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Diastereoselective synthesis of 1-(tetrahydrofuran-3-yl)-1,3-dihydroisobenzofuran derivatives via Prins bicyclization

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ABSTRACT

The homoallylic alcohol tethered with a benzylic hydroxyl group, that is, (*E*)-4-(2-(hydroxymethyl)-phenyl)but-3-en-1-ol undergoes smooth Prins bicyclization with various aldehydes in the presence of 20 mol % $Sc(OTf)_3$ and 4 Å MS at 80 °C to afford a novel series of 1-(tetrahydrofuran-3-yl)-1,3-dihydroisobenzofuran derivatives in good yields with high diastereoselectivity.

The five-membered oxygen containing heterocycles are often present in many natural products such as lignans, polyether ionophores, and macrodiolides.[1] These molecules are known to exhibit various biological activities such as antitumor, antimalarial, and antimicrobial behavior.[2] In particular, 1,3-dihydroisobenzofuran core is found in naturally occurring molecules such as flavimycins **A** and **B**.[3] The flavimycins **A** and **B** (Fig. 1) are novel dimeric 1,3-dihydroisobenzofurans isolated, as inhibitors of peptide deformylase, from cultures of *Aspergillus flavipes*. These compounds are found to inhibit the staphylococcus aureus peptide deformylase with IC_{50} values of 35.8 and 100.1 μM, respectively.

Prins cyclization has emerged as a powerful strategy for the synthesis of a wide range of substituted tetrahydropyran derivatives and related compounds.[4,5] In addition to this, bicyclic tetrahydropyran derivatives are reported using Prins bicyclization strategy.[6] However, the formation of the tetrahydrofuran ring is unusual under Prins cyclization.[7] In a few cases, the tetrahydrofuran ring is formed through the five-membered oxocarbenium ion that can be trapped by a nucleophile.[8] To the best of our knowledge, there are no reports on the synthesis of tetrahydrofuranyl substituted 1,3-dihydroisobenzofurans via Prins bicyclization.

Following our interest on Prins cyclization,[9] we herein report a novel strategy for the synthesis of 1-(tetrahydrofuran-3-yl)-1,3-dihydroisobenzofuran derivatives by means of Prins bicyclization.

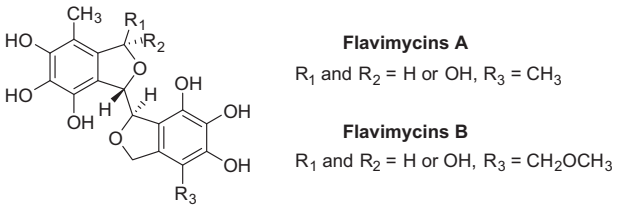

Figure 1. Naturally occuring flavimycins **A** and **B**.

Accordingly, we first attempted the Prins cyclization of (*E*)-4-(2-(hydroxymethyl)phenyl)but-3-en-1-ol (**1**) with 2,5-dimethoxybenzaldehyde (**2a**) using 20 mol % $Sc(OTf)_3$ in the presence of 4 Å MS in 1,2-dichloroethane. The reaction was found to be very sluggish at room temperature. But by increasing the temperature from 25 to 80 °C, the corresponding product, 1-(tetrahydrofuran-3-yl)-1,3-dihydroisobenzofuran **3a** was obtained in 78% yield as a major diastereomer (Scheme 1, Table 1, entry a). The diastereomeric ratio (95:5) was determined on the basis of ^1H NMR spectrum of a crude product. The two diastereomers could easily be separated by silica gel column chromatography.

The stereochemistry of **3a** was assigned by extensive NMR experiments including 2-D nuclear overhauser effect spectroscopy (NOESY) and double quantum filtered correlation spectroscopy (DQFCOSY). The assignments were made with a help of DQFCOSY

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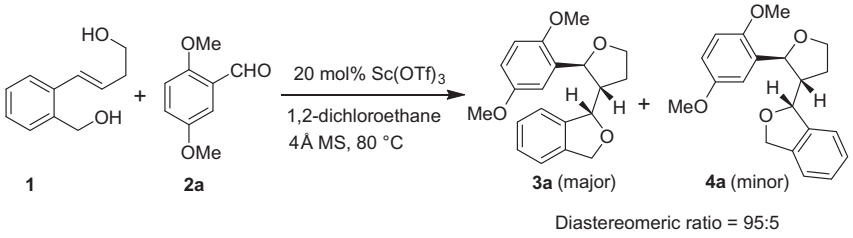
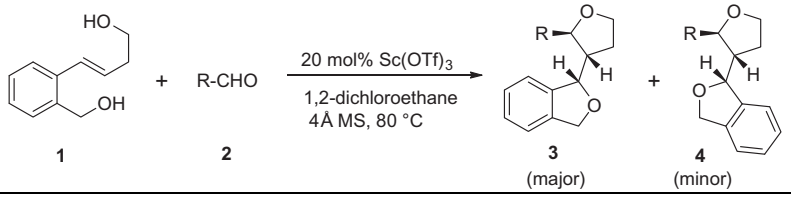


Scheme 1. Reaction of 4-(2-(hydroxymethyl)phenyl) but-3-en-1-ol with 2,5-dimethoxybenzaldehyde.

Table 1
$Sc(OTf)_3$-catalyzed preparation of 1-(tetrahydrofuran-3-yl)-1,3-dihydroisobenzofurans[a]



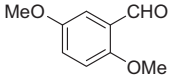
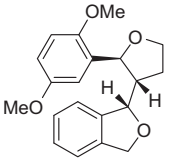
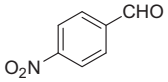
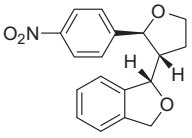
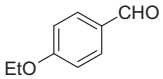
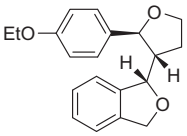
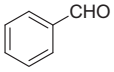
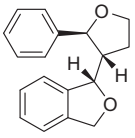
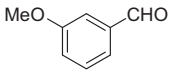
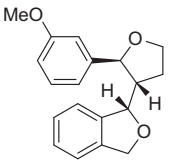
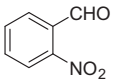
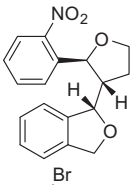
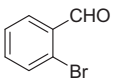
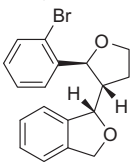
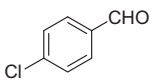
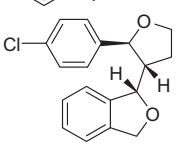
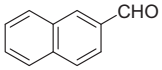
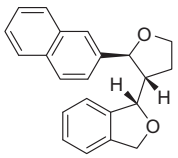
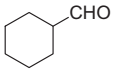
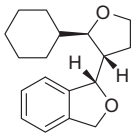
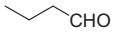
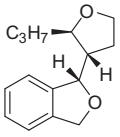
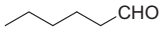
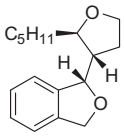
Entry	Aldehyde (**2**)	Product (**3**)[b]	Time (h)	Yield[c] (%)	Diastereomeric ratio
a			9	78	95:5
b			10	56	70:30
c			9	68	90:10
d			8	68	85:15
e			10	62	80:20
f			10	59	75:25
g			8	55	78:22
h			8	70	85:15

Table 1 (*continued*)

Entry	Aldehyde (**2**)	Product (**3**)[b]	Time (h)	Yield[c] (%)	Diastereomeric ratio
i			7	72	90:10
j			6	74[d]	68:32
k			5	70[d]	70:30
l			6	75[d]	75:25

[a] Reaction was performed with 0.5 mmol olefin, 0.55 mol % aldehyde and 20 mol% $Sc(OTf)_3$.
[b] All the products were characterized by ^1H and ^{13}C NMR, IR, and mass spectroscopy.
[c] Yield refers to pure single diastereomers after column chromatography.
[d] Combined yield of two diastereomers which were inseparable on column chromatography.

experiment in which doublet was assigned to H1 proton at δ 5.36 with J_{H1-H2} = 6.2 Hz. The coupling constant J_{H2-H5} = 2.0 Hz corresponds to dihedral angle H2–C2–C5–H5 ≈ 58° (but in compound **3a** it is found to be 49°) also indicating the cis orientation of H2 and H5 protons. The following nOe correlations H1/H5, H1/H4′, H2/H11, H3′/H6′, H5/H10, H6/H7, and H4/H11 support the proposed structure. All the couplings and nOes are in good agreement with the proposed structure as shown in Figure 2. The double-edged arrows show characteristic nOe correlations of **3a**.[10]

Likewise, the coupling of 4-nitrobenzaldehyde (**2b**) with a homoallylic alcohol (**1**) under similar reaction conditions afforded the diastereomeric products **3b** (major, 56% yield) and **4b** (minor, 24% yield) (Table 1, entry b). These diastereomers could easily be separated by silica gel column chromatography. The stereochemistry of **3b** and **4b** was also characterized by extensive NMR experiments like **3a**. In the case of compound **3b**, J_{H2-H5} = 2.5 Hz corresponds to dihedral angle H2–C2–C5–H5 ≈ 55° (but in com-

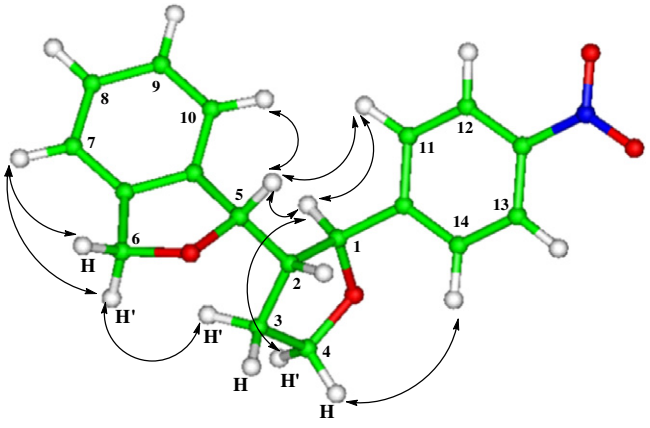


Figure 3. Characteristic nOes and energy minimized structure of **3b**.

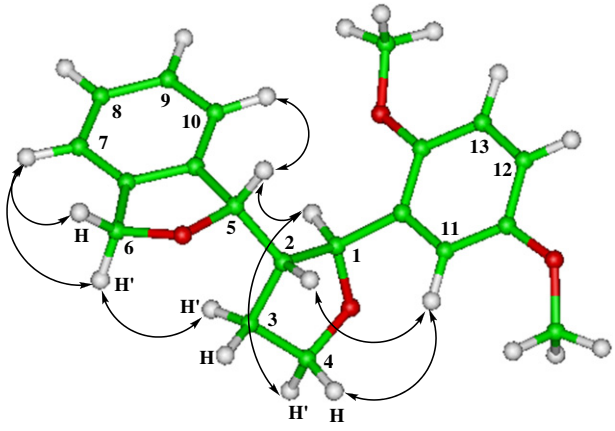


Figure 2. Characteristic nOes and energy minimized structure of **3a**.

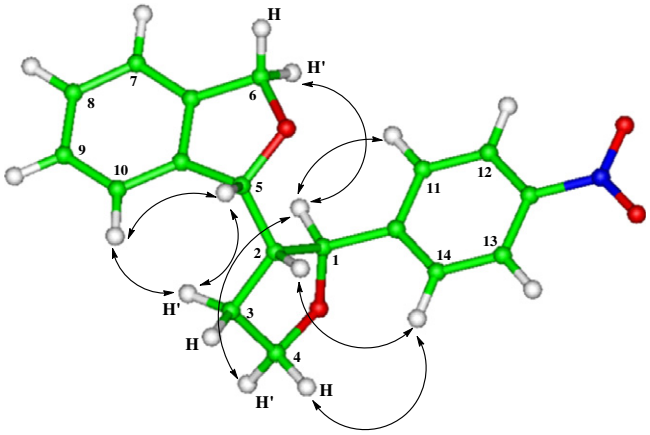
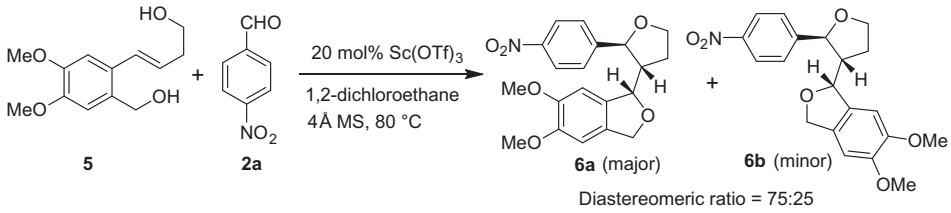
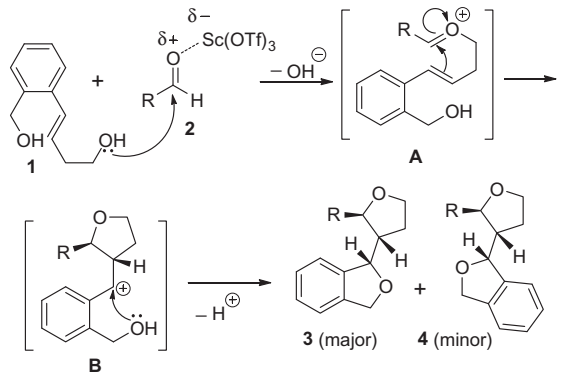


Figure 4. Characteristic nOes and energy minimized structure of product **4b**.



Scheme 2. Reaction of (*E*)-4-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)but-3-en-1-ol with 4-nitrobenzaldehyde.



Scheme 3. A plausible reaction pathway.

pound **3b** it is found to be 44°) also indicating the cis orientation of H2 and H5 protons. The following nOe correlations H1/H5, H1/H11, H1/H4′, H5/H11, H5/H10, H3′/H6′, H4/H14, and H6/H7 support the proposed structure. All the couplings and nOes are perfectly matching with the structure as shown in Figure 3.[10]

For compound **4b**, the presence of a strong nOe correlation between H1/H6′ and H3′/H10 suggests that C2–C5 bond is constrained. The energy minimized structure shown in the Figure 4 is well supported by H5/H3′, H5/H10, H1/H11, H1/H4′, H4/H14, and H2/H14 nOe correlations. The value of 30° for the dihedral angle H2–C2–C5–H5 corresponds to $^{3}J_{H2-H5}$ = 5.2 Hz (using Karplus relations), which is similar to the experimental value of 5.2 Hz. Compound **4b** differs from compound **3b** by configuration change at the C5 carbon. The double-edged arrows show characteristic nOe correlations of **4b** (Fig. 4).[10]

The scope of the reaction is illustrated with other aromatic aldehydes and the results are summarized in Table 1.[11] Interestingly, several aromatic aldehydes such as 4-ethoxybenzaldehyde, benzaldehyde, 3-methoxybenzaldehyde, 2-nitrobenzaldehyde, 2-bromobenzaldehyde, and 4-chlorobenzaldehyde underwent a smooth Prins bicyclization with a homoallylic alcohol (**1**) to furnish the respective 1-(tetrahydrofuran-3-yl)-1,3-dihydroisobenzofuran derivatives (Table 1, entries c–i) in moderate to good yields. The reaction was successful with both electron-deficient and electron-rich aromatic aldehydes. Interestingly, aliphatic aldehydes such as cyclohexanecarboxaldehyde, *n*-butanal, and *n*-hexanal gave the corresponding alkyl substituted 1-(tetrahydrofuran-3-yl)-1,3-dihydroisobenzofuran derivatives in good yields (Table 1, entries j–l). Therefore, the present method works not only with aromatic aldehydes but also with aliphatic aldehydes. In all cases, the product was formed as a mixture of two diastereomers. In the case of aliphatic aldehydes, the diastereomers were inseparable by silica gel column chromatography.

Next attempt was made to study the effect of substituent on the aromatic ring of homoallylic diol. Thus treatment of (*E*)-4-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)but-3-en-1-ol (**5**) with 4-nitrobenzaldehyde under similar reaction conditions gave the diastereomeric products **6a** (major, 45% yield) and **6b** (minor, 15% yield) as depicted in Scheme 2. The diastereomers could easily be separated by silica gel column chromatography.

All the products were characterized and confirmed by NMR, IR, and mass spectrometry. The effect of various acid catalysts such as TsOH, $In(OTf)_3$, and $Sc(OTf)_3$ was studied for this conversion. Among them, $Sc(OTf)_3$ was found to give the best results in terms of yields. As solvent, 1,2-dichloroethane gave the best results.

The reaction was assumed to proceed via the formation of oxocarbenium ion **A** generated from hemi-acetal which is in turn formed by the reaction of homoallylic alcohol **1** with aldehyde **2** likely after activation through Sc(III). This is followed by the attack of an internal olefin resulting in the formation of more stable benzylic carbocation **B** which is simultaneously trapped by a tethered hydroxyl group, leading to the formation of 1-(tetrahydrofuran-3-yl)-1,3-dihydroisobenzofuran **3**. The intermediate **B** has more flexibility in terms of C–C bond rotation therefore which can result in the formation of **3** and **4**. In contrast, a thermodynamically more stable diastereomer **3** can form predominantly (Scheme 3).

In summary, we have developed a novel strategy for the synthesis of 1-(tetrahydrofuran-3-yl)-1,3-dihydroisobenzofuran derivatives by means of $Sc(OTf)_3$ catalyzed Prins bicyclization. The end products are structural analogues of flavimycins **A** and **B** and hence can be evaluated for biological activity.

Acknowledgements

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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.org/10.1016/j.tetlet.2013.01.006.

References and notes

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10. The energy-minimization of the structures was done with steepest descent followed by conjugate gradient methods in Insight II/Discover program employing an SGI workstation.
11. *General experimental procedure*: To a stirred solution of (*E*)-4-(2-(hydroxymethyl)phenyl)but-3-en-1-ol (**1**) (89 mg, 0.5 mmol), 2,5-dimethoxy benzaldehyde (**2a**) (91 mg, 0.55 mmol) and 4 Å MS in anhydrous 1,2-dichloroethane (5 mL) was added $Sc(OTf)_3$ (20 mol %) under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 7 h. After completion of the reaction as indicated by TLC, the mixture was quenched with sat. aqueous $NaHCO_3$ solution (2 mL) and then extracted with dichloro methane (2x10 mL). The organic extracts were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by column chromatography (silica gel, 100–200 mesh) using a gradient mixture of ethyl acetate/hexane to afford the pure product **3a** (126 mg, 78%). Spectral data for selected compounds.
(S)-1-((2S*,3R*)-2-(2,5-Dimethoxyphenyl)tetrahydrofuran-3-yl)-1,3-dihydroisobenzofuran (***3a**;Table 1 *entry a)*: Yield, 78%; Viscous liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28–7.21 (m, 3H), 7.13–7.10 (m, 1H), 7.07 (d, J = 3.2 Hz, 1H), 6.82 (d, J = 8.9 Hz, 1H), 6.78 (dd, J = 8.9 and 3.2 Hz, 1H), 5.57–5.54 (m, 1H), 5.36 (d, J = 6.2 Hz, 1H), 5.21–5.13 (m, 2H), 4.11–4.07 (m, 1H), 4.03–3.98 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.62–2.57 (m, 1H), 1.78–1.68 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 153.8, 150.9, 141.2, 139.6, 132.9, 127.5, 127.3, 121.3, 121.0, 112.7, 112.5, 111.5, 83.6, 78.1, 73.4, 68.9, 55.9, 55.8, 52.8, 26.5; IR (neat): ν_{max} 2926, 2858, 1497, 1271, 1049, 755 cm^{-1}; MS (ESI): m/z 349 $(M+Na)^+$. HRMS (ESI) calcd for $C_{20}H_{22}O_4Na$: 349.1416 $(M+H)^+$, found 349.1425.