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SHORT STEREOSELECTIVE SYNTHESES OF (-)-AJMALICINE, (-)-3-ISO-AJMALICINE AND THEIR 5-METHOXYCARBONYL DERIVATIVES FROM SECOLOGANIN

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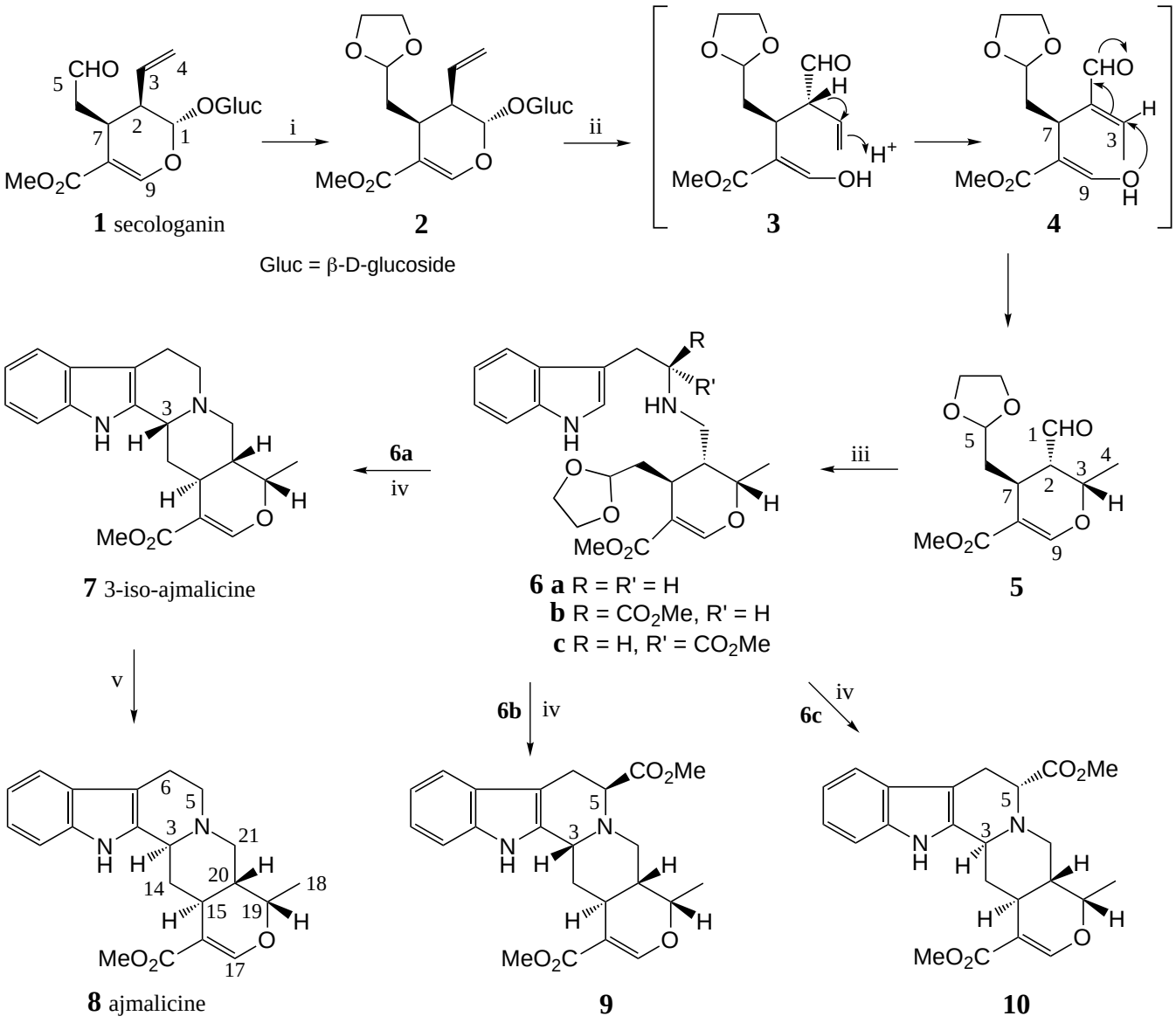
Abstract - Enzymatic hydrolysis of secologanin ethylene acetal at pH 5.0 resulted in stereoselective rearrangement of its aglucone to a dihydropyran aldehyde, which on reductive amination with tryptamine and cyclisation afforded 3-iso-ajmalicine, subsequently inverted to ajmalicine; analogous use of methyl *S*-tryptophanate gave 5*S*-methoxycarbonyl-3-iso-ajmalicine, whereas the *R*-enantiomer rather surprisingly yielded the ajmalicine derivative, whose anomalous CD spectrum has been rationalised.

Largely because of its medicinal use, ajmalicine (raubasine) (**8**) is probably one of the most important heteroyohimbine alkaloids, and has been a perennial synthetic target.[1,2a] In the past we have prepared various members of this group from their biological precursors tryptamine and secologanin (**1**), initially following the *in vivo* sequence, *i.e*. Pictet-Spengler condensation, hydrolysis of the glucoside, subsequent rearrangement of the aglucone and reduction.[2a,b] Latterly, we considered it might be more efficient to carry out the cyclisation to the indole not as the first step but rather as the last, since this should achieve better control over the C-3 stereochemistry. Thus by converting the aldehyde in **1** to a methyl ester, we obtained methyl elenolate from which 3*S*-heteroyohimbines could be prepared, but unfortunately only as mixtures of C-19 and 20 stereoisomers due to equilibration, and a selective synthesis of ajmalicine still eluded us.[2c] We therefore looked to a variant of this approach, in particular using a C-5 acetal of secologanin which we have found to be effective in synthesising other indole alkaloids, not least because acid catalysed removal of the acetal also promoted concomitant stereoselective Pictet-Spengler cyclisation.[3] The results of our subsequent successful work are summarised in Scheme 1.



Scheme 1. Reagents and conditions: (i) $(CH_2OH)_2$/THF/TFA/Al_2O_3, 55-60° C, 3 h; (ii) β-glucosidase/pH 5.0 aq. buffer, 37° C, 3 d; (iii) tryptamine or methyl *S*- or *R*-tryptophanate/MeOH/$NaCNBH_3$, 2 d; (iv) 1M HCl/1:1 aq. Me_2CO, 56° C, 1.5 h; (v) AcOH, 140 °C or a) $Pb(OAc)_4$/AcOH, b) $NaBH_4$.

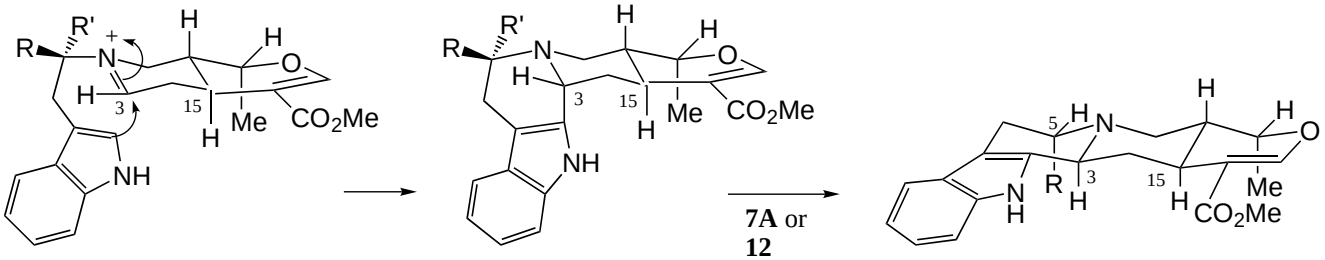
Reaction of secologanin with ethylene glycol in presence of acid and alumina gave the amorphous ethylene acetal (**2**), $[\alpha]_D$ -7° (MeOH). Subsequent hydrolysis with β-glucosidase in pH 5.0 buffer at 37° C for three days resulted in rearrangement of the aglucone, and after chromatography on silica with 3:1 $CHCl_3/Et_2O$, afforded in 50-70% yield a dihydropyran aldehyde [M^+ 270.1099 ($C_{13}H_{18}O_6$); λ_{max}(MeOH): 236 nm; ν_{max} ($CHCl_3$) 2720, 1703, 1630 cm^{-1}]. Its structure (**5**) was indicated by the ^{1}H NMR spectrum[9] with *inter alia* a doublet at δ 9.67 for the C-1 aldehyde, a singlet at δ 7.67 for the alkene H-9 and a doublet at δ 1.57 for the C-4 methyl group, and confirmed by the eventual conversion into ajmalicine. On some occasions,

formation of a minor amount (~10%) of the C-3 epimer was observed. The highly stereoselective transformation is considered to occur by migration of the double bond into conjugation with the aldehyde in the ring opened aglucone (**3**) with preferential formation of an *E*-alkene (**4**), and subsequent Michael addition of the C-9 enol to C-3 from the upper face, protonation of C-2 generating the more stable 2,7-*trans* geometry. Supporting evidence for the intermediacy of **4** has come from other work on secologanin derivatives, where an analogous conjugated aldehyde was isolated and shown to be the more stable *E*-alkene from the chemical shift of the aldehyde proton at δ 9.3 rather than the δ 10.1 expected for a *Z*-alkene.[4] Significantly, it cyclised exclusively to a heterocycle with the same 3*S* configuration as **5**. Hence any C-3 epimer of **5** would arise from a *Z*-alkene, formed before or after equilibration with **4**, perhaps by an analogous process to that found for cathenamine.[2b]

3-Iso-ajmalicine and ajmalicine

Reductive amination of the aldehyde (**5**) with tryptamine and sodium cyanoborohydride in methanol afforded in 85% yield the coupled amine (**6a**), whose structure was corroborated by the ^{1}H NMR spectrum with signals for both indole [δ 8.29 (br s, HN-1), 7.7-7.1 (m, *ar*H$_4$), 7.10 (d, *J*=2 Hz, H-2)] and monoterpene [δ 4.16 (qd, *J*=18, 2 Hz, H-19), 4.87 (dd, *J*=5.5, 4 Hz, H-3), 4.82 (s, CO_2Me)] moieties (indole alkaloid numbering). Heating the crude **6a** in a 1:1 mixture of acetone and 10% aq. hydrochloric acid under reflux for ninety min, followed by chromatography on silica with 5:4 $CHCl_3$/Me_2CO, gave a 75% yield of an amorphous product $[\alpha]_D$ -10^o (MeOH). That hydrolysis of the acetal and subsequent cyclisation to a heteroyohimbine had occurred was indicated *inter alia* by the mass spectrum with M^+ 352.1783 ($C_{21}H_{24}N_2O_3$) and characteristic fragments at *m/z* 184, 170, 169, 156, and by the loss of the NMR signal for the indolic H-2 in **6a**. A complete analysis of its ^{1}H NMR spectrum[10] established the structure as 3-iso-ajmalicine (**7**). Thus H-20 (δ 2.05) had a small *cis-ae* coupling of 3.5 Hz with H-19 (δ 4.48) and a *trans-aa* coupling of 11.5 Hz with H-15 (δ 1.95), which in turn had a *trans-aa* coupling of 12 Hz with H-14$_{ax}$ (δ 1.59); with the last H-3 (δ 4.56) had a *cis-ae* coupling of 5 Hz, so that the absolute stereochemistry must be as depicted in *cis*-quinolizidine (**7A**). Furthermore, the configuration at C-3 was corroborated as *R* from a negative Cotton effect at 286 nm in the CD spectrum (-4.7 x 10^3 cm^2 dmol^{-1}).[5] As we had anticipated, exclusive generation of this stereochemistry in **7A** during the Pictet-Spengler cyclisation was attributable to kinetic axial attack by the indole at a C-3/N-4 iminium ion in an intermediate (**11a**) held in a chair-like conformation by equatorial C-15 and 20 substituents (Scheme 2).[3] Finally, heating **7** in glacial acetic acid[3a] epimerised C-3 largely to the thermodynamically preferred *trans*-

quinolizidine (**8A**), producing a 85:15 mixture from which ajmalicine (**8**), mp 252-253° C, $[\alpha]_D$ -66° ($CHCl_3$) was obtained by recrystallisation from ethanol. It was characterised by a broadened doublet at δ 3.43 for H-3 with a *trans-aa* coupling of 12 Hz to H-14_{ax} in the NMR spectrum[10] and a positive Cotton effect at 285 nm in the CD spectrum (+2.9 x 10^3 cm^2 $dmol^{-1}$), and identified by direct comparison (mixed mp) with an authentic sample. Inversion of 3-isoajmalicine to ajmalicine was also achieved by the standard method of lead tetra-acetate oxidation followed by sodium borohydride reduction.



11 a R = R' = H
b R = CO_2Me, R' = H
c R = H, R' = CO_2Me

7A R = R' = H
9A R = CO_2Me, R' = H
12 R = H, R' = CO_2Me

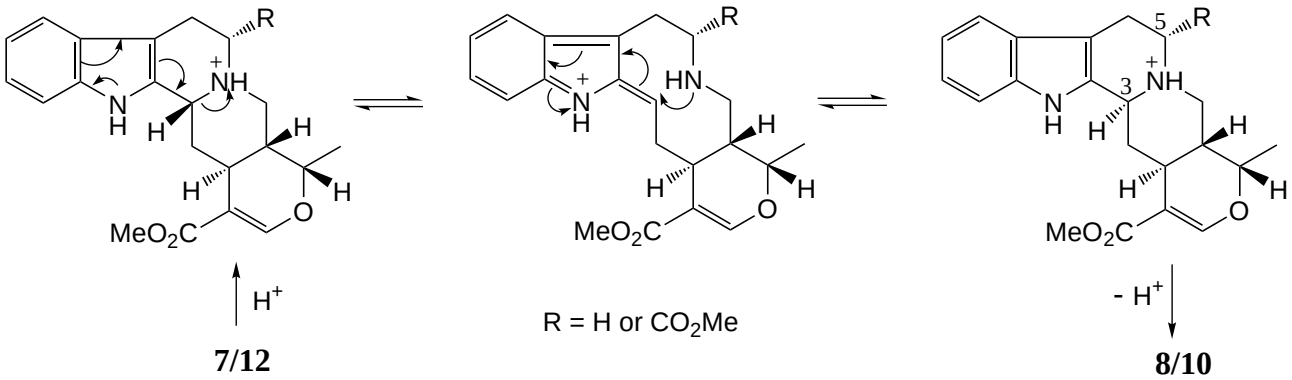
8A R = H
10A R = CO_2Me
13 R = CH_2OH

Scheme 2

5-Carboxy alkaloids

Some years ago we discovered the first members of a parallel series of monoterpenoid indole carboxy-alkaloids derived from L(*S*)-tryptophan rather than tryptamine, including one heteroyohimbine, 5*S*-carboxytetrahydroalstonine, isolated as its methyl ester.[2a,6] With the aldehyde (**5**) to hand, we now saw the opportunity to synthesise another stereoisomer likely to correspond to a natural product. Indeed, repetition of the sequence substituting methyl *S*-tryptophanate for tryptamine afforded **6b** and thence, after chromatography on silica with EtOAc, the amorphous 5*S*-methoxycarbonyl-3-iso-ajmalicine (**9**), as shown by M^+410.1844 ($C_{23}H_{26}N_2O_5$), a negative Cotton effect in the 280 nm region of the CD spectrum, and analysis of its ^{1}H NMR spectrum.[10] Such was expected from our rationale that cyclisation of the indole onto a piperideine ring in a chair-like conformation (**11b**) would necessarily involve stereoelectronic control with *trans-aa* addition leading to a C-3 configuration with an equatorial hydrogen as in **9A** (Scheme 2). Furthermore, the 3,5 *trans* geometry was in accord with that which we long since had found to be generated preferentially in Pictet-Spengler cyclisations of tryptophan, or exclusively with N_b-benzyl derivatives.[7]

On the other hand, with the enantiomeric methyl *R*-tryptophanate these two controlling effects would be opposed, although we suspected that the former might predominate, since there were no obvious structural disadvantages with **12**, the 5*R*-epimer of **9**. In the event, *via* **6c** a single product was obtained, after chromatography on silica with 1:1 $CHCl_3$/PhMe, in *ca.*70% yield, mp 244-246^o C (from MeOH) with M^+410, combustion analysis for $C_{23}H_{26}N_2O_5$ and a negative CD curve betwen 300 and 270 nm corresponding to the anticipated structure. However, a complete analysis of the ^{1}H NMR spectrum[10] revealed from the series of *trans-aa* couplings of *ca.*13 Hz between H-3, 14_{ax}, 15, 20 and 21_{ax} that it was actually 5*R*-methoxycarbonyl-ajmalicine (**10**) with 3*S* configuration. This result was somewhat unexpected, since under the same conditions the tryptamine and *S*-tryptophan derivatives above had afforded only the *3R* isomers, and epimerisation of 3-iso-ajmalicine required prolonged treatment with acid under more drastic conditions. Direct cyclisation to **10** could be discounted since it would invoke an unfavourable twist-boat intermediate. It would seem that the 3*R* isomer (**12**) was formed as the initial product from intermediate (**11c**) and then epimerised to **10**, in all likelihood *via* acid-catalysed C-3/N-4 cleavage, a process that can occur under surprisingly mild conditions with favourable substrates (Scheme 3).[8] In this case (R = CO_2Me) concomitant generation of the preferred 3,5 *trans* geometry provides an additional driving force to the conversion to an equatorial indole moiety that occurs with ajmalicine (R = H), and thus accounts for the relative ease and completeness of the transformation to **10**.



Scheme 3

Consequently both H-3 and the C-5 methoxycarbonyl group are pseudo-axial as in **10A**, the resulting 1,3-diaxial interaction accounting for the ~1ppm deshielding of the H-3 NMR signal (δ 4.4 in $CDCl_3$) relative to ajmalicine. The apparently anomalous negative Cotton effect can also be attributed to this feature: the axial C-5 ester with its π electron system interacts more strongly with the indole chromophore than the

remainder of the molecule, and from the opposite face, thus reversing the usual sign. If this were the case, then removal of the carbonyl function should restore standard behaviour. Indeed, when the C-5 ester was reduced by brief treatment with lithium aluminium hydride in ether to the primary alcohol (**13**) [M^+382] the CD spectrum became very similar to that of ajmalicine with a positive Cotton effect at 285 nm, in accord with 3*S* stereochemistry. Incidentally, these results re-emphasise the need for careful choice of reference model in assigning configurations from CD spectra, even when there is restricted conformational mobility. Finally, **10** would seem to be a thermodynamic product, since it was apparently unchanged (TLC, NMR) with no inversion of C-5 on prolonged treatment with sodium methoxide in methanol. Interestingly, under the same conditions the methyl ester of the isomeric natural alkaloid, 5*S*-methoxycarbonyl-tetrahydroalstonine, retained its 3,5 *cis* geometry, presumably due to competing interactions with the axial C-20 substituent.

Thus from secologanin we have achieved short, stereoselective, enantiospecific syntheses of ajmalicine and some of its congeners, which are efficient, practical and suitable for large-scale production, unlike virtually all previous syntheses. Obviously, our approach can be readily adapted to a range of natural and unnatural analogues by appropriate selection of tryptamine or arylethylamine derivatives. Again, we have prepared further potential representatives of the small but increasing number of carboxy monoterpenoid indole alkaloids, which are now likely to be found as natural products.

ACKNOWLEDGEMENTS

We thank the EPSRC for Studentships (S.B.P., P.R.) and the Commonwealth Commission for a Scholarship (B.E.N.D.).

Dedication

To Professor J. P. Kutney on the occasion of his 70th birthday.

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9. ^{1}H NMR spectrum (secologanin numbering):

   5 (300 MHz, $CDCl_3$) δ 9.67 (d, *J*=2.5 Hz, H-1), 7.67 (s, H-9), 4.98 (dd, *J*=5.5, 3.5 Hz, H-5), 4.30 (dd, *J*=7, 2 Hz, H-3), 4.00-3.80 (m, OCH_2CH_2O), 3.75 (s, OMe), 3.15 (ddd, *J*=10, 3.5, 2.5 Hz, H-7), 2.92 (td, *J*=2.5, 2 Hz, H-2), 2.81 (dt, *J*=14.5, 3 Hz, H-6_a), 1.60 (ddd, *J*=14.5, 10, 5.5 Hz, H-6_b).
10. ^{1}H NMR spectra (alkaloid numbering):

    7 (400 MHz, d_6-Me_2CO) δ 8.51 (br s, NH), 7.54 (s, H-17) 7.52-7.17 (m, *ar*-H_4), 4.69 (ddd, *J*=4, 2, 1.5 Hz, H-3), 4.30 (qd, *J*=7, 3 Hz, H-19), 3.94 (d, *J*=7 Hz, H-5), 3.80 (s, OMe), 3.78 (s, OMe), 3.26 (dd, *J*=17, 1.5 Hz, H-6_{eq}), 3.16 (ddd, *J*=17, 7, 1.5 Hz, H-6_{ax}), 2.68 (dd, *J*=11, 4 Hz, H-21_{eq}), 2.50 (t, *J*=11 Hz, H-21_{ax}), 2.15 (tdd, *J*=11, 4, 3 Hz, H-20), 2.00 (tdd, *J*=11, 4, 1.5 Hz, H-15), 1.69(td, *J*=11, 4 Hz, H-14_{ax}), 1.22 (ddd, *J*=11, 4, 2 Hz, H-14_{eq}), 0.88 (d, *J*=7 Hz, H_3-18).

    8 (300 MHz, $CDCl_3$) δ 8.04 (br s, NH), 7.80 (s, H-17), 7.75-7.12 (m, *ar*-H_4), 4.38 (qd, *J*=7, 4 Hz, H-19), 3.77 (s, OMe), 3.43 (ddt, *J*=12, 2, ~1 Hz, H-3), 3.25 (ddd, *J*=12, 3.5, 2 Hz, H-14_{eq}), *ca*. 3.15 (m, H-5_a), *ca*. 3.08 (m, H-6_a), 3.00 (dd, *J*=10, 3 Hz, H-21_{eq}), *ca*. 2.88 (m, H-6_b), *ca*. 2.70 (m, H-5_b), 2.46 (td, *J*=12, 3.5 Hz, H-15), 2.28(t, *J*=10 Hz, H-21_{ax}), 2.18 (dddd, *J*=12, 10, 4, 3 Hz, H-20), 1.34 (q, *J*=12 Hz, H-14_{ax}), 1.11 (d, *J*=7 Hz, H_3-18).

9 (300 MHz, $CDCl_3$) δ 8.51 (br s, NH), 7.54 (s, H-17), 7.53-7.17 (m, *ar*-H_4), 4.69 (ddt, *J*=4, 2, 1.5 Hz, H-3), 4.30 (qd, *J*=7, 3 Hz, H-19), 3.94 (d, *J*=7 Hz, H-5), 3.80 (s, OMe), 3.78 (s, OMe), 3.26 (dt, *J*=17,1.5 Hz, H-6_{eq}), 3.16 (ddd, *J*=17, 7, 1.5 Hz, H-6_{ax}), 2.68 (dd, *J*=11, 4 Hz, H-21_{eq}), 2.50 (t, *J*=11 Hz, H-21_{ax}), 2.15 (tdd, *J*=11, 4, 3 Hz, H-20), 2.00 (tdd, *J*=11, 4, 1.5 Hz, H-15), 1.69 (td, *J*=11, 4 Hz, H-14_{ax}), *ca*. 1.22 (ddd, *J*=11, 4, 2 Hz, H-14_{eq}), 0.88 (d, *J*=7 Hz, H_3-18).

10 (300 MHz, 4:1 $CDCl_3/C_6D_6$) δ 8.00 (br s, NH), 7.73 (br d, *J*=7 Hz, *ar*-H), 7.63 (s, H-17), 7.52-7.28 (m, *ar*-H_3), 4.73 (ddm, *J*=13, 2.5 Hz, H-3), 4.63 (qd, *J*=7, 3.5 Hz, H-19), 4.07 (dd, *J*=5.5, 2.5 Hz, H-5), 3.95 (s, OMe), 3.81 (s, OMe), *ca*. 3.5 (m, H_2-6, H-14_{eq}), 3.27 (t, *J*=13 Hz, H-21_{ax}), 3.04 (dd, *J*=13, 4.5 Hz, H-21_{eq}), 2.80 (tdd, *J*=13, 4, 1.5 Hz, H-15), 2.31 (tdd, *J*=13, 4.5, 3.5 Hz, H-20), 1.47 (q, *J*=13 Hz, H-14_{ax}), 1.42 (d, *J*=7 Hz, H_3-18).