Pergamon

Tetrahedron Letters 41 (2000) 8861–8865

TETRAHEDRON LETTERS

Short syntheses of 16-methoxycarbonyl-16,17-dehydro-antirhine and its 10-oxy derivatives from secologanin

Richard T. Brown,* Bukar E. N. Dauda, Simon B. Jameson and Cid A. M. Santos†

Department of Chemistry, The University of Manchester, Manchester M13 9PL, UK

Received 1 September 2000; accepted 18 September 2000

Abstract

Stereoselective, enantiospecific syntheses of 16-methoxycarbonyl-16,17-dehydro-antirhine, its 10-hydroxy and 10-glucosyloxy derivatives have been realised from the corresponding tryptamines and the ethylene acetal of the monoterpenoid glucoside secologanin via hydrolysis and selective reduction of the aglucone with baker's yeast. © 2000 Published by Elsevier Science Ltd.

Keywords: alkaloids; glycoside; indole; micro-organism; stereoselection; reduction; terpene.

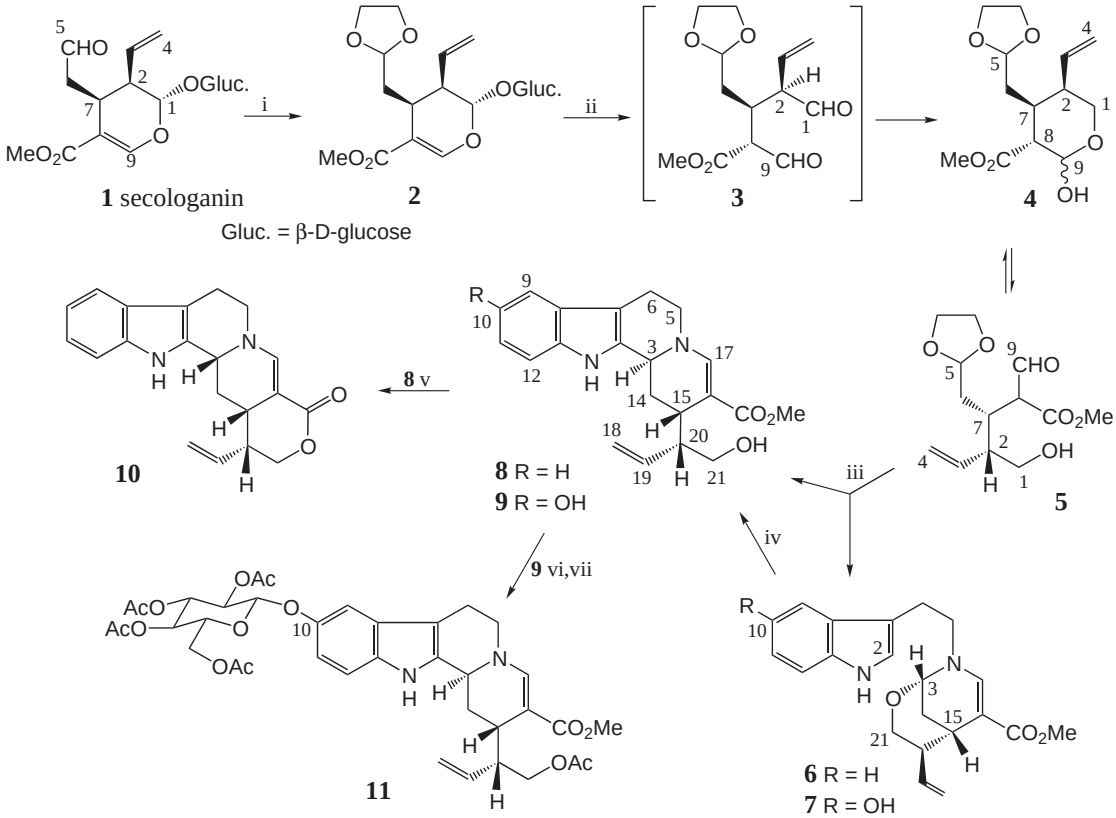
The numerous monoterpenoid indole alkaloids are derived biogenetically from the monoterpene glucoside secologanin **1**, which condenses with tryptamine to form the universal precursor, strictosidine.[1] Our group has carried out several stereoselective syntheses of indole alkaloids from secologanin C-5 derivatives which necessarily involved hydrolysis with β-glucosidase and concomitant or subsequent rearrangement of the aglucones.[2] We found that the structure of the predominant product was crucially dependant on the pH of the medium: at pH 5.0 a dihydropyran aldehyde was formed, from which heteroyohimbine alkaloids could be prepared, whereas at pH 7.0 an alternative cyclohexene aldehyde was formed, from which yohimbines were obtained.[2b,e]

When baker's yeast (*Saccharomyces cerevisae*) was used as a glucosidase source with secologanin ethylene acetal **2** in pH 7.5 buffer at 25°C, a cyclohexene aldehyde was again obtained, but, interestingly, at pH 6.4 selective reduction of the C-1 aldehyde in the aglucone **3** occurred to afford a lactol **4** as a gum in 60–80% yield. It had a molecular ion at m/z 272.1254 ($C_{13}H_{20}O_6$), and showed hydroxyl and non-conjugated ester carbonyl IR bands at 3425 and 1735 cm^{-1} (film), the former being lost on acetylation to a monoacetate [M^+ 314.1363 ($C_{15}H_{22}O_7$) ν_{max}

* Corresponding author. Tel: +44 161 275 4632; fax: +44 161 275 4939; e-mail: r.t.brown@man.ac.uk
† On sabbatical leave from Universidade Federal do Paraná, Curitiba, PR, Brazil.

0040-4039/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01616-6

1733 cm^{-1}]. Under neutral conditions in MeOH there was no UV chromophore, but on addition of alkali a peak appeared at 270 nm, attributable to an anion from a β-aldehydo-ester **5** formed by opening of the lactol ring. Brief treatment with TFA led to elimination of water and formation of a derivative [M^+ 254.11653 ($C_{13}H_{18}O_5$)] containing a β-alkoxy-α,β-unsaturated ester chromophore with λ_{max} 237 nm, which gave no base shift. Final confirmation of structure and stereochemistry as a 9:1 *R*/*S* mixture of C-9 epimers came from analysis of the ^1H NMR spectra of **4** and its derivatives.[5] In particular, H-9 was identified from the ~1 ppm shift on acylation, and for the major epimer had a 9 Hz *trans-aa* coupling with H-8 (3.5 Hz *cis-ae* for the minor epimer), which in turn had a further *trans-aa* coupling of 10 Hz with H-7. Significantly, H-2 had negligible coupling with H-7 and only small ~2 Hz *ae*/*ee* couplings with the C-1 methylene protons, proving that it was equatorial and thus that the 2,7-*cis* geometry of secologanin had been conserved. It was necessary to confirm this as we had observed that a 2,7-*trans* isomer can be formed on occasion: if an acidic pH were not maintained, reversible enolisation of the C-1 aldehyde in the ring-opened aglucone **3** resulted in appreciable epimerisation of C-2 before reduction. Hence, in this case the labile hydrogen and the chiral centre at C-2 were retained, in contrast to the above rearranged aglucones (Scheme 1).



Scheme 1. Reagents and conditions: (i) $(CH_2OH)_2$/THF/TFA/Al_2O_3, 55–60°C, 3 h; (ii) baker's yeast/pH 6.4 aq. buffer, 25°C, 7 days; (iii) tryptamine or 5-hydroxytryptamine/Me_2CO/pH 3.5 aq. buffer, 56°C, 3–5 h; (iv) Me_2CO/pH 3.5 aq. buffer, 56°C, 5 h; (v) MeOH/3% aq. HCl, 65°C, 1 h; (vi) 1-bromo-2,3,4,6-tetra-acetyl-α-D-glucose/1 equiv. LiOH/MeOH, 25°C, 6 h; (vii) Ac_2O/py, 25°C, 12 h

In 1992 the alkaloid glabratine was isolated from the Sumatran plant *Uncaria glabrata* D.C. (Rubiaceae) and shown to be a 9-β-D-glucosyloxy derivative of the unknown 16-methoxycarbonyl-16,17-dehydro-antirhine **8**.[3] It was unique in having the same unusual N-4/C-17 ring as antirhine but retaining the methoxycarbonyl group lost with the latter. Although synthesis of glabratine itself was not immediately feasible because the required 4-hydroxytryptamine was not readily available, we envisaged that it might be possible to prepare the parent structure **8** in one step from lactol **4** and tryptamine. Likewise, serotonin (5-hydroxytryptamine) should afford the 10-hydroxy **9** and 10-glucosyloxy derivatives **11**, which we anticipated as also likely to be natural products due to the wide occurrence of 10-oxygenated indole alkaloids.

In preliminary condensation experiments, tryptamine and the lactol were heated in pH 3.5 aq. acetone buffer under reflux for three hours. Chromatography of the crude product on silica gel with 3:2 ethyl acetate/chloroform afforded two amorphous compounds in 30 and 36% yield, both of which had molecular ions at m/z 352 analysing for $C_{21}H_{24}N_2O_3$, and UV spectra constituting the sum of indolic and β-amino-acrylate chromophores (λ_{max} 222, 290 nm). The less polar minor product had corresponding IR bands at ν_{max} 3327, 1666 and 1611 cm^{-1}, and was distinguished by a large peak in the mass spectrum at m/z 130 characteristic of an uncyclised tryptamine derivative. This was confirmed by the presence of an indolic α proton at δ 7.0 in the NMR spectrum,[6] which showed clearly that while the acetal had been cleaved, Pictet–Spengler cyclisation had not taken place. Both H-3 at δ 4.53 and H-15 at δ 2.89 appeared as broadened singlets with only small ^3J couplings to adjacent protons and a significant mutual ^4J W coupling of 1.5 Hz, which were consistent with the bridged amino-ether structure **6**.

The mass spectrum of the more polar major product had a base peak at m/z 284 attributable to the loss of a homoallylic alcohol side chain, and a broad IR band at 3560–3250 cm^{-1} indicated the likely presence of OH, as well as indolic NH groups. In this case Pictet–Spengler cyclisation had been achieved, since there was no signal for any indolic α proton in its NMR spectrum,[6] which also confirmed the structure and stereochemistry as 16-methoxycarbonyl-16,17-dehydro-antirhine **8**. A broadened doublet at δ 4.90 assigned to H-3 had a large *trans-aa* coupling of 12 Hz to H-14$_{ax}$ (δ 1.82), and this in turn had an *ae* coupling of 4 Hz to H-15 (δ 3.26) which must thus be equatorial. Hence the cyclisation had occurred with complete stereoselectivity to give the 3,15-*trans* product in a *trans*-quinolizidine conformation with an axial C-15 substituent (Fig. 1). A chair-like iminium intermediate would presumably have this substituent equatorial and the indole would add axially to afford an initial *cis*-quinolizidine, which then flips to the observed *trans* conformation. Interestingly, simply on acetylation of the alcohol, H-3 became a broad singlet at δ 4.80, indicating that it was equatorial and that the acetate preferred a *cis*-quinolizidine conformation (Fig. 2). Formation of the minor product **6** must involve trapping of the intermediate by competitive addition of the C-21 alcohol to the iminium ion, a process likely to be reversible, and on heating under the same conditions as above it was indeed converted into **8**.

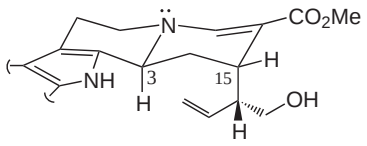


Figure 1.

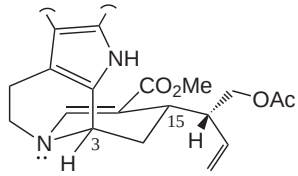


Figure 2.

Again, with 3,15-*trans* stereochemistry **8** must be the kinetic product, since a *cis* isomer with both substituents pseudo-equatorial would be thermodynamically preferred. Accordingly, when **8** was heated in stronger acid, 3% HCl in aq. methanol, for an hour it lactonised and C-3 was largely epimerised to form the *cis* product **10** [M^+ 320.1524 ($C_{20}H_{20}N_2O_2$); λ_{max} 219, 298 nm; ν_{max} 3270, 1730, 1660 cm^{-1}] as indicated by *trans-trans-aaa* couplings in its NMR spectrum between H-3, H-14_{ax} and H-15; the last had an *ae* coupling of 5 Hz with H-20, which again corroborated the retention of secologanin stereochemistry throughout.

Likewise, heating the lactol **4** and serotonin (as the creatinine sulfate) in aq. acetone at pH 3.5 under reflux and nitrogen for five hours, followed by chromatography on silica with ethyl acetate, afforded in 50% yield 10-hydroxy-16-methoxycarbonyl-16,17-dehydro-antirhine $[\alpha]_D$ +40 (CH_2Cl_2) [M^++H 369.1810 ($C_{21}H_{25}N_2O_4$); λ_{max} 217, 301 nm with a shift to 312 nm on addition of alkali; ν_{max} 3280, 1722 and 1660 cm^{-1}]. Confirmation of the structure **9** came from its NMR spectrum, which (except for the aromatic region) was very similar to that for **8**, with a *trans*-quinolizidine conformation again indicated from the broadened doublet at δ 4.89 for H-3 with a 12 Hz *aa* coupling. A minor amount (8%) of the intermediate **7** $[\alpha]_D$ +160 ($CHCl_3$) was also obtained.

Adapting a procedure[4] for β-glycosidation of a phenol in presence of an alcohol, **9** was treated with an equivalent of lithium hydroxide and excess 2,3,4,6-tetra-acetyl-1-bromo-α-D-glucopyranose in methanol for six hours. The crude product was then acetylated and chromatography on silica with 1:1 ethyl acetate/chloroform afforded in ca. 20% yield a 10-glucosyloxy derivative as the amorphous penta-acetate **11** $[\alpha]_D$ +120 ($CHCl_3$) [$[\alpha]_{max}$ 225, 269, 294 nm; ν_{max} 3205, 1750, 1680 cm^{-1}]. The molecular ion at m/z 740.2698 ($C_{37}H_{44}N_2O_{14}$) corresponded to formation of a monoglucoside, and significantly, no base shift was observed in the UV spectrum even after alkaline hydrolysis, showing that the link was to the phenol and not the alternative C-21 alcohol. The expected additional signals were present in the ^1H NMR spectrum for the acetylated sugar moiety, and a broad singlet for H-3 at δ 4.78 again indicated a preferred *cis*-quinolizidine conformation for a C-21 acetate.

We have thus prepared a series of 16-methoxycarbonyl-16,17-dehydro-antirhines, which are likely to be found eventually as natural products. A similar short synthetic route can be used for the glucoalkaloid glabratine when the requisite hydroxytryptamine is available.

Acknowledgements

We thank the EPSRC for a Quota Studentship (S.B.J.), the Commonwealth Commission for a Scholarship (B.E.N.D.) and CAPES, Brazil for financial support (C.A.M.S.).

References

1. Nagakura, N.; Rüffer, M.; Zenk, M. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2308–2312.
2. (a) Brown, R. T. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; John Wiley: New York, 1983; pp. 135–139, 192–194. (b) Brown, R. T.; Chapple, C. L.; Duckworth, D. M.; Platt, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 160–163. (c) Brown, R. T.; Dauda, B. E. N.; Santos, C. A. M. *Chem. Commun.* **1991**, 825–826. (d) Brown, R. T.; Kandasamy, M. *Tetrahedron Lett.* **2000**, *41*, 3547–3550. (e) Brown, R. T.; Pratt, S. B.; Richards, P. *Tetrahedron Lett.* **2000**, *41*, 5627–5630.
3. Arbain, D.; Byrne, L. T.; Putra, M. M.; Sargent, M. V.; Syarif, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 665–666.
4. (a) Fischer, E.; Armstrong, E. F. *Berichte* **1901**, *34*, 2885–2900. (b) Berrang, B.; Twine, C. E.; Henessee, G. L.; Carroll, F. I. *Synth. Commun.* **1975**, *5*, 231–236.
5. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) (secologanin numbering). Compound **4**: δ 6.00 (m, $J=17$, 10 Hz, H-3), 5.33 (d, $J=3.5$ Hz, H-9$_{min}$), 5.23 (m, H_2-4), 4.96 (dd, $J=6$, 5 Hz, H-5$_{min}$), 4.88 (dd, $J=6$, 5 Hz, H-5$_{maj}$), 4.85 (d, $J=9$ Hz, H-9$_{maj}$), 3.95–3.75 (m, H_2-1, $(CH_2O)_2$), 3.72 (s, OMe), 2.76 (dd, $J=10$, 3.5 Hz, H-8$_{min}$), 2.68 (m, $J=10$ Hz, H-7$_{min}$), 2.42 (dd, $J=10$, 9 Hz, H-8$_{maj}$), 2.35 (m, $J=2.5$, 2 Hz, H-2), 2.30 (td, $J=10$, 6 Hz, H-7$_{maj}$), 1.77 (ddd, $J=15$, 10, 6 Hz, H-6$_a$), 1.38 (ddd, $J=15$, 6, 5 Hz, H-6$_b$).
6. ^{1}H NMR spectra (300 MHz, $CDCl_3$) (alkaloid numbering). Compound **6**: δ 8.05 (bs, NH), 7.64 (s, H-17), 7.4–7.1 (m, ArH_4), 7.0 (d, $J=2$ Hz, H-2), 6.09 (m, $J=16$, 10 Hz, H-19), 5.23 (m, H_2-18), 4.53 (bs, $J=1.5$, 1.5 Hz, H-3), 3.8–3.4 (m, H_2-21, H_2-5), 3.71 (s, OMe), 3.08 (m, H_2-6), 2.89 (bs, $J=4$, 3, 1.5 Hz, H-15), 2.22 (dm, $J=14$, 3, 1.5 Hz, H-14$_a$), 2.09 (bs, H-20), 1.16 (bd, $J=14$, 4 Hz, H-14$_b$). Compound **8**: δ 8.07 (bs, NH), 7.75 (s, H-17), 7.5–7.1 (m, ArH_4), 5.58 (m, $J=16$, 9, 8 Hz, H-19), 5.22 (dd, $J=16$, 2.5 Hz, H-18$_a$), 5.08 (dd, $J=9$, 2.5 Hz, H-18$_b$), 4.90 (bd, $J=12$, 3, 2 Hz, H-3), 3.72 (s, OMe), 3.68 (dd, $J=14$, 4 Hz, H-5$_{eq}$), 3.62 (dd, $J=14$, 4.5 Hz, H-5$_{ax}$), 3.41 (d, $J=8$ Hz, H_2-21), 3.26 (bs, $J=4$, 3 Hz, H-15), 2.94 (m, $J=13$, H-6$_{ax}$), 2.78 (bd, $J=13$, 4.5 Hz, H-6$_{eq}$), 2.53 (m, $J=8$, 8, 3 Hz, H-20), 2.26 (ddd, $J=13$, 4, 2 Hz, H-14$_{eq}$), 1.82 (ddd, $J=13$, 12, 4 Hz, H-14$_{ax}$).