The first stereospecific synthesis of michellamine B

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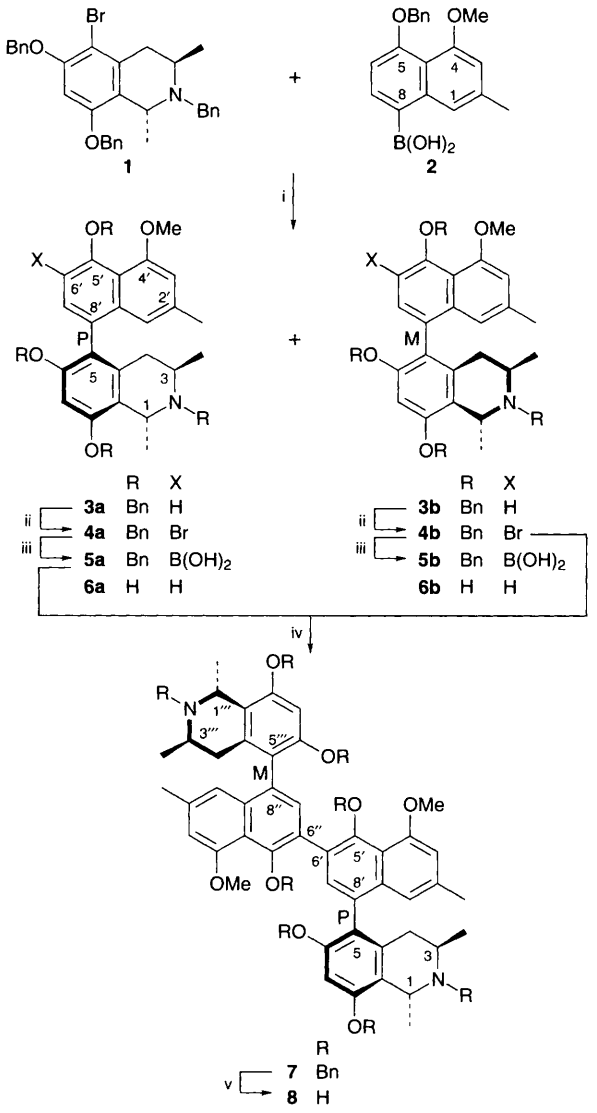
The dimeric alkaloid michellamine B is synthesized stereospecifically by the palladium-catalysed cross-coupling of the 6′-naphthaleneboronic acid of the tetrabenzylated derivative of korupensamine A and the 6′-bromo analogue of the tetrabenzylated derivative of korupensamine B, both of which are prepared by total synthesis.

The anti-viral activity of the dimeric michellamine alkaloids[1,2] was discovered in the United States National Cancer Institute program to identify from natural products novel antiviral agents for the treatment of acquired immunodeficiency syndrome. The isomeric michellamines A, B and C, which were isolated from the Cameroonian liana *Ancistrocladus korupensis*, demonstrated activity against human immunodeficiency virus (HIV)-1 and HIV-2 strains, including HIV-1 resistant to 3′-azido-3′-deoxythymidine, completely inhibiting viral cytopathic effects in infected human lymphoblastic cell lines[3,4] and inhibiting recombinant HIV reverse transcriptase activity.[3,5]

The michellamines possess two stereogenic centres in each of their two tetrahydroisoquinoline rings (at 1, 3, 1‴ and 3‴) and two stereogenic biaryl bonds between these rings and the central binaphthalene ring system, arising from restricted rotation about these bonds (at 5–8′ and 8″–5‴). The relative configurations of the michellamines A (5–8′P, 8″–5‴P), B **8** (5–8′P, 8″–5‴M) and C (5–8′M, 8″–5‴M) were established from their ^{1}H NMR spectra,[2] while their absolute configurations were determined by degradation to (*R*)-alanine and (*R*)-3-aminobutyric acid.[6] The previously reported syntheses of the michellamines by the Bringmann, Kelly and Hoye groups[7–9] were non-stereoselective and gave product mixtures that required separation by HPLC. Because michellamine B **8** was the most potent of the three dimers,[3] we undertook its stereospecific synthesis (Scheme 1), which we describe here.

The biosynthesis of the michellamines probably occurs through dimerization of korupensamines A **6a** and B **6b**, which were isolated from the same vine,[10] then subsequently synthesized by the Bringmann and Kelly groups.[11] We adapted the strategy to develop routes for the stereospecific syntheses of each of the michellamine isomers by first independently synthesizing the protected korupensamine derivatives **3a** and **3b**, then introducing appropriate functionality in each separate atropisomer in order to form the michellamine 6′–6″ binaphthalene bond by a palladium- catalysed heterobiaryl coupling reaction. To achieve this goal, the tetrabenzyl derivatives of korupensamine A **3a** and B **3b** were prepared (82%)† using a Suzuki heterobiaryl coupling {$Pd[P(C_6H_5)_3]_4$, aq. $Ba(OH)_2$, DME, 85 °C, 37 h}[12,13] of the (1*R*,3*R*)-5-bromotetrahydroisoquinoline **1**[5] and the 8′-naphthaleneboronic acid **2**, which was prepared as follows: i, bromination ($C_6H_5NMe_3Br_3$, THF, 3 h) of 8-methoxy-6-methyl-1-tetralone[14] to give the 2-bromo-1-tetralone (92%); ii, dehydrobromination (DBU, CH_2Cl_2, room temp., 2 h) of the bromotetralone to afford 4-methoxy-2-methyl-5-naphthol (98%); iii, *para*-bromination (Bu_4NBr_3, $CHCl_3$, −5 °C, 1.5 h) to the 8-bromo-5-naphthol (75%); iv, benzylation (BnBr, K_2CO_3, Me_2CO, reflux, 24 h) to the 5-benzyl ether (89%); and v, conversion (BuLi, THF, −78 °C, 7 min; $B(OPr^i)_3$; aq. NH_4Cl) to 5-benzyloxy-4-methoxy-2-methyl-8-naphthaleneboronic acid **2** (70%). The coupled products (82% of 3:2 **3a** and **3b**) were characterized after separation by HPLC (Novapak 4-μ silica, 10% EtOAc/hexanes). The geometries about the 5–8′ bonds were assigned after conversion of **3a** to korupensamine A **6a**,[10] which was isolated as the formate salt.‡ The free base (86%) generated from the salt (20% MeOH/$CHCl_3$ extraction from aq. NH_4OH, pH 10.5) had an ^{1}H NMR spectrum identical to that reported for the natural product.[10]



Scheme 1 The synthesis of michellamine B **8**. *Reagents and conditions*: i, $Pd[P(C_6H_5)_3]_4$, $Ba(OH)_2$, aq. DME, 85 °C, 37 h; ii, $C_5H_5NHBr_3$, $CHCl_3$–HOAc, 17 h; iii, BuLi, 2-MeTHF, −95 °C, 12 min; $B(OPr^i)_3$, −95 to −15 °C; aq. NH_4Cl; iv, $Pd[P(C_6H_5)_3]_4$, K_3PO_4, DMF, 90 °C, 16 h; v, 8.8% HCO_2H–MeOH, Pd, 45 °C, 3 h.

Bromination (1 equiv. pyridinium bromide perbromide–HOAc, $CHCl_3$, 17 h) of the **3a** and **3b** mixture afforded the readily separable (silica gel, 6–12% EtOAc–25% toluene–hexanes; then 3.5% EtOAc–toluene for **4b**) 6′-bromo-8′-tetrahydroisoquinolinylnaphthalenes **4a** (26%) and **4b** (18%). Byproducts, including those resulting from bromination on the benzyl protecting groups, were recycled by dehalogenation (5 equiv. BuLi, 2-MeTHF, −95 °C, 12 min; followed by MeOH). Attempted conversion of **4a** to the 6′-naphthaleneboronic acid **5a** using standard conditions [BuLi, THF, −78 °C, 30 min; $B(OMe)_3$; aq. NH_4Cl] produced predominantly the 5′-*O*-(1-phenylpentyl) analogue of **3a** (59%), which apparently arose from the rapid deprotonation of the *ortho* 5′-benzyl ether methylene group by the 6′-aryllithium derived from **4a**, followed by the alkylation of the resultant benzyllithium by 1-bromobutane generated in the halogen–metal exchange reaction. Only 14% of **5a** was isolated. In contrast, the 4′-desmethoxy-2′-desmethyl analogue of **4a** was readily converted to its corresponding 6′-naphthaleneboronic acid (64%).[5] Fortunately, we were able to circumvent this difficulty by modifying the reaction conditions, including lowering the reaction temperature (4 equiv. BuLi, 2-MeTHF, −95 °C, 12 min) to decrease proton transfer and using $B(OPr^i)_3$[15] (−95 to −15 °C) in place of $B(OMe)_3$ to decrease formation of the diarylborinic acid, to obtain **5a** (71%). The 5–8′M isomer **5b** of **5a** was prepared in an identical manner from the 6′-bromonaphthalene **4b** for coupling with **4a**.

Suzuki heterobiaryl coupling of the 6′-bromonaphthalene **4b** and the 6′-naphthaleneboronic acid **5a** under the aqueous conditions used to produce **3a** and **3b** afforded octabenzylmichellamine B **7** (61%). The yield of **7** was enhanced (76%) using nonaqueous heterobiaryl coupling conditions {$Pd[P(C_6H_5)_3]_4$, K_3PO_4,[13] DMF, 90 °C, 18 h}. At ambient temperature, the ^1H NMR spectrum (C_6D_6) of **7** showed broadened signals (presumably from hindered rotation about the 6′–6″ bond), which were also observed in the spectrum of the 4′,4″-didesmethoxy-2′,2″-didesmethyl analogue.[5] The proton signals appreciably sharpened at 50 °C to provide a well-resolved spectrum.

Debenzylation (8.8% HCO_2H/MeOH,[16] 45 °C, 3 h) of **7** yielded michellamine B as the diformate salt (98%), which was spectrally identical (except for the counterion resonance) with a sample of natural michellamine B diacetate. In contrast, deprotection at ambient temperature proved to be much slower and produced a tetrabenzylated intermediate (as established by electrospray mass spectrometry), which underwent further deprotection slowly. The ^1H NMR spectrum of synthetic michellamine B as the free base, which was obtained from the diformate salt (20% MeOH–$CHCl_3$ extraction from aq. NH_4OH, pH 10.5)[1] was identical with that reported[1] for the natural product. The retention times (t_R = 10.0 min) of synthetic and natural michellamine were identical on reversed-phase HPLC [Zorbax C_8, 4.6 × 250 mm, 0.01 mol dm^{-3} CF_3CO_2H in (55% MeOH–H_2O), 0.6 ml min^{-1}, 260 nm].

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Footnotes

† Characterization of all new compounds included 300 MHz ^1H NMR and high-resolution mass spectrometry, IR and UV spectroscopy, and optical rotation.

‡ ^1H NMR (CD_3OD) δ 1.13 (d, *J* 6.3 Hz, 3 H, 3-Me), 1.61 (d, *J* 6.6 Hz, 3 H, 1-Me), 1.99 (dd, *J* 17.8, 11.5 Hz, 1 H, H-4_a), 2.30 (s, 3 H, 2′-Me), 2.53 (dd, *J* 17.8, 4.6 Hz, 1 H, H-4_e), 3.52 (m, 1 H, H-3), 4.06 (s, 3 H, 4′-OMe), 4.67 (q, *J* 7.6 Hz, 1 H, H-1), 6.44 (s, 1 H, H-7), 6.71 (s, 1 H, H-1′), 6.76 (d, *J* 1.1, 1 H, H-3′), 6.78 (d, *J* 7.9 Hz, 1 H, H-6′), 7.08 (d, *J* 7.8 Hz, 1 H, H-7′), and 8.54 (s, 1 H, HCO_2).

References

1 K. P. Manfredi, J. W. Blunt, J. H. Cardellina II, J. B. McMahon, L. L. Pannell, G. M. Cragg and M. R. Boyd, *J. Med. Chem.*, 1991, **34**, 3402.
2 M. R. Boyd, Y. F. Hallock, J. H. Cardellina II, K. P. Manfredi, J. W. Blunt, J. B. McMahon, R. W. Buckheit Jr., G. Bringmann, M. Schäffer, G. M. Cragg, D. W. Thomas and J. G. Jato, *J. Med. Chem.*, 1994, **37**, 1740.
3 J. B. McMahon, M. J. Currens, R. J. Gulakowski, R. W. Buckheit Jr., C. Lackman-Smith, Y. F. Hallock and M. R. Boyd, *Antimicrob. Agents Chemother.*, 1995, **39**, 484.
4 J. G. Supko and L. Malspeis, *Antimicrob. Agents Chemother.*, 1995, **39**, 9.
5 V. Upender, D. J. Pollart, P. D. Hobbs, J. Liu, W. Chao, C. Olsen, B. Bowden, D. W. Thomas, A. Pandey, J. A. Lawson and M. I. Dawson, submitted for publication.
6 G. Bringmann, R. Zagst, M. Schäffer, Y. F. Hallock, J. H. Cardellina II and M. R. Boyd, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1190.
7 G. Bringmann, S. Harmsen, J. Holenz, T. Geuder, R. Götz, P. A. Keller, R. Walter, Y. F. Hallock, J. H. Cardellina II and M. R. Boyd, *Tetrahedron*, 1994, **50**, 9643.
8 T. R. Kelly, A. Garcia, F. Lang, J. J. Walsh, K. V. Bhaskar, M. R. Boyd, R. Götz, P. A. Keller, R. Walter and G. Bringmann, *Tetrahedron Lett.*, 1994, **35**, 7621.
9 T. R. Hoye, M. Chen, L. Mi, and O. P. Priest, *Tetrahedron Lett.*, 1994, **35**, 8747.
10 Y. F. Hallock, K. P. Manfredi, J. W. Blunt, J. H. Cardellina II, M. Schäffer, K. P. Gulden, G. Bringmann, A. Y. Lee, J. Clardy, G. Francois and M. R. Boyd, *J. Org. Chem.*, 1994, **59**, 6349.
11 G. Bringmann, R. Götz, P. A. Keller, R. Walter, P. Henschel, M. Schäffer, M. Stäblein, T. R. Kelly and M. R. Boyd, *Heterocycles*, 1994, **39**, 503.
12 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
13 T. Watanabe, N. Miyaura and A. Suzuki, *Synlett.*, 1992, 207.
14 B. Tamchompoo, C. Thebtaranonth and Y. Thebtaranonth, *Synthesis*, 1986, 785.
15 W. J. Thompson and J. Gaudino, *J. Org. Chem.*, 1984, **49**, 5237.
16 B. El Amin, G. M. Anantharamaiah, G. P. Royer and G. E. Means, *J. Org. Chem.*, 1979, **44**, 3442.

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