$BF_3.OEt_2$-catalyzed synthesis of 1-(tetrahydropyran-3-yl)-1,3-dihydroisobenzofuran and *trans*-fused hexahydropyrano[3,2-*c*]chromene derivatives

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Graphical Abstract

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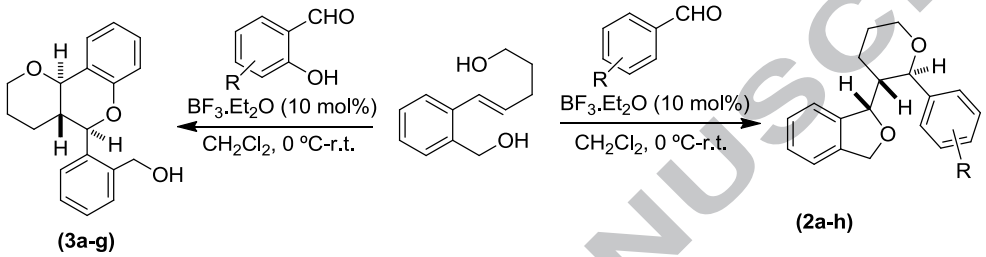

(3a-g) (2a-h)

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ABSTRACT

A novel intramolecular Prins cyclization of (*E*)-5-(2-(hydroxymethyl)phenyl)pent-4-en-1-ol with aldehydes has been achieved using 10 mol% $BF_3.Et_2O$ to produce the 1-(tetrahydropyran-3-yl)-1,3-dihydroisobenzofuran derivatives in good to excellent yields with high selectivity. Similar type of coupling with salicylaldehydes provides the *trans*-fused hexahydropyrano[3,2-*c*]chromene derivatives in excellent yields.

The *trans*-fused hexahydropyrano[3,2-*c*]pyran moiety is a core structure of blepharocalyxin D (Figure 1). It is a unique member of dimeric diarylheptanoid natural products isolated from the seeds of *Alpinia blepharocalyx* and is used in the Chinese traditional medicine for the treatment of stomach disorders.[1] It also acts as an antiproliferative agent (ED_{50} 3.61 mμ) against murine colon 26-L5 carcinoma cells.[2]

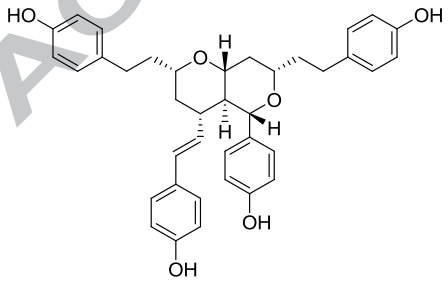

Figure 1. Structure of blepharocalyxin D

Prins cyclization is a simple method for the stereoselective synthesis of functionalized tetrahydropyran rings, which are core structural units of many natural products.[3,4] It has been successfully employed for the total synthesis of tetrahydropyran (THP)-containing polyether antibiotics and other complex natural products.[5,6] Recently, an intramolecular version of Prins cyclization has been developed through the trapping of carbenium ion with tethered nucleophiles like hydroxyl and aryl groups to afford the corresponding heterobicycles and tricycles respectively.[7,8] However, there are no reports on the synthesis of 1-(tetrahydropyran-3-yl)-1,3-dihydroisobenzofurans and *trans*-fused hexahydropyrano[3,2-*c*]chromenes through a Prins cascade process.

Following our interest on Prins type cyclizations,[9] we herein report an efficient approach for the stereoselective synthesis of fused tetrahydropyran derivatives namely, 1-(tetrahydropyran-3-yl)-1,3-dihydroisobenzofurans and *trans*-fused hexahydropyrano[3,2-*c*]chromenes by means of Prins bicyclization. As a preliminary experiment, we performed the

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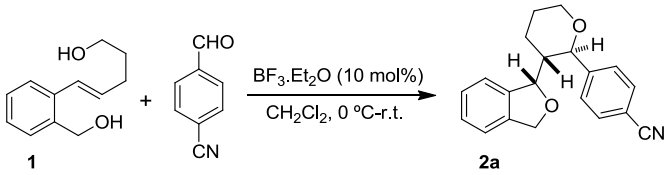
coupling of (*E*)-5-(2-(hydroxymethyl)phenyl)pent-4-en-1-ol with 4-cyanobenzaldehyde in the presence of 10 mol% $BF_3.Et_2O$ in dichloromethane. Interestingly, the reaction proceeded smoothly at room temperature affording the corresponding 1-(tetrahydropyran-3-yl)-1,3-dihydroisobenzofuran **2a** as a sole product in 80% yield (Scheme 1).



Scheme 1. Synthesis of 1-(te trahydropyran-3-yl)-1,3-dihydroiso-benzofuran **2a**

The structure and stereochemistry of **2a** were confirmed by X-ray crystallography (Figure 2).[10]

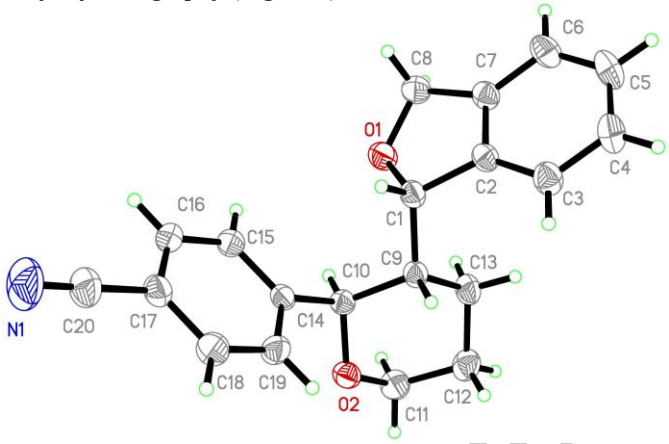


Figure 2. ORTEP diagram of **2a**

To evaluate the efficacy of the catalyst, various Lewis and Brønsted acids were screened for this conversion and the results are summarized in Table 1. Among them, 10 mol% $BF_3.Et_2O$ was found to be most effective to furnish the product **2a** (entry c, Table 1). Other Lewis acids like $InCl_3$, $ZnCl_2$, $In(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$) and Brønsted acids such as TsOH, CSA, benzoic acid) were found to be ineffective for this reaction. Next, we examined the effect of solvents such as dichloromethane, acetonitrile and tetrahydrofuran. Of these, dichloromethane gave the best results.

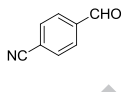
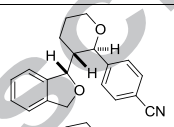
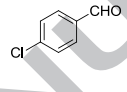
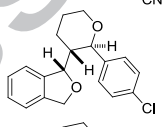
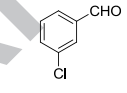
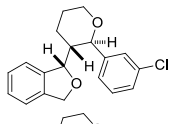
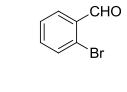
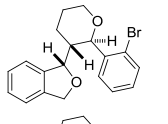
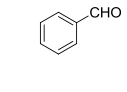
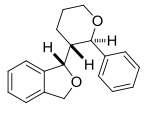
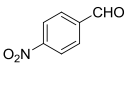
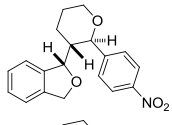
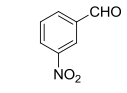
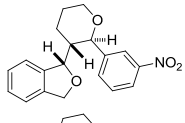
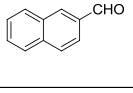
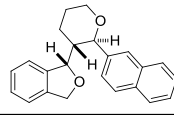
Table 1. Catalyst Optimization in the formation of **2a**[a]

Entry	Catalyst	Time (h)	Yield (%)[b]
a	$InCl_3$	4	70
b	$ZnCl_2$	4	52
c	$BF_3.Et_2O$	3	80
d	$Sc(OTf)_3$	3	75
e	$In(OTf)_3$	4	48
f	$Yb(OTf)_3$	6	45
g	TsOH	6	35
h	CSA	6	38
i	Benzoic acid	6	30

[a]Reaction was performed at 0.5 mmol scale with respect to aldehyde
[b]Isolated yield

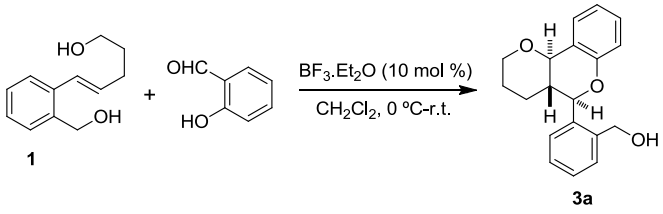
After optimizing the reaction conditions, we extended this process to other aldehydes and the results are summarized in Table 2. The substituents present on aromatic ring had shown some effect on the conversion. It was observed that aromatic aldehydes bearing strong electron-withdrawing substituents such as cyano- and nitro- groups (entries a, f and g, Table 2) gave the products in slightly lower yields than halogenated aromatic counterparts (entries b, c and d, Table 2). Remarkably, a sterically hindered 2-naphthaldehyde also afforded the desired product in good yield (entry h, Table 2).

Table 2. Synthesis of 1-(tetrahydropyran-3-yl)-1,3-dihydroiso-benzofurans[a]

Entry	Aldehyde	Product (2)	Time (h)	Yield (%)
a			3	80
b			4	85
c			4	83
d			4	87
e			3	82
f			4	78
g			4	77
h			3	85

[a]Reaction was performed at 0.5 mmol scale with respect to aldehyde
[b]Isolated yield

The above results provided a gateway to extend this process to various salicylaldehydes. Accordingly, treatment of (*E*)-5-(2-(hydroxymethyl)phenyl)pent-4-en-1-ol (**1**) with salicylaldehyde under similar conditions gave the *trans*-fused hexahydropyrano[3,2-*c*]chromene **3a** in 82% yield (Scheme 2).



Scheme 2. Synthesis of *trans*-fused hexahydropyrano-[3,2-*c*]chromene derivatives

The relative stereochemistry of **3a** was confirmed by extensive NMR experiments including 2D double quantum

filtered correlation spectroscopy (DQFCOSY) and nuclear Overhauser effect spectroscopy (NOESY). The assignments were made with the help of DQFCOSY and NOESY experiments (Figure. 3). The large coupling constants between H5-H6 (δ 4.44 ppm, $^{3}J_{H5\text{-}H6}$ = 9.9 Hz), H5-H10 (δ 5.74 ppm, $^{3}J_{H5\text{-}H10}$ = 10.8 Hz) along with the presence of NOE cross peaks between H6/H10, H5/H(*ortho*-Ph) suggest that H5, H6 and H10 are relatively in *trans* orientation to each other as represented in Figure 3.

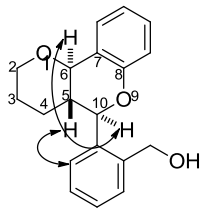
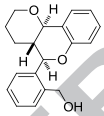
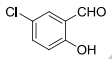
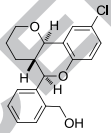
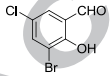
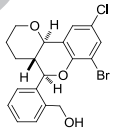
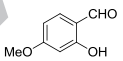
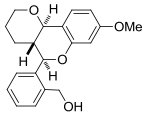
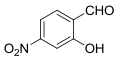
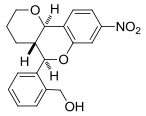
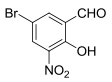
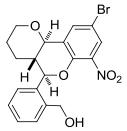
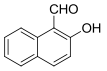
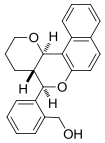


Figure 3. Characteristic NOE cross correlations of **3a**

Encouraged by the above results, we extendend our efforts to study the effect of various salicyladehydes containing different electron withdrawing and donating substituents. As shown in Table 3, the corresponding *trans*-fused hexahydropyrano[3,2-*c*]chromene derivatives were obtained in good to excellent yields. The substituents present on the aromatic ring had shown some effect on the conversion. It was observed that both activated (entry d, Table 3) and deactivated salicylaldehydes (entry e, Table 3) gave the products in slightly lower yields than halogenated aromatic counterparts (entries b and c, Table 3).

Table 3. Synthesis of hexahydropyrano[3,2-*c*]chromenes[a]

Entry	Aldehyde	Product (3)	Time (min)	Yield (%)[b]
a			15	82
b			20	85
c			20	84
d			15	80
e			20	78
f			20	79
g			15	86

[a]Reaction was performed at 0.5 mmol scale with respect to aldehyde
[b]Isolated yield

As depicted in Table 3, 2-hydroxy-1-naphthaldehyde (entry g, Table 3) gave higher yields than simple salicylaldehyde (entry a, Table 3).

This method provides a variety of 1-(tetrahydropyran-3-yl)-1,3-dihydroisobenzofuran and hexahydropyrano[3,2-*c*]chromene derivatives in good yields with excellent diastereoselectivity. The high stereoselectivity is achieved by the trapping of a more stable benzylic carbocation with a tethered hydroxyl group approaching from the less sterically hindered equatorial side of the more stable chair conformation. Furthermore, intramolecular cyclizations are highly favorable and faster than the intermolecular reactions. All the products were characterized and confirmed by NMR, IR and mass spectrometry.[11]

In conclusion, we have demonstrated an intramolecular version of Prins cyclization for the stereoselective synthesis of 1-(tetrahydropyran-3-yl)-1,3-dihydroisobenzofuran and *trans*-fused hexahydropyrano[3,2-*c*]chromene derivatives under mild conditions. This approach generates two heterocyclic rings with three new stereogenic centers in a one-pot operation.

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Supplementary data

Supplementary data (compound characterization) associated with this article can be found, in the online version, at http://dx.doi.

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10. CCDC-992340 contains supplementary crystallographic data for compound **2a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
11. **Typical procedure for the intramolecular Prins cyclization:** To a stirred solution of homoallylic diol (**1**, 0.50 mmol) and aldehyde (0.60 mmol) or salicylaldehyde (0.60 mmol) in dry 1,2-dichloromethane (5 mL) was added $BF_3.Et_2O$ (0.05 mmol). The resulting mixture was stirred at room temperature under nitrogen atmosphere for the specified time (Table 2 or Table 3). After completion of the reaction, as indicated by TLC, the mixture was quenched with saturated aqueous $NaHCO_3$ solution (0.5 mL) and extracted with dichloromethane (2x10 mL). The organic phases were combined, washed with brine (3x2 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (60-120 mesh) using ethyl acetate/hexane as eluent to afford pure product 2 or 3 (Table 2 or Table 3).