Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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The stereoselective synthesis of cis-/trans-fused hexahydropyrano[4,3-b]chromenes via Prins cyclization trapping by a tethered nucleophile


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1. Preparation of starting materials

A. Synthesis of (Z)-2-(5-hydroxypent-2-yl)phenol (1):

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\text{CH} & \quad \text{CH} \\
\text{OBn} & \quad \text{OBn}
\end{align*}
\]

\[
\text{OBn} \quad \text{OBn}
\]

\[
\text{Z-Olefin}
\]

\[
\text{Na/lq. NH}_2
\]

\[
\text{Dry THF, -78 °C to r.t.}
\]

\[
\text{HO}
\]

\[
\text{HO}
\]

**Procedure for the synthesis of (Z)-1-(benzyloxy)-2-(5-(benzyloxy)pent-2-yl)benzene by C3 Wittig Olefination:**

To a stirred solution of (3-(benzyloxy)propyl)triphenylphosphonium iodide (20 mmols, 2 equiv.) in anhydrous THF (60 mL) was added n-BuLi (1.6 M in hexane, 2.5 equiv.) dropwise at -78°C under argon atmosphere. The resulting orange ylide solution was stirred for 30 minutes and then to that a solution of the 2-(2(benzyloxy)phenyl)acetaldehyde (10 mmols, 1 equiv.) in anhydrous THF (20 mL) was added drop wise at -78 °C. The reaction mixture was stirred at this temperature for 30 min. and then was allowed to warm slowly to room temperature for 4h and was quenched with saturated NH₄Cl after completion as indicated by TLC. The reaction mixture was extracted with ether (3x25 mL). The organic layers were combined and washed with brine (2x15 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The resulting crude product was obtained as a 92:8% mixture of Z and E isomers (confirmed by the ¹H NMR spectra of the crude product). The two isomers could be easily separable by silica gel column chromatography. The purification of the crude product by the silica gel column chromatography using ethyl acetate/n-hexane gradients afforded the pure product (Z)-1-(benzyloxy)-2-(5-(benzyloxy)pent-2-yl)benzene as a liquid. Yield, 3.0 gram, 84%. ¹H NMR (500 MHz, CDCl₃): 7.50-7.27 (m, 10H), 7.23-7.13 (m, 2H), 6.97-6.87 (m, 2H), 5.76-5.67 (m, 1H), 5.61-5.51 (m, 1H), 5.11 (s, 2H), 4.52 (s, 2H), 3.55-3.46 (m, 4H), 2.53-2.44 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): 156.3, 138.5, 137.3, 129.6, 129.5, 128.4,
128.3, 128.1, 127.7, 127.6, 127.4, 127.1, 127.0, 126.5, 120.7, 111.5, 72.8, 69.9, 69.8, 28.0, 27.9; IR (KBr): v 2858, 1492, 1452, 1238, 1106, 1022, 744, 698 cm\(^{-1}\); ESI-MS: \(m/z\) 359 (M+H\(^{+}\)).

**Procedure for the synthesis of (Z)-2-(5-hydroxypent-2-enyl)phenol (1):**

![Chemical structure of (Z)-2-(5-hydroxypent-2-enyl)phenol (1)](image)

To a solution of (Z)-1-(benzylxy)-2-(5-(benzyloxy)pent-2-enyl)benzene obtained as above (9 mmol, 1 equiv.) in THF (18 mL) was added liquid NH\(_3\) (45 mL) followed by the addition of sodium metal (45 mmol, 5 equiv.).\(^{3}\) The blue coloured reaction mixture was allowed to stir for 30 minutes. After the completion of the reaction, the reaction was quenched by NH\(_4\)Cl and ammonia was allowed to evaporate. Then the reaction mixture was filtered with hot EtOAc and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography using ethyl acetate/n-hexane gradients to afford pure product (Z)-2-(5-hydroxypent-2-enyl)phenol (1) as a viscous liquid. Yield, 1.35 gram, 90%. \(^1\)H NMR (500 MHz, CDCl\(_3\)): 7.13 (d, \(J = 7.9\) Hz, 1H), 7.10 (t, \(J = 7.9\) Hz, 1H), 6.86 (t, \(J = 7.9\) Hz, 1H), 6.79 (d, \(J = 7.9\) Hz, 1H), 5.69-5.61 (m, 1H), 5.54-5.46 (m, 1H), 3.77 (t, \(J = 5.9\) Hz, 2H), 3.44 (d, \(J = 6.9\) Hz, 2H), 2.54-2.47 (m, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): 154.2, 131.5, 130.4, 127.6, 126.6, 126.2, 120.5, 115.8, 61.8, 30.0, 29.5; IR (KBr): v 3413, 1460, 1249, 1055, 753 cm\(^{-1}\); ESI-MS: \(m/z\) 179 (M+H\(^{+}\));
B. Synthesis of \((E)-2-(5\text{-hydroxypent-2-enyl})\text{phenol (4)}:\)

![Chemical structure diagram]

**Procedure for the synthesis of \((E)-1-(benzyloxy)-2-(5-(benzyloxy)pent-2-enyl)\text{benzene by Julia Olefination:}\)**

A solution of 5-(3-(benzyloxy)propylsulfonfyl)-1-phenyl-1H-tetrazole\(^4\), a sulfone (12 mmol, 1.2 equiv.) in THF (75 mL) was cooled to \(-78\ \degree\)C, and a solution of lithium bis(trimethylsilyl)amide (15 mmol) in THF (10 mL) was added slowly. The resulting solution was stirred at \(-65\ \degree\)C for 1h, and then a solution of 2-(2(benzyloxy)phenyl)acetaldehyde\(^2\) (10 mmols, 1 equiv.) in THF (10 mL) was added at a rate such that the temperature remained below \(-65\ \degree\)C. The orange solution was stirred for an additional hour at \(-65\ \degree\)C and then allowed to warm to room temperature over 15 h. Water (60 mL) was added and the resulting mixture stirred for 1h. The reaction was transferred to a separatory funnel, extracted with Et\(_2\)O (3 x 30 mL), dried (Na\(_2\)SO\(_4\)), filtered, and concentrated to afford a yellow oil. The resulting crude product was obtained as a 85:15% mixture of \(E\) and \(Z\) isomers (confirmed by the \(^1\)H NMR spectra of the crude product). The two isomers could be easily separable by silica gel column chromatography. The purification of the crude product by the silica gel column chromatography using ethyl acetate/\(n\)-hexane gradients afforded the pure product \((E)-1-(benzyloxy)-2-(5-(benzyloxy)pent-2-enyl)\text{benzene}\) as a liquid. Yield, 2.75 gram, 77%. \(^1\)H NMR (500 MHz, CDCl\(_3\)): 7.52-7.45 (m, 2H), 7.45-7.28 (m, 8H), 7.25-7.18 (m, 2H), 7.00-6.92 (m, 2H), 5.80-5.71 (m, 1H), 5.63-5.53 (m, 1H), 5.12 (s, 2H), 4.55 (s, 2H), 3.54 (t, \(J = 6.9\) Hz, 2H), 3.47 (dd, \(J = 6.9\) and 1.0 Hz, 2H), 2.44-2.36 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 156.2, 138.5, 137.4, 130.3, 129.7, 128.4, 128.3, 127.7, 127.6, 127.4, 127.1, 127.0, 126.4, 120.7, 111.6, 72.8, 70.1, 69.8, 33.2, 33.0; IR (KBr): v 2856, 1493, 1452, 1240, 1104, 747, 697 cm\(^{-1}\); ESI-MS: \(m/z\) 359 (M+H)\(^+\).
Procedure for the synthesis of (E)-2-(5-hydroxypent-2-enyl)phenol (4):

\[
\text{\includegraphics[width=0.2\textwidth]{structure.png}}
\]

To a solution of (E)-1-(benzylloxy)-2-(5-(benzylloxy)pent-2-enyl)benzene obtained as above (7.6 mmol, 1 equiv.) in THF (15 mL) was added liquid NH₃ (40 mL) followed by the addition of sodium metal (38 mmol, 5 equiv.).³ The blue coloured reaction mixture was allowed to stir for 30 minutes. After the completion of the reaction, the reaction was quenched by NH₄Cl and ammonia was allowed to evaporate. Then the reaction mixture was filtered with hot EtOAc and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography using ethyl acetate/n-hexane gradients to afford pure product (E)-2-(5-hydroxypent-2-enyl)phenol (4) as a viscous liquid. Yield, 1.22 gram, 90%.

¹H NMR (500 MHz, CDCl₃): 7.16-7.05 (m, 2H), 6.90-6.83 (m, 1H), 6.82-6.76 (m, 1H), 5.79-5.71 (m, 1H), 5.58-5.49 (m, 1H), 3.66 (t, J = 6.4 Hz, 2H), 3.39 (d, J = 6.4 Hz, 2H), 2.37-2.26 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): 154.2, 131.7, 130.4, 127.9, 127.7, 126.0, 120.7, 115.8, 61.6, 35.6, 34.2; IR (KBr): v 3351, 2925, 1454, 1238, 753 cm⁻¹; ESI-MS: m/z 179 (M+H)⁺;

References:

2. Copies of $^1$H and $^{13}$C NMR spectra of products 3a-3j and 5a-5j

Product 3a (Table 2, Entry a):

$^1$H NMR, 300 MHz, CDCl$_3$
Product 3b (Table 2, Entry b):
Product 3c (Table 2, Entry c).

$^1$H NMR, 300 MHz, CDCl$_3$. 
Product 3d (Table 2, Entry d):

\[ ^1H \text{NMR, } 300 \text{ MHz, } \text{CDCl}_3 \]
Product 3e (Table 2, Entry e).

$^1$H NMR, 300 MHz, CDCl$_3$
Product 3f (Table 2, Entry f):

$^1$H NMR, 300 MHz, CDCl$_3$
Product 3g (Table 2, Entry g):

$^1$H NMR, 300 MHz, CDCl$_3$
Product 3b (Table 2, Entry b):
Product 31 (Table 2, Entry 1):

\[
\text{H}^1 \text{NMR, } 300 \text{ MHz, CDCl}_3
\]
Product 3j (Table 2, Entry j):

$^1$H NMR, 300 MHz, CDCl$_3$
Product 5a (Table 3, Entry a):

$^1$H NMR, CDCl$_3$, 300 MHz
Product 5b (Table 3, Entry b):

$^1$H NMR, CDCl$_3$, 300 MHz
Product 5c (Table 3, Entry c):

$^1$H NMR, CDCl$_3$, 300 MHz
Product 5d (Table 3, Entry d):

$^1$H NMR, CDCl$_3$, 300 MHz

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Product 5e (Table 3, Entry e):

$^{1}$H NMR, CDCl$_3$, 300 MHz
Product 5g (Table 3, Entry g):

$^1$H NMR, CDCl$_3$, 300 MHz
Product 5h (Table 3, Entry h):

$^1$H NMR, CDCl$_3$, 300 MHz
Product 5i (Table 3, Entry i):

$^1$H NMR, CDCl$_3$, 300 MHz