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Enantiospecific, diastereoselective synthesis of *Aspidosperma* alkaloid analogues from secologanin

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Abstract

Pure enantiomers of two diastereomeric *Aspidosperma* alkaloid analogues antipodal at the spiro and adjacent centres have been prepared, as kinetic and thermodynamic products, respectively, in a biomimetic sequence via a secodine-like intermediate from a secologanin derivative and Kuehne's indolo-azepine. © 2000 Elsevier Science Ltd. All rights reserved.

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Both enantiomeric series of *Aspidosperma* alkaloids, exemplified by vincadifformine **1**, occur in nature, even though they are derived from one enantiomer of the universal monoterpenoid indole alkaloid precursor, strictosidine, formed by condensation of tryptamine and secologanin **3**.[1] This dichotomy was plausibly attributed to the intervention of an achiral intermediate, e.g. secodine **2**, with cyclisation to one enantiomer or the other of **1** being controlled by the chiral environment of an enzyme specific to the individual plant (Scheme 1). Presumably due to its high reactivity, no secodine could be isolated in vivo, although related dimers and dihydrosecodine have been discovered.[1] Eventually, Kuehne and co-workers substantiated the proposed pathway by elegant in vitro syntheses of a transient secodine **2** with biomimetic cyclisation in high yield to racemic vincadifformine.[2] In subsequent work, their indolo-azepine methodology was used in enantioselective syntheses of (+)- and (−)-vincadifformine in high enantiomeric excess.[3]

Our group has carried out several stereoselective syntheses of *Corynanthé* alkaloids from secologanin in which the asymmetric centre at C-7 played a key role in inducing chirality at other centres.[4] We considered that the C-7 centre might also direct stereoselectivity in cyclisation of secodine-like intermediates formed, by analogy with Kuehne's work, from indolo-azepine **7** and aldehydes derived from secologanin and hence generate a novel series of chiral *Aspidosperma* alkaloid analogues (Scheme 2).

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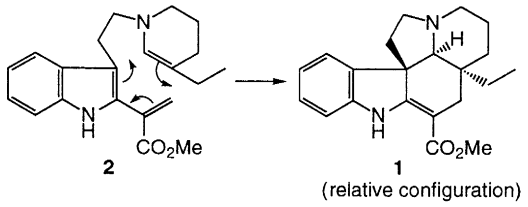
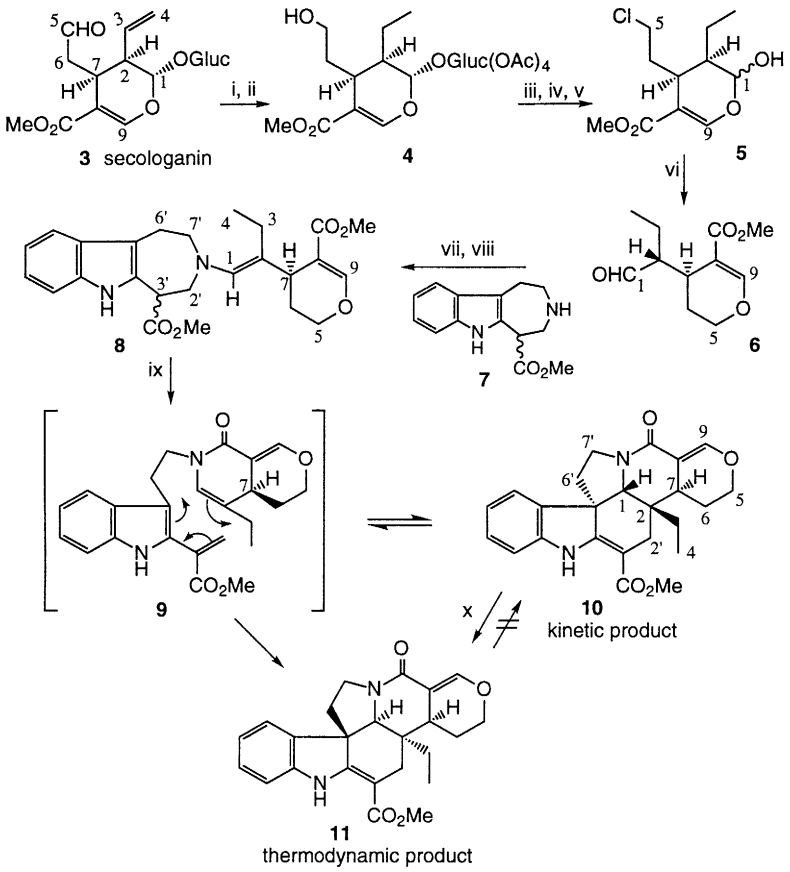


Scheme 1.



Scheme 2. Reagents and conditions: (i) Ac_2O/py, 12 h; (ii) H_2/Pd/EtOAc/H_2O, 48 h; (iii) $SOCl_2$/DCM, 15 min; (iv) NaOMe, MeOH, 1.5 h; (v) β-glucosidase, pH 5 aq. buffer, 37°C, 2 days; (vi) pH 7 aq. Me_2CO, 37°C, 3 days; (vii) MeOH, Δ, 2–4 days; (viii) silica chromatography; (ix) $CHCl_3$, 7 days; (x) MeOH, Δ, 6 days

Thus, acetylation and catalytic hydrogenation of secologanin **3** afforded tetrahydrosecologanin tetra-acetate **4** [M^+ 560.2105 ($C_{25}H_{36}O_{14}$); λ_{max}(MeOH): 238 nm; ν_{max} ($CHCl_3$): 3500, 1750, 1720, 1630 cm^{-1})] which was converted with $SOCl_2$ in DCM to the 5-chloro derivative, mp 125°C, as indicated inter alia by loss of the OH peak in the IR spectrum and elemental analysis for $C_{25}H_{35}O_{13}Cl$. Zemplen deacetylation and hydrolysis with β-glucosidase then gave in 42% overall yield from **3** the 5-chloro-aglucone **5** [M^+ 248.0817 ($C_{11}H_{17}O_4{}^{35}Cl$); ν_{max} ($CHCl_3$): 3415, 1703, 1630 cm^{-1}]. Removal of the sugar was confirmed by a shift in the UV maximum from 238 to 272 nm on addition of alkali, due to opening of the hemi-acetal ring and formation of a conjugated enolate anion, and the ^1H NMR spectrum which also showed **5** to be a pair of C-1 epimers from two H-9 singlets at δ 7.51 and 7.48. After

some experimentation, it was found that on standing in aq. acetone at pH 7 and 37°C for three days, an intramolecular displacement of the chlorine at C-5 by the C-9 enol could be achieved to give, in 80% yield, the C-1 aldehyde **6**. The molecular ion at *m/z* 212.103 ($C_{11}H_{16}O_4$) indicated loss of HCl, and the UV maximum at 237 nm was attributable to a β-alkoxyacrylate chromophore, but the lack of a shift with alkali indicated that the product was not a hemi-acetal. Accordingly, no OH signal was present in the IR spectrum, but there were now two C=O bands at 1750 and 1710 cm^{-1}, confirmation of the former as the C-1 aldehyde and hence structure **6** coming from its ^1H NMR spectrum.[7]

The indolo-azepine **7**[5] and aldehyde **6** were then heated under reflux in MeOH for four days, and subsequent chromatography afforded two isomeric products, characterised as lactams **A**, mp 238–240°C $[\alpha]_D$ +150°, and **B**, mp 205–207°C $[\alpha]_D$ −131°, in ca. 10 and 20% unoptimised yield, respectively. For both products the UV absorption with λ_{max} 226, 296, 326 nm was no longer indolic but corresponded to a combination of β-anilinoacrylate and β-alkoxyacrylamide chromophores, as did two C=O IR bands at ca. 1710 and 1650 cm^{-1}; molecular ions at *m/z* 406 analysing for $C_{24}H_{26}O_4N_2$ and the presence of only one methyl ester in the NMR spectra were consistent with formation of a lactam. In both mass spectra the base peak at *m/z* 214 plus an ion at *m/z* 192 corresponded to a fragmentation by retro Diels–Alder and allylic cleavage characteristic of an *Aspidosperma* skeleton.

Lactam **A** was assigned structure **10** and relative stereochemistry from a complete analysis of the ^1H NMR spectrum[7] with decoupling and NOE experiments. The ethyl group was shown to be *cis* to H-1 and *trans* to H-7 when irradiation of both C-3 protons gave enhancement of the former (3.1/2.5%) but not the latter, whereas irradiation of H-7 did enhance one of the C-7′ protons, showing that the ethanamine bridge and H-7 were on the same side. Finally, the absolute configuration of the spiro centre in lactam **10** was established as *S* and C-1 as *R* from correlation of the positive optical rotation and, more specifically, the associated positive Cotton effect at 326 nm in the CD spectrum with those of known alkaloids of the vincadifformine group.[6] For lactam **B** structure **11** was deduced in a similar way from ^1H NMR[7] and CD spectra. Salient points were that a negative Cotton effect established spiro *R* and C-1 *S* chirality, and that substantial, reciprocal NOE enhancements observed between H-1, H-7 and the protons of the ethyl group showed that they were all on the same side of the molecule. Since on heating lactam **10** in refluxing MeOH it was slowly converted into **11**, but the latter gave no indication of reverting to **10** under the same conditions, lactam **10** must be the kinetic and **11** the thermodynamic product. Molecular modelling indicated that the difference in stability could be attributed essentially to an eclipsing interaction along the 2–7 bond in **10** that was relieved on conversion to **11**.

After condensing **7** and **6** in MeOH for a shorter time of two days, chromatography afforded the intermediate enamine **8** as a ca. 9:1 mixture of isomers, probably 3′-epimers, in ca. 15% unoptimised yield [M^+ 438.2149 ($C_{25}H_{30}O_5N_2$); λ_{max} 224, 282, 291 nm]. The structure was established from the ^1H NMR spectrum[7] with signals for both indolo-azepine and monoterpene moieties, and characterised in particular by a singlet for the enamine H-1 at δ 6.81. Furthermore, NOE studies not only showed that the major enamine had *E* 1,2-geometry, but also that it was the *E* N,1-rotamer: irradiation of H-1 enhanced H-7 (4.5%), 9 (2.6%) and 2a′ (9.7%) but not any protons of the ethyl group, whereas irradiation of H_a-3 gave enhanced peaks for protons on C-7′ (5.2%) but not C-2′.

Significantly, on standing in $CHCl_3$ for seven days the enamine **8** was *quantitatively* converted into a single product, the kinetic lactam **10**. These results can be rationalised by invoking a secodine-type intermediate **9** formed by retro-Michael fragmentation and lactamisation of **8**, after *E/Z* isomerisation of the enamine. At room temperature, cyclisation is then directed by the C-7 chiral centre to the less hindered face of the enamide ring to afford the kinetic lactam **10** exclusively. However, at 65°C reversal to **9** must occur and thus permit a slow accumulation of the thermodynamic lactam **11** by attack from the more hindered face, a process that is apparently irreversible under these conditions.

We have thus achieved the synthesis from a single chiral precursor of two diastereomeric *Aspidosperma* alkaloid analogues that are antipodal at every centre except one, the original C-7 centre of secologanin. If this asymmetric centre were eliminated (e.g. by dehydrogenation) then we would have the prospect of readily controlled selective syntheses for both enantiomeric series. A further possibility is the use of secologanin itself with the indolo-azepine and hence a route to novel hybrid *Aspidosperma–Corynanthé* structures.

Acknowledgements

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7. ^{1}H NMR spectra (300 MHz, $CDCl_3$) (numbering based on secologanin): **6** δ 9.68 (d, *J*=3 Hz, H-1), 7.62 (s, H-9), 4.14 (m, *J*=12, 4.5, 1.5 Hz, H-5_{eq}), 3.92 (m, *J*=12, 10.5, 4 Hz, H-5_{ax}), 3.70 (s, OMe), 3.00 (m, *J*=1.5 Hz, H-7), 2.47 (m, *J*=3 Hz, H-2), 1.9–1.7 (m, H_2-6, H-3_b), 1.35 (m, H-3_a), 0.93 (t, *J*=7 Hz, H_3-4). **8** (major isomer) δ 8.63 (NH), 7.48 (s, H-9), 7.1–7.6 (m, *ar*-H_4), 6.81 (s, H-1), 4.25 (dd, *J*=5, 2.5 Hz, H-3′), 4.07 (m, H-5_a), 3.79 (m, H-5_b), 3.72 (s, OMe), 3.69 (s, OMe), 3.5–3.7 (m, H_2-7′), 3.16 (m, *J*=10.5, 2.5 Hz, H-2_a′), 2.97 (bd, *J*=2.5 Hz, H-7), 2.64 (m, *J*=10.5, 5 Hz, H-2_b′), 2.5–2.3 (m, H_2-6′), 2.15 (m, H-3_a), 1.97 (m, H-6_b), 1.7–1.5 (m, H-6_a, H-3_b), 1.00 (t, *J*=7 Hz, H_3-4). **10** δ 8.95 (NH), 7.38 (d, *J*=2.5 Hz, H-9), 6.9–7.2 (m, *ar*-H_4), 4.28 (td, *J*=12, 4 Hz, H-5_a), 4.00 (td, *J*=12, 12, 4 Hz, H-5_b), 3.96 (ddd, *J*=12, 8, 2.5 Hz, H-7_a′), 3.81 (s, OMe), 3.59 (d, *J*=2.5 Hz, H-1), 3.48 (ddd, *J*=12, 11, 6 Hz, H-7_b′), 2.70 (dd, *J*=16, 2.5 Hz, H-2_a′), 2.47 (ddd, *J*=10, 6, 2.5 Hz, H-7), 2.16 (d, *J*=16 Hz, H-2_b′), 1.9–2.1 (m, H-6_b′, H_2-6), 1.90 (ddd, *J*=12, 6, 2.5 Hz, H-6_a′), 1.22 (m, H-3_b), 0.97 (m, H-3_a), 0.68 (t, *J*=7 Hz, H_3-4). **11** δ 8.93 (NH), 7.70 (d, *J*=2.5 Hz, H-9), 6.9–7.2 (m, *ar*-H_4), 4.67 (td, *J*=10.5, 2.5 Hz, H-7_a′), 4.36 (td, *J*=10.5, 2.5 Hz, H-5_a), 4.04 (d, *J*=1.5 Hz, H-1), 3.95 (m, H-5_b), 3.75 (s, OMe), 3.16 (dm, *J*=10.5 Hz, H-7_b′), 2.85 (dt, *J*=9, 2.5 Hz, H-7), 2.46 (dd, *J*=16, 2.5 Hz, H-2_b′), 2.04 (d, *J*=16 Hz, H-2_a′), 1.9–2.0 (m, H-6_b′, H_2-6), 1.90 (ddd, *J*=12, 6, 2.5 Hz, H-6_a′), 1.22 (m, H-3_b), 0.97 (m, H-3_a), 0.68 (t, *J*=7 Hz, H_3-4).