural products, nucleoside analogues, and pharmaceutical molecules. This report addresses the unmet challenge in preparing *C*-acyl furanosides by developing a cross-coupling reaction between glycosyl esters and carboxylic acids. A key step is the photoredox activation of the glycosyl ester, which promotes the homolysis of the strong anomeric C–O bond through CO_2 evolution to afford glycosyl radicals. This method embraces a large scope of furanoses, pyranoses, and carboxylic acids, and is readily applicable to the synthesis of a thymidine analogue and diplobifuranylone B, as well as the late-stage modification of (+)-sclareolide. The convenient preparation of the redox active glycosyl ester from native sugars and the compatibility with common furanoses exemplifies the potential of this method in medicinal chemistry.

Introduction

C-Acyl glycosides are versatile synthetic intermediates to natural products, nucleoside analogues, and pharmaceutical molecules (Scheme 1A).[1] Downstream derivatives of *C*-acyl glycosides, including *C*-alkyl glycosides,[2] diazo derivatives,[3] alcohols,[4] nucleoside analogues,[5] and cyclopentitols,[6] display significant potentials in drug discovery and utilities in chemical biology and biochemistry studies. A *C*-glycoside linkage confers *in vivo* stability towards hydrolysis and enzymatic degradation.[7] Therefore, *C*-furanosides, including nucleoside analogues in particular, have been extensively explored as antiviral drug candidates. In addition, unnatural nucleosides are essential tools for studying the origins of mutagenicity and the mechanism of replication and evolution.[8] *C*-acyl furanosides serve as a convenient intermediate to nucleoside analogues through formation of heterocycles at the anomeric position *via* condensation and cyclization.[5]

Synthetic efforts towards *C*-acyl glycosides have been primarily focused on pyranosides. Conventional methods include the nucleophilic addition of glycosyl lithium[9] or samarium[10] reagents to carbonyl compounds and the functionalization of *C*-nitriles,[4a,11] *C*-allyls,[4b] *C*-allenes[3,12] and benzothiazoles (Scheme 1A).[13] Recent cross-coupling approaches employ stannane reagents[14] and glycosyl bromides[15] to deliver a broad range of *C*-acyl pyranoside products. In contrast to the widespread means to prepare *C*-acyl pyranosides, access to *C*-acyl furanosides is limited and lacks a robust scope.[16] For



Scheme 1 Strategies in *C*-acyl furanoside synthesis.

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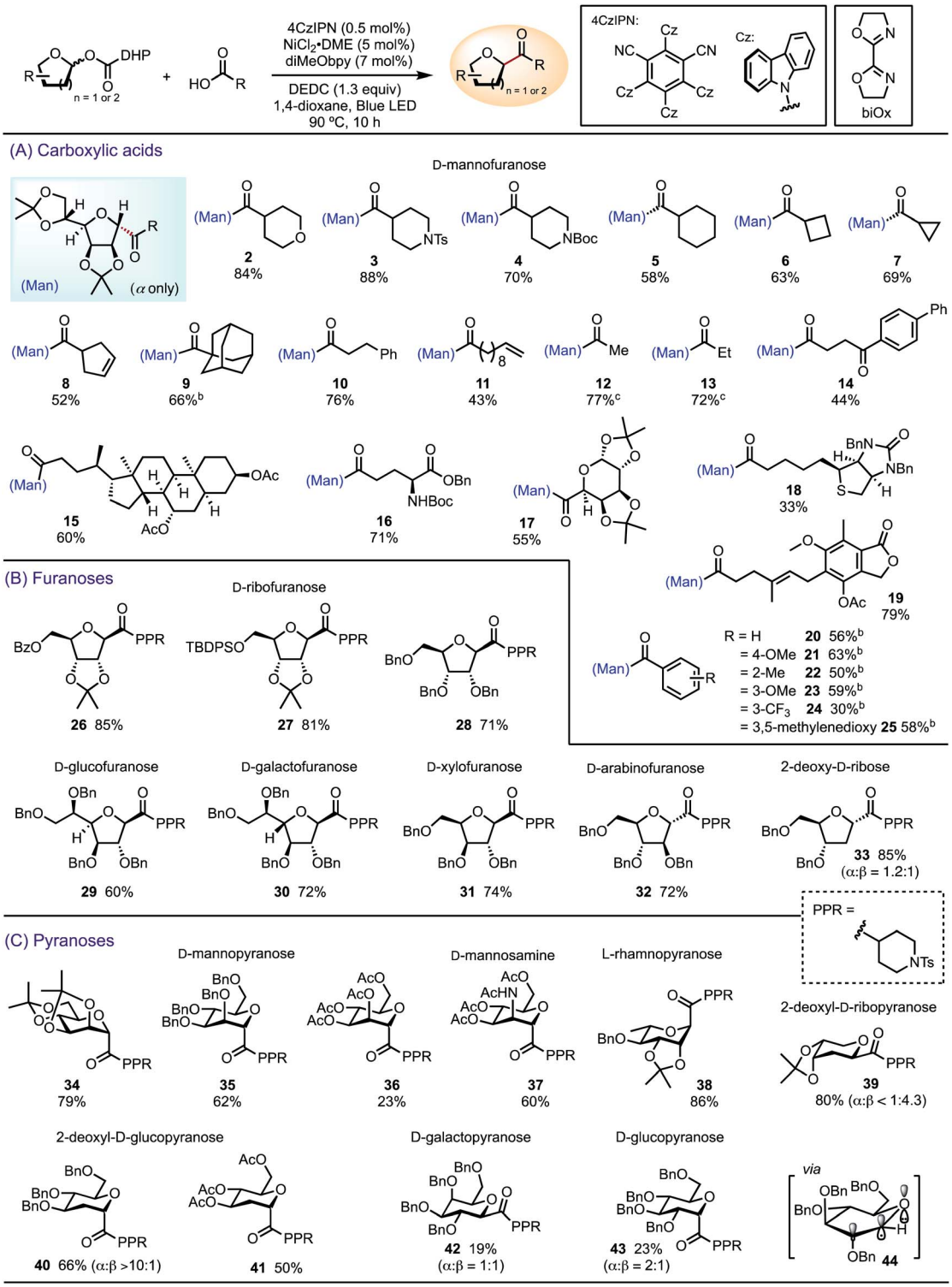
Table 1 Scope of *C*-acyl glycosylation with DHP-derived glycosyl esters[aa]



[a] Isolated yields. The major anomer was isolated as a pure product, unless specified. Stereochemistry of the products was assigned based on NOESY and COSY experiments. Reaction conditions: carboxylic acid (0.20 mmol), glycosyl ester (0.26 mmol, 1.3 equiv.), 1,4-dioxane (4.8 mL). [b] 2,2′-Bi-2-oxazoline (biOx) as the ligand, $NiBr_2$·diglyme (5 mol%), 4CzIPN (0.25 mol%), glycosyl ester (1.2 equiv.), LiBr (2.5 mol%), 86 °C. [c] The corresponding anhydride was used as the electrophile without DEDC, 1,4-dioxane (3.2 mL).

example, furanosyl stannane reagents have not yet been reported. Furanosyl bromides, especially 2-deoxy derivatives, are often unstable and have not been applied to *C*-acyl furanoside synthesis. Currently, the best way to prepare *C*-acyl furanosides is through the nucleophilic addition of metal reagents to glycosyl nitriles,[17] but this method requires multiple steps and precludes base-sensitive functional groups.

The dearth of furanosylation methods may be associated with the lack of furanosyl radical precursors that can be used for cross-coupling. Pyranosyl radicals have been generated from various unnatural glycosyl derivatives, including bromides,[18] xanthates,[19] glycals,[20] stannanes,[21] thiol ethers,[22] acyl tellurides,[23] and trifluoroborates.[24] Precursors to furanosyl radicals, however, are limited to unnatural tetrahydrofuran derivatives with a carboxylic acid at the C1 position, restricting the scope of carbohydrate substrates.[25] Furthermore, redox auxiliaries based on C–C bond homolysis can only substitute at the C5 of furanosides and the C6 of pyranosides, not allowing for anomeric functionalization.[26] The most ideal glycosyl radical precursor is the native carbohydrate, but the BDE of the anomeric C–O bond (99 kcal mol^{-1}) is even higher than that of a typical alcohol (96 kcal mol^{-1}).[27] Thus, formation of glycosyl radicals *via* anomeric C–O bond homolysis represents a significant fundamental challenge.

Herein, we report a solution to the unmet challenge of *C*-acyl furanoside synthesis by utilizing redox auxiliary **1** to generate furanosyl radicals from furanosyl esters and cross-coupling them to carboxylic acids (Scheme 1B). Inspired by the success of alkyl dihydropyridine (DHP) as a radical precursor[28] and its utility in C5- and C6-functionalization of glycosides,[26a,b] we developed DHP-based redox auxiliary **1** by incorporating a carbonyl group between DHP and the glycoside, which can induce the homolysis of the strong anomeric C–O bond through CO_2 evolution.[29] The favorable condensation between **1** and furanoses and pyranoses readily furnishes glycosyl esters that are bench stable and compatible with all common native carbohydrates.

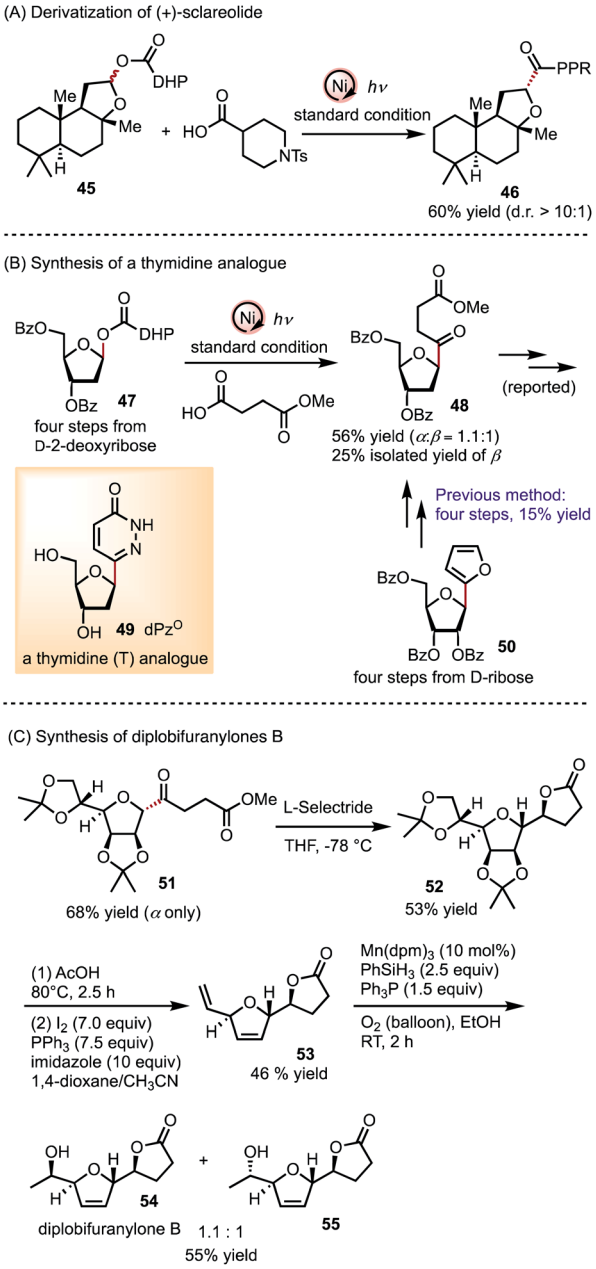
Results and discussion

We performed *C*-acylation of glycosides by cross-coupling glycosyl DHP carboxylate esters with carboxylic acids under modified photoredox-nickel dual catalytic conditions, with diethyl dicarbonate (DEDC) as an activator for the carboxylic acids (Table 1).[30] The elevated temperature of 90 °C was necessary to facilitate DHP fragmentation and the subsequent decarboxylation. Lower temperature led to incomplete decarboxylation and the formation of glycosyl ester as a byproduct. We first evaluated the scope with respect to carboxylic acids coupling to diacetonide-protected D-mannofuranosyl DHP carboxylate ester (Table 1A). Aliphatic carboxylic acids containing various functional groups, including amines, alkenes, and ketones, underwent efficient coupling to afford *C*-acyl D-mannosides **2–13**. The scope of the carboxylic acids extends to biologically active substrates, including fenbufen **14**, ursodeoxycholic acid **15**, L-glutamic acid (Glu) **16**, α-D-galactopyranuronic acid **17**, D-biotin **18**, and mycophenolic acid **19**. The high yield of **16** suggests that this method shows promise for glyco-peptide synthesis by allowing conjugation of glutamic acid with a variety of carboxylic acids. The coupling of D-mannofuranosyl DHP ester to benzoic acids utilizes a variant of the standard conditions that employs unsubstituted 2,2′-bi-2-oxazoline (biOx) as the ligand to afford products **20–25**. Electron-deficient benzoic acids gave lower yields than electron-rich derivatives. In all reactions, the α-anomer was isolated as the predominant product due to the approach of the incoming catalyst from the α-face, as the β-face was hindered by the C2-substituent. Alternatively, it is possible that the capture of glycosyl radical by Ni is reversible.[31] Under the Curtin–Hammett condition, the stereoselectivity is determined by a faster reductive elimination of the α-product relative to the β-product.

We then investigated the scope with respect to furanoses and the compatibility of protecting groups using 4-piperidinecarboxylic acid (PPR–CO_2H) as the coupling partner (Table 1B). D-Ribofuranoses bearing common protecting groups, such as benzoyl **26**, *tert*-butyldiphenylsilyl (TBDPS) **27**, and benzyl **28**, afforded the corresponding β-*C*-acyl ribofuranosides in good yields. Other furanosides also underwent smooth *C*-acylation to generate D-glucofuranoside **29**, D-galactofuranoside **30**, D-xylofuranoside **31**, and D-arabinofuranoside **32**. The stereoselectivity appears to be governed by the stereochemistry at C2, favoring the entering group from the opposite face of the C2-substituent. While the β-anomer was favored by most products, D-arabinofuranoside **32** was formed as the α-anomer. Benzyl-protected 2-deoxy-D-ribose generated a mixture of α and β anomers of **33** in a ratio of 1.2 : 1, presumably due to the lack of steric hindrance at C2 to distinguish the α from the β face.

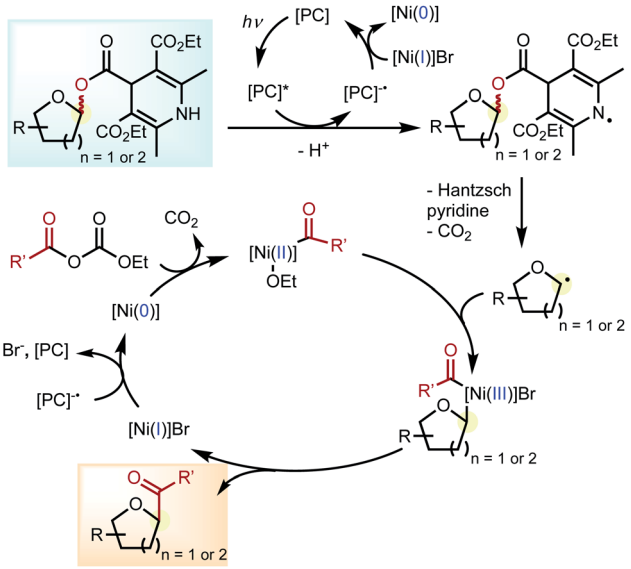
A variety of pyranoses were transformed to *C*-acyl glycosides **34–41** under the standard conditions (Table 1C). α-Anomers were favored for D-mannopyranoses **34–36**, D-mannosamine **37**, L-rhamnopyranose **38**, and 2-deoxy-D-glucopyranosides **40** and **41**, as determined by the kinetic anomeric effect, namely the stabilization of the transition state by the donation of the lone electron pair on the ring oxygen to the anti-bonding orbital of the newly-formed σ bond ($\sigma^{*\ddagger}$) in the axial position.[32] Both anomers were observed for 2-deoxy-D-ribopyranoside **39**, with the β-anomer favored due to the steric hindrance remotely imparted by C3 and C4 substituents. *C*-Acylation of D-galactopyranose and D-glucopyranose was less effective and afforded a mixture of α- and β-anomers **42** and **43** in low yields. We attribute this limitation to the contradictory preferences of the steric and stereoelectronic effects. In the preferred boat conformation **44**,[32] β-attack of the glycosyl radical intermediate is favored due to the steric hindrance at C2, whereas the transition state of α-attack is stabilized by the kinetic anomeric effect.

The generality of this *C*-acylation method prompted us to explore its application to derivatize natural products and synthesize biologically relevant molecules (Scheme 2). A (+)-sclareolide derivative **45** can be readily coupled with 4-piperidinecarboxylic acid to afford **46** in 60% yield with a diastereomeric ratio (d.r.) higher than 10 : 1 (Scheme 2A). This late-stage modification can be extended to natural and synthetic molecules containing hemiacetal functionality, in light of a large variety of



Scheme 2 Synthetic applications of *C*-acylation of furanosides.

commercially available carboxylic acids. A thymidine (T) analogue dPz^{O} **49** has attracted considerable attention,[5a] as the corresponding nucleotide can be incorporated into DNA by Klenow fragments and forms a Watson–Crick base pair with adenine (A).[5b] *C*-Acylation of D-2-deoxyribosyl ester **47** accomplishes a more efficient formal synthesis of **48** compared to a previous route from **50** (Scheme 2B).[5a] Alternatively, a better overall yield may be achieved by conducting the *C*-acylation of D-ribose (74% yield, α only, *cf.* compound **S7** in the ESI†), followed by reduction at C2.[5b] Finally, we demonstrate that acyl mannofuranose **51**, obtained in 68% yield, can lead to natural product diplobifuranylone B **54** [33] in a concise synthetic route (Scheme 2C).[34] The structure of **55** was assigned to diplobifuranylone A in the original report of these molecules, produced by fungus pathogens,[33]



Scheme 3 Proposed catalytic cycle.

but a discrepancy between the spectroscopic data of **55** and that of diplobifuranylone A suggests that the original structural assignment requires reconsideration.

Based on literature precedents and a previous radical trapping experiment,[29] we propose that the reaction follows the photoredox-nickel dual catalytic cycles shown in Scheme 3. The key step involves the subsequent fragmentation of the DHP ester to afford the glycosyl radical upon release of Hantzsch pyridine and CO_2. The carboxylic acid coupling partner is activated by DEDC by forming the corresponding anhydride.

Conclusions

We developed a cross-coupling reaction to prepare *C*-acyl furanosides and pyranosides from glycosyl esters and carboxylic acids. Upon photoredox activation, the glycosyl ester can fragment to generate a glycosyl radical through CO_2 evolution. This method tolerates a broad scope of carboxylic acids, furanoses, and pyranoses to deliver products with excellent diastereoselectivity, governed by the stereochemistry at C2. The reaction is particularly useful for the synthesis of unnatural nucleosides and the late-stage modification of natural products. The convenient preparation of the redox active glycosyl esters, their stability, and their compatibility with common carbohydrates exemplifies the potential of this method in medicinal chemistry.

Data availability

All experimental procedures and spectroscopic data can be found in the ESI.†

Author contributions

Y. W. and T. D. conceived the idea. Y. W. optimized the conditions. Y. W. and J. L. explored the scope. T. D. supervised the project and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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