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Rapid Assembly of Functionalized Hydrodibenzofurans via Semipinacol Rearrangements

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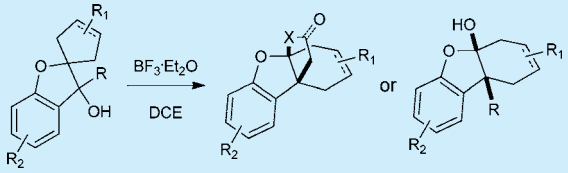
Supporting Information

ABSTRACT: A distinct strategy via unprecedented semipinacol rearrangements for the synthesis of functionalized hydrodibenzofurans is reported. The versatile reactivity of benzofuran-3-one as a building block enabled the convergent coupling of simple starting materials and, thus, allowed for the facile variation of R group and the construction of hydrodibenzofurans with fused rings.



Compound collections based on the scaffolds of bioactive natural products can be regarded as *biologically relevant* and *prevalidated* and thus serve as valuable starting points for medicinal chemistry and chemical biology research.[1] The rapid assembly of such compound collections would be of great importance and calls for the development of efficient and convergent strategies allowing for diverse structural variation, which is often not the major focus of target oriented complex natural product synthesis.

The hydrodibenzofuran nucleus (Figure 1) with a congested all-carbon quaternary stereogenic center represents the key structural feature of a diverse group of natural products,[2] including the galanthamine-type *Amaryllidaceae*, *Lunaria*, and *Opium alkaloids*. The intricate polycyclic structures and medicinal importance of these complex natural products have attracted significant attention from synthetic chemists since the early 1950s, leading to the discovery of a number of novel synthetic strategies.[3] While these approaches have tremendously facilitated the target oriented synthesis via linear synthetic routes, a convergent method that could allow for the diverse variation of the R group is rare (Figure 1). Moreover, while synthetic methods for the preparation of fused indolines based on the hydrocarbazole framework have been well established,[4] the construction of their oxygen analogues, the fused hydrodibenzofurans, such as that shown in the thebinan type natural product (Figure 1),[5] cannot be achieved by existing methods. Herein, we report a distinct strategy via semipinacol rearrangements for the synthesis of a diverse range of functionalized hydrodibenzofurans.

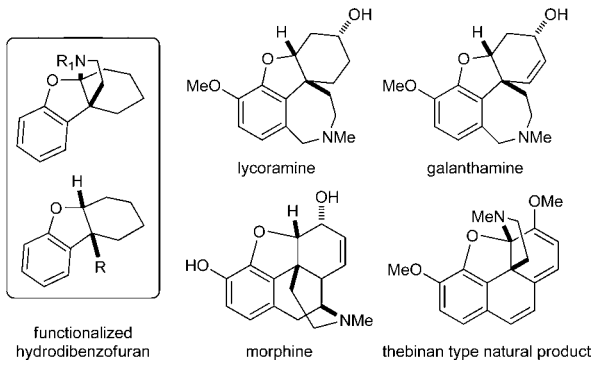
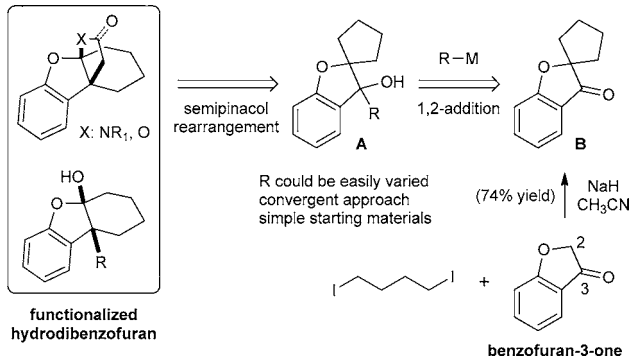


Figure 1. Representative natural products containing hydrodibenzofuran nucleus.

Our convergent synthetic strategy is depicted in Scheme 1. We conceived that the shown hydrodibenzofurans could be furnished by the semipinacol rearrangements[6] of the tertiary alcohol **A**, which in turn could be easily generated by the reaction of ketone **B** with a variety of readily available organometallic reagents via 1,2-addition. The synthesis of **B** can be achieved using benzofuran-3-one as a building block through simple double alkylation. Thus, the versatile reactivity

Scheme 1. Synthetic Strategy to Functionalized Hydodibenzofurans *via* Semipinacol Rearrangements



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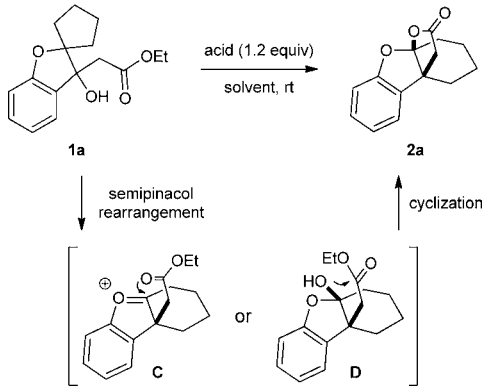
of benzofuran-3-one (nucleophilic C2 and electrophilic C3)[7] could be utilized for the efficient coupling of simple starting materials, enabling the diverse variation of the R group, which then could be transferred into the functionalized hydrodibenzofurans via semipinacol rearrangements. While Tu and co-workers have elegantly demonstrated the synthetic power of semipinacol rearrangements in the construction of hydrodibenzofurans,[8] our synthetic strategy employs totally different bond disconnections, allowing for the facile variation of the R group and the construction of hydrodibenzofurans with additional fused rings.

A model reaction of **1a** was carried out first to identify the optimized reaction conditions (Table 1). This single step

Table 1. Optimization of Reaction Conditions[a]



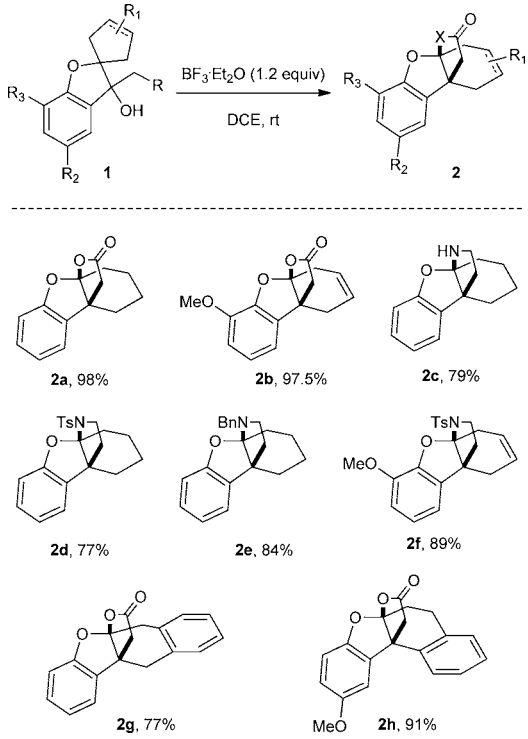
entry	acid	solvent	yield of **2a**[b]
1	TFA	DCM	0
2	$SnCl_4$	DCM	81
3	TMSOTf	DCM	93
4	$BF_3{\cdot}Et_2O$	DCM	96
5	$BF_3{\cdot}Et_2O$	toluene	74
6	$BF_3{\cdot}Et_2O$	CCl_4	95
7	$BF_3{\cdot}Et_2O$	DCE	98

[a]Reaction conditions: To a solution of **1a** (42.0 mg, 0.15 mmol) in the solvent (1.5 mL) was added the specified acid (1.2 equiv). The resulting mixture was stirred at rt for 12 h. [b]Isolated yield after silica gel chromatography.

transformation features a cascade reaction sequence involving semipinacol rearrangement followed by lactonization. Mechanistically either the oxonium **C** or hemiketal **D** could be a possible intermediate, leading to the formation of the hydrodibenzofuran with a fused lactone (**2a**). In the presence of Bronsted acids, such as TFA, alkene formation via dehydration was the major pathway. Gratifyingly, after several attempts, we found that Lewis acids were superior to Bronsted acids in promoting the desired transformation. Among the Lewis acids tested, $BF_3{\cdot}Et_2O$ was chosen due to the high yield of the reaction and operational simplicity. Further screening of different solvents led to the identification of the optimized reaction conditions: the reaction was carried out at rt in the presence of 1.2 equiv of $BF_3{\cdot}Et_2O$ using DCE as the reaction medium, producing **2a** in 98% yield.

Under the optimized reaction conditions, the substrate scope of the semipinacol rearrangements was next investigated. Substrates bearing a suitable R group that could interact with the oxonium or hemiketal intermediate to form additional fused rings were tested first (Scheme 2). When R is an ester, the hydrodibenzofurans with a fused lactone were

Scheme 2. Synthesis of Hydrodibenzofurans with Fused Rings



obtained with good to excellent yields (**2a**, **2b**, **2g**, **2h**). In addition, the hydrodibenzofurans with a fused pyrrolidine ring, the key structural feature of the thebinan type natural product, could be generated from tertiary alcohols containing the amine side chains (**2c**, **2d**, **2e**, **2f**). The protecting groups on nitrogen could be varied, providing more options for synthetic design. The substituents on the phenyl ring and decoration of the five-membered ring were also well tolerated, furnishing products with increased complexity. Importantly, alkene functionality could be introduced into the products, which could be used for further structural variation (**2b**, **2f**). **2h** was isolated as the major product, highlighting the excellent regioselectivity of the semipinacol rearrangement. It should be noted that the hydrodibenzofuran with a fused hydrofuran ring could not be produced with a substrate containing the alcohol side chain.

The semipinacol rearrangements with substrates without interacting side chains also proceeded very well, furnishing the functionalized hemiketals with good to excellent yields (Scheme 3). Aryl substitution patterns and electronic properties (both electron-donating and -withdrawing substituents) were well tolerated (**2i**–**2m**). A medicinally important motif, tetrazole, was successfully introduced into the product with a good yield (**2n**). When R was alkyl, no significant steric effect was observed (**2o**–**2r**). The reaction proceeded well with a substituent on the phenyl ring and decoration of the five-membered ring (**2s**–**2v**). Moreover, **2u** and **2v** were isolated as the major products, indicating that the semipinacol rearrangements were both diastereo- and regioselective. It should be noted that functional groups, such as alkene and ketal, were compatible with the reaction conditions, furnishing molecules with handles for further elaboration (**2s**, **2u**).

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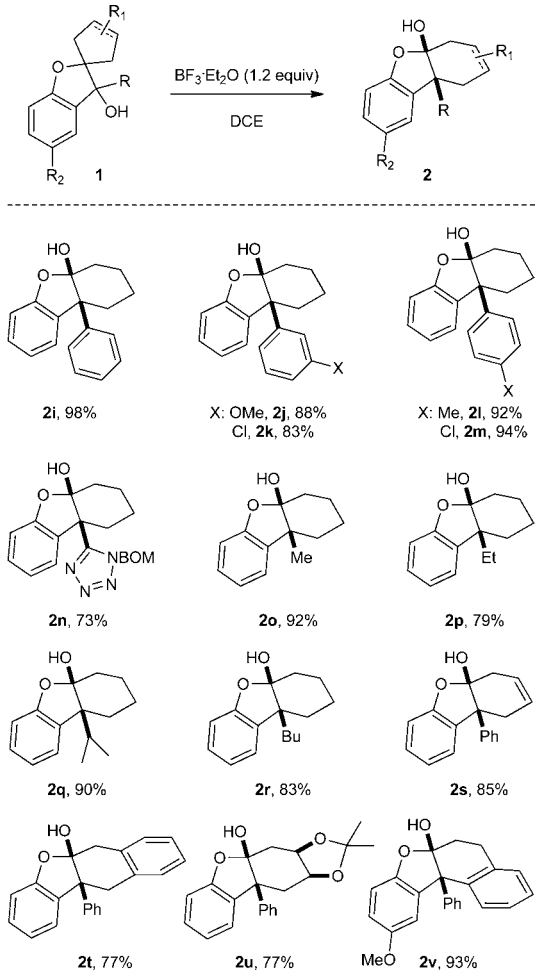
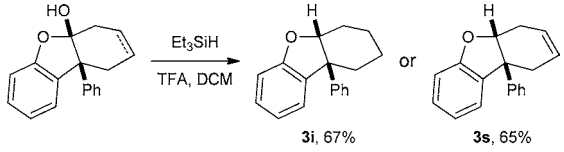
Scheme 3. Synthesis of Functionalized Hemiketals



The hemiketals formed by the semipinacol rearrangements not only served as possible reactive intermediates for the formation of fused hydrodibenzofurans, as demonstrated in Scheme 2, but also could be easily reduced to deliver functionalized hydrodibenzofurans (Scheme 4). For example,

Scheme 4. Reduction of the Hemiketals



3i and **3s** were prepared in good yields using Et_3SiH as the reducing reagent.[9] It should be noted that the alkene functionality remained untouched during the reduction.

In conclusion, we have developed a distinct strategy via unprecedented semipinacol rearrangements for the synthesis of functionalized hydrodibenzofurans. The versatile reactivity of benzofuran-3-one as a building block enabled the convergent coupling of simple starting materials and, thus, allowed for the facile structural variation of the products. Moreover, hydrodibenzofurans with additional fused rings, which have been challenging to access by existing approaches, were successfully constructed with high efficiency.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02202.

Detailed experimental procedures, characterization data, and copies of ^1H and ^{13}C spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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