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Enantiospecific synthesis of (–)-3-iso-19,20-dehydro-β-yohimbine from secologanin: a route to *normal* and *pseudo* stereoisomers of yohimbine

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Abstract

Hydrolysis of secologanin ethylene acetal at pH 7 resulted in stereoselective aldol cyclisation to a cyclohexene aldehyde, which, on reductive amination and cyclisation with tryptamine afforded (–)-3-iso-19,20-dehydro-β-yohimbine, converted into various *normal* and *pseudo* isomers of yohimbine.

Keywords: Aldol; alkaloids; biomimetic; indole; stereoselection; terpene.

The pentacyclic series of *Corynanthé* indole alkaloids, exemplified by yohimbine **8**, have been known for well over a century, and, because of their pharmacological properties, have been targets for many syntheses.[1] In nature they occur as various stereoisomers, but all have a common H-15α (*S*) configuration derived from C-7 in the monoterpenoid secologanin **1**, which condenses with tryptamine to form the universal indole alkaloid precursor, strictosidine.[2] Our group has carried out several stereoselective syntheses of alkaloids from secologanin derivatives in which the asymmetric centre at C-7 played a role in inducing chirality at other centres.[3] Thus, conversion of the C-5 aldehyde in **1** to a methyl ester and hydrolysis with β-glucosidase at pH 5.0 resulted in rearrangement of the aglucone largely to the known methyl elenolate, from which ajmalicine and other heteroyohimbine alkaloids could be prepared.[4] We found that precise control of the pH was crucial to optimise the yield of the desired aglucone, and a significant discovery was that at pH 7.0 an alternative rearrangement via a vinylogous aldol reaction predominated to give an epimeric pair of cyclohexene aldehydes, from which yohimbine and β-yohimbine were obtained.[5] However, although the results were interesting as a biomimetic analogy, the methyl ester did not afford a really satisfactory synthetic route because it gave mixtures at various stages. It was also a rather cumbersome way of protecting the aldehyde, in that it involved oxidation and reduction of C-5, so we therefore looked to an alternative.

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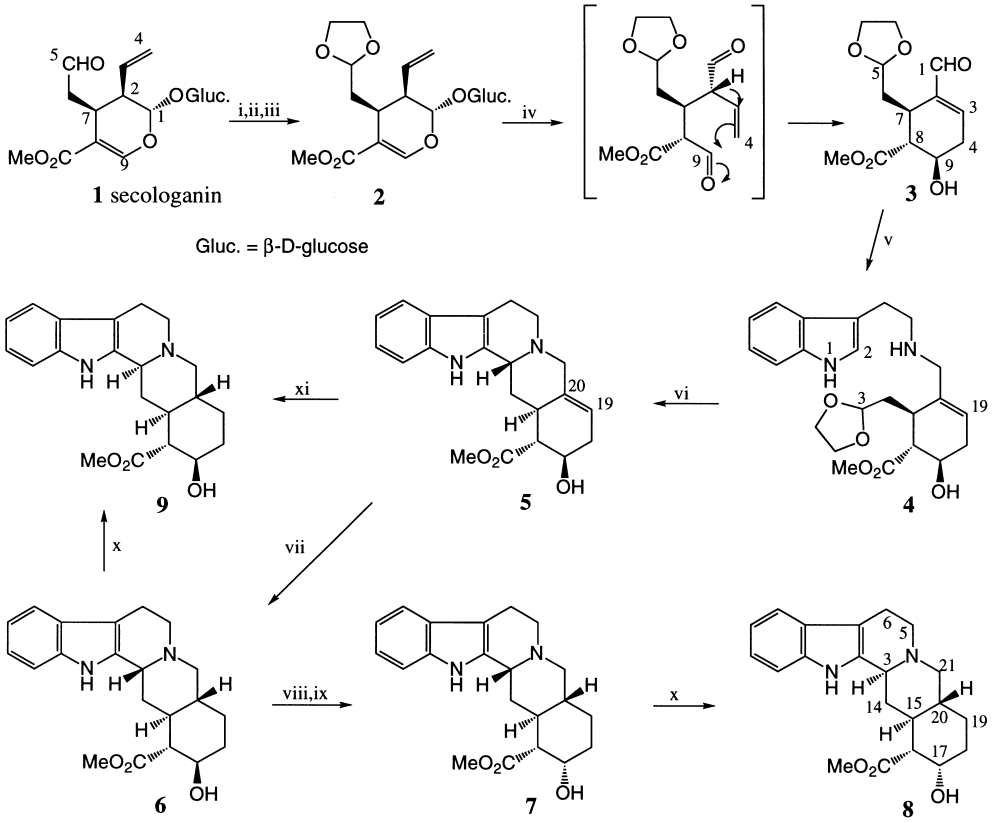
An acetal was intrinsically attractive since acid catalysed removal could in principle also promote Pictet–Spengler cyclisation to the required pentacyclic system. Thus, acetylation of secologanin followed by ethylene glycol in the presence of acid gave the tetra-acetate of ethylene acetal **2**, mp 125°C $[\alpha]_D$ –100 ($CHCl_3$). Zemplen deacetylation and subsequent hydrolysis with β-glucosidase in pH 7.0 buffer at 37°C for 4 days afforded in 70% yield the cyclohexene aldehyde **3** $[\alpha]_D$ +11.5 ($CHCl_3$) [M^+ 270.1109 ($C_{13}H_{18}O_6$); λ_{max} (MeOH): 228 nm; ν_{max} ($CHCl_3$) 3450, 2720, 1725, 1685, 1630 cm^{-1}]. Importantly, on the basis of the ^1H NMR spectrum,[8] **3** consisted of essentially only one C-9 stereoisomer (unlike the previous analogues) with *trans–trans* C-7, 8, 9 stereochemistry. Hence, with the C-5 acetal the vinylogous aldol cyclisation (Scheme 1) has achieved virtually complete stereoselection with the single chiral centre at C-7 (*S*) inducing *R* chirality at both C-8 and C-9 in **3**, a result attributable to a chair-like transition state with all the 7, 8 and 9 substituents equatorial.

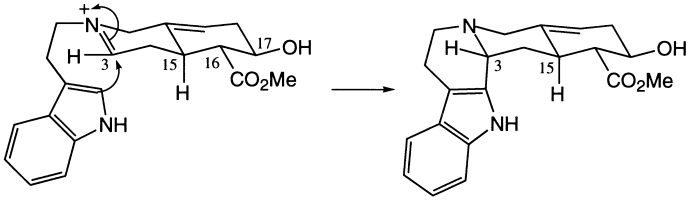


Scheme 1. Reagents and conditions: (i) Ac_2O/py, 12 h; (ii) $(CH_2OH)_2$/THF/TFA, Δ, 1 h; (iii) NaOMe/MeOH, 12 h; (iv) β-glucosidase/pH 7.0 aq. buffer, 37°C, 4 days; (v) tryptamine, MeOH/$NaCNBH_3$, 2 days; (vi) 10% aq. HCl:Me_2CO 1:1, Δ, 2 h; (vii) H_2/Pd/MeOH, 12 h; (viii) DMSO/Ac_2O, 16 h; (ix) $NaBH_4$, *i*PrOH, 20 h; (x) AcOH, Δ, 2–4 days; (xi) H_2/PtO_2/Et OH, 24 h

The next step was reductive amination of the aldehyde with tryptamine, a reaction which had previously been problematic due to mixtures formed by competing conjugate reduction under a variety of conditions and reducing agents. However, in this case over-reduction was essentially avoided by the use of sodium cyanoborohydride in methanol to afford in ca. 85% yield the

desired amine **4** [M^+ 414.2170 ($C_{23}H_{30}N_2O_5$); λ_{max}: 226, 283, 292 nm; ν_{max}: 3470, 1730 cm^{-1}] together with a probable boron complex. The structure **4** was corroborated by the ^1H NMR spectrum (300 MHz, $CDCl_3$) with signals for both indole [δ 8.29 (s, HN-1), 7.7–7.1 (m, 4 *ar*H), 7.10 (bs, H-2)] and monoterpene [δ 5.59 (bd, H-19), 4.79 (t, H-3), 4.83 (s, CO_2Me)] moieties.

Heating the above crude product in a 1:1 mixture of acetone and 10% aq. hydrochloric acid under reflux for 2 hours gave, in 75% yield on crystallisation from acetone, a single compound, mp 140–142°C $[\alpha]_D$ –73 (MeOH); [λ_{max} (MeOH): 227, 283, 291 nm; ν_{max} ($CHCl_3$): 3470, 1730 cm^{-1}]. That hydrolysis of the acetal and subsequent cyclisation to a 19,20-dehydroyohimbine had occurred was indicated inter alia by the mass spectrum with M^+ 352.1777 ($C_{21}H_{24}N_2O_3$) and several characteristic peaks, including an ion at m/z 156 that was much more intense than that at m/z 184,[6] and by the loss of the NMR signal for the indolic H-2 in **4**. The structure and relative stereochemistry was established as 3-iso-19,20-dehydro-β-yohimbine **5** from a complete analysis of the the ^1H NMR spectra[9] of the product and its 17-*O*-acetate. Diaxial couplings of 10 Hz confirmed that the H-15, 16, 17 *trans–trans* stereochemistry had been retained, whereas the small *ae* and *ee* couplings of 5 and 2.5 Hz to the C-14 methylene protons showed that H-3 was equatorial, establishing a 3–15 *trans* orientation. From the known absolute stereochemistry of C-7 in secologanin, this would correspond in **5** to a 3-β(*R*) configuration, which was confirmed by a –ve Cotton effect (-2.7×10^4 cm^{-2} $dmol^{-1}$) at 280 nm in the CD spectrum.[7] Exclusive generation of this stereochemistry in the Pictet–Spengler cyclisation can be attributed to kinetic axial attack by the indole at a C-3/N-4 iminium in a chair-like intermediate with equatorial C-15, 16 and 17 substituents to give a *cis*-quinolizidine (Scheme 2). Because this was a kinetic product, in addition to the 3β(*R*) series, it afforded routes to the thermodynamically preferred *trans*-quinolizidine alkaloids with 3α(*S*) configuration.



Scheme 2.

Thus, catalytic hydrogenation of the 19,20 double bond in **5** with Pd/C occurred only from the top face to give a quantitative yield of pseudo-β-yohimbine **6**, mp 135–138°C $[\alpha]_D$ +68 (MeOH), as indicated by M^+ 354.1939 ($C_{21}H_{26}N_2O_3$) and the NMR spectrum[9] with three large *trans*-diaxial couplings to H-20 from protons on C-15, 19 and 21; small couplings to H-3 showed retention of an equatorial β-configuration which was corroborated by a –ve Cotton effect at 280 nm in the CD spectrum. Moffit oxidation of **6** gave the 17-ketone, mp 220–223°C [M^+ 352.1787 ($C_{21}H_{24}N_2O_3$)] which was reduced stereoselectively with sodium borohydride in isopropanol to only pseudoyohimbine **7**, mp 250–253°C [M^+ 354.1927 ($C_{21}H_{26}N_2O_3$)]. Its NMR spectrum[9] was similar to that of **6**, except for small couplings to H-17 in accord with inversion to an axial OH group. Subsequent heating in glacial acetic acid epimerised C-3 to give the *trans*-quinolizidine yohimbine **8** [M^+ 354.1943 ($C_{21}H_{26}N_2O_3$)], characterised by a broadened doublet for H-3 with a *trans* diaxial coupling of 11 Hz in the NMR spectrum,[9] and a +ve Cotton effect at 280 nm in the CD spectrum,[7] and identified by comparison with an authentic sample. A similar epimerisation of **6** afforded β-yohimbine **9** [M^+ 354.1924 ($C_{21}H_{26}N_2O_3$)], which was also produced directly by

hydrogenation of **5** with Adams' catalyst. Again, oxidation of **9** to yohimbone, mp 245–248°C [M^+ 352.1783 ($C_{21}H_{24}N_2O_3$)] and subsequent reduction gave yohimbine.

Hence, we have synthesised, in ca. 40% overall yield from secologanin, (–)-3-iso-19,20-dehydro-β-yohimbine **5**, an example (as yet unknown in nature) of a rare type of indole alkaloid, and used it to prepare selectively four of the *normal* and *pseudo* stereoisomers of yohimbine. Its further conversion into *epiallo* and *allo* isomers is discussed in the following paper.[10]

Acknowledgements

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8. ^{1}H NMR spectrum (300 MHz, d_6-Me_2CO) (numbering based on secologanin). Compound **3**: δ 9.50 (s, H-1), 6.91 (ddd, J = 5, 3, 1 Hz, H-3), 4.92 (dd, J = 5.5, 5 Hz, H-5), 4.12 (ddd, J = 8, 7.5, 5 Hz, H-9), 4.0–3.8 (m, OCH_2CH_2O), 3.71 (s, OMe), 3.15 (m, J = 8, 7.5, 3.5, 1 Hz, H-7), 3.08 (dd, J = 8, 7.5 Hz, H-8), 2.44 (ddt, J = 19.5, 7.5, 3 Hz, H-4$_b$), 2.69 (dtd, J = 19.5, 5, 1.5 Hz, H-4$_a$), 2.29 (ddd, J = 14, 8, 5 Hz, H-6$_a$), 1.80 (ddd, J = 14, 5.5, 3.5 Hz, H-6$_b$).
9. Selected ^{1}H NMR spectra (300 MHz, $CDCl_3$) (numbering based on yohimbine). Compound **5**: δ 8.14 (bs, NH), 7.49–7.13 (m, *ar*-H_4), 5.47 (d, J = 5.5 Hz, H-19), 4.42 (ddd, J = 5, 2.5, 2 Hz, H-3), 3.86 (ddd, J = 10.5, 10, 5 Hz, H-17), 3.81 (s, OMe), 3.34 (d, J = 13 Hz, H-21$_{eq}$), 3.27 (m, H_2-5), 3.07 (d, J = 13 Hz, H-21$_{ax}$), 3.01 (dm, J = 17 Hz, H-6$_{eq}$), 2.59 (ddd, J = 17, 4.5, 2.5 Hz, H-6$_{ax}$), 2.35–2.40 (m, H-14$_{eq}$, H-15, H-16, H-18$_{eq}$), 2.10 (ddd, J = 17.5, 10.5, 3 Hz, H-18$_{ax}$), 1.81 (ddd, H-14$_{ax}$). Compound **5** *O*-acetate: δ 5.50 (d, J = 4.5 Hz, H-19), 4.98 (ddd, J = 10.5, 10, 5 Hz, H-17), 4.54 (ddd, J = 5, 2.5, 2 Hz, H-3), 3.76 (s, OMe), 3.40 (dm, J = 13, ~3, ~1 Hz, H-21$_{eq}$), 3.3 (m, H_2-5), 3.14 (d, J = 13 Hz, H-21$_{ax}$), 3.02 (dm, J = 17 Hz, H-6$_{eq}$), 2.63 (ddd, J = 17, 4.5, 2.5 Hz, H-6$_{ax}$), 2.50 (dm, J = 17.5, 10, ~3, ~1 Hz, H-18$_{eq}$), 2.54 (t, J = 10 Hz, H-16), 2.48 (ddd, J = 11.5, 10, 4.5 Hz, H-15), 2.32 (ddd, J = 13.5, 4.5, 2.5 Hz, H-14$_{eq}$), 2.12 (ddm, J = 17.5, 10.5, ~3 Hz, H-18$_{ax}$), 1.87 (ddd, J = 13.5, 11.5, 5 Hz, H-14$_{ax}$). Compound **6**: δ 4.47 (dd, J = 4, 1.5 Hz, H-3), 3.84 (s, OMe), 3.58 (td, J = 11, 4 Hz, H-17), 4.41 (m, H_2-5), 3.02 (tdd, J = 12, 6, 2.5 Hz, H-6$_a$), 3.74 (dm, J = 12 Hz, H-6$_b$), 2.76 (dd, J = 12, 5 Hz, H-21$_{eq}$), 2.53 (t, J = 12 Hz, H-21$_{ax}$), 2.16 (t, J = 11 Hz, H-16), 2.10 (dtd, J = 11, 9, 2.5 Hz, H-15), 2.1–2.0 (m, H_2-14, H-18$_{eq}$), 2.12 (dtd, J = 16, 12, 2.5 Hz, H-18$_{ax}$), ca. 1.6 (m, H-19$_{eq}$, H-20), 1.39 (dtd, J = 16, 12, 2.5 Hz, H-18$_a$), 0.92 (dtd, J = 16, 12, 2.5 Hz, H-19$_a$). Compound **7**: δ 4.75 (ddd, J = 5, 2.5, 1.5 Hz, H-3), 4.29 (bs, J = 3, 2.5, 2 Hz, H-17), 3.92 (s, OMe), 3.44 (m, H_2-5), 3.07 (dm, J = 16 Hz, H-6$_a$), ca. 2.8 (dm, J = 16 Hz, H-6$_b$; dd, J = 12, 3.5 Hz, H-21$_{eq}$), 2.68 (t, J = 12 Hz, H-21$_{ax}$), 2.34 (dd, J = 12, 3 Hz, H-16), 2.30 (dm, J = 12, 3, 2.5 Hz, H-14$_{eq}$), 2.00 (td, J = 12, 5 Hz, H-14$_{ax}$), 1.87 (dm, J = 12, ~3 Hz, H-18$_{eq}$), 1.78–1.55 (tm, J = 12 Hz, H-15; tm, J = 12 Hz, H-18$_{ax}$; td, J = 12, 3.5 Hz, H-20), 1.30 (bq, J = 12 Hz, H-19$_{ax}$), 0.92 (dbd, J = 12, 3 Hz, H-19$_{eq}$). Compound **8**: δ 4.35 (dm, J = ~3 Hz, H-17), 3.72 (s, OMe), 3.43 (bd, J = 11 Hz, H-3), 3.01 (dd, J = 11, 3 Hz, H-21$_{ex}$), 2.65 (t, J = 11 Hz, H-21$_{aq}$), 2.38 (dd, J = 11, 3 Hz, H-16), 1.45 (tm, J = 11 Hz, H-15), 1.26 (q, J = 11 Hz, H-14$_{ax}$). Compound **9**: δ 3.81 (ddd, J = 5, 2.5, 1 Hz, H-17), 3.78 (s, OMe), 3.22 (dd, J = 11, 2.5 Hz, H-3).
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