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$InBr_3$-catalyzed stereoselective synthesis of trans-2,6-disubstituted 3,6-dihydro-2*H*-pyrans

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Abstract

A new method for the stereoselective synthesis of trans-2,6-disubstituted 3,6-dihydro-2*H*-pyrans with a variety of substitution patterns is described, involving Lewis acid induced tandem allylation or cyanation of δ-hydroxy-α,β-unsaturated aldehydes to produce dihydropyrans in good yields and with trans-selectivity. This method is very useful for the synthesis of trans-2,6-disubstituted dihydropyran ring-containing natural products such as laulimalide, scytophycin C and many others.
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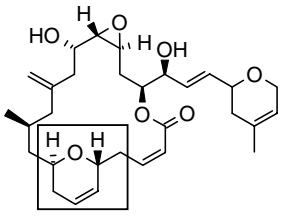
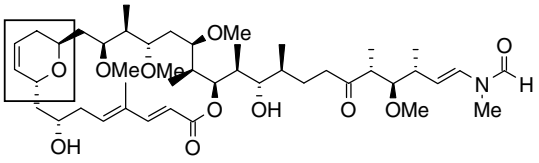
Keywords: Dihydropyrans; δ-Hydroxy-α,β-unsaturated aldehydes; Allylation; Cyanation

The 2,6-disubstituted dihydropyran ring system is frequently found in various natural products, examples include swinholide,[1,2] scytophycin C[3,4] and laulimalide (Fig. 1).[5]

2,6-Disubstituted dihydropyrans are also synthetically useful intermediates in the preparation of polysubstituted tetrahydropyran ring systems, such as those found in the pseudomonic acids.[6] As a result, several approaches[7–13] have been reported for the preparation of dihydropyrans, and some of the more varied methodologies include electrophile-initiated alkylation of glycals,[14] hetero-Diels–Alder cycloadditions,[15–18] olefin metathesis,[19] Prins-cyclizations of cyclopropyl carbinols,[20] or homoallylic alcohols,[21] and an intramolecular silyl-modified Sakurai reaction (ISMS).[22,23] Many of these reactions have limitations, such as the need for strictly anhydrous conditions, stoichiometric quantities of a Lewis acid initiator, or delivery of a strong Lewis acid at a low temperature. Recently, indium tribromide has received increasing attention as a water-tolerant, green Lewis acid catalyst for organic synthesis demonstrating highly chemo-, regio- and stereoselective results.[24,25] Compared to conventional Lewis acids, it has advantages of water stability, recyclability, operational simplicity, strong tolerance to oxygen and nitrogen-containing substrates and functional groups, and it can often be used in catalytic amounts.[26–28] In continuation of our interest in the synthesis of scytophycin C,[29] we disclose



Laulimalide



Scytophycin C

Fig. 1. Structures of laulimalide and scytophycin C.

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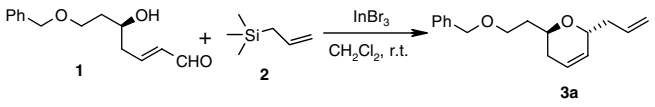
herein a novel protocol for the construction of trans-2,6-disubstituted dihydropyrans.

Following our interest in the catalytic uses of indium tribromide,[30–36] we describe an efficient method for the preparation of trans-2,6-disubstituted dihydropyrans through a tandem allylation/cyanation of δ-hydroxy-α,β-unsaturated aldehydes. To the best of our knowledge, no synthesis of C6-(allyl)- or C6-(cyano)-3, 6-dihydropyrans from δ-hydroxy-α,β-unsaturated aldehydes has been reported. In a model reaction, δ-hydroxy-enal **1** was treated with allyltrimethylsilane **2** using 5 mol % of indium(III) bromide as a catalyst. Interestingly, product 6-allyl-2-[2-(benzyloxy)ethyl]-3,6-dihydro-2*H*-pyran **3a** was isolated in 82% yield with trans-selectivity (Scheme 1).

The structure of product **3a** was established using NMR, the proton assignment was achieved with a QCOSY experiment. The presence of NOE's between the C-2 proton and the C-7 protons suggests that the stereochemistry at C-6 is *R* (a single enantiomer) and that the protons at C-2 and C-6 are trans to each other (Fig. 2).

No cis-diastereoisomer was observed in the ^{1}H NMR spectrum of the crude products obtained from the C-allylation of δ-hydroxy-enals. This result provided the incentive for a further study of reactions with various δ-hydroxy-enals. Interestingly, a diverse range of hydroxy-enals participated well in this reaction to afford the corresponding trans-2,6-disubstituted dihydropyrans in good yields (Table 1). Enantiomerically pure aldehydes gave optically pure products (Table 1, entries a–d). Trimethylsilyl cyanide also participated effectively in this reaction (Scheme 2).

However, *ortho*-hydroxy *trans*-cinnamaldehyde and allylsilane did not give the desired product under similar reaction conditions. Furthermore, α,β-unsaturated aldehydes without a δ-hydroxyl group failed to give the expected products, although, homoallylic alcohols were obtained in good yields. A possible reaction mechanism is illustrated in Scheme 3. The reaction proceeds with activation of aldehyde by indium(III) bromide and subsequent formation of an oxonium intermediate in which stereoelectronic and/or steric factors dictate the direction of the incoming nucleophile.



Scheme 1. A tandem allylation.

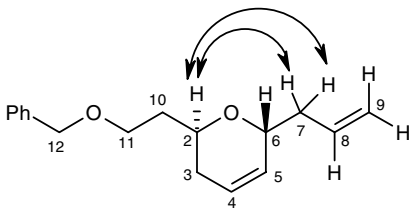
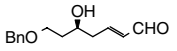
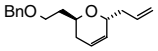
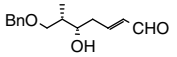
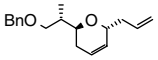
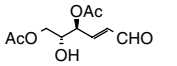
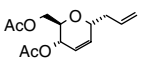
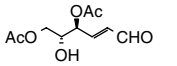
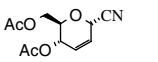
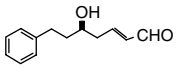
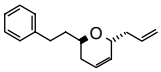
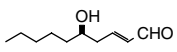
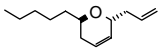
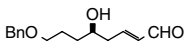
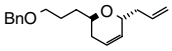
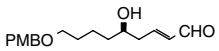
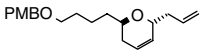
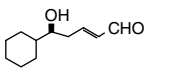
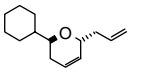
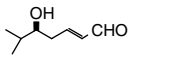
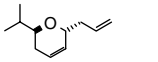
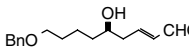
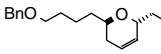
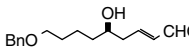
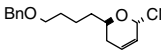
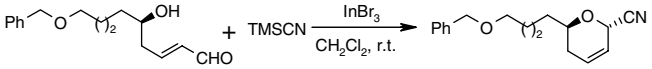


Fig. 2. Characteristic NOE's of product **3a**.

Table 1
$InBr_3$-catalyzed synthesis of trans-2,6-disubstituted 3,6-dihdro-2*H*-pyrans

Entry	Substrate **1**	Product[a] **3**	Time (h)	Yield[b] (%)
a			1.0	82
b			0.5	85
c			0.5	88
d			0.5	70
e			2.0	85
f			2.0	70
g			1.5	85
h			1.0	75
i			1.5	70
j			2.0	70
k			1.0	82
l			1.0	72

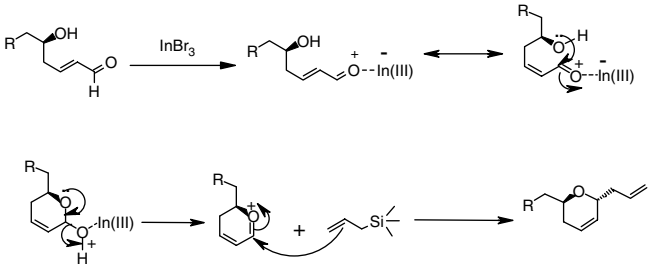
[a] The products were characterized ^{1}H NMR, IR and mass spectrometry.
[b] Yield refers to pure products after chromatography.



Scheme 2. A tandem cyanation.

The scope and generality of this process is illustrated in Table 1.

Various indium(III) reagents such as $InBr_3$, $InCl_3$, $In(OTf)_3$ and $In(ClO_4)_3$ were screened for this transformation. Of these catalysts, indium tribromide was found to be



Scheme 3. A plausible reaction mechanism.

most effective in terms of conversion and selectivity. For example, treatment of aldehyde **1a** with allyltrimethylsilane in the presence of 5 mol % of $InBr_3$ and 5 mol % of $InCl_3$ for 1 h afforded **3a** in 82% and 70% yields, respectively. In addition, this method is useful for the direct synthesis of 2,3-dideoxy C-glycoside analogues (Table 1, entries c and d). This method facilitates the introduction of an allyl or cyano functionality on the pyran ring system in one-pot, making it an efficient pathway for producing 6-allyl- or 6-cyano-3,6-dihydro-2*H*-pyrans, which can be further modified to give biologically important natural products.

In summary, we have demonstrated an efficient protocol for the synthesis of trans-2,6-disubstituted dihydropyrans from δ-hydroxy-α,β-unsaturated aldehydes and allyltrimethylsilane in a highly regio- and stereoselective manner. We believe that this new method will find applications in the synthesis of biologically active natural products that contain a dihydropyran ring system.

General procedure: A mixture of the δ-hydroxy-α,β-unsaturated aldehyde (1 mmol), allyltrimethylsilane or trimethylsilyl cyanide (1.2 mmol) and indium tribromide (5 mol %) in dichloromethane (10 mL) was stirred at room temperature. After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure dihydropyran.

Spectroscopic data for selected compounds: Compound **3a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.23 (m, 5H, Ar-H), 5.85 (m, 1H), 5.81 (m, 1H), 5.70 (m, 1H), 5.07 (m, 2H), 4.50 (2 × d, $J = 12.0$ Hz, 2H), 4.19 (m, 1H), 3.88 (tt, $J = 4.4$, 8.8 Hz, 1H), 3.62 (m, 1H), 3.59 (m, 1H), 2.40 (m, 1H), 2.24 (m, 1H), 2.05–1.74 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.9, 35.7, 38.9, 64.9, 67.1, 72.5, 73.2, 116.9, 124.5, 127.7, 127.9, 128.5, 129.3, 135.3, 138.7 IR (KBr) Neat: ν_{max}: 3445, 2924, 2856, 1728, 1635, 1451, 1279, 1082, 760 cm^{-1}. ESI-HRMS [M+Na] found 281.1517, $C_{17}H_{22}O_2Na$ requires 281.1508. Compound **3b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.22 (m, 5H, Ar-H), 5.89–5.64 (m, 3H), 5.10–5.03 (m, 2H), 4.48 (s, 2H), 4.18 (m, 1H), 3.56 (m, 1H), 3.42 (dd, $J = 6.6$, 9.0, 2H), 2.45–2.32 (m, 1H), 2.26–2.16 (m, 1H), 2.01–1.93 (m, 2H), 1.91–1.77 (dq, $J = 4.4$, 6.6 Hz, 1H) 0.98 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 29.9, 38.6, 38.8, 68.9, 72.9, 73.1, 116.8, 124.7, 125.0, 127.5, 127.7, 128.4, 129.4, 135.5, 139.0. IR (KBr) Neat: ν_{max}: 3448, 2924, 2854, 1638, 1456, 1215, 1082, 758 cm^{-1}. ESI-HRMS [M+Na] found 295.1673, $C_{18}H_{24}O_2Na$ requires 295.1661. Compound **3e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.12 (m, 5H, Ar-H), 6.01–5.68 (m, 3H), 5.26–4.97 (m, 2H), 4.26 (m, 1H), 3.71 (tt, $J = 4.0$, 8.5 Hz, 1H), 2.88 (ddd, $J = 5.2$, 9.5, 13.7 Hz, 1H), 2.67 (ddd, $J = 7.0$, 9.5, 13.7 Hz, 1H), 2.46 (m, 1H), 2.35–2.21 (m, 1H), 2.12–1.95 (m, 2H), 1.95–1.86 (m, 1H), 1.86–1.70 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.8, 32.2, 37.3, 39.1, 67.4, 72.4, 117.0, 124.4, 125.9, 128.5, 128.6, 129.4, 135.3, 142.5. IR (KBr) Neat: ν_{max}: 3446, 2925, 2855, 1637, 1457, 1216, 1082, 761 cm^{-1}. ESI-HRMS [M+Na] found 251.1411, $C_{16}H_{20}ONa$ requires 251.1402.

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