Synthetic studies directed towards the potent cytotoxic natural product ottelione A: stereoselective construction of the complete framework

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A stereoselective strategy for the rapid acquisition of the complete framework (dideoxyottelione A) of the promising cytotoxic agent ottelione A, with four contiguous stereogenic centres on a hydrindane skeleton and a sensitive 4-methylene-cyclohex-2-enone functionality, from the readily available Diels–Alder adduct of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and norbornadiene, is delineated.

Towards the end of 1998, the isolation and structure determination of two novel, diastereomeric 4-methylene-cyclohex-2-enone moiety-bearing natural products, otteliones A and B, from the fresh water plant Ottelia alismoides that grows partially under water, was reported.1 While ottelione B was assigned structure 1, even the most incisive analyses of the NMR data and modelling did not permit unambiguous assignment to ottelione A. For ottelione A, structures 2a and 2b were considered and on the basis of available data 2a was very much favoured without fully ruling out 2b.1 Ottelione A was also found to be identical with the compound reported earlier in the patent literature by Leboul and Provost at Rhone-Poulenc Rorer.2 Our interest in otteliones A and B was aroused by the observation of remarkable antitumor and antileukemia activity exhibited by them.1–3 It was shown that 1 and 2 inhibit tubulin polymerisation into microtubules in a manner reminiscent of colchicine, vincristine and vinblastine. When subjected to in vitro screening against a panel of ca. 60 human tumor cell lines at NCI, both 1 and 2 showed remarkable cytotoxicity against most of the cell lines at nM–pM concentrations.1 Such a promising biological activity profile, the unusual bicyclic structure with four stereogenic centres, the presence of a sensitive 4-methylene-cyclohex-2-enone moiety4 and the uncertainty associated with the structure assigned to ottelione A 2 prompted us to explore synthetic approaches towards this novel molecule. Herein, we describe a stereoselective and flexible approach, targeted towards the favoured formulation 2a for
ottelione A, which has resulted in the acquisition of the complete framework of ottelione A and set the stage for the synthesis of the natural product.

The key element of our projected synthesis of ottelione A 2a was the identification of the stereochemically well-defined tricyclic compound 3,5 readily available through inverse electron demand Diels–Alder reaction between 1,2,3,4-tetra-chloro-5,5-dimethoxycyclopentadiene and norbornadiene, as a propitious starting point (Scheme 1). In the bicyclic hydridane framework as well as all the four stereogenic centres present in ottelione A are firmly imbedded (see bold lines in 3) and the main task was to disengage the requisite framework from 3, preserving the stereochemical features, and sequentially generate the complex and extensive functionalization pattern present in the target molecule 2a.

Regioselective OsO₄-mediated dihydroxylation of the unsubstituted norbornene double bond in 3⁵ and reductive dehalogenation furnished the cis-diol 4. Periodate cleavage led to the dialdehyde 5 which was directly subjected to controlled mono-Wittig olefination and the remaining aldehyde functionality was reduced to furnish 6. Tosylation of the hydroxy group in 6 to 7 and Cu⁰ mediated cross-coupling reaction with PhMgBr and acetal deprotection readily led to 8 with the correct stereochemical disposition at all the four stereogenic centres (cf. 1, 3, 3a and 7a positions in 2a) and the desired two substituents on the five-membered ring. The hydridane framework from the key compound 8 was extracted through Baeyer–Villiger oxidation to two regioisomeric lactones (55:45) and LAH reduction to furnish the diols 9 and 10, respectively. PDC oxidation of 9 and 10 led to the enones 11 and 13, respectively, and extensive high field 2D NMR studies on these enones established their structural identity. The sensitive 4-methyleneencyclohex-2-ene moiety from 11 was generated quite uneventfully through conversion of the primary hydroxy group to the mesylate and DBU mediated elimination to yield dideoxyottelione A 12 (Scheme 1). The 1H and 13C NMR data for 12 exhibited remarkable similarity to that of the natural product 2a, as the only difference between them is the presence of the aromatic substitution in the latter. In a similar manner, enone 13 was transformed to 14, a regioisomer of the natural series in which the benzyl and vinyl moieties are interchanged.

In short, we have outlined a simple and flexible strategy, emanating from abundantly available starting materials, towards a promising cytotoxic natural product ottelione A 2a. Our approach can be readily adapted to the synthesis of 2a itself through minor tactical modifications and is inherently well-suited to delivering a variety of analogues for biological evaluation. Efforts along these lines are underway and will be reported shortly.

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Notes and references

6 All compounds were fully characterized on the basis of their spectral and analytical data. Selected data for 2a: δ(CHCl₃) 7.31–7.13 (m, 5H), 6.42 (dd, 1H, J 6.9, 3.6), 6.28 (dd, 1H, J 6.9, 3.6), 5.80 (ddd, 1H, J 17.7, 10.2, 7.2), 5.02–4.92 (m, 2H), 2.96 (m, 1H), 2.81 (m, 1H, J 13.2, 6.0), 2.58 (dd, 1H, J 13.2, 8.4), 2.47–2.27 (m, 3H), 2.04–1.95 (m, 1H, J 18.0–16.3 (m, 2H), 1.27–1.16 (m, 1H); δCl(CDCI₃) 203.2, 141.1, 141.0, 132.9, 132.4, 128.6 (2C), 128.4 (2C), 126.0, 113.8, 51.2, 50.4, 47.1, 47.0, 46.3, 44.7, 41.1, 40.1; m/z (70 eV, El) 264 (M⁺). For 12: δ(CHCl₃) 7.36–7.18 (m, 5H, arom), 6.97 (d, 1H, J 10, Hα), 5.93 (d, 1H, J 10, Hα), 5.67 (ddd, 1H, J 17.2, 10.2, 8.2, Hβ), 5.39 (s, 1H, Hβ), 5.25 (s, 1H, Hβ), 5.02 (d, 1H, J 10.2, Hγ), 4.90 (d, 1H, J 17.1, Hδ), 3.02 (d of quintet, 1H, J 7, 3.4, Hγ), 2.94 (dd, 1H, J 15, 7.2, Hγ), 2.78 (dd, 1H, J 10.8, 8.5, Hα), 2.70 (dd, 1H, J 13.6, 8.7, Hα), 2.62 (dd, 1H, J 18.2, 3.5, Hβ), 2.30–2.23 (m, 1H, J 17.2, Hβ), 2.03–1.97 (m, 1H, Hγ), 1.25 (ddd, 1H, J 13.1, 10.5, 7.5, Hδ); δCl(CDCI₃) 199.7 (C quat.), 145.6 (CH), 140.5 (2C, C quat.), 140.4 (CH), 129.0 (2C, CH), 128.3 (2C, CH), 126.4 (CH), 126.0 (CH), 115.9 (CH₂), 53.7 (CH), 50.1 (CH), 48.7 (CH₂), 42.5 (CH), 41.2 (CH), 37.5 (CH₂), m/z (70 eV, El) 264 (M⁺). For 14: δ(CHCl₃) 7.26–7.10 (m, 5H, arom), 7.01 (d, 1H, J 10.2, Hγ), 5.92 (d, 1H, J 10, Hα), 5.87 (ddd, 1H, J 17.2, 10.7, Hβ), 5.44 (s, 1H, Hδ), 5.35 (s, 1H, Hβ), 5.04 (d, 1H, J 17.2, Hδ), 4.97 (d, 1H, J 10, Hα), 3.18–3.10 (m, 1H, J 17.2, Hβ), 2.98 (dd, 1H, J 13.4, 4.1, Hα), 2.78 (t, 1H, J 8.3, Hα), 2.70 (dd, 1H, J 7.9, 4.3, Hα), 2.34 (ddd, 1H, J 13.3, 10.3, Hβ), 2.05–1.90 (m, 2H, Hβ, Hα), 1.22 (ddd, 1H, J 13.1, 9.5, 7.5, Hβ); δCl(CDCI₃) 199.5 (C quat.), 145.6 (CH), 142.2 (CH), 141.8 (CH₂), 140.6 (Cquat.), 128.7 (2C, CH), 128.3 (2C, CH), 126.5 (CH), 126.0 (CH), 121.4 (CH₂), 113.3 (CH₃), 55.1 (CH), 49.3 (CH), 46.3 (CH), 43.7 (CH), 40.5 (CH₂), 37.1 (CH); m/z (70 eV, El) 264 (M⁺).