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Novel protocol for the synthesis of octahydropyrano- and thiopyrano[4,3-*a*]carbazole derivatives via Prins/Friedel–Crafts cyclization

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ABSTRACT

A novel Prins/Friedel–Crafts cyclization of (*Z*)-6-(1-methyl-1*H*-indol-3-yl)hex-3-en-1-ol with aldehydes has been achieved using a catalytic amount of $BF_3{\cdot}OEt_2$ under mild reaction conditions to produce the corresponding octahydropyrano[4,3-*a*]carbazole derivatives in good yields with high diastereoselectivity. The cross-coupling of (*Z*)-6-(1-methyl-1*H*-indol-3-yl)hex-3-ene-1-thiol with aldehydes affords the corresponding octahydrothiopyrano[4,3-*a*]carbazole derivatives under similar conditions.

The carbazole core is often found in various natural products.[1] In particular, pyranocarbazole alkaloids are very attractive due to their fascinating structural features and potential biological activity.[2] Furthermore, pyranocarbazole core is present in several alkaloids such as heptazolicine, euchrestifoline, *cis*-dihydroxygirinimbine, clausine-T, and many others (Fig. 1).[3] Some of these alkaloids are known to exhibit antidiarrheal and antitumor activities.[4,5]

In recent years, the Prins cyclization has received special attention because of its versatility for the construction of tetrahydropyran scaffolds.[6] In particular, intramolecular version of Prins cyclization is very useful for the stereoselective construction of fused heterobicycles and tricycles.[7,8] Inspired by inherent biological properties of carbazoles, we were interested to develop a novel strategy for the synthesis of octahydropyrano- and thiopyrano[4,3-*a*]carbazole derivatives. However, to the best of our knowledge, there have been no reports on the preparation of thiopyrano[4,3-*a*]carbazole derivatives via a tandem Prins/Friedel–Crafts cyclization.

In continuation of our research findings on Prins cyclization,[9] we herein report a novel strategy for the synthesis of octahydropyrano- and thiopyrano[4,3-*a*]carbazole derivatives via Prins- and thia-Prins/Friedel–Crafts cyclization, respectively. Accordingly, we first attempted the cross-coupling of (*Z*)-6-(1-methyl-1*H*-indol-3-yl)hex-3-en-1-ol (**1**) with benzaldehyde (**2**) using $BF_3{\cdot}OEt_2$ in dichloromethane. The reaction went to completion within 10 min at room temperature and the desired product, 4-phenyl-octahydropyrano[4,3-*a*]carbazole **3a** was isolated in 87% yield with *cis*-selectivity (Scheme 1).

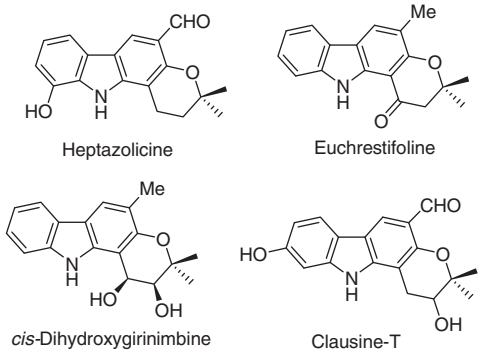

Figure 1. Naturally occurring pyrano[3,2-*a*]carbazole alkaloids.

The *cis*-stereochemistry of **3a** was established by ^1H NMR experiments. The coupling between Ha–Hb (J_{Ha-Hb} = 1.9 Hz) and Hb–Hc (J_{Hb-Hc} = 4.5 Hz) indicates that Ha, Hb, and Hc are in *cis*-orientation. This is further confirmed by the presence of nOe cross peaks between Ha–Hb, Hb–Hc, and Ha–Hc as depicted in Figure 2.

The geometry of the olefin controls the stereoselectivity of the reaction. It is known that *cis*-olefin gives the *cis*-fused product exclusively whereas the *trans*-olefin provides the *trans*-fused product predominantly.[8d] Unlike, classical Prins cyclization, no formation of 4-fluoro- or 4-hydroxytetrahydropyrans was observed in

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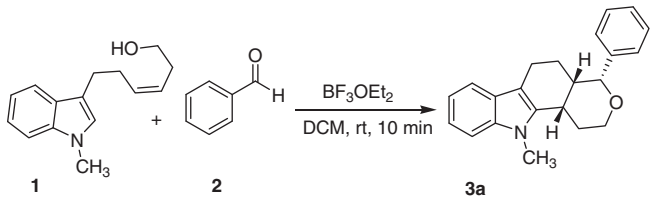


Scheme 1. Reaction of (*Z*)-6-(1-methyl-1*H*-indol-3-yl)hex-3-en-1-ol with benzaldehyde.

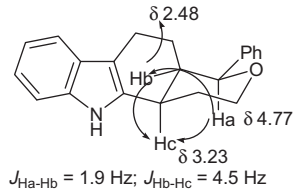
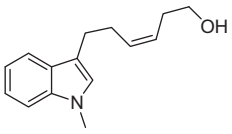
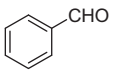
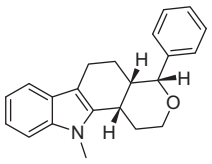
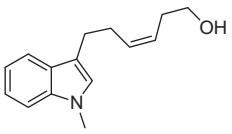
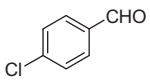
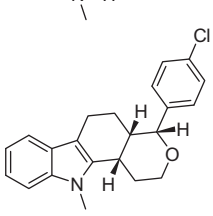
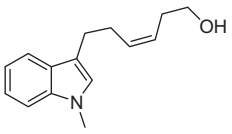
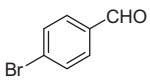
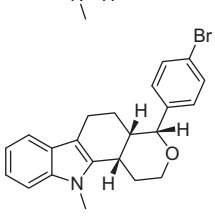
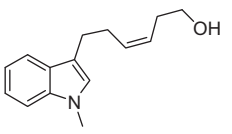
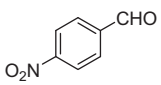
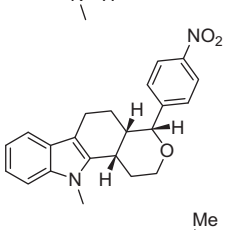
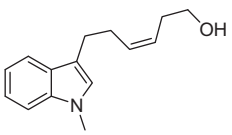
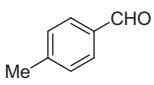
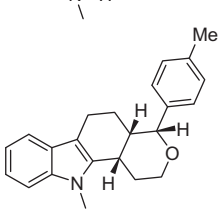
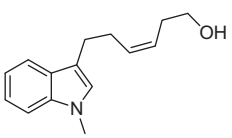
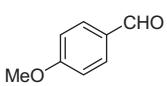
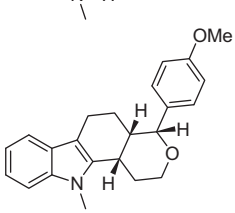


Figure 2. Characteristic nOes of **3a**.

this reaction. Inspired by the above results, we extended this process for other substituted aldehydes. The scope of the reaction is illustrated with respect to various aldehydes and the results are summarized in Table 1. The cross-coupling of (*Z*)-6-(1-methyl-1*H*-indol-3-yl)hex-3-en-1-ol (**1**) with *p*-bromobenzaldehyde under the above conditions gave the corresponding *cis*-fused octahydropyrano[4,3-*a*]carbazole (**3c**) in 83% yield (Table 1, entry c). The structure of **3c** was confirmed by X-ray crystallography (Fig. 3).[10]

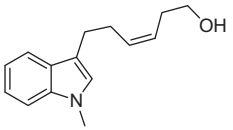
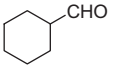
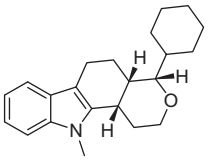
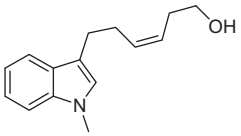
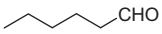
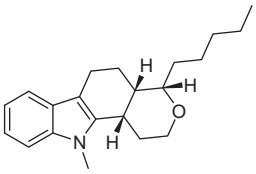
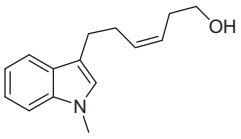
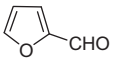
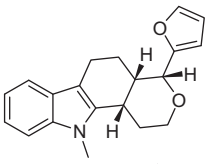
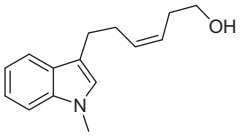
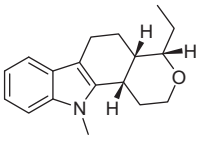
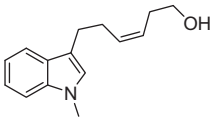
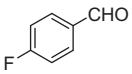
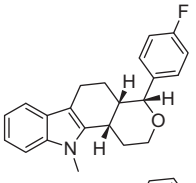
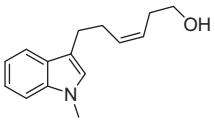
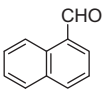
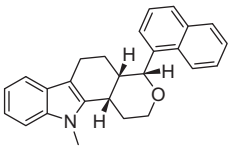
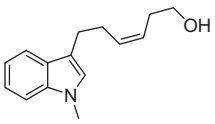
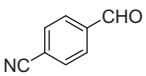
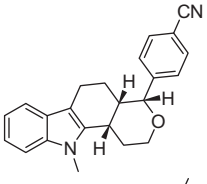
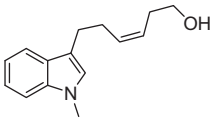
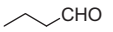
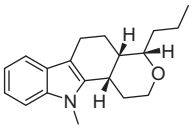
Various substituted aromatic aldehydes such as *p*-chloro-, *p*-nitro-, *p*-methyl-, *p*-methoxy-, *p*-fluoro-, and *p*-cyano-benzaldehydes participated well in this reaction. As seen from Table 1, both electron-rich and electron-deficient aldehydes gave the desired products in good yields (Table 1). Furthermore, acid sensitive furan-2-carboxaldehyde also underwent a smooth coupling with (*Z*)-6-(1-methyl-1*H*-indol-3-yl)hex-3-en-1-ol (**1**) to give the corresponding *cis*-4-furanyl-octahydropyrano[4,3-*a*]carbazole in 85% yield (Table 1, entry i). Notably, a sterically hindered α-naphthaldehyde also gave the product **3l** in excellent yield (Table 1,

Table 1
$BF_3{\cdot}OEt_2$ catalyzed tandem Prins/Friedel–Crafts cyclization

Entry	Alcohol (**1**)	Aldehyde (**2**)	Product (**3**)[a]	Time (min)	Yield[b] (%)
a				10	87
b				10	85
c				15	83
d				20	85
e				10	90
f				10	87

(*continued on next page*)

Table 1 (*continued*)

Entry	Alcohol (**1**)	Aldehyde (**2**)	Product (**3**)[a]	Time (min)	Yield[b] (%)
g				10	90
h				10	87
i				10	85
j				10	90
k				10	87
l				10	90
m				10	89
n				10	80

[a] All products were characterized by ^{1}H NMR, IR, and mass spectrometry.
[b] Yield refers to pure products after chromatography.

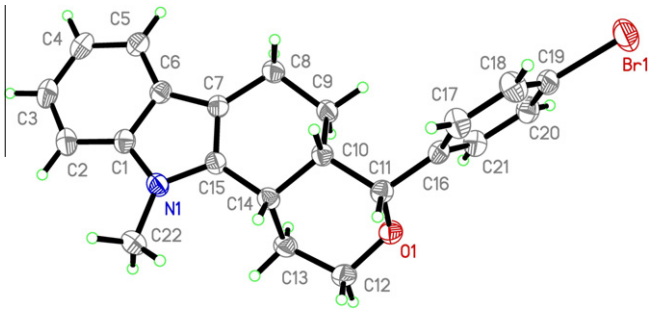


Figure 3. ORTEP diagram of **3c**.

entry l). The structure of **3l** was confirmed by X-ray crystallography (Fig. 4).[10]

This method works well not only with aromatic aldehydes but also with aliphatic aldehydes like cyclohexanaldehyde, *n*-hexanal, *n*-propanal, and *n*-butanal. In case of aliphatic aldehydes, the corresponding alkyl-substituted octahydropyrano[4,3-*a*]carbazole derivatives were obtained in good yields (Table 1, entries g, h, j, and n). Thus, it provides a diverse range of *cis*-fused octahydropyrano[4,3-*a*]carbazole derivatives in a single-step operation.

Next attempt was made to examine the reactivity of (*Z*)-4-methyl-*N*-(6-(1-methyl-1*H*-indol-3-yl)hex-3-enyl)benzenesulfonamide (**4**) and (*Z*)-6-(1-methyl-1*H*-indol-3-yl)hex-3-ene-1-thiol (**5**). Surprisingly, (*Z*)-4-methyl-*N*-(6-(1-methyl-1*H*-indol-3-yl)hex-3-enyl)benzenesulfonamide (**4**) failed to give the desired product

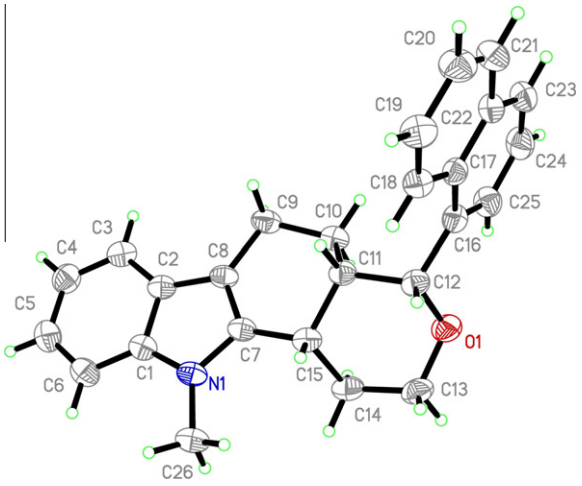
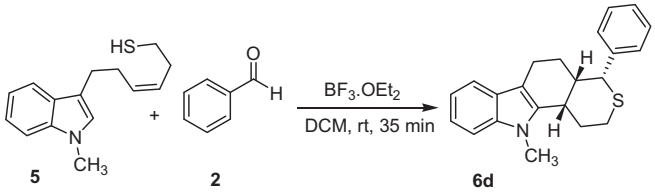
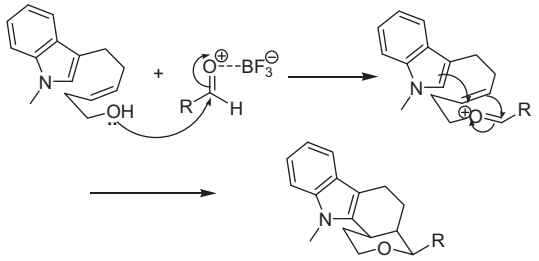


Figure 4. ORTEP diagram of **3l**.



Scheme 2. Reaction of (*Z*)-6-(1-methyl-1*H*-indol-3-yl)hex-3-ene-1-thiol with benzaldehyde.

under the influence of acid catalysts such as $Sc(OTf)_3$, $Sc(OTf)_3$/*p*-TSA, $InCl_3$, $In(OTf)_3$, $InBr_3$, and $BF_3{\cdot}OEt_2$ in various amounts ranging from catalytic to stoichiometric even at reflux temperature in dichloroethane. However, the cross-coupling of (*Z*)-6-(1-methyl-1*H*-indol-3-yl)hex-3-ene-1-thiol (**5**) with benzaldehyde in the presence of $BF_3{\cdot}OEt_2$ at room temperature gave the corresponding octahydrothiopyrano[4,3-*a*]carbazole (**6d**) in 75% yield (Scheme 2, Table 2).

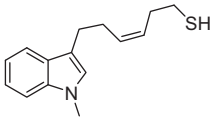
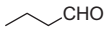
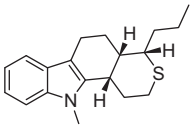
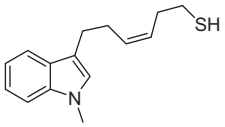
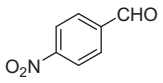
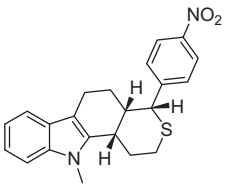
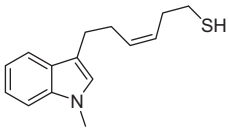
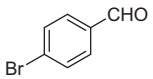
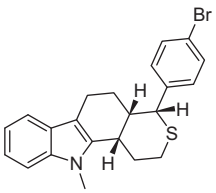
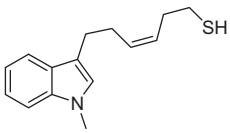
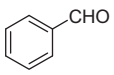
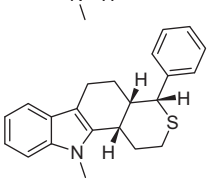


Scheme 3. A plausible reaction pathway.

The scope of thia-Prins cyclization with various aldehydes like *n*-butanal, *p*-nitrobenzaldehyde, and *p*-bromobenzaldehyde is illustrated in Table 2 (entries a–d).[11] The structure of the products was established by NMR, IR, and mass spectroscopy. The effect of various Lewis acids such as $Sc(OTf)_3$, $In(OTf)_3$, $La(OTf)_3$, and $InBr_3$ as well as Bronsted acids such as *p*-TSA and CSA were screened for this conversion. Of these, $BF_3{\cdot}OEt_2$ was found to give the best results in Prins- and thia-Prins/Friedel–Crafts cyclization. As a solvent, dichloromethane gave the best results.

The reaction was expected to proceed via the formation of oxocarbenium ion from hemi-acetal which is formed in situ from an aldehyde and a homoallylic alcohol, likely after activation through $BF_3{\cdot}OEt_2$. This is followed by the attack of an internal olefin resulting in the formation of carbocation which is simultaneously trapped by an indolyl group leading to the formation of octahydropyrano[4,3-*a*]carbazole as depicted in Scheme 3.

Table 2
$BF_3{\cdot}OEt_2$ catalyzed tandem thia-Prins/Friedel–Crafts cyclization

Entry	Thiol (**5**)	Aldehyde (**2**)	Product (**6**)[a]	Time (min)	Yield[b] (%)
a				45	80
b				40	75
c				30	83
d				35	75

[a] All products were characterized by ^1H NMR, IR, and mass spectrometry.
[b] Yield refers to pure products after chromatography.

In summary, we have developed a novel strategy for the synthesis of octahydropyrano- and thiopyrano[4,3-*a*]carbazole derivatives in a highly diastereoselective manner via a cascade of Prins cyclization using a catalytic amount of $BF_3{\cdot}OEt_2$. This method provides a rapid access to the synthesis of a wide range of pyrano- and thiopyrano[4,3-*a*]carbazole derivatives in good yields with excellent selectivity.

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Supplementary data

Supplementary data (spectral data and NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.113.

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10. CCDC-909200 (**3c**) and CCDC-909201 (**3l**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
11. *General procedure:* To a stirred solution of aldehyde (1 mmol), homoallylic alcohol, or thiol (1 mmol) in anhydrous dichloromethane (5 mL) was added a catalytic amount of $BF_3.OEt_2$ (10 mol %). The resulting mixture was stirred at room temperature under nitrogen atmosphere for the specified time (Table 1). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ and extracted with dichloromethane (2×15 mL). The combined organic layers were concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate/hexane, 1:9) to afford the pure product.