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A novel tandem ene/Prins cyclization for the synthesis of octahydropyrano[2,3-*c*]pyrrole derivatives

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ABSTRACT

A tandem ene/Prins cyclization of olefin tethered aldehyde with an aldehyde has been accomplished using 5 mol % scandium triflate at ambient temperature to afford a novel series of *cis*-fused octahydropyrano[2,3-*c*]pyrrole derivatives in good yields with high selectivity. This is the first report on a tandem cyclization of 4-methyl-*N*-(3-methylbut-2-enyl)-*N*-(2-oxoethyl)benzenesulfonamide with aldehydes.

Tetrahydropyran ring is often found in many marine- and terrestrial-originated biologically active natural products.[1] In particular, 2,6-disubstituted *exo*-methylene pyran ring is an important component of biologically important natural products such as dactylolide and zampanolide (Fig. 1).[2]

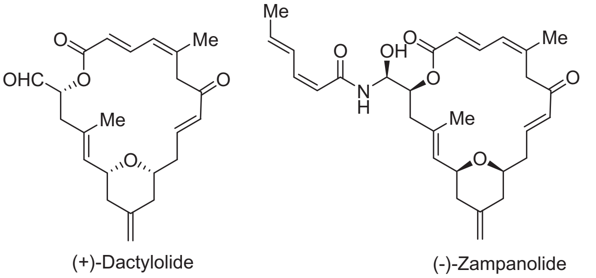
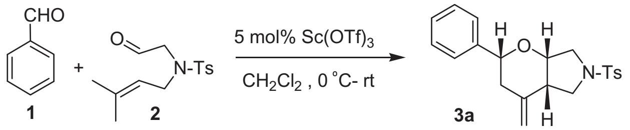


Figure 1. Representative examples of *exo*-methylene pyran ring containing natural products.

The *exo*-methylene compounds are generally prepared by means of an intramolecular ene reaction.[3] Acid-catalyzed intramolecular carbonyl-ene cyclization is one of the most attractive methods for ring closure, leading to the formation of a homoallylic alcohol with two contiguous stereocenters with a high degree of stereoselectivity.[4] On the other hand, Prins cyclization is one of the elegant methods for the construction of tetrahydropyran skeleton.[5] Generally, acid catalysts are known to catalyze both ene and Prins cyclizations.[6–8] Inspired by an intramolecular ene reaction,[3] we attempted one-pot ene/Prins cyclization to construct the fused tetrahydropyran scaffolds.[9] However, to the best of our knowledge, there are no reports on one-pot ene/Prins cyclization of *N*-prenyl tethered aldehyde with aldehydes.

Following our interest on Prins type cyclizations,[10] we herein report a novel strategy for the synthesis of *cis*- fused octahydropyrano[2,3-*c*]pyrrole derivatives through a tandem ene/Prins cyclization. The homoallylic alcohol required for Prins cyclization was generated in situ from olefin tethered aldehyde by means of an intramolecular ene cyclization. At first, we attempted an intramolecular ene reaction of an olefin tethered aldehyde **2** in the presence of 5 mol % $Sc(OTf)_3$ in dichloromethane. Interestingly, compound **2** underwent smooth intramolecular ene reaction at room temperature to afford the desired homoallylic alcohol predominantly as a *cis*-isomer (Scheme 1).



Scheme 1. A tandem ene/Prins reaction for the formation of **3a**.

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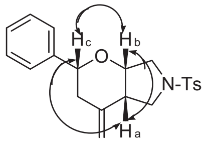
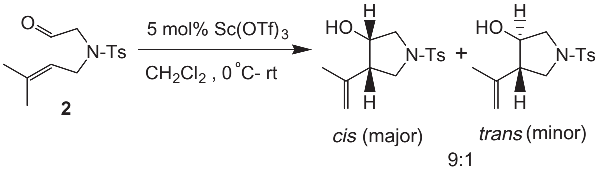


Figure 2. Characteristic nOe's of product **3a**.



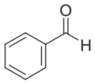
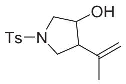
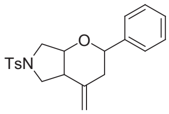
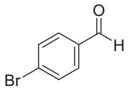
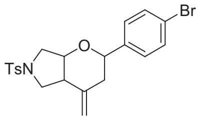
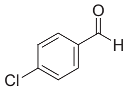
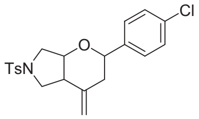
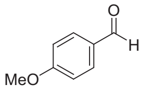
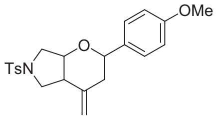
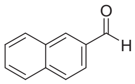
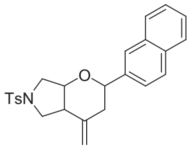
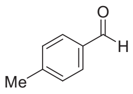
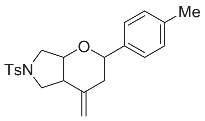
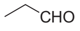
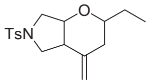
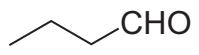
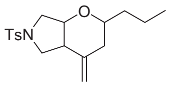
Thus formed homoallylic alcohol was then subjected to Prins cyclization to afford the corresponding tetrahydropyran derivative. Next, we attempted one-pot synthesis of tetrahydropyran derivatives from *N*-prenyl tethered aldehyde and aldehydes. Accordingly, the treatment of benzaldehyde (**1**) with *N*-prenyl tethered aldehyde (**2**) in the presence of 5 mol % scandium triflate in dichloromethane gave the corresponding *cis*-fused tetrahydropyran derivative **3a** predominantly in an 88% yield (Scheme 1).

The tandem reaction proceeds well at room temperature in a one-pot way hence it doesnot require the isolation of in situ formed homoallylic alcohol. The stereochemistry of **3a** was established and confirmed by nOe studies. The presence of strong nOe crosses peaks between Ha–Hb and Ha–Hc clearly suggests that Ha/Hb and Ha/Hc are in *cis*-orientation (Fig. 2).

To study the scope, we extended this methodology to various aldehydes. Interestingly, several aromatic aldehydes underwent smooth Prins cyclization with homoallylic alcohol generated in situ from olefin tethered aldehyde **2** to furnish the aryl substituted octahydropyrano[2,3-*c*]pyrrole scaffolds (Table 1, entries b–f). Notably, a sterically hindered 2-naphthaldehyde also participated well in this reaction. This method works not only with aromatic aldehydes but also with aliphatic aldehydes. Indeed, aliphatic aldehydes such as propanaldehyde, butyraldehyde, *n*-hexanal, isovelaraldehyde, *n*-decanal, and cyclohexanecarboxaldehyde also gave the corresponding alkyl substituted octahydropyrano[2,3-*c*]pyrrole derivatives in good yields (Table 1, entries g–l). In the absence of the catalyst, no ene reaction was observed under similar conditions. As solvent, dichloromethane was found to give the best results. All the products were characterized and confirmed by NMR, IR, and mass spectrometry. The scope and generality of this process is illustrated with respect to various aldehydes and the results are presented in Table 1.[11]

Mechanistically, the reaction was assumed to proceed via an intramolecular ene reaction of *N*-prenyl tethered aldehyde **2** to generate a homoallylic alcohol. Thus formed homoallylic alcohol reacts subsequently with an aldehyde to afford the desired tetrahydropyran derivative **3**.

Table 1
Intra-ene/Prins cyclization for *cis*-fused octahydropyrano[2,3-*c*]pyrrole derivatives

Entry	Aldehyde	Homoallylic alcohol	Product (**3**)[a]	Time (h)	Yield[b] (%)
a				12	87
b		–		12	85
c		–		12	78
d		–		14	75
e		–		13	77
f		–		14	82
g		–		14	72
h		–		13	70

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