Tetrahedron Letters 50 (2009) 7089–7092

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The structures of three new Galbulimima alkaloids

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ARTICLE INFO

Article history:
Received 27 August 2009
Revised 23 September 2009
Accepted 2 October 2009
Available online 14 October 2009

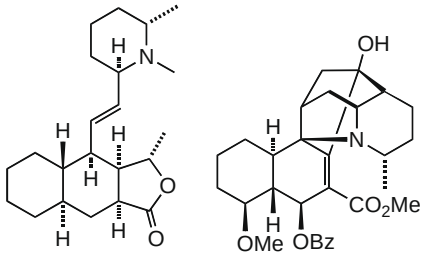
Keywords:
Galbulimima belgraveana
Alkaloids
Novel structures
Biosynthesis

ABSTRACT

The structures of three new alkaloids isolated from the bark of the rain forest tree *Galbulimima belgraveana*, have been determined by a combination of NMR spectroscopy and X-ray crystallography. One of the alkaloids, himgrine (**5**), was shown to be an oxygenated derivative of himbacine (**1**), while the second, GB16, (**8**) proved to be identical with a degradation product from himgaline (**4**). The remaining alkaloid, GB17 (**12**) possesses an entirely new and unexpected skeleton.

The structures have been determined for 22 unique alkaloids isolated from the bark of the rain forest tree *Galbulimima belgraveana* which is found in Northern Australia, Papua New Guinea and Indonesia.[1,2] The alkaloids form three distinct groups: Class I represented by himbacine (**1**) (four members), Class II typified by himandrine (**2**) (15 members) and Class III represented by GB13 (**3**) and himgaline (**4**) (three members).[3] Himbacine (**1**) was found to have strong antispasmodic activity[4] and was later shown to be a potent cardio-selective muscarinic antagonist,[5] due to its ability to bind selectively with M_2/M_4 muscarinic receptors.[6] Thus, it became a lead compound in the search for new drugs for the treatment of neurodegenerative conditions such as Alzheimer's disease. While interest in himbacine has waned, a synthetic analogue has been shown to be a potent orally active thrombin receptor (PAR-1) antagonist and is presently undergoing stage 3 clinical trials for the treatment of acute coronary syndrome and for secondary-prevention in patients who have had a prior myocardial infarct or stroke.[7]

The combination of novel structures with promising biological activity has attracted the attention of several synthesis groups and led to numerous total syntheses of himbacine (**1**),[8–16] four of GB13 (**3**),[17–20] two of himgaline (**4**)[19,20] and one of himandrine (**2**).[21] Our current interest in these alkaloids is concerned with their biosynthesis. Ritchie and Taylor proposed a polyketide origin (nona-acetate + pyruvate equivalent),[2] and Baldwin et al. extended the hypothesis to include an intramolecular Diels–Alder (IMDA) reaction, thereby forming an advanced precursor to himbacine (**1**) (Scheme 1); they then carried out an elegant biomimetic synthesis.[16]



The pathway to the more complex alkaloids would appear to involve a Michael reaction followed by a proton shift and an enamine-based aldol reaction (Scheme 2), and in their total syntheses of **4**, Evans[20] and Movassaghi[21] showed that such a sequence was feasible.[20] Conversion of **3** into **4** by intramolecular conjugate addition of the amino group to the enone function was demonstrated during the original structural studies,[22] and more recently

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✠ Deceased January 1, 2009.

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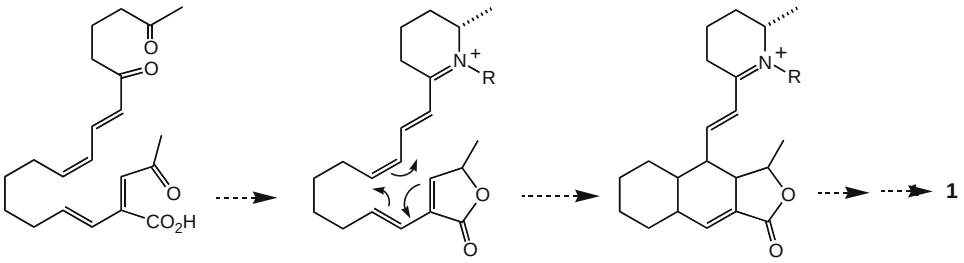
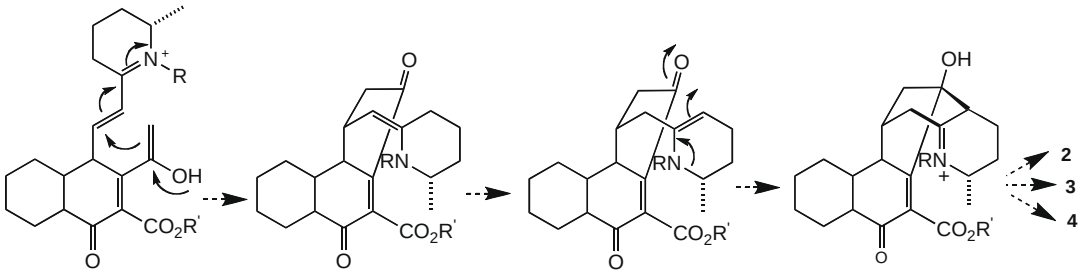
doi:10.1016/j.tetlet.2009.10.019



Scheme 1. Baldwin's hypothesis for the biosynthesis of Class 1 alkaloids.



Scheme 2. Hypothesis for the biosynthesis of Class II and III alkaloids.

with the total synthesis of **4**.[20,21] However, the route to the himandrine (**2**) type is less obvious. Baldwin et al. have proposed a possible route similar to that outlined in Scheme 2,[16] but the very recent biomimetic synthesis of **4** reported by Movassaghi et al.,[21] provides a more convincing hypothesis. In order to shed more light on these processes, we have revisited the structural studies carried out in the early sixties with the hope of identifying missing links in the biosynthetic sequences. In addition to the 22 alkaloids described at that time, a further six alkaloids of unknown constitution were reported.[3] In this Letter, we describe the structure determination of three of these compounds, namely himgrine, GB16 and GB17.

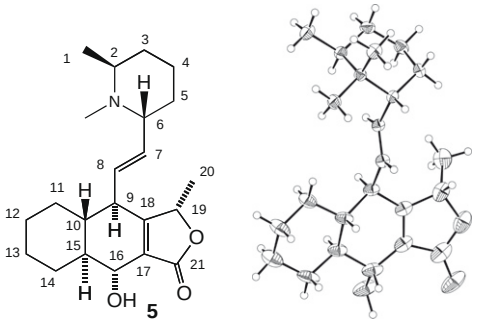
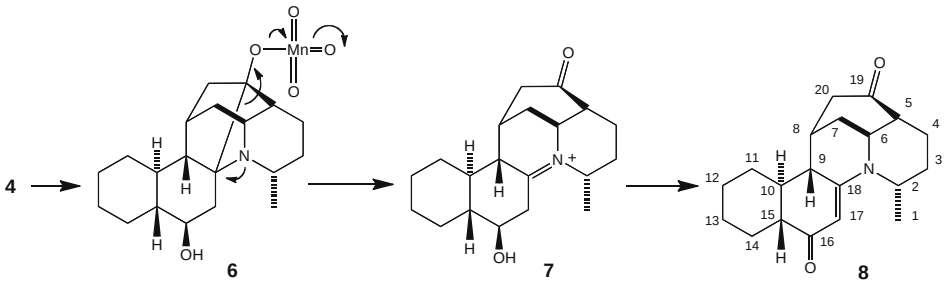


Figure 1. Structure of himgrine (5) and the ORTEP representation of himgrine methiodide.

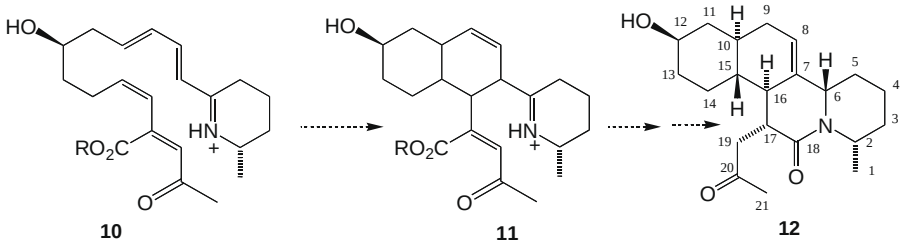
When NMR spectra from the alkaloid himgrine[23] were compared with those of himbacine (**1**), it was apparent that like **1**, himgrine possessed a 2,6-disubstituted piperidine ring, a secondary methyl group, an *N*-methyl group, a lactone ring and a trans disubstituted double bond. However, the ^{13}C NMR spectrum showed a second double bond (tetra-substituted and probably conjugated to a carbonyl group) and a secondary hydroxy substituent, probably allylic (δ_H 4.22). We were then able to arrive at a gross structure, but to make unequivocal stereochemical assignments we resorted to X-ray crystal analysis on the derived methiodide, enabling us to assign structure **5** (including the absolute configuration) to the parent alkaloid (Fig. 1).[24]

NMR spectra[25] showed alkaloid GB16 to possess two carbonyl groups (δ_C 207.7 and δ_C 197.8), one of which appeared to be conjugated to a trisubstituted double bond. Although the frequencies for the latter at δ_C 104.8 and δ_C 158.5 were puzzling at first, they could be rationalised, by assuming that a nitrogen atom was attached to the β carbon of the enone functionality. When we discovered that the new alkaloid was identical with a degradation product derived from himgaline (**4**) by oxidation with $KMnO_4$,[26] we were able to arrive at structure **8**, the mechanism for the formation of which is proposed in Scheme 3.

NMR spectra of GB17[27] indicated two carbonyl groups (δ_C 208.1 and δ_C 171.8), a trisubstituted double bond (δ_C 138.3 and δ_C 121.2;



Scheme 3. Oxidation of himgaline (**4**) to form GB16 (**8**).



Scheme 4. Structure of GB17 (**12**) and its speculative biosynthesis from **10**.

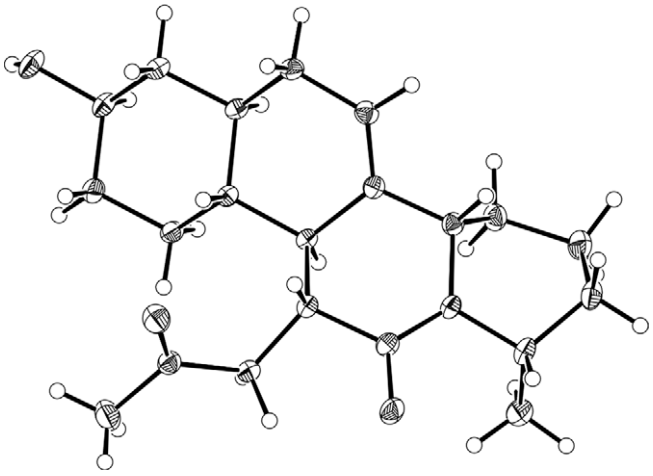
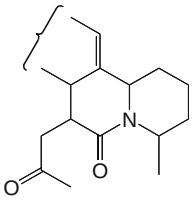


Figure 2. ORTEP of GB17 (**12**).



9

Figure 3. Partial structure of GB17.

δ_H 5.75), a secondary hydroxy (δ_C 70.0; δ_H 3.56), two CH's bonded to nitrogen (δ_C 59.7; δ_H 4.02, and δ_C 52.1; δ_H 3.72), a methyl group as part of an acetyl group (δ_C 30.9, δ_H 2.21), a methylene group adjacent to a carbonyl group (δ_C 42.8, δ_H 2.86, dd, J = 16.9, 7.8; δ_H 2.74, J = 16.9, 3.7) and a secondary methyl (δ_C 19.9, δ_H 1.33). Noting that the CH-N resonances were significantly down field from those recorded for himbacine (δ_H 3.00 and δ_H 2.81), we concluded that the nitrogen was amidic, consistent with the carbonyl peak observed at δ_C 171.8. HMBC spectra then enabled the connectivity to be established between the amide CHs, the double bond and the acetyl group as indicated by partial structure **9** (Fig. 3). When this structure would not fit on to any of the templates for the three established classes of alkaloid discovered to date, we entertained the possibility of an alternative IMDA process applied to a polyene structure such as **10** (similar to that invoked by Baldwin). In this way we arrived at the intermediate **11** from which an azachrysene framework could plausibly be formed (Scheme 4). The full structure **12** for GB17 was then established by X-ray crystal analysis of the hydrate (Fig. 2).[28] The absolute stereochemistry depicted for **12** is based on the presumption that it would have the same absolute configuration for C-2 (namely *S*) possessed by all twenty two of the alkaloids known to date.[29]

We are still searching for alkaloids that could be intermediates in the biosynthesis of the Class II and III structures via the pathways outlined in Scheme 2. The discovery of alkaloid **12**, however, adds a new and exciting dimension to these explorations, especially to the early stages of biosynthesis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.019.

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23. *Himgrine* (**5**): mp (methiodide) 222 °C, IR 3683, 3620, 1741, 1684 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 5.76 (dd, J = 15.4, 8.9 Hz, 1H, H7), 5.20 (dd, J = 15.3, 9.6 Hz, 1H, H8), 4.82 (ddq, J = 0.8, 2.5, 6.7 Hz, 1H, H19), 4.15 (dt, J = 2.6, 8.8 Hz, 1H, H16), 3.21 (m, 1H, OH), 3.08 (m, 1H, H6), 2.84 (m, 1H, H6), 2.68 (dt, J = 2.6, 9.1 Hz, 1H, H9), 2.38 (m, 1H), 1.95 (m, 1H), 1.79 (m, 2H), 1.71 (m, 2H), 1.58 (m, 2H), 1.53 (m, 2H), 1.45 (m, 3H) 1.37 (d, J = 6.8 Hz, 3H, CH_3-20), 1.35 (m, 1H), 1.25 (m, 4H), 1.01 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H, CH_3-1). ^{13}C NMR (150.86 MHz, $CDCl_3$) δ = 172.2 (C21), 166.4 (C18), 137.5 (C7), 129.1 (C8), 127.1 (C17), 78.4 (C19), 68.1 (C16), 60.8 (C6), 53.2 (C2), 45.8 (C9), 45.1 (C15), 42.1 (C10), 40.9 (N-Me), 33.0 (C5), 32.9 (C3), 30.9 (C11), 29.8 (C14), 25.8, 25.4 (C12, C13), 18.8 (C4), 16.9 (C20) 14.0 (C1). MS *m/z* (EI) 359 (M^+, 32%), 345 (43),

344 (100), 138 (18), 112 (43). EI-HRMS $C_{22}H_{33}NO_3$ [M^+]: calcd 359.2460; found 359.2446.

24. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 745550. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
25. *GB16* (**8**): mp 203–204 °C, IR 1715, 1635, 1560 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 5.38 (s, 1H, H17), 3.80 (m, 1H, H6), 3.38 (dddq, *J* = 14.3, 9.3, 2.2, 7.2 Hz, 1H, H2), 2.7 (m, 1H, H8), 2.63 (ddd, *J* = 15.9, 2.9, 2.5 Hz, 1H, H20), 2.54 (m, 1H, H4), 2.46 (m, 1H, H5), 2.38 (dd, *J* = 15.9, 5.6 Hz, 1H, H′20), 2.36 (m, 1H, H7), 2.33 (m, 1H, H9), 2.29 (m, 1H, H14), 2.26 (m, 1H, H′7), 2.05 (dq, *J* = 4.7, 12.3 Hz, 1H, H3), 1.87 (m, 2H), 1.82 (dd, *J* = 11.7, 3.7 Hz, 1H, H15), 1.78 (m, 1H), 1.47 (d, *J* = 7.2 Hz, 3H, CH_3-1), 1.55 (m, 1H, H10), 1.33 (m, 1H, H′3), 1.20 (m, 2H), 1.12 (m, 2H), 0.98 (1H, H11). ^{13}C NMR (150.86 MHz, $CDCl_3$) δ = 207.7 (C19), 197.8 (C16), 158.5 (C18), 104.8 (C17), 63.2 (C6), 62.5 (C2), 51.1 (C5), 48.2 (C15), 46.6 (C9), 42.1 (C20), 39.2 (C10), 33.4 (C7), 30.1 (C11), 29.9 (C8), 25.9 (C14), 25.6 (C13), 25.4 (C12), 24.4 (C3), 23.8 (C4), 20.5 (C1). MS *m/z* (EI) 313 (M^+ 100%), 298 (15), 285 (28), 270 (15), 256 (14), 242 (15), 230 (9), 216 (8), 202 (19), 188 (10), 177 (24), 160 (12), 146 (12), 132 (12), 120 (15), 107 (9), 91 (20), 79 (20), 67 (23), 55 (42), 41 (50). ESI-HRMS $C_{20}H_{28}O_2$ [M+H^+]: calcd 314.2120; found 314.2114.
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27. *GB17* (**12**): mp 115 °C (monohydrate), IR 3684, 3620, 1713, 1627 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ = 5.75 (d, *J* = 6.1 Hz, 1H) 4.02 (m, 1H, H6), 3.72 (dddq, *J* = 13.5, 9.2, 3.0, 6.8 Hz, 1H, H2), 3.56 (tt, *J* = 10.9, 4.3 Hz, 1H, H12), 2.86 (dd, *J* = 16.9, 7.8 Hz, 1H, H19), 2.74 (dd, 16.9, 3.9 Hz, 1H, H19), 2.44 (ddd, 11.5, 7.8, 3.7 Hz, 1H, H17), 2.21 (s, 3H, CH_3-21), 2.20 (br t, *J* = 8.7, 1H, H16) 1.96 (m, 3H), 1.83 (m, 5H), 1.81 (m, 1H, H4), 1.71 (dddd, *J* = 14.2, 11.1, 7.6, 3.1 Hz, 1H, H4), 1.58 (m, 1H), 1.55 (m, 1H), 1.33 (d, *J* = 6.7 Hz, 3H, CH_3-1), 1.27 (m, 2H), 1.08 (m, 2H), 0.95 (m, 1H, H15). ^{13}C NMR (150.86 MHz, CD_3OD) δ = 208.1 (C20), 171.8 (C18), 138.3 (C7), 121.2 (C8), 70.0 (C12), 59.7 (C6), 52.1 (C2), 48.3 (C17), 42.8 (C19), 42.4 (C15), 42.3, (C11), 38.9 (C16), 37.7 (C10), 35.5 (C13), 32.6 (C5), 32.3 (C9), 31.7 (C14) 30.9 (C21), 27.8 (C3), 19.9 (C1), 19.2 (C4). MS *m/z* (EI) 345 (M^+ 8%), 330 (8), 302 (10), 288 (100), 272 (11), 247 (8). ESI-HRMS $C_{21}H_{32}NO_3$ [M+H^+]: calcd 346.2382; found 346.2374.
28. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 745551. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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