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$Sc(OTf)_3$-catalyzed sugar based tandem ene-Prins cyclization: a novel synthesis of hexahydro-2*H*-furo[3,2-*b*]pyranopyran scaffolds

B. V. Subba Reddy *, A. V. Ganesh, A. Siva Krishna, G. G. K. S. Narayana Kumar, J. S. Yadav

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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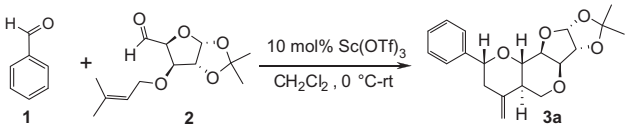
ABSTRACT

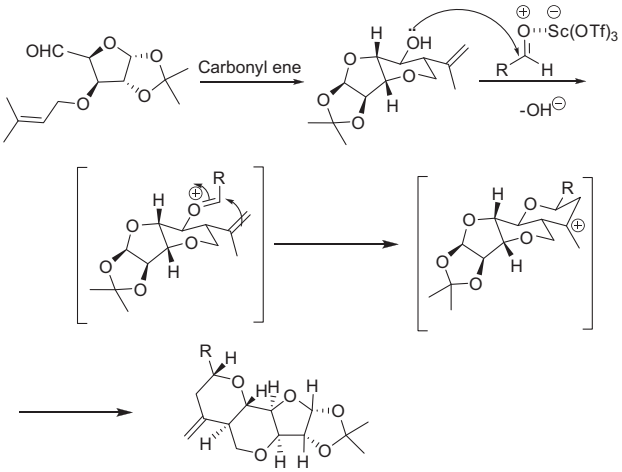
Ttandem ene-Prins cyclization between an aldehyde and an olefin tethered sugar aldehyde has been achieved using a catalytic amount of scandium triflate (10 mol %) at ambient temperature to give a novel series of sugar annulated pyranopyran derivatives in good yields with high selectivity. This is the first report on sugar based ene-Prins cyclization between an aldehyde and *O*-prenyl derivative of a sugar aldehyde.

The development of new synthetic strategies to construct the fused ring systems continues to be an attractive target in organic synthesis.[1] In this context, 'tandem' reactions, in which multiple reactions are combined into single operation in a convergent way, have been reported for the synthesis of a wide range of organic molecules.[2] The advantages of tandem reactions are the formation of several bonds with high degree of selectivity, efficiency, and atom-economy by a single catalyst in one-pot operation. The Lewis acid-catalyzed intramolecular carbonyl-ene reaction is one of the most attractive methods for ring closure, leading to the formation of two contiguous stereocentres with high degree of stereoselectivity.[3] The Prins cyclization is one of the elegant methods for the construction of tetrahydropyran ring system.[4] Generally, Lewis acids and Brønsted acids are known to catalyze the Prins cyclization to produce a wide range of tetrahydropyran scaffolds under mild conditions.[5–7] However, to the best of our knowledge, there are no reports on tandem ene-Prins cyclization between an aldehyde and *O*-prenyl tethered sugar aldehyde derived from D-glucose.

In continuation of our interest on Prins-cyclization,[8] we herein report a novel method for the synthesis of sugar fused pyranopyran derivatives by means of Prins cyclization of aldehydes with homoallyl alcohol generated in situ from olefin tethered sugar aldehyde via an intramolecular ene reaction. Initially, we have attempted the coupling of benzaldehyde (**1**) with *O*-prenyl tethered sugar aldehyde (**2**) in the presence of 10 mol % of scandium triflate in dichloromethane. The reaction proceeded smoothly at room temperature



Scheme 1. ene-Prins cyclization of prenyl tethered sugar aldehyde **2** with benzaldehyde.



Scheme 2. A plausible reaction mechanism.

* Corresponding author. Tel.: +91 40 27193535; fax: +91 40 27160512.
E-mail address: basireddy@iict.res.in (B.V.S. Reddy).

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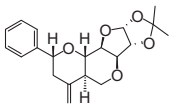
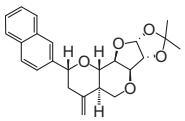
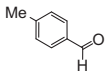
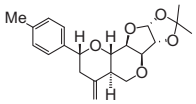
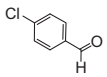
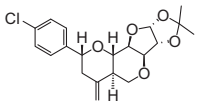
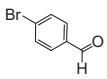
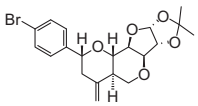
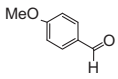
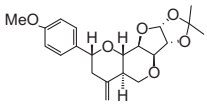
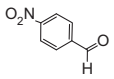
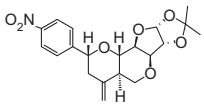
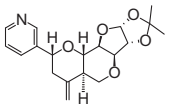
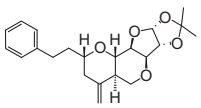
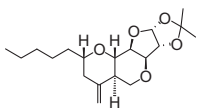
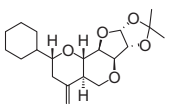
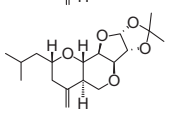
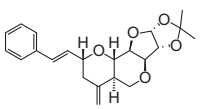
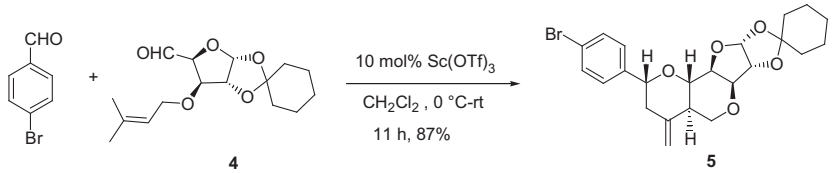
Table 1
$Sc(OTf)_3$-catalyzed ene-Prins cyclization with glucose-aldehyde (**1**) and various aldehydes

Entry	Aldehyde(**2**)	Alkene (**3**)[a]	Time (h)	Yield[b] (%)
a			10.0	88
b			10.5	86
c			10.5	83
d			11.0	82
e			10.0	84
f			12.0	78
g			13.0	76
h			14.0	70
i			10.5	90
j			10.0	90
k			11.0	88
l			10.0	86
m			12.0	80

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



Scheme 3. ene-Prins cyclization of cyclohexylidene protected sugar with *p*-bromobenzaldehyde.

and the corresponding product **3a** was obtained in 88% yield with high selectivity (Scheme 1).

The stereochemistry of the product was confirmed by NOE studies.[9] This result provided the incentive for further study of reactions with various aromatic aldehydes, such as 2-naphthaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, *p*-bromobenzaldehyde, *p*-anisaldehde and *p*-nitrobenzaldehyde.

The aromatic aldehydes underwent smooth coupling with a homoallyl alcohol generated in situ via an intramolecular ene reaction of **2** to furnish a variety of aryl substituted furopyranopyran derivatives (Table 1, entries b–g). Like aromatic aldehydes, pyridin-2-carboxaldehyde also participated well in this reaction (Table 1, entry h). Furthermore, aliphatic substrates, such as hydrocinnamaldehyde, hexanaldehyde, cyclohexanecarboxaldehyde and isovelaraldehyde also gave the desired products in good yields (Table 1, entries i–l). Notably, acid sensitive *trans*-cinnamaldehyde also participated effectively in this cyclization (Table 1, entry m). In the absence of a catalyst, no 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. Probably, the reaction proceeds via an intramolecular ene reaction of *O*-prenyl derivative of a sugar aldehyde to generate a homoallyl alcohol. Thus in situ formed homoallylic alcohol may undergo Prins cyclization with an aldehyde to afford the desired product (Scheme 2).

The scope and generality of this process is illustrated with respect to various aldehydes and the results are presented in Table 1.[10] Eventually, we attempted the coupling of *p*-bromobezaldehyde with cyclohexylidene protected *O*-prenyl tethered sugar aldehyde. The reaction was also successful with cyclohexylidene protected sugar derivative to furnish the corresponding cyclized product **5** in 87% yield under similar conditions (Scheme 3).

In summary, we have demonstrated a novel approach for the synthesis of sugar annulated pyranopyran derivatives via a tandem ene-Prins cyclization using a catalytic amount of $Sc(OTf)_3$. In situ generated homoallyl alcohol, by means of intramolecular ene cyclization of *O*-prenyl derivative of a sugar aldehyde was successfully coupled with various aldehydes to produce a novel class of sugar fused pyranopyran derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.077.

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10. *General procedure*: To a solution of *O*-prenyl tethered sugar aldehyde (5.0 mmol), in dichloromethane (10 mL) was added scandium triflate (0.5 mmol) at rt. After completion of the ene reaction (1.5 h) as indicated by TLC, aldehyde (5.0 mmol) in dichloromethane (6 mL) was added to the reaction mixture at the same temperature. The reaction mixture was stirred at room temperature for a specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 1.0–9.0) gave the pure products. **3a**: $[\alpha]_D^{25}$ +47.6 (*C* 1.00, $CHCl_3$); IR (KBr): ν_{max} 3066, 2932, 2858, 1636, 1608, 1542, 1329, 1290, 1164, 1089, 964, 821, 738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39–7.19 (m, 5H), 5.82 (d, J = 3.8 Hz, 1H), 4.99 (s, 1H), 4.89 (s, 1H), 4.44–4.40 (m, 1H), 4.39 (dd, J = 2.9, 11.6 Hz, 1H), 4.15–4.09 (m, 1H), 4.08–4.05 (m, 1H), 4.01–3.96 (m, 1H), 3.84 (t, J = 11.6 Hz, 1H), 3.49–3.44 (m, 1H), 2.76–2.67 (m, 1H), 2.40–2.25 (m, 2H), 1.46 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 141.6, 128.4, 127.8, 125.6, 112.8, 111.7, 104.7, 83.7, 80.5, 76.4, 75.9, 72.5, 64.6, 40.0, 39.8, 26.6, 26.1. LCMS: *m*/*z*: 367 (M+Na). HRMS Calcd for $C_{20}H_{24}O_5Na$ (M+Na): 367.1521. Found: 367.1526. **3l**: $[\alpha]_D^{25}$ +19.8 (*C* 1.00, $CHCl_3$); IR (KBr): ν_{max} 2962, 2916, 2850, 1638, 1606, 1440, 1364, 1316, 1243, 1134, 1076, 1018, 960, 886 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.81 (d, J = 3.4 Hz, 1H), 4.88 (s, 1H), 4.80 (s, 1H), 4.44–4.34 (m, 1H), 4.06–3.91 (m, 2H), 3.80–3.73 (m, 1H), 3.71–3.61 (m, 1H), 3.43–3.29 (m, 2H), 2.64–2.52 (m, 1H), 2.13–1.97 (m, 1H), 1.88–1.72 (m, 1H), 1.62–1.52 (m, 1H), 1.49 (s, 3H), 1.29 (s, 3H), 1.34–1.14(m, 2H), 0.92 (d, J = 6.2 Hz), 0.89 (d, J = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0, 112.0, 111.5, 104.5, 83.7, 77.0, 76.2, 76.0, 71.9, 64.3, 45.1, 40.2, 38.0, 26.5, 25.9, 24.1, 23.0, 22.2. LCMS: *m*/*z*: 347 (M+Na). HRMS Calcd for $C_{18}H_{28}O_5Na$(M+Na):347.1834. Found:347.1836.