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Graphical Abstract

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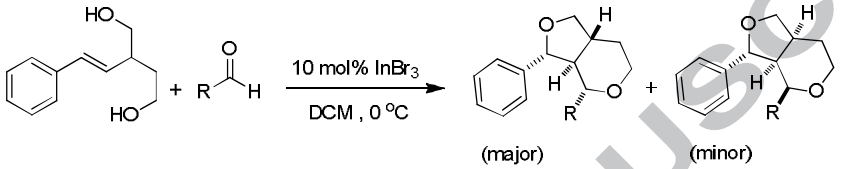

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$InBr_3$-catalyzed stereoselective synthesis of 3,4- disubstituted hexahydro-1*H*-furo[3,4-*c*]pyran derivatives

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ABSTRACT

An ϒ,δ-unsaturated alcohol tethered with a hydroxyl group, i.e. (*E*)-2-styrylbutane-1,4-diol (**1**) undergoes a smooth bicyclization with various aldehydes in the presence of 10 mol% $InBr_3$ and at 0 °C to afford a novel series of hexahydro-1*H*-furo[3,4-*c*]pyran derivatives in good yields with high diastereoselectivity.

Prins cyclization is one of the useful methods for the synthesis of a broad range of substituted tetrahydropyran derivatives (THP).[1,2] In particular, an intramolecular Prins cyclization is a versatile strategy for the stereoselective synthesis of fused heterocycles.[3] Recently, we reported an intramolecular version of Prins cyclization by trapping the carbenium ion with tethered nucleophiles like hydroxyl, *N*-tosylamide and aryl group to generate the corresponding heterobicycles.[4] To the best of our knowledge, there are no reports on the synthesis of 3,4-disubstituted hexahydro-1*H*-furo[3,4-*c*]pyrans from the easily accessible aldehydes and a hydroxyl tethered ϒ,δ-unsaturated alcohol. Furthermore, hexahydrofuropyran motif is a core structure of many natural products such as triFA1[5] and rubioncolin B.[6] Rubioncolin B belongs to a class of naphthohydroquinone family isolated from the roots of *Rubia oncotricha* and *R. cordifolia*[7a] and is used in the Chinese traditional medicine (Figure 1).[7b]

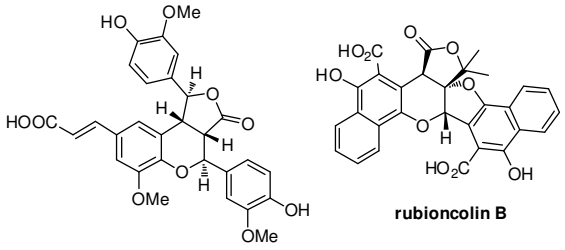

Figure 1. Biologically active furopyranone derivatives

In continuation of our research on Prins type cyclizations,[8] we herein report a novel Prins bicyclization for the stereoselective synthesis of *trans*-fused 3,4-disubstituted hexahydro-1*H*-furo[3,4-*c*]pyran derivatives. The starting material (**1**) was prepared from the allylic alcohol (**1a**) through a Johnson–Claisen rearrangement. Reduction of the ester (**1b**) with LAH, followed by silyl deprotection afforded the desired alcohol (**1**) in good yield (Scheme 1).

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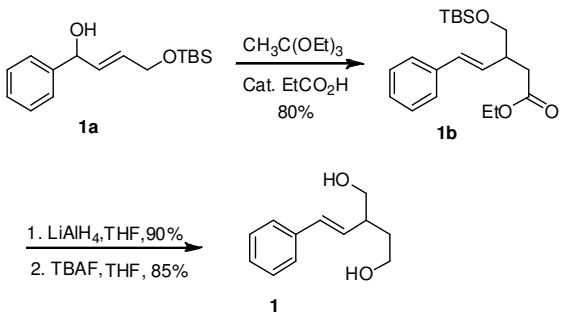
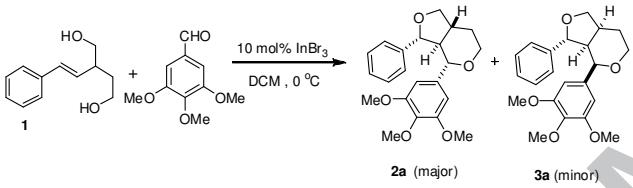


Scheme 1. Preparation of the starting material (**1**)

In a model reaction, we treated (*E*)-2-styrylbutane-1,4-diol (**1**) with 3,4,5-trimethoxybenzaldehyde in the presence of 10 mol $InBr_3$ in dichloromethane. The reaction proceeded smoothly at 0 °C affording the corresponding product **2a** in 90% yield with a high *trans*-selectivity (95:5, Scheme 2, entry b, Table 1). The ratio of *trans*/*cis*-isomers was determined by ^{1}H NMR spectrum of a crude mixture. The diastereomers could easily be separated by silica gel column chromatography.



Scheme 2. Synthesis of furo[3,4-*c*]pyran derivatives **2a/3a**

The structure and stereochemistry of 3-phenyl-4-(3,4,5-trimethoxyphenyl)hexahydro-1*H*-furo[3,4-*c*]pyran **2a** were established by X-ray crystallography (Figure 2).[9]

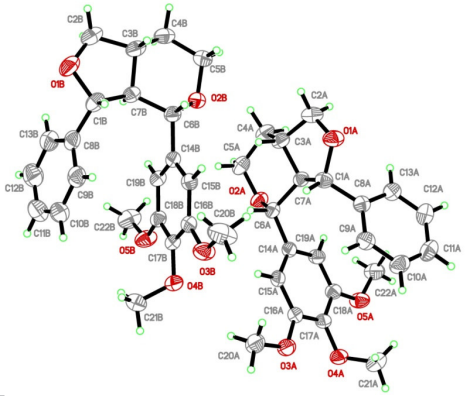


Figure 2. ORTEP diagram of product **2a**

The efficiency of various other Lewis and Brønsted acids was tested for this conversion, and the results are presented in Table 1. Of various acids tested, 10 mol% of $Sc(OTf)_3$ was found to be equally effective to $InBr_3$ for this conversion to furnish the product **2a** in 80% yield (entry c, Table 1). Furthermore, 10 mol% of $In(OTf)_3$ also afforded the product **2a** in 75% yield (entry a, Table 1). Other Lewis acids ($B(Ph)_3$, $Yb(OTf)_3$) and Brønsted acids (TsOH, CSA, benzoic acid) were found to be ineffective (Table 1).

Table 1. Screening of catalysts in the formation of **2a**[a]

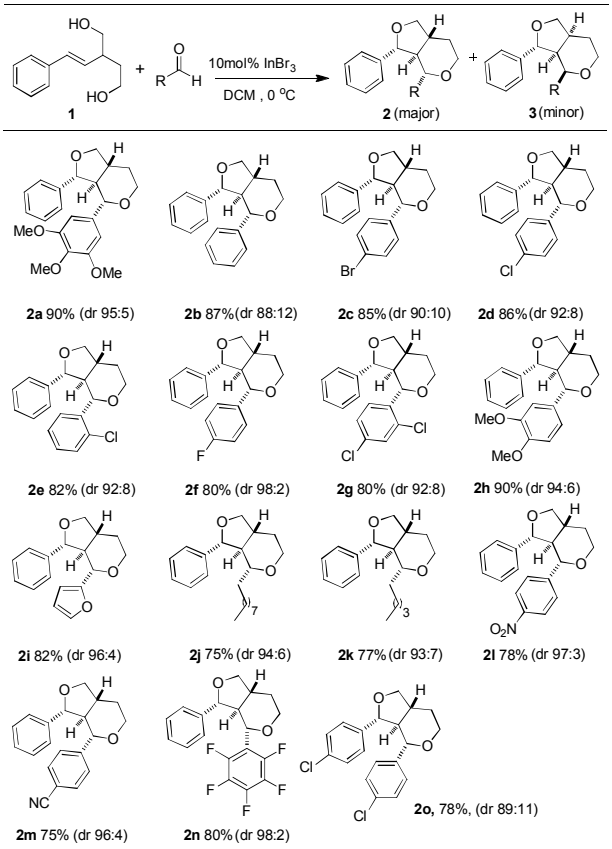
Entry	Catalyst	Mol%	Time (h)	Yield (%)[b]
a	$In(OTf)_3$	10	1	75
b	$InBr_3$	"	1	90
c	$Sc(OTf)_3$	"	1	80
d	$B(Ph)_3$	"	6	20
e	$Yb(OTf)_3$	"	4	30
f	$InCl_3$	"	4	55
g	TsOH	"	5	40
h	CSA	"	8	30
i	benzoic acid	"	8	10

[a]Reaction was performed at 0.5 mmol scale with respect to olefin. [b] Yield of *trans*- and *cis*-fused isomers (95:5) after column chromatography.

Next, we examined the effect of solvents such as toluene, benzene, dichloroethane, chloroform, acetonitrile, tetrahydrofuran and dichloromethane (Table 2, supporting information). Among them, dichloromethane gave the best results.

Inspired by the above results, we extended this method to other aromatic aldehydes such as 4-bromo-, 4-chloro-, 2-chloro-, 4-fluoro-, 2,4-dichloro-, 3,4-dimethoxy-, 4-nitro-, 4-cyano-, and 2,3,4,5,6-pentafluorobenzaldehydes. In all cases, the corresponding *trans*-fused furo[3,4-*c*]pyran derivatives were obtained in good to excellent yields with high selectivity (Table 3). This method works not only with aromatic aldehydes but also with aliphatic aldehydes. The efficacy of this approach was also tested by performing the reaction with heteroaromatic aldehyde like furan-2-carboxaldehyde (Table 3).

Table 3. Synthesis of 3,4-substituted hexahydro-1*H*-furo[3,4-*c*]pyran derivatives[a,b]



[a]Reaction was performed at 0.5 mmol scale with respect to olefin.[b]Combined yield of *trans*- and *cis*-fused products after column chromatography.

The structure and stereochemistry of a minor diastereomer, i.e. *cis*-fused hexahydro-1*H*-furo[3,4-*c*]pyran **3c** were confirmed by X-ray crystallography (Figure 3).[9]

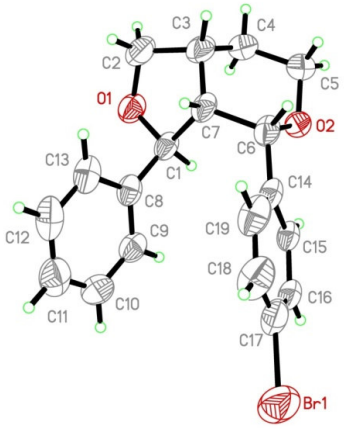


Figure 3. ORTEP diagram of product **3c**

The above results provided a gateway to extend this process to other substrates such as (*E*)-2-(4-chlorostyryl)butane-1,4-diol (**5**). Accordingly, the coupling of (*E*)-2-(4-chlorostyryl)butane-1,4-diol (**5**) with 4-chlorobenzaldehyde under similar conditions afforded the corresponding product as a mixture of **2o** and **3o** in 78% yield with 89:11 ratio Table 3). The structure and stereochemistry of a minor isomer **3o** were established by X-ray crystallography (Figure 4).[9]

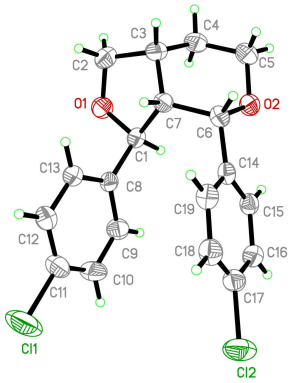
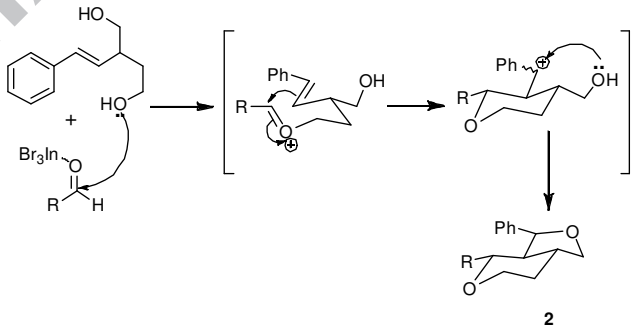


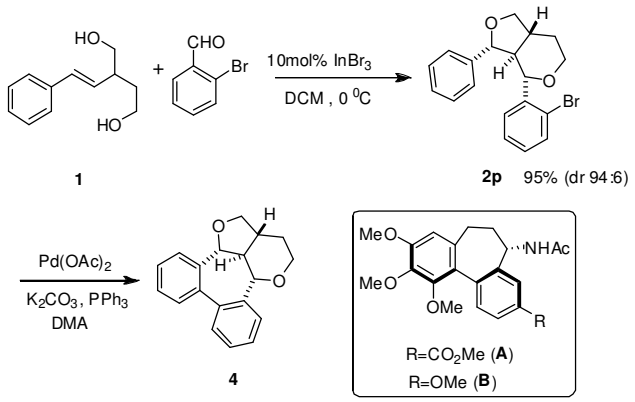
Figure 4. ORTEP diagram of product **3o**

The reaction is expected to proceed *via* the formation of an oxocarbenium ion which is formed *in situ* from the aldehyde and ϒ,δ-unsaturated alcohol, likely after activation with $InBr_3$. The *E*-oxocarbenium ion is trapped with an internal olefin resulting in the formation of benzylic carbocation, which is simultaneously trapped by a tethered hydroxyl group leading to the formation of furopyrans as depicted in Scheme 3.[10]



Scheme 3. A plausible reaction pathway

To demonstrate the synthetic utility, we applied this method to generate allocolchicine analogues. Accordingly, the product **2p** was transformed into polycyclic compound **4** *via* aryl-aryl bond formation[11] using $Pd(OAc)_2$ (10 mol%), triphenylphosphine (10 mol%) and K_2CO_3 (2 equiv) in DMA at 130 °C. The desired product **4** was obtained in 75% yield (Scheme 4). The 6-7-6 carbocyclic framework is a common structural core of allocolchicine (**A**) and *N*-acetyl colchinol-*O*-methyl ether (NCME) (**B**). The allocolchicines are seven-membered biaryl derivatives of naturally occurring colchicines, which are potent tubulin inhibitors.[12]



Scheme 4. Synthesis of seven-membered biaryl derivative **4**

In conclusion, a novel Prins bicyclization strategy has been developed for the synthesis of hexahydro-1*H*-furo[3,4-*c*]pyran derivatives. This is the first report on the synthesis of furopyrans *via* tandem Prins cyclization.[13] This approach generates two heterocyclic rings with four new stereogenic centers in a one pot operation.

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Supplementary data

Experimental details, characterization data, copies of ^{1}H and ^{13}C NMR spectrum of products can be found, in the online version, at http:// dx.doi.org/

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13. *General procedure:* To a stirred solution of ϒ,δ-unsaturated alcohol (**1**, 0.5 mmol) and aldehyde (0.6 mmol) in dry dichloromethane (5 mL) at 0 °C was added 10 mol% $InBr_3$. The resulting mixture was stirred at the same temperature under nitrogen atmosphere. After completion of the reaction as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ solution (1 mL) and extracted with dichloromethane (2x5 mL). The combined

organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography with ethyl acetate/hexane as eluent to afford the pure product (**2** and **3**).