Pergamon

Tetrahedron Letters 41 (2000) 5631–5635

TETRAHEDRON LETTERS

Synthesis of 18*R*-hydroxy-*epiallo*-yohimbines from (–)-3-iso-19,20-dehydro-β-yohimbine: an enantiospecific route to deserpidine and reserpine analogues from secologanin

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Received 19 May 2000; accepted 1 June 2000

Abstract

(–)-3-Iso-19,20-dehydro-β-yohimbine has been converted into *epiallo*-yohimbines and, via a novel regio- and stereoselective hydration, into the 18*R*-hydroxy derivative, an analogue of deserpidine. Its 11-methoxy derivative, also prepared from secologanin, is a potential precursor for a reserpine analogue.

Keywords: addition reaction; alkaloids; indole; regioselection; stereoselection; terpene.

Because of their therapeutic uses, deserpidine **1** and reserpine **2** are the most familiar members of the small group of 18-hydroxy-*epiallo*-yohimbine alkaloids, and have been targets for a variety of synthetic approaches.[1] Common to all of these was the necessity for *epiallo* stereochemistry, i.e. 3β, 15α, 20α, around ring D, which was generally achieved by using intermediates with the eventual H-15 and H-20 *cis* and then exercising stereocontrol in generation of the *trans* H-3 relative configuration. This was not a trivial task, essentially because there is usually not much difference in energy between the available conformations of the C-3 *epiallo* and *allo* epimers. However, our synthesis[2] of (–)-3-iso-19,20-dehydro-β-yohimbine **3** from secologanin offered the opportunity for an alternative approach, in that H-3 and H-15 now had the desired *trans* geometry and it remained to introduce H-20 selectively *cis* to H-15. In this case the choice was between *pseudo* (3β, 15α, 20β) and *epiallo* stereochemistry, whence conformational analysis led us to consider that the latter should be thermodynamically preferred. Furthermore, the presence of a 19,20 double bond meant that it should be possible to introduce an oxygenated functionality at the allylic C-18 position.

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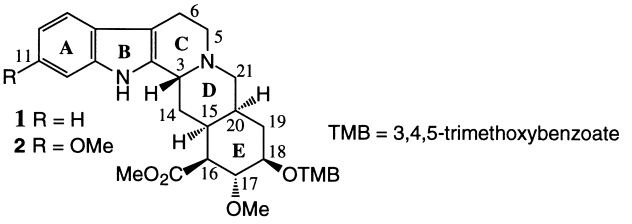
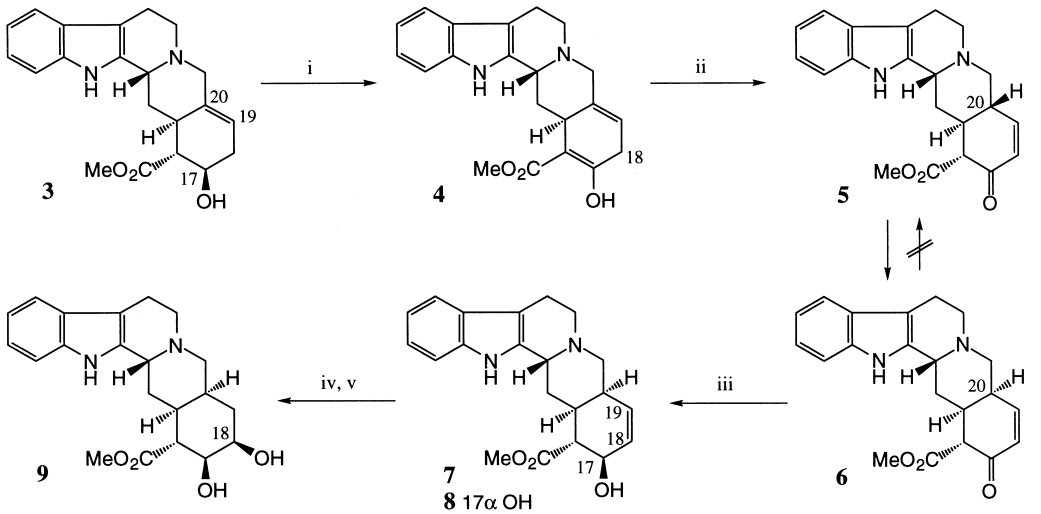
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00913-8



We envisaged that the required H-20 stereochemistry might be achieved by oxidation of the C-17 alcohol in **3** and subsequent isomerisation of the 19,20 alkene into conjugation with the 17-ketone (Scheme 1). Initial attempts to obtain the ketone were thwarted by the ease of aromatisation to a phenol, but Swern oxidation with DMSO/$(COCl)_2$ afforded in 87% yield an amorphous product [M^+ 350.1628 ($C_{21}H_{22}N_2O_3$); λ_{max} (MeOH): 225, 273, 291 nm; ν_{max} ($CHCl_3$): 3500–3200, 1732, 1657, 1619 cm^{-1}]. A large base shift of the UV spectrum indicated the anticipated β-keto-ester, shown to be virtually completely enolised by lack of an H-16 signal and the presence of an exchangeable one-proton signal at δ 12.47 in the ^1H NMR spectrum,[5] which also confirmed the structure as **4**.



Scheme 1. Reagents and conditions: (i) DMSO/$(COCl)_2$/CH_2Cl_2, –50°C, 0.5 h; (ii) DBU/MeCN, 24 h; (iii) $NaBH_4$/$CeCl_3$/MeCN/MeOH, 1 h; (iv) $Hg(O_2CCF_3)_2$/MeCN/aq.TFA, 24 h; (v) $NaBH_4$/aq. NaOH, 5 min

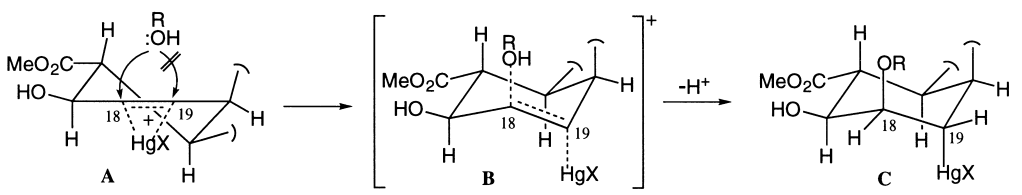
As the next step of alkene isomerisation entailed the deprotonation of C-18 in the presence of this much more acidic enol, several acids and bases were tried as catalysts, with disappointing results. In particular, compound **4** was susceptible to β-dicarbonyl cleavage, reacting to give conjugated ketones but only with concomitant decarbomethoxylation. Eventually, it was found that DBU in acetonitrile at room temperature for 24 hours achieved the double bond migration with retention of the ester, giving an 80% yield of two separable isomers in a ca. 8:1 ratio. The structure of the major product $[\alpha]_D$ +19 (EtOH) [M^+ 350.1632 ($C_{21}H_{22}N_2O_3$); ν_{max}: 1737, 1677 cm^{-1}] was shown to be the desired 18,19-dehydro-epialloyohimbone **6** from inter alia a detailed analysis of its ^1H NMR spectrum.[5] There were two alkene protons at δ 5.86 and 6.10 assigned to H-18 and H-19 respectively; H-3 was a broadened doublet at δ 3.27 with a *trans-aa* coupling of 12

Hz to H-14$_{ax}$; H-16 was a doublet at δ 3.60 with a *trans-aa* coupling of 12 Hz to H-15 at δ 2.77, which in turn had only a small *ae* coupling of 2 Hz with H-20, in accord with their *cis* geometry, and small *ae* and *ee* couplings with both C-14 protons. These data established an *epiallo* configuration and also a *trans*-quinolizidine conformation, the latter feature corroborated by characteristic IR bands at ca. 2735 cm^{-1}.

As anticipated, the minor product $[\alpha]_D$ –34 (EtOH) [M^+ 350.1630 ($C_{21}H_{22}N_2O_3$); ν_{max}: 1732, 1675 cm^{-1}] was found to be the alternative 20-epimer, 18,19-dehydro-pseudoyohimbone **5**. In its NMR spectrum[5] H-15 was observed at δ 1.65 with *trans-aa* couplings of 11, 11 and 12 Hz to H-14$_{ax}$, H-16 and H-20, respectively, whereas H-3 was a broad singlet at δ 4.18 with only small *ae* and *ee* couplings with the C-14 protons, in accord with an equatorial orientation. Hence, a *pseudo* configuration was confirmed with a corresponding *cis*-quinolizidine conformation, as also indicated by the absence of any *trans* IR bands. We rationalised that the *cis*-quinolizidine **5** was an initial kinetic product from the deprotonation/reprotonation process but that it was gradually isomerised into the more stable *trans*-quinolizidine **6**. Accordingly, when pure samples of **5** and **6** were treated with DBU in acetonitrile, **5** was indeed slowly converted into **6**, but there was no sign of the reverse even after several weeks.

To obtain a C-18 hydroxyl with β(*R*) configuration a regioselective and stereoselective addition of water to the 18,19 alkene was required. Our initial strategy envisaged use of a β C-17 hydroxyl to direct oxygen addition to the *re* face of C-18 via a cyclic acetal, and hence generate a *cis*-diol by analogy with a literature procedure using Hg^{2+} and chloral.[3] Thus, borohydride reduction of **6** in methanol/acetonitrile in the presence of $CeCl_3$ afforded a 78% yield of a separable epimeric pair (4:1 ratio) of allylic alcohols. The major product $[\alpha]_D$ +19 (EtOH) [M^+ 352.1793 ($C_{21}H_{24}N_2O_3$)] was shown to be 18,19-dehydro-epiallo-β-yohimbine **7** from its NMR spectrum[5] with a large *trans*-diaxial coupling of 11 Hz between H-17 and H-16, which in turn also had another *trans-aa* coupling with H-15. On the other hand, the minor alcohol $[\alpha]_D$ +12 (EtOH) [M^+ 352.1780 ($C_{21}H_{24}N_2O_3$)] was 18,19-dehydro-epialloyohimbine **8**, as indicated by a *cis-ae* coupling of 4 Hz between H-16 and H-17. In both cases the structures were confirmed by catalytic hydrogenation with Pd–C of the 18,19-alkene to the known alkaloids.

However, all attempts to form a cyclic acetal from **7** failed, and a variant involving cyclisation of a urethane apparently resulted in bonding of the nitrogen rather than the oxygen to C-18. Nevertheless, since the latter indicated that mercuration was at least occurring, we devised a new strategy. Considering the concave shape of the D/E rings imposed by the *cis* ring junction, the mercury ion should attack the alkene from the less hindered convex face to give an intermediate cation, which would prefer to have a half-chair conformation **A** with three substituents pseudo–equatorial rather than axial as in the alternative (Scheme 2). Crucially, if the reactions were under stereoelectronic control, obligatory *trans*-diaxial addition would mean that the nucleophile (e.g. ROH) must approach from the upper *re* face on a trajectory towards C-18, rather than C-19, to



Scheme 2.

ensure a chair-like transition state **B**, rather than an unfavourable boat-like transition state. The net result should be formation of the organomercurial **C**, and hence 18*R* alcohol **9**.

After some experimentation, treatment of **7** with mercuric trifluoroacetate in presence of water and TFA (to minimise oxidation of N-4), followed by reduction of the organomercury intermediate with sodium borohydride, afforded a single product, mp 158–160°C [M^+ 370.1875 ($C_{21}H_{26}N_2O_4$); λ_{max}: 229, 286, 290 nm; ν_{max}: 3600–3260, 1714 cm^{-1}] in 50% yield. That it was a diol was shown by the formation of a diacetate [M^+ 454.2099 ($C_{25}H_{30}N_2O_6$); ν_{max}: 3250, 1725 cm^{-1}], analysis of whose NMR spectrum[5] established that the addition of water to **7** had indeed proceeded with the desired regio- and stereochemistry to give **9**. In particular, a double doublet at δ 5.32 was identified as H-17 with a large *trans-aa* coupling to H-16 and a small *cis-ae* coupling to H-18, attributed from its chemical shift at δ 5.63; in turn, H-18 had only small *ae* and *ee* couplings to the C-19 methylene group, confirming its equatorial disposition. Interestingly, an identical addition also occurred with the minor epimer **8**, showing that H-bonding of the nucleophile ROH with the 17-alcohol was not an essential requirement for the reaction.

Thus, from **3** we have produced 18*R*-hydroxy-epiallo-β-yohimbine **9**, an analogue of deserpidine **1** with the correct absolute stereochemistry at C-3, 15, 18 and 20. Indeed, elimination of water from C-16/17 would give a compound which has been converted into **1** by Szantay and co-workers.[4] The 11-methoxy derivative of **3** has also been made for conversion into a similar analogue of reserpine **2**. Furthermore, inversion of C-3 by standard methods[1b] would give access to the corresponding *allo* series of yohimbines from the *epiallo* compounds.

Acknowledgements

We thank the EPSRC for a Postdoctoral Research Assistantship (F.B.) and the Commonwealth Commission for a Scholarship (B.E.N.D.).

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5. ^{1}H NMR spectra (300 MHz). Compound **4**: (C_6D_6) δ 12.47 (s, OH), 7.76 (bs, NH), 7.25–7.70 (m, *ar*-H_4), 5.48 (bs, H-19), 4.42 (dd, J = 6, 3 Hz, H-3), 3.90 (s, OMe), 3.82 (bd, J = 16.5 Hz, H-21$_{eq}$), 3.80 (dm, J = 13 Hz, H-5$_{eq}$), 3.59 (ddd, J = 13, 12, 2 Hz, H-5$_{ax}$), 3.1–2.9 (m, H-6$_{eq}$, H_2-18, H-21$_{ax}$), 2.82 (bd, J = 12 Hz, H-15), 2.48 (dd, J = 12, 3 Hz, H-14$_{eq}$), 2.20 (ddd, J = 15, 12, 5 Hz, H-6$_{ax}$), 1.62 (td, J = 12, 6 Hz, H-14$_{ax}$). Compound **5**: (C_6D_6) δ 7.95 (bs, NH), 7.68–7.12 (m, *ar*-H_4), 6.10 (dd, J = 10, 5 Hz, H-19), 5.86 (d, J = 10 Hz, H-18), 3.65 (s, OMe), 3.27 (bd, J = 12 Hz, H-3), 3.02 (dd, J = 12, 3 Hz, H-6$_{ax}$), 2.77 (ddm, J = 12, 2 Hz, H-15), 2.65 (m, H-5$_{eq}$, H-6$_{eq}$), 2.4–2.3 (m, H-20, H-5$_{ax}$, H-21$_{ax}$), 1.65 (dm, J = 12 Hz, H-14$_{eq}$), 1.57 (m, H-14$_{eq}$, H-21$_{eq}$). Compound **6**: (C_6D_6) δ 7.48 (bs, NH), 7.63–7.19 (m, *ar*-H_4), 5.76 (d, J = 10 Hz, H-18), 5.70 (dd, J = 10, 5 Hz, H-19), 4.18 (bs, H-3), 3.60 (s, OMe), 3.05 (m, H_2-5), 2.95 (d, J = 11 Hz, H-16), 2.84 (dbd, J = 15, 10 Hz, H-6$_{ax}$), 2.38 (dbd, J = 15, 4 Hz, H-6$_{eq}$), 2.29 (dd, J = 11, 4 Hz, H-21$_{eq}$), 2.18 (dd, J = 11, 10 Hz, H-21$_{ax}$), 1.65 (m, H-14$_{eq}$, H-15), 1.52 (dbd, J = 14, 11 Hz, H-14$_{ax}$). Compound **7**: ($CDCl_3$) δ 8.07 (bs, NH), 7.47–7.15 (m, *ar*-H_4), 5.72 (dd, J = 10, 1 Hz, H-18), 5.65 (ddd, J = 10, 4, 1 Hz, H-19), 4.60 (d, J = 11 Hz, H-17), 3.85 (s, OMe), ca. 3.8 (m, H_2-5), 3.45 (dbd, J = 12, 4.5 Hz, H-3), ca. 3.0 (m, H_2-6), 2.85 (dd, J = 13, 11 Hz, H-16), 2.87 (dm, J = 12 Hz, H-20), 2.64 (bd, J = 12 Hz, H-21$_{eq}$), 2.34 (dm, J = 13 Hz, H-15), 2.24 (bt,

$J = 12$ Hz, H-21$_{ax}$), ca. 1.85 (m, H_2-14). Compound **8**: ($CDCl_3$) δ 7.83 (bs, NH), 7.56–7.14 (m, *ar*-H_4), 5.95 (dd, $J = 10.5$, 5.5 Hz, H-19), 5.65 (dd, $J = 10.5$, 5 Hz, H-18), 4.46 (dd, $J = 5$, 4 Hz, H-17), 3.84 (s, OMe), ca. 3.8 (m, H_2-5), 3.42 (bd, $J = 12.5$ Hz, H-3), ca. 3.0 (m, H_2-6), 3.10 (dd, $J = 13$, 4 Hz, H-16), 2.94 (dd, $J = 11$, 5 Hz, H-21$_{eq}$), ca. 2.65 (m, H-15, H-20), ca. 2.22 (m, H-14$_{eq}$, H-21$_{ax}$), 1.93 (ddd, $J = 12.5$, 11, 5 Hz, H-14$_{ax}$). Compound **9**: (C_6D_6) δ 7.65 (bs, NH), 7.62–7.16 (m, *ar*-H_4), 5.63 (dt, $J = 4$, ~2 Hz, H-18), 5.32 (dd, $J = 11.5$, 4 Hz, H-17), 3.62 (dbd, $J = 13$, 3 Hz, H-3), 3.52 (dd, $J = 14$, 11.5 Hz, H-16), 3.51 (s, OMe), 3.08 (ddd, $J = 17$, 10, 5.5 Hz, H-6$_{ax}$), 2.88 (dd, $J = 13$, 10 Hz, H-21$_{ax}$), 2.63 (dbd, $J = 17$, 4 Hz, H-6$_{eq}$), 2.53 (td, $J = 10$, 5.5 Hz, H-5$_{ax}$), 2.45 (dd, $J = 13$, 4 Hz, H-21$_{eq}$), ca. 2.0 (m, H-15, H-20), ca. 1.4 (m, H_2-19).