A One-Pot Methodology for the Synthesis of the Yohimban Skeleton

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General Methods.

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions. Drying of organic extracts during workup of reactions was performed over anhydrous MgSO4. Evaporation of solvents was accomplished with a rotary evaporator. Analytical thinlayer chromatography was performed on SiO2 (Merck silica gel 60 F254) and the spots were located with aqueous KMnO4. Chromatography refers to flash chromatography and was carried out on SiO2 (SDS silica gel 60 ACC, 35-75 μm, 230-240 mesh ASTM) or Al2O3 (Aluminium oxide neutral, 63-200 μm). NMR spectra were recorded in CDCl3 on a Varian Mercury 400 MHz or Varian VNMRS 400 MHz. Chemical shifts of 1H and 13C NMR spectra are reported in ppm downfield (δ) from Me4Si. All NMR data assignments are supported by COSY and HSQC experiments.
To a stirred solution of NaH (60% mineral oil, 490 mg, 20.2 mmol) in THF (20 mL) at 0 °C was added tert-butyl acetoacetate (1.07 g, 6.74 mmol). The resulting mixture was stirred at 0 °C for 10 min before slow addition of a solution of n-butyllithium (3.3 mL of 2.6 M in hexanes, 7.09 mmol). The resulting orange solution was stirred at 0 °C for 10 min before slow addition of a solution of 4-bromo-1-butene (1.00 g, 7.41 mmol) in THF (1.5 mL) whereupon the color of the dianion faded immediately. The reaction mixture was stirred at room temperature for 15 min and then quenched by addition of sat. aq. NH₄Cl (2 mL), water (5 mL) and then diluted with Et₂O (15 mL). The organic phase was washed with water, dried, concentrated and purified by chromatography (0→10→25→50% EtOAc/hexane) to give β-keto ester 2 (0.990 g, 73%) as a yellow oil. \(^1\)H NMR (400 MHz, COSY) δ 1.47 (s, 9H, CH₃), 1.70 (quint, J = 7.6 Hz, 2H, H-5), 2.07 (qt, J = 7.6, 1.6 Hz, 2H, H-5), 2.54 (t, J = 7.2 Hz, 2H, H-4), 3.33 (s, 2H, H-2), 5.00 (m, 2H, H-8), 5.76 (ddt, J = 13.6, 10.4, 6.8 Hz, 1H, H-7), \(^13\)C NMR (400 MHz, HSQC) δ 22.4 (C-5), 27.9 (CH₃), 32.8 (C-6), 41.9 (C-4), 50.6 (C-2), 81.8 (C), 115.3 (C-8), 137.7 (C-7), 166.4 (C-1), 203.1 (C-3). HRMS calcd for C₁₂H₂₁O₃ [M+H]⁺ 213.1491, found 213.1485.

\[ \text{tert-butyl 3-oxo-7-octenoate (2) (Method B).} \]

\[^1\] Compound 2 was prepared according to a modified version of a previously reported procedure see: Haddad, N.; Abramovich, Z. J. Org. Chem. 1995, 60, 6883.
To a stirred solution of Meldrum’s acid (630 mg, 4.38 mmol, 1.0 equiv), 1-hexenoic acid (0.52 mL, 4.38 mmol, 1.0 equiv), and DMAP (590 mg, 4.82 mmol, 1.1 equiv) in CH₂Cl₂ at 0 ºC was slowly added a solution of DCC (994 mg, 4.82 mmol, 1.1 equiv) in CH₂Cl₂ (4.4 ml). The reaction mixture was warmed to r.t and stirred for 16 h. The precipitated solid was removed by filtration and washed thoroughly with CH₂Cl₂. The filtrate was subsequently washed with 1 M aq. NaHSO₄ (2 x 30 mL), brine (30 mL), dried and concentrated. The residue was immediately dissolved in tert-butanol (28 mL) and the solution refluxed for 5 h. The volatiles were removed and the residue purified by chromatography (1→2.5→5% EtOAc/hexane) to give 2 (750 mg, 81%) as a yellow oil.

\[ N-[2-(1H-Indol-3-yl)ethyl]-3-oxooct-7-enamide (3)^2 \]

A stirred solution of β-keto ester 2 (625 mg, 2.94 mmol) and tryptamine (471 mg, 2.94 mmol) in dioxane (100 mL) was stirred at reflux until all the amine was consumed (approximately 2 h, monitored by TLC). Concentration and purification by chromatography (0→25→50→100% EtOAc/hexane) gave 3 as a white solid (755 mg, 86%). ¹H NMR (400 MHz, COSY) δ 1.62 (quint, \( J = 14.8, 7.6 \) Hz, 2H, H-5), 2.01 (q, \( J = 6.8 \) Hz, 2H, H-6), 2.24 (t, \( J = 7.2 \) Hz, 2H, H-4), 2.96 (t, \( J = 6.8 \) Hz, 2H, NHCH₂), 3.27 (s, 2H, H-2), 3.59 (q, \( J = 7.2 \) Hz, 2H, ArCH₂), 4.99 (m, 2H, H-8), 5.72 (ddt, \( J = 13.6, 10.4, 6.8 \) Hz, 1H, H-7), 6.95 (br, 1H, NH), 7.00 (d, \( J = 2.0 \) Hz, 1H, H-2’), 7.10 (td, \( J = 8.0, 1.2 \) Hz, 1H, H-5’), 7.18 (td, \( J = 8.0, 1.2 \) Hz, 1H, H-6’), 7.33 (d, \( J = 8.4 \) Hz, 1H, H-7), 7.58 (d, \( J = 8.0 \) Hz, 1H, H-4’), 8.36 (br, 1H, NH); ¹³C NMR (400 MHz, HSQC) δ 22.3 (C-6), 25.2, 32.8 (C-5), 39.9, 42.9 (C-4), 49.1 (C-2), 111.3 (C-7 Ar), 112.6 (C-3 Ar), 115.5 (C-8), 118.6 (C-4 Ar), 119.3 (C-5 Ar), 122.0 (C-6 Ar), 122.2 (C-

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² Under more concentrated conditions (0.2 M) the reaction did not go to completion and led to more by-products. The same was observed using only a stoichiometric quantity of tryptamine.
2 Ar), 127.3 (C-3a Ar), 136.4 (C-7a Ar), 137.6 (C-7), 165.7 (C-1), 206.6 (C-3). HRMS calcd for C$_{18}$H$_{23}$N$_{2}$O$_{2}$ [M+H]$^+$ 299.1759, found 299.1754.

**Evaluation of the Cross Metathesis/Tandem Cyclisation process**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions for Part I (CM)$^a$</th>
<th>Conditions for Part ii$^b$</th>
<th>Ratio$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A (10%), CH$_2$Cl$_2$, r.t., 5 h</td>
<td>-</td>
<td>1  4/5  6  7  25  45  15  15</td>
</tr>
<tr>
<td>2</td>
<td>A (20%), CH$_2$Cl$_2$, reflux, 48 h</td>
<td>-</td>
<td>20  20  30  30</td>
</tr>
<tr>
<td>3$^a$</td>
<td>B (2.5%), CH$_2$Cl$_2$, 5 h reflux</td>
<td>-</td>
<td>65  -  -  -</td>
</tr>
<tr>
<td>4</td>
<td>B (2.5%), CH$_2$Cl$_2$, Cul (1%), 5 h reflux</td>
<td>-</td>
<td>94  -  4  2</td>
</tr>
<tr>
<td>5</td>
<td>As entry in 4</td>
<td>Silica (excess), CH$_2$Cl$_2$</td>
<td>26  23  33  16</td>
</tr>
<tr>
<td>6</td>
<td>As entry in 4</td>
<td>Alumina (excess), CH$_2$Cl$_2$</td>
<td>5  95  -  -</td>
</tr>
<tr>
<td>7</td>
<td>As entry in 4</td>
<td>TFA (1 equiv), CH$_2$Cl$_2$</td>
<td>-  -  50  50</td>
</tr>
<tr>
<td>8</td>
<td>As entry in 4</td>
<td>BzCl (1.2 equiv), CH$_2$Cl$_2$, -78 °C to r.t</td>
<td>-  -  60  40</td>
</tr>
<tr>
<td>9</td>
<td>As entry in 4</td>
<td>AcCl (10 equiv), CH$_2$Cl$_2$</td>
<td>-  -  10  90</td>
</tr>
<tr>
<td>10</td>
<td>As entry in 4</td>
<td>Cul (1 equiv), CH$_2$Cl$_2$</td>
<td>-  -  55  45</td>
</tr>
</tbody>
</table>

$^a$ 5 equivalents of crotonaldehyde were used. $^b$ All reactions were run for 18 h at r.t unless otherwise stated and a solvent concentration of 0.1 M was used. $^c$ Ratios were determined approximately from crude spectra. $^d$ The remaining composition of the mixture could not be ascertained but could not be attributed to the other compounds in the scheme above.
(E)-N-[2-(1H-Indol-3-yl)ethyl]-3,9-dioxonon-7-enamide (1)

To a degassed solution of alkene 3 (115 mg, 0.385 mmol) in Et₂O was added crotonaldehyde (81 mg, 1.156 mmol), Grubbs-2 catalyst B (8.0 mg, 9.6 μmol, 2 mol %), and Cul (3.0 mg, 15.4 μmol, 3 mol %) and the mixture was heated at reflux for 5 h. After cooling to room temperature, the reaction mixture was concentrated to give enal 1 (~90-95% pure by NMR), which was used directly in any further steps without further purification. ¹H NMR (400 MHz, COSY) δ 1.70 (quint, J = 7.3 Hz, H-5), 2.45 (quint, J = 7.3 Hz, 2H, H-6), 2.68 (t, J = 7.4 Hz, 2H, H-4), 2.97 (t, J = 6.8 Hz, 2H, H-2'), 3.30 (s, 2 H, H-2), 3.60 (dt, J = 12.6, 6.7 Hz, 2H, H-1'), 6.05 (dd, J = 18.0, 7.0 Hz, 1H, H-8), 6.75 (dt, J = 18.0, 7.5 Hz, 1H, H-7), 7.05 (s, 1H, H-2 Ar), 7.11 (t, J = 8.0 Hz, 1H, H-5 Ar), 7.19 (t, J = 8.0 Hz, 1H, H-6 Ar), 7.36 (d, J = 8.1 Hz, 1H H-7 Ar), 7.59 (d, J = 7.6 Hz, 1H, H-4 Ar), 8.50 (br, 1H, NH), 9.45 (d, J = 7.0 Hz, 1H, CHO); ¹³C NMR (400 MHz, HSQC) δ 21.2 (C-5), 25.1 (C-2'), 31.6 (C-6), 39.9 (C-4), 42.4 (C-1'), 49.6 (C-2), 111.4 (C-7 Ar), 112.5 (C-3 Ar), 118.6 (C-4 Ar), 119.3 (C-5 Ar), 122.10 (C-6 Ar), 122.3 (C-2 Ar), 127.3 (C-3a Ar), 133.2 (C-7a Ar), 136.4 (C-8), 157.5 (C-7), 165.6 (C-1), 194.1 (C-9), 205.3 (C-3).

³ The amount of enal 1 was found to vary from batch to batch. In some runs as much as 30% of cyclised products were seen to have formed.
Evaluation of the Organocatalytic Step

**General method:** To a stirred solution of the crude metathesis product \(1\) in the corresponding solvent (0.1 M) at r.t was added the organocatalyst (see table). After 18 h, AcCl (10 equiv) was added and the reaction was stirred for an additional 18 h. Work-up and purification by column chromatography gave 7 which was then analysed by HPLC (*for conditions see spectra section*).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysta</th>
<th>Solvent</th>
<th>e.r</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C</td>
<td>CH(_2)Cl(_2)</td>
<td>48:51</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>CH(_2)Cl(_2)</td>
<td>47:53</td>
</tr>
<tr>
<td>3</td>
<td>E</td>
<td>CH(_2)Cl(_2)</td>
<td>52:48</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>CH(_2)Cl(_2)</td>
<td>56:44</td>
</tr>
<tr>
<td>5</td>
<td>G</td>
<td>CH(_2)Cl(_2)</td>
<td>70:30</td>
</tr>
<tr>
<td>6</td>
<td>G</td>
<td>Toluene(^{c,d})</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 20% of catalyst was used in each case. \(^b\) No reaction \(^c\) Concentration of (0.33 M) used. \(^d\) Solvent was evaporated prior to addition of CH\(_2\)Cl\(_2\) and AcCl.

\(^4\) All catalysts were commercially available with the exception of G, which was prepared according to the following procedure: Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem., Int. Ed.* 2007, 46, 8431.
(3β)-Yohimban-19,21-dione (6)

To the crude enal 1 (0.282 mmol)\textsuperscript{5} in CH\textsubscript{2}Cl\textsubscript{2} (0.3 mL) at -78 °C was added benzoyl chloride (48 mg, 0.338 mmol). The resulting mixture was stirred for 3 h at -78 °C then warmed to room temperature overnight. The reaction mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} washed with 2N NaOH (aq) (3 x 2 mL), dried, and concentrated. Purification by chromatography (0→10→25→50→100% EtOAc/hexane) gave 6 and 7 (24 mg, 40%) as a yellow solid in a 2:1 ratio. NMR data\textsuperscript{6} for compound 6: \textsuperscript{1}H NMR (400 MHz, COSY) δ 1.25 (m, 1H, H-18), 1.50 (m, 1H, H-17), 1.80-1.85 (m, 2H, H-17, H-18), 1.91 (m, 1H, H-14), 2.20-2.30 (m, 2H, H-2H-16), 2.30-2.35 (m, 2H, H-2H-15) 2.70 (m, 1H, H-6), 3.00-3.05 (m, 2H, H-5,H-6), 4.92 (br d, J = 5.6 Hz, 1H, H-3), 5.10 (br d, J = 13.0 Hz, 1H, H-5), 7.12 (td, J = 7.2, 0.8 Hz, 1H, H-10), 7.19 (td J = 6.8, 1.2 Hz, 1H, H-11), 7.35 (d, J = 8.0 Hz, 1H, H-12), 7.48 (d, J = 7.6 Hz, 1H, H-9), 7.81 (br, 1H, NH) \textsuperscript{13}C NMR (400 MHz, HSQC) δ 21.2 (C-6), 21.6 (C-17), 28.9 (C-16), 29.0 (C-14), 29.9 (C-18), 31.9 (C-15), 43.1 (C-5), 53.9 (C-3), 99.3 (C-20), 111.1 (C-7), 111.2 (C-12), 118.5 (C-9), 120.1 (C-10), 122.2 (C-11), 127.4 (C-8), 132.9 (C-2), 135.7 (C-13), 169.9 (C-19), 170.1 (C-21). HRMS calcd for C\textsubscript{19}H\textsubscript{21}N\textsubscript{2}O\textsubscript{2} [M+H]\textsuperscript{+} 309.1602, found 309.1598.

\textsuperscript{5} Assuming quantitative yield from the metathesis reaction.
\textsuperscript{6} Biogenetic numbering was used.
Yohimban-19,21-dione (7)

To crude enal 1 (0.083 mmol) in CH₂Cl₂ (0.1 mL) at room temperature was added acetyl chloride (65 mg, 0.83 mmol) and the resulting mixture stirred overnight. The reaction mixture was diluted with CH₂Cl₂, washed with 2 N NaOH (3 x 1 mL), dried and concentrated. Careful purification by chromatography (0→10→25→50→100% EtOAc/hexane) gave 7 (14 mg, 54%), as a yellow solid. ¹H NMR (400 MHz, COSY) δ 1.18-1.25 (m, 1H, H-16), 1.25-1.32 (m, 1H, H-17), 1.50 (q, J = 12.8 Hz, 1H, H-14), 1.62-1.71 (m, 1H, H-18), 1.87-1.94 (m, 2H, H-16 and H-18), 2.26-2.36 (m, 1H, H-17), 2.39 (dt, J = 12.4, 3.2 Hz, 1H, H-14eq), 2.61 (t, J = 12.8 Hz, 1H, H-15), 2.82 (ddt, J = 6.0, 4.0, 2.0 Hz, 2H, H-6), 2.85-2.93 (m, 1H, H-5eq), 4.82 (dd, J = 11.6, 2.8 Hz, 1H, H-3), 5.08 (ddd, J = 12.0, 4.0, 2.0 Hz, 1H, H-5eq), 7.13 (td, J = 7.6, 0.8 Hz, 1H, H-10), 7.19 (td J = 7.2, 1.2 Hz, 1H, H-11), 7.33 (d, J = 8.0 Hz, 1H, H-12), 7.51 (d, J = 7.2 Hz, 1H, H-9), 7.75 (br, 1H, NH) ¹³C NMR (400 MHz, HSQC) δ 21.1 (C-6), 21.3 (C-16), 29.0 (C-17), 30.0 (C-18), 32.1 (C-15), 36.7 (C-14), 39.3 (C-5), 53.4 (C-3), 98.8 (C-20), 109.5 (C-7), 110.8 (C-12), 118.4 (C-9), 119.9 (C-10), 122.2 (C-11), 126.8 (C-8), 133.0 (C-2), 136.2 (C-13), 169.1 (C-19), 169.6 (C-21). HRMS calcd for C₁₉H₂₁N₂O₂ [M+H]⁺ 309.1602, found 309.1598.
One-pot synthesis of 7

To a stirred solution of β-keto ester 2 (400 mg, 1.88 mmol) in 1,4 dioxane (64 mL) was added tryptamine (392 mg, 2.44 mmol, 1.3 equiv) and the resulting mixture was heated at reflux until all of 2 was consumed (approximately 2 h, monitored by TLC). The excess tryptamine was removed by infusing the reaction mixture with a permeable cellulose bag “tea-bag” containing (0.85 g, 1.68 mmol, ~3 equiv with respect to residual tryptamine) of p-toluenesulfonic acid polymer bound resin7 (see figure 1). After 30 min, when no tryptamine was visible by TLC (see Figure 2), the “tea bag” was removed from the solution and washed with CH$_2$Cl$_2$ (2 × 10 mL) into the reaction flask. The solvent was evaporated on a rotary evaporator and the alkene 3 (~1.88 mmol) was dissolved in Et$_2$O (13.4 mL) and the resulting solution was degassed for 5 min with argon before addition of crotonaldehyde (659 mg, 0.735 mL, 9.4 mmol, 5 equiv), Grubbs-2 catalyst B (32 mg, 0.036 mmol, 0.02 equiv), and Cul (10 mg, 0.054 mmol, 0.03 equiv). The resulting mixture was heated at reflux for 5 h, cooled to room temperature and the reaction mixture concentrated. To the crude

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7 The resin was obtained from Aldrich chemical company (catalogue number: 532312) - Toluene sulfonic acid, polymer-bound Macroporous, 30-60 mesh, extent of labeling: 2.0-3.0 mmol/g loading.
enal 1 was added CH₂Cl₂ (2.2 mL) followed by acetyl chloride (1.43 g, 1.3 mL, 18 mmol, 10 equiv) and the resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH₂Cl₂ (60 mL) washed with 2 N NaOH (3 x 5 mL), dried and concentrated. Purification by chromatography (0→10→25→50% EtOAc/hexane) gave 7 (249 mg, 43% overall yield from β-keto ester 2) as a yellow solid.

**Figure 1:** Removal of excess tryptamine with acidic resin

![Removal of excess tryptamine with acidic resin](image1)

**Figure 2:** TLC of solution (a) before addition of acidic resin (b) after addition of acidic resin

![TLC of solution](image2)

1: Tryptamine reference sample  
2: Cross spots  
3: Reaction mixture
$^1$H NMR (400 MHz, CDCl$_3$) spectrum for 2
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum for 2
$^1$H NMR (400 MHz, CDCl$_3$) spectrum for 3
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum for 3
$^1$H NMR (400 MHz, CDCl$_3$) spectrum for 1
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum for 1
$^1$H NMR (400 MHz, CDCl$_3$) spectrum for 6

![Chemical Structure of 6]
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum for 6
$^1$H NMR (400 MHz, CDCl$_3$) spectrum for 7
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum for 7
1H COSY (400 MHz, CDCl₃) spectrum for 7
1H-13C HSQC spectrum for 7
HPLC\textsuperscript{8} of racemic 7 (isocratic MtBE\_EtOH 95/5):

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{hplc_racemic_7}
\caption{HPLC analysis of racemic 7.}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{RT} & \textbf{Area} & \textbf{\% Area} & \textbf{Height} \\
\hline
1 & 4.796 & 14112507 & 50.64 & 1249808 \\
2 & 5.380 & 13758226 & 49.36 & 2934832 \\
\hline
\end{tabular}
\caption{Processed Channel Descrip. for HPLC of racemic 7.}
\end{table}

HPLC of 7 using organocatalyst G (isocratic MtBE\_EtOH 95/5)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{hplc_7}
\caption{HPLC analysis of 7 with organocatalyst G.}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{RT} & \textbf{Area} & \textbf{\% Area} & \textbf{Height} \\
\hline
1 & 4.830 & 2926320 & 29.24 & 332682 \\
2 & 5.735 & 7082584 & 70.76 & 757032 \\
\hline
\end{tabular}
\caption{Processed Channel Descrip. for HPLC of 7 with organocatalyst G.}
\end{table}

\textsuperscript{8} HPLC analyses for the determination of enantiomeric excess were carried out using a DAICEL CHIRALPAK IC column (250×4.6 mm I.D., 5 μm; Chiral Technologies Europe) on a Waters model 2487 Dual Absorbance Detector and set at the wavelength of 254 nm.