COMMUNICATION

Rapid and convergent assembly of the polycyclic framework assigned to the cytotoxic marine alkaloid halitulin

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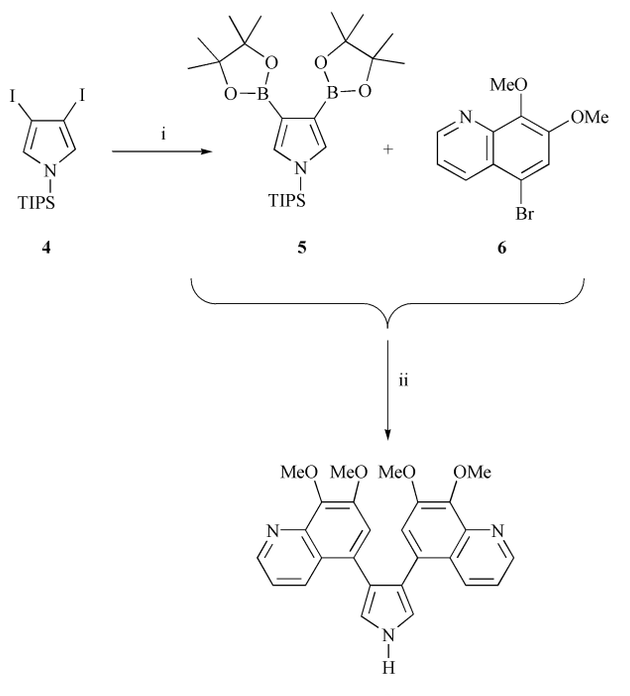
Received (in Cambridge, UK) 14th December 2001, Accepted 15th April 2002
First published as an Advance Article on the web 10th May 2002

Compound 3, representing the tetra-*O*-methyl ether derivative of structure, 1, assigned to the cytotoxic marine alkaloid halitulin, has been assembled in a convergent manner from the readily available building blocks 5, 6 and 11.

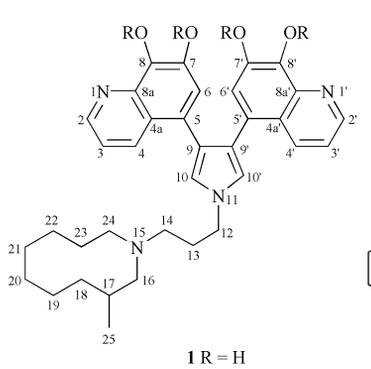
The marine natural product halitulin has recently been isolated from the sponge *Haliclona tulearensis* (collected in Sodwana Bay, Durban, South Africa) and assigned[1] structure **1** which incorporates the 3,4-bis(7′,8′-dihydroxyquinolin-5′-yl)pyrrole unit as a key motif. Significantly, halitulin was found to be cytotoxic against several tumour cell lines (*e.g.* P-388, A-549, HT-29 and MEL-28) with IC_{50} values in the 12–25 ng mL^{-1} range.[1] Such properties, coupled with the unique structure assigned to this marine alkaloid, prompted a patent-filing[2] claiming 3,4-bis(7′,8′-dihydroxyquinolin-5′-yl)pyrroles as anti-tumour agents. Consequently, and as part of a general program directed toward the total synthesis of biologically active, pyrrole-containing natural products and their analogues,[3–6] we were attracted to compound **1** as a novel synthetic target. In preliminary work directed toward this end, we have recently detailed[7] an unambiguous synthesis of compound **2**, the structure of which has been assigned to haliclorensin,[8] another (albeit biologically inactive) marine alkaloid also isolated from the sponge *Haliclona tulearensis*. On the basis of our work, and in keeping with the slightly earlier report of Steglich and Heinrich,[9] we concluded[7] that diamine **2** does not represent the true structure of haliclorensin. Whilst such results might cast some doubt on the related 3′-methylazacyclodecanyl substructure allegedly incorporated within halitulin, compound **1** remains an attractive target because accessing it would enable evaluation of the therapeutic potential of various 3,4-bis(7′,8′-dihydroxyquinolin-5′-yl)pyrroles. Of course, acquisition of target **1** should also assist in establishing the correct structure of halitulin. It is against this background that we now describe a strategy for the rapid and convergent assembly of the polycyclic framework associated with structure **1**, as highlighted by the ready acquisition of the tetra-*O*-methyl ether derivative **3**.

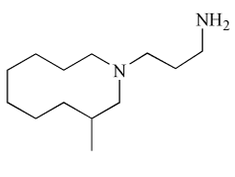
Initial studies were focused on the construction of the 3,4-diquinolin-5′-ylpyrrole pharmacophore and it was anticipated that the pivotal sub-target **7** (Scheme 1) could be assembled *via* palladium[0]-mediated cross-coupling of the known[10] 5-bromoquinoline **6** with an appropriately 3,4-difunctionalised pyrrole such as **5**. To these ends the readily available[11] 3,4-diiodopyrrole **4** was subjected to reaction with pinacolborane in the presence of $PdCl_2(dppf)$[12] under conditions described by Masuda *et al.*[13] In this manner the requisite cross-coupling partner **5**† was obtained, albeit as a chromatographically inseparable admixture with significant quantities of the corresponding mono-borolated material. Nevertheless, unpurified samples of compound **5** readily engaged in a Suzuki–Miyaura cross-coupling reaction[14] with bromoquinoline **6** to give the desilylated product **7** (29% *ex.* compound **4**, mp 242–245 °C) the structure of which was confirmed by single-crystal X-ray analysis‡ (Fig. 1).



Scheme 1 *Reagents and conditions*: (i) pinacolborane (6 mole equiv.), $PdCl_2(dppf)$ (14 mol%), Et_3N (10 mole equiv.), 1,4-dioxane, 85 °C, 24 h; (ii) Compound **6** (1.4 mole equiv.), $Pd(PPh_3)_4$ (10 mol%), 2 M Na_2CO_3 (10 mole equiv.), 6 : 5 v/v PhMe–MeOH, *ca.* 65 °C, 24 h. [dppf = 1,1-bis(diphenylphosphino)ferrocene].

Attachment of the required *N*-propyl-3-methylcycloazadecane subunit to the pyrrole nitrogen of compound **7** required access to the triflate§ **11** (Scheme 2) and this was prepared by initial treatment of the previously reported[7] amine **8** with methyl acrylate in the presence of acetic acid. The resulting Michael addition product **9** (>65%) was subject to reduction with lithium aluminium hydride and the ensuing 1°-alcohol **10** (100%) reacted with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine to give the required electrophile **11**





 DOI: 10.1039/b111401h

Table 1 Comparison of ^{1}H NMR spectral data derived from compounds **3** and **7** with those reported[1] for halitulin

δ_H Compound **3**[a]	Assign[b]	δ_H Compound **7**[c]	Assign[b]	δ_H Halitulin **1**[a]	Assign[d]
—	—	9.48 (br s, 1H)	H11	—	—
8.78 (dd, *J* 4.1 and 1.3, 2H)	H2/2′	8.80 (dd, *J* 4.1 and 1.8, 2H)	H2/2′	8.56 (d, *J* 4.9, 2H)	H2/2′
8.28 (dd, *J* 8.6 and 1.3, 2H)	H4/4′	8.29 (dd, *J* 8.6 and 1.8, 2H)	H4/4′	8.51 (d, *J* 8.3, 2H)	H4/4′
7.03 (dd, *J* 8.6 and 4.1, 2H)	H3/3′	7.14 (d, *J* 2.6, 2H)	H10/10′	7.28 (br s, 2H)	H6/6′
7.00 (s, 2H)	H6/6′	7.05 (dd, *J* 8.6 and 4.1, 2H)	H3/3′	7.20 (dd, *J* 8.3 and 4.9, 2H)	H3/3′
6.96 (s, 2H)	H10/10′	7.04 (s, 2H)	H6/6′	7.04 (br s, 2H)	H10/10′
4.12 (m, 2H)	H12	—	—	4.23 (t, *J* 6.3, 2H)	H12
2.77 (m, 1H)	H24	—	—	3.75 (m, 1H)	H24
2.62 (m, 1H)	H14	—	—	3.40 (m, 1H)	H24
2.40 (t, *J* 12.5, 1H)	H16	—	—	3.27 (m, 1H)	H16
2.28 (m, 2H)	H14/24	—	—	3.23 (m, 2H)	H14
2.14 (m, 3H)	H13/16	—	—	2.97 (m, 1H)	H16
1.92 (m, 1H)	H17	—	—	2.56 (m, 2H)	H13
1.82 (m, 2H)	—	—	—	2.32 (m, 1H)	H17
1.73–1.58 (m, 3H)	—	—	—	1.96 (m, 2H)	H23
1.56–1.38 (m, 7H)	—	—	—	1.62–1.36 (m, 8H)	H20
0.82 (d, *J* 7.0, 3H)	H25	—	—	1.60 (m, 2H)	H18
4.02 (s, 6H)	C8/8′ OMe	4.03 (s, 6H)	C8/8′ OMe	1.09 (br s, 3H)	H25
3.61 (s, 6H)	C7/7′ OMe	3.63 (s, 6H)	C7/7′ OMe	Signals due to OH protons not reported	—

[a] Spectra recorded in $CDCl_3$ at 500 MHz. [b] Made with the assistance of HMBC, HMQC, COSY and TOCSY experiments. [c] Spectrum recorded in $CDCl_3$ at 300 MHz. [d] Taken from Reference 1.

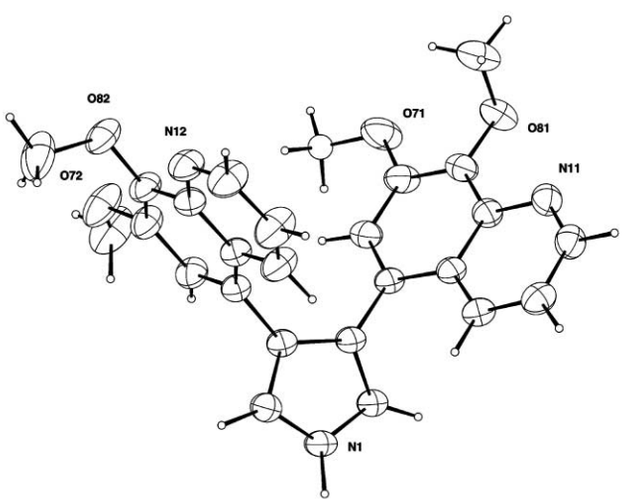
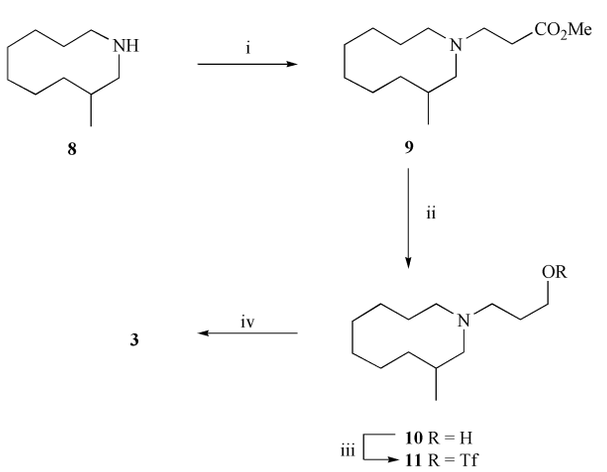


Fig. 1 Anisotropic Displacement Ellipsoid Plot (ADEP) (with 50% probability ellipsoids) of compound **7** derived from X-ray crystallographic data.



Scheme 2 *Reagents and conditions*: (i) methyl acrylate (excess), AcOH (2 mole equiv.), reflux, 16 h; (ii) $LiAlH_4$ (2 mole equiv.), THF, 18 °C, 16 h; (iii) Tf_2O (1.2 mole equiv.), 2,6-di-*tert*-butyl-4-methylpyridine (2.5 mole equiv.), CH_2Cl_2, 0 °C, 1 h; (iv) compound **7** (1.0 mole equiv.), KHMDS (1.2 mole equiv.), THF, 0 °C, 0.10 h then compound **11** (1.2 mole equiv.), 0 °C, 0.15 h. KHMDS = potassium hexamethyldisilazide.

(100%). Being rather unstable, triflate **11** was immediately reacted with the potassium salt of pyrrole **7** (generated by reacting compound **7** with KHMDS) and, in this manner, target **3** (87%) was obtained as a bright yellow oil.

Spectroscopic analysis of compound **3** provided data in full accord with the assigned structure. Unfortunately, all attempts thus far to effect the exhaustive demethylation of compound **3** and thereby generate congener **1** have been unsuccessful. Nevertheless, detailed spectroscopic analysis of compound **3**¶ and appropriate collation of the derived data with those reported[1] for halitulin allow some conclusions to be drawn. For example, comparisons of the ^{1}H NMR data for compound **3**, (and precursor **7**) with those for the natural product (Tables 1 and 2) are not especially favorable even when allowance is made for the fact that parallels are being drawn between a bis-*O*-methyl ether and the corresponding free catechol. Similar concerns arise in making analogous comparisons of the ^{13}C NMR data obtained for compounds **3** and **7** with those reported for halitulin (Table 2). Significantly, these "discrepancies" involve BOTH the cyclic amine and the 3,4-diquinolin-5-ylpyrrole portions of structure **1**. The foregoing assessments raise some concerns regarding the assigned structure of halitulin. However, definitive conclusions in this regard must await the unambiguous synthesis of compound **1** and/or the re-collection of halitulin and its subjection to further spectroscopic studies. Efforts directed toward the former end are now underway in these laboratories. Biological evaluations of compounds **3** and **7** are also being undertaken. Results will be reported in due course.

Experimental

3,4-Bis(7′,8′-dimethoxyquinolin-5′-yl)pyrrole (7)

4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (333 mg, 2.60 mmol, ex Aldrich) was added, dropwise, to a magnetically stirred solution of pyrrole **5**[11] (206 mg, 0.43 mmol), $PdCl_2$(dppf)[12] (21 mg, 0.03 mmol) and triethylamine (439 mg, 4.34 mmol) in 1,4-dioxane (5 mL) maintained at 18 °C under an atmosphere of nitrogen. The resulting mixture was heated at 85 °C for 24 h then cooled, quenched with distilled water (20 mL) and extracted with $CHCl_3$ (4 × 20 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a tan-coloured oil. This material was taken up in ethyl acetate–hexane (15 mL of a 1 : 10 v/v mixture) and the resulting solution filtered through a small pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to afford a *ca.* 3 : 1 mixture (as judged by ^{1}H

Table 2 Comparison of ^{13}C NMR spectral data derived from compounds **3** and **7** with those reported[1] for halitulin

δ_C Compound **3**[a]	Assign[b]	δ_C Compound **7**[c]	Assign	δ_C Halitulin (**1**)[a]	Assign[d]
150.4	C7	150.7	C7	148.1	C7
149.8	C2	149.9	C2	145.1	C2
143.2	C8a	143.3	C8a	141.6	C4
141.3	C8	141.3	C8	131.2	C8
134.3	C4	134.8	C4	130.1	C8a
129.3	C4a	129.9	C4a	126.7	C5
122.9	C5	123.3	C5	123.2	C6
121.0	C9	121.0	C9	122.9	C4a
120.8	C3	119.0	C3	122.6	C10
118.4	C6	118.7	C6	118.8	C9
116.6	C10	116.9	C10	117.1	C3
60.5	C16	—	—	57.7	C16
53.1	C24	—	—	54.4	C14
52.0	C14	—	—	50.9	C24
48.2	C12	—	—	46.8	C12
31.7	C18	—	—	32.7	C18
29.8	C17	—	—	28.3	C17
28.7	C13	—	—	26.1	C13
26.2	CH_2	—	—	24.4	C19
25.7	CH_2	—	—	24.2	C20
24.4	CH_2	—	—	23.9	C21
24.2	CH_2	—	—	23.6	C22
22.0	CH_2	—	—	22.0	C23
19.2	C25	—	—	20.7	C25
61.4	OMe	61.7	OMe	—	—
56.3	OMe	56.4	OMe	—	—

[a] Spectra recorded in $CDCl_3$ at 125 MHz. [b] Made with the assistance of HMBC, HMQC and APT experiments. [c] Spectrum recorded in $CDCl_3$ at 75 MHz. [d] Taken from Reference 1.

NMR analysis) of compound **6** and its mono-borolated counterpart (130 mg). This material was used without purification in the next step of the reaction sequence.

A solution of Na_2CO_3 (290 mg, 2.74 mmol) in water (1.4 mL) was added, in one portion, to a solution of the above-mentioned product mixture (130 mg), 5-bromo-7,8-dimethoxyquinoline (**6**)[10] (161 mg, 0.60 mmol) and $Pd(PPh_3)_4$ (32 mg, 0.027 mmol) in toluene–methanol (11 mL of a 6 : 5 v/v mixture). The resulting solution was deoxygenated under reduced pressure (16 mmHg) and back filled with nitrogen. This procedure was repeated five times. The ensuing and magnetically stirred solution was heated at reflux for 24 h then cooled to 18 °C and diluted with water (20 mL). The resulting mixture was extracted with $CHCl_3$ (4 × 30 mL) and the combined organic phases dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of this material to flash chromatography (silica gel, 5 : 95 v/v methanol–$CHCl_3$ elution) and concentration of the appropriate fractions (R_f 0.2) then afforded pyrrole **7** (56 mg, 29% from **5**) as yellow crystalline masses, mp 242–245 °C (Found: $M^{+\bullet}$, 441.1701. $C_{26}H_{23}N_3O_4$ requires $M^{+\bullet}$, 441.1689). ν_{max} (KBr)/cm^{-1} 2934, 1599, 1474, 1332, 1155, 1079, 991, 752; δ_H—see Table 1; δ_C—see Table 2; *m*/*z* (EI, 70 eV) 441 ($M^{+\bullet}$, 17%), 371 (74), 313 (23), 157 (41), 101 (100).

Acknowledgements

We thank the Institute of Advanced Studies for financial support. We are also grateful to the Australian Research Council for providing an APA(I) to DJW and Professor Y. Kashman (University of Tel-Aviv) for copies of the ^1H NMR spectra derived from halitulin. Many useful discussions with Professor Wolfgang Steglich (LMU–Muenchen) are warmly acknowledged.

References and notes

† All new and stable compounds had spectroscopic data [IR, UV, NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high-resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

‡ *Crystal data for compound* **7**: $C_{26}H_{23}N_3O_4$, $M = 441.487$, $T = 200(1)$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 8.12680(10)$, $b = 21.0119(4)$, $c = 18.7505(3)$ Å, $\beta = 95.1067(8)°$, $V = 3189.12(9)$ Å^3, $D_x = 0.92$ g cm^{-3}, $F(000) = 940$, 6514 unique data ($\theta_{max} = 26.42°$), 5203 with $I > 3\sigma(I)$; $R = 0.0774$, $R_w = 0.0732$, $S = 0.9986$.

Images were measured on a Nonius Kappa CCD diffractometer (Mo-Kα graphite monochromator, $\lambda = 0.71073$ Å) and data extracted using the DENZO package.[15] Structure solution was by direct methods (SIR92)[16] and refinement was by full matrix least-squares on *F* using the CRYSTALS program package.[17] The SQUEEZE routine of PLATON[18] was used to account for the electron density of the highly disordered solvent void. CCDC reference number 177294. See http://www.rsc.org/suppdata/p1/b1/b111401h/ for crystallographic files in .cif or other electronic format.

§ The IUPAC name for triflate is trifluoromethanesulfonate.

¶ *Selected spectral data for compound* **3**: ν_{max} (neat, NaCl)/cm^{-1} 2930, 1598, 1496, 1472, 1346, 1331, 1297, 1256, 1156, 1105, 1078, 789; δ_H—see Table 1; δ_C—see Table 2; *m*/*z* (EI, 70 eV) 636.3678 ($C_{39}H_{48}N_4O_4$ requires 636.3676, $M^{+\bullet}$, 100%), 621 [$(M - H_3C^{\bullet})^+$, 7], 455 [$(M - C_{12}H_{23}N^{\bullet})^+$, 42], 440 [$(M - C_{13}H_{26}N^{\bullet})^+$, 19], 168 [$(C_{11}H_{22}N)^{+\bullet}$, 28].

1 Y. Kashman, G. Koren-Goldshlager, M. D. Garcia Gravalos and M. Schleyer, *Tetrahedron Lett.*, 1999, **40**, 997.
2 Y. Kashman, G. Koren-Goldshlager and M. D. Garcia Gravalos, WO 00/20411; (*Chem. Abstr.*, 2000, **132**, 260678).
3 M. G. Banwell, B. L. Flynn and D. C. R. Hockless, *Chem. Commun.*, 1997, 2259.
4 M. G. Banwell, B. L. Flynn, E. Hamel and D. C. R. Hockless, *Chem. Commun.*, 1997, 207.
5 M. G. Banwell, A. M. Bray, A. C. Willis and D. J. Wong, *New J. Chem.*, 1999, **23**, 687.
6 M. G. Banwell, A. Edwards, J. Smith, E. Hamel and P. Verdier-Pinard, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1497.
7 M. G. Banwell, A. M. Bray, A. J. Edwards and D. J. Wong, *New J. Chem.*, 2001, **25**, 1347.
8 G. Koren-Goldshlager, Y. Kashman and M. Schleyer, *J. Nat. Prod.*, 1998, **61**, 282.
9 M. R. Heinrich and W. Steglich, *Tetrahedron Lett.*, 2001, **42**, 3287 . The correct structure for haliclorensin has now been established, M. R. Heinrich, Y. Kashman, P. Spiteller and W. Steglich, *Tetrahedron*, 2001, **57**, 9973.
10 F. Trécourt, M. Mallet, F. Mongin and G. Quéguiner, *Synthesis*, 1995, 1159.
11 B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, R. D. Artis and J. M. Muchowski, *J. Org. Chem.*, 1990, **55**, 6317.

12 L. Brandsma, S. F. Vasilevsky and H. D. Verkruijsse, *Application of Transition Metal Catalysts in Organic Synthesis*, Springer-Verlag, Berlin, 1998, p. 5.
13 M. Murata, T. Oyama, S. Watanabe and Y. Masuda, *J. Org. Chem.*, 2000, **65**, 164.
14 T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508.
15 DENZO-SMN: Z. Otwinowski and W. Minor, *Processing of X-ray diffraction data collected in oscillation mode, Methods in Enzymology, Volume 276: Macromolecular Crystallography*, Part A, eds. C. W. Carter Jr. and R. M. Sweets, Academic Press, 1997, pp. 307–326.
16 A. Altomare, G. Cascarano, C. Giacovazzo and A. Guagliardi, *J. Appl. Crystallogr.*, 1993, **26**, 343.
17 D. J. Watkin, C. K. Prout, J. R. Carruthers and P. W. Betteridge, *CRYSTALS*, Chemical Crystallography Laboratory, Oxford, UK, Issue 10, 1966 .
18 A. L. Spek, *Acta Crystallogr., Sect. A*, 1990, **46**, C34.