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Straightforward and highly diastereoselective synthesis of 2,2-di-substituted perhydrofuro[2,3-*b*]-pyran (and furan) derivatives promoted by $BiCl_3$†

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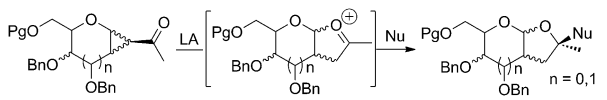
An effective and facile method for the synthesis of 2,2-di-substituted perhydrofuro[2,3-*b*]pyran (and furan) derivatives is described. The cyclization of 1,2-cyclopropanated sugars with olefins in the presence of $BiCl_3$ is highly diastereoselective. 2,2-Di-substituted cyclization products were obtained in good to excellent yields.

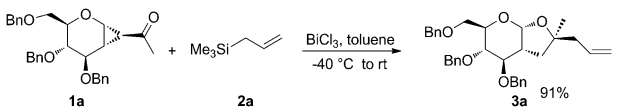
Perhydrofuro[2,3-*b*]pyran (and furan) subunits are extensively found in a large number of natural products with a broad-range of biological activities.[1,2] Fascinated by the complex skeletons and excellent bioactivity, much effort has been devoted to developing creative strategies for the architecture of such fused-cycle motifs.[3,4] Among the myriad methods, ring closure by intramolecular coupling reaction is one of the most efficient and direct methods. Although many strategically novel methods have been developed for the synthesis of diverse perhydrofuro[2,3-*b*]pyrans (and furans), the development of a more stereoselective and efficient strategy to afford such C(2) position active functional groups in substituted perhydrofuro[2,3-*b*]pyran (and furan) skeletons remains a challenge.

Highly strained cyclopropane derivatives, which can serve as versatile C3 building blocks for the construction of various ring systems, have been extensively studied in recent years. So far, cyclopropane derivatives substituted with a wide range of activating functional groups have been successfully used in cyclization and cycloaddition reactions.[5] Among them, some interesting transformation reactions using cyclopropyl carbonyls (aldehydes or ketones) have also been reported.[5d] However, the majority of these studies centre on the ring-expansion to construct dihydrofuran derivatives or the [3+2] addition to synthesize cyclopentanes.[5d,6] By contrast, there have been precious few research studies on ring-expansion, followed by intermolecular nucleophilic addition to furnish multi-substituted fused-ring compounds. Furthermore, in the previous studies, the carbohydrate-based cyclopropanes were usually used as glycosyl donors for synthesis of C(2)-branched glycoside, ring expanded oxepanes.[7] Recently, NIS-mediated ring opening of carbohydrate-based cyclopropyl methanol or cyclopropanecarboxylate offered easy access to 3-iodo-perhydrofuro[2,3-*b*]-pyran derivatives,[8] but it is still a challenge to install an active functional group at the C(2) of the fused perhydrofuro[2,3-*b*]pyrans (and furans). In continuation of our previous work on the stereoselective synthesis of glycosides,[9] we disclose our results on highly diastereoselective synthesis of 2,2-disubstituted perhydrofuro [2,3-*b*]-pyrans (and furans) from cyclopropanated sugars *via* a $BiCl_3$ promoted cyclopropane ring-opening and recyclization–addition tandem strategy (Scheme 1). Such a reaction constructed a quaternary carbon center in a stereoselective manner, which is perceived as a challenging problem in organic synthesis.[10] Besides, these carbohydrate-based fused-ring compounds could be tested as potential inhibitors of *O*-GlcNAcase.[11]

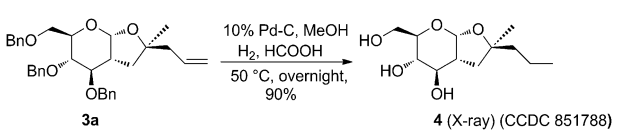
The initial experiments were performed with 1,2-cyclopropanated sugar **1a** and allyltrimethylsilane **2a** as model substrates. To our delight, after a series of trials, we found that



Scheme 1 Proposed synthetic route for 2,2-di-substituted perhydrofuro[2,3-*b*]-pyran (and furan) derivatives.



Scheme 2 $BiCl_3$-promoted reaction of **1a** and allyltrimethylsilane (**2a**).



Scheme 3 The corresponding hydrogenated product.

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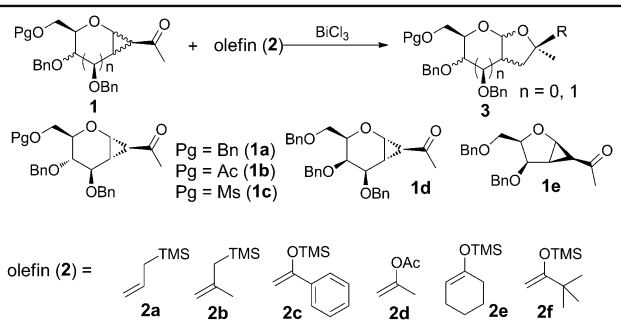
2.5 equiv. of $BiCl_3$ in toluene was the optimal condition for this transformation (Scheme 2).[12]

The stereochemistry of the perhydrofuro[2,3-*b*]pyran **3a** was confirmed by extensive studies of the ^{1}H NMR and NOE, and determined by X-ray crystallographic analysis of the corresponding hydrogenated product **4** (Scheme 3).

Under the optimal reaction conditions, the scope of substrates was then evaluated, and the results are provided in Table 1. Firstly, a wide variety of nucleophilic organosilicon reagents including allyltrimethylsilane (**2a**), and its analogue (**2b**), silyl enol ether derivatives (**2c**, **2e** and **2f**) were investigated (Table 1, entries 1–3, 5 and 6). Interestingly, $BiCl_3$ mediated reaction was very efficient for

Table 1 The reaction of 1,2-cyclopropanated sugars and olefins using $BiCl_3$ as a promoter[a]



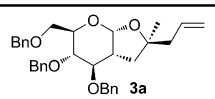
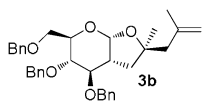
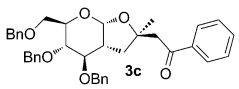
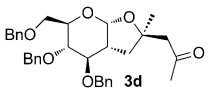
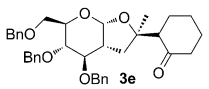
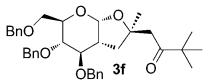
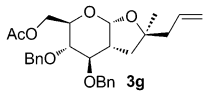
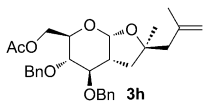
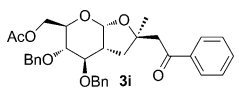
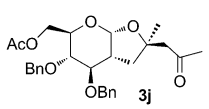
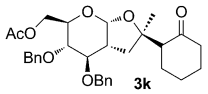
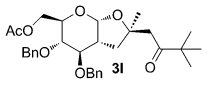
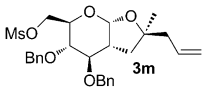
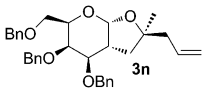
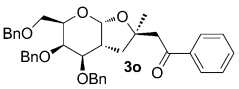
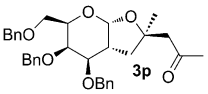
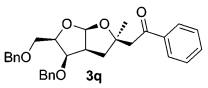
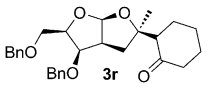
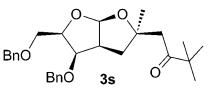
Entry	Substrate	Olefin	Product	Yield[b] (%)
1	**1a**	**2a**		91
2	**1a**	**2b**		75
3	**1a**	**2c**		66
4	**1a**	**2d**		86
5	**1a**	**2e**		88
6	**1a**	**2f**		70
7	**1b**	**2a**		85
8	**1b**	**2b**		83
9	**1b**	**2c**		71
10	**1b**	**2d**		64

Table 1 (*Continued*)

Entry	Substrate	Olefin	Product	Yield[b] (%)
11	**1b**	**2e**		85
12	**1b**	**2f**		72
13	**1c**	**2a**		90
14	**1d**	**2a**		85
15	**1d**	**2c**		80
16	**1d**	**2d**		74
17	**1e**	**2c**		78
18	**1e**	**2e**		73
19	**1e**	**2f**		65

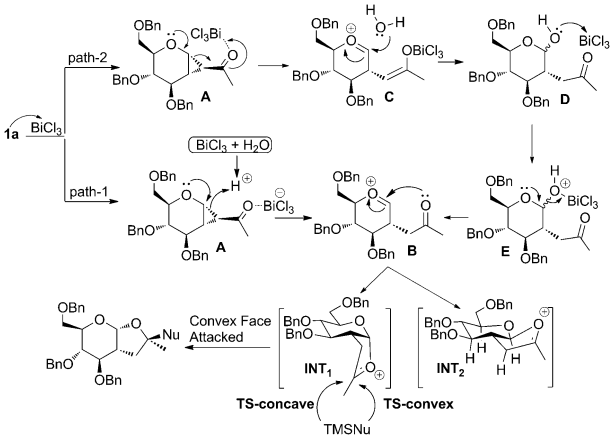
[a] All reactions were carried out using 0.1 mmol 1,2-cyclopropanated sugar, 0.4 mmol nucleophile and 0.25 mmol $BiCl_3$ in 1 mL toluene unless otherwise noted. [b] Isolated yield.

synthesis of perhydrofuro[2,3-*b*]pyran derivatives with only one diastereomer as the product. Obviously, other olefin derivatives such as isopropenyl acetate (**2d**) could also be used in this reaction (Table 1, entries 4 and 10). Furthermore, it is worthwhile to mention that a nucleophile with a bulky group (**2f**) could be employed in the coupling reaction to furnish the fused-cycle product in 70% yield (Table 1, entry 6). In addition, the prochiral ketone precursor (**2e**) gave the perhydrofuro[2,3-*b*]pyran derivative as a single diastereomer as well (Table 1, entry 5).

Then, different protection groups in 1,2-cyclopropanated sugars were used for the transformation. Therefore, 6-*O*-Ac and 6-*O*-Ms-1,2-cyclopropanated sugars were also used as donors to test the feasibility of the reaction (Table 1, entries 7–13). Obviously, the 6-*O*-participation group (Ac) (Table 1, entries 7–12) and the 6-*O*-electron-withdrawing group (Ms) did not affect the reaction (Table 1, entry 13).[13]

Finally, the scope of the reaction was further investigated by using other cyclopropanated sugar derivatives (**1d** and **1e**). Satisfactorily, the galactose-based perhydrofuro[2,3-*b*]pyrans can be obtained in good yield (Table 1, entries 14–16) under the same conditions, and the multi-substituted perhydrofuro[2,3-*b*]furans are obtained in a moderate yield with only one diastereoisomer (Table 1, entries 17–19).

On the basis of the above results, a plausible mechanism is proposed for the formation of perhydrofuro[2,3-*b*]pyran (and furan)



Scheme 4 Plausible mechanism of $BiCl_3$ promoted cyclization *via* oxocarbenium ion intermediates.

derivatives under the $BiCl_3$ promoted conditions (Scheme 4). Along path-1, partial $BiCl_3$ coordinated to the carbonyl oxygen, and activated the cyclopropane, while the remaining $BiCl_3$ reacted with H_2O generated hydrogen ions,[14] which worked as electrophiles bonded to C(7), followed by the ring opening of 1,2-cyclopropanated sugar and formation of the pyran oxocarbenium ion **B**. Subsequently, carbonyl oxygen could serve as a nucleophile intramolecularly attacking the anomeric carbon to form six-five fused ring oxocarbenium ion intermediates **INT1** and **INT2**. DFT calculations[15] at the B3LYP/6-31+G** level in toluene showed that **INT1** is 8.7 kcal mol^{-1} more stable than **INT2**. Therefore, the formation of **INT1** is dominant. A second possible reaction pathway to form **INT1** (Scheme 4, path-2) is that after the $BiCl_3$ activation and ring opening of 1,2-cyclopropanated sugar, H_2O attacked the anomeric carbon generated 2-*C*-branched hemiacetal **D**, which was further activated by $BiCl_3$ produced 2-*C*-branched pyran oxocarbenium ion **B**, and then formed the bicyclic oxocarbenium ion **INT1**. Lastly, **INT1** is trapped by the nucleophiles, affording the perhydrofuro[2,3-*b*]pyran derivatives. Theoretically, the nucleophiles can approach the cation from either the convex face or the concave face, which will lead to the formation of products in two different conformations. To disclose the origin of the selectivity, the transition states of trimethylsilyl attack from the convex face (TS-convex) and the concave face (TS-concave) were calculated. The results show that the TS-convex is 2.7 kcal mol^{-1} more favorable than the TS-concave, which are consistent with the experimental observations. In the TS-concave, hydrogen atom H_a on the trimethylsilyl nucleophile is very close to H_b on the six-membered ring (1.936 Å), which is shorter than the van der Waals distance between two hydrogen atoms (2.18 Å), indicating that there is steric repulsion. Therefore, it is more convenient for a nucleophile trapping the six-five fused ring oxocarbenium ion from the convex face to offer diastereomeric perhydrofuro[2,3-*b*]pyran derivatives. In order to further test our hypothesis, some parallel experiments were designed and the results have shown that this cascade reaction proceeded *via* a stepwise process.[15]

In conclusion, we have developed a cyclization reaction promoted by $BiCl_3$ using 1,2-cyclopropanated sugars as a new type of reagent. The cyclization is efficient and provides a method for highly diastereoselective synthesis of 2,2-di-substituted perhydrofuro[2,3-*b*]pyran (and furan) derivatives with good to excellent yields. Preliminary mechanistic studies indicated that the reaction proceeded *via* a stepwise process. Further investigations of the scope of this reaction are in progress.

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