COMMUNICATION

Studies towards the taxane ring system *via* a cascade macrocyclisation–transannulation strategy

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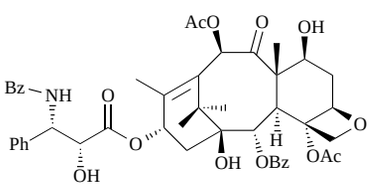
Treatment of the ω-iodoacetylene 6 with Bu_3SnH–AIBN produces the taxane ring system 9 (45–60%) by way of transannular cyclisation from the macrocyclic vinyl radical intermediate 8, whereas the analogous iodoacetylenes 5a, 11 and 13a, together with the iodopolyenones 12a, 14a and 17, failed to give corresponding taxane systems, *i.e.* 7, 16 and 19 on similar treatment; instead only products resulting from direct reduction of the carbon–iodine bonds in these substrates were obtained.

The discovery of the potent anticancer properties of Taxol **1**,



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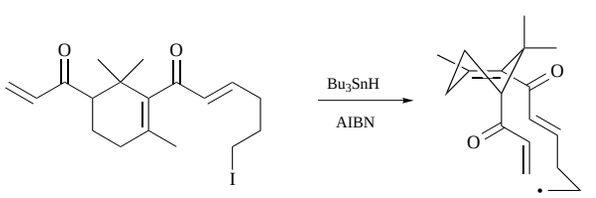
with its novel tricyclo[9.3.1.$0^{3,8}$]pentadecene framework, has acted as an immense spur to synthetic chemists—luring and seducing them into designing and developing routes to this important and challenging target. As a consequence, an avalanche of subtle and intriguing synthetic designs towards the taxane carbon framework have been forthcoming in recent years,[1] with four of them culminating in the total synthesis of Taxol itself.[2] A few years ago our research group described its own distinctive approach to the taxanes based on a cascade radical-mediated macrocyclisation–transannulation stategy from an appropriately substituted A-ring precursor, *viz*. **2**→**4**, *via*



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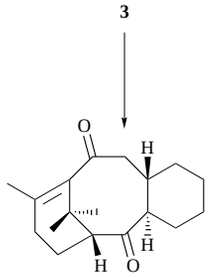

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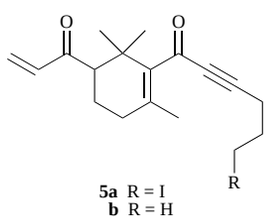
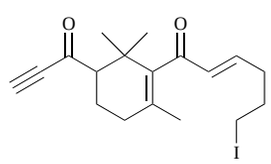
3.[3] Since this time we have examined a variety of alternative precursors, analogous to **2**, in order to develop and refine this synthetic approach to the taxane ring system. In this communication we describe the outcome of using alkyne electrophores in place of alkene electrophores in the aforementioned radical cascade, together with the results of incorporating methyl group substitution on the disubstituted alkene electrophore in **2** and, finally the outcome of a complementary radical-mediated cascade sequence to the taxane ring system from the iodotrienone **17**.

At the outset of our investigations, although not unknown, alkynes had been used less frequently than alkenes as electrophores in radical cyclisations.[4,5] We surmised that replacement of either of the enone electrophores in **2** by alkynones, *viz*. **5a** and **6**, would have a beneficial effect on the efficacy of the cascade macrocyclisation–transannulation processes and, in addition, lead to more unsaturated taxane products (*e.g.* **7** from **5a**) thereby facilitating further synthetic transformations in the tricyclic products.



5a R = I
b R = H



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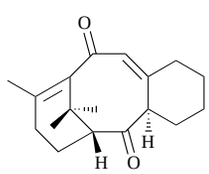

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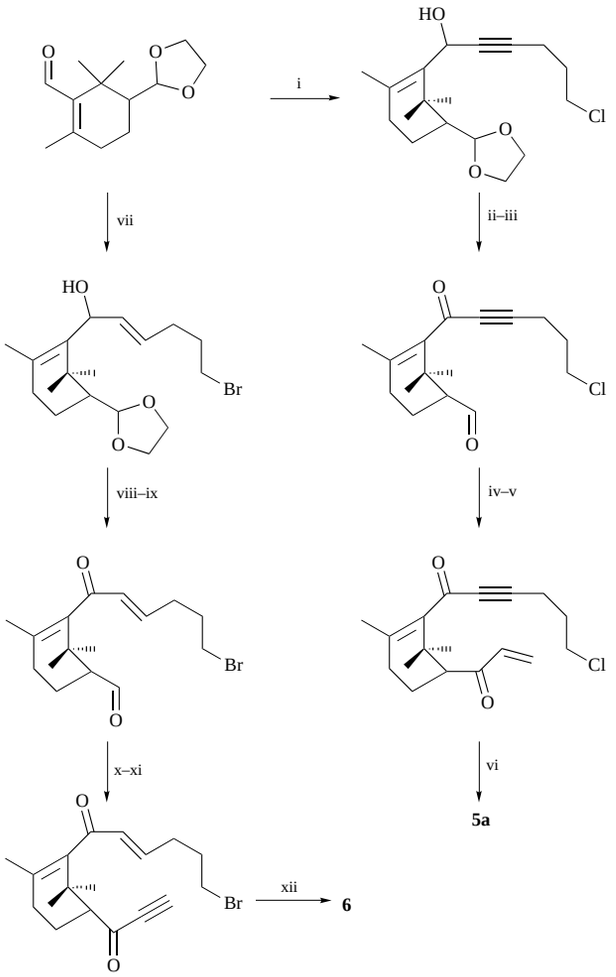
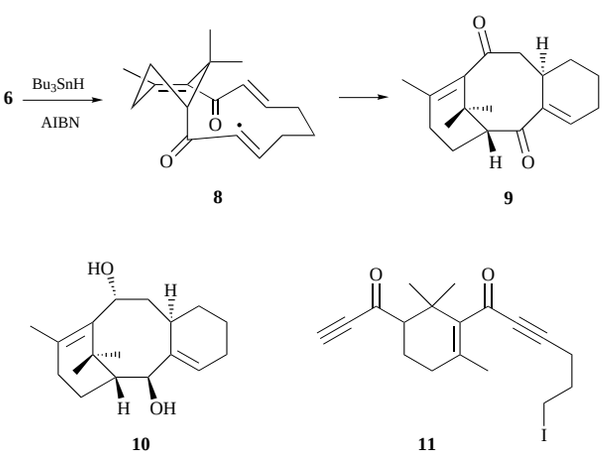
The iododienynedione isomers, **5a** and **6**, were synthesised from essentially the same substituted ring-A precursor, as highlighted in Scheme 1.[6] Whereas the substrate **2** underwent radical cascade cyclisation in the presence of Bu_3SnH–AIBN to produce largely the diastereoisomer **4** of the corresponding taxane, the alkyne analogue **5** failed to undergo any intramolecular cyclisation at all, and instead gave only the product of direct reduction of the carbon–iodine bond, **5b** (21%).[6] To our pleasure however, when the iododienynedione **6** incorporating a terminal ynone electrophore was treated with Bu_3SnH–AIBN[7] it underwent a facile cascade 12-*endo*-*dig* macrocyclisation (to **8**) followed by a 6-*exo*–8-*endo* transannulation producing the tricyclo[9.3.1.$0^{3,8}$]pentadecadienedione **9** in a satisfying 45–60% yield. The structure of **9** followed from analysis of its NMR spectroscopic data whereas its stereochemistry was secured from an X-ray crystal structure determination of the 1,5-diol **10** produced from reduction of the dione **9** with DIBAL.[8]

The differing outcomes of the attempted cascade cyclisations of **2**, **5a** and **6** are surely interesting, but attempts to rationalise the results using computer modelling and energy



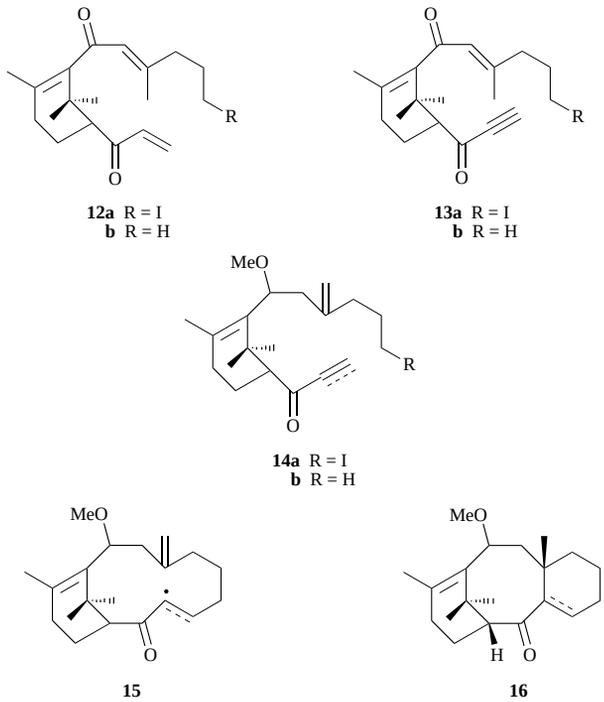
Scheme 1 *Reagents, conditions and yields:* i, BuLi, $HCC(CH_2)_3Cl$, THF, −78 °C, 96%; ii, TPAP, NMO, CH_2Cl_2, 0 °C, 98%; iii, CSA, THF, H_2O, reflux, 98%; iv, $H_2C{=}CHMgBr$, THF, −78 °C, 98%; v, TPAP, NMO, CH_2Cl_2, 0 °C, 89%; vi, NaI, EtCOMe, reflux, 94%; vii, BuLi, *E*-$Bu_3SnCH{=}CH(CH_2)_3Br$, THF, −84 °C, 81%; viii, TPAP, NMO, CH_2Cl_2, room temp., 89%; ix, CSA, THF, H_2O, reflux, 89%; x, HCCMgBr, THF, room temp., 81%; xi, $BaMnO_4$, CH_2Cl_2, room temp., 59%; xii, NaI, EtCOMe, reflux, 99%

minimisation data on ill-defined processes and reactive intermediates were less than successful.[9] Perhaps not too surprisingly the ambitious double cyclisation of the enediynedione **11**



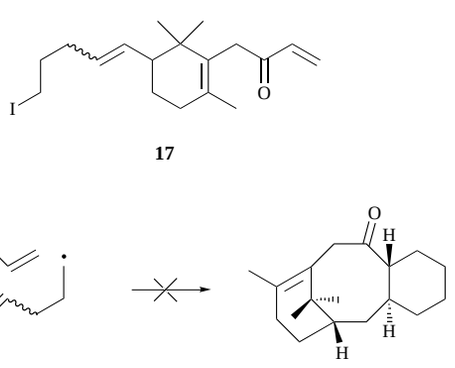
also failed in the presence of Bu_3SnH–AIBN with only the product of carbon–iodine bond reduction (~21%) being identified amongst the products.

In ramifications of the successful cascade macrocyclisation–transannulation reactions **2**→**4** and **6**→**9**, we examined the corresponding cyclisations of the vinyl methyl substituted analogues **12a** and **13a**, together with the exo-methylene containing substrate **14a**.[10] Each of these precursors however led



only to the products of direct reduction of their carbon–iodine bonds, *i.e.* **12b**, **13b** and **14b**, on treatment with Bu_3SnH–AIBN. Whilst this outcome was not too surprising in the cases of **12a** and **13a**, where facile 1,5-hydrogen abstraction by the precursor radical from the vinyl methyl group might be expected,[11] we were more optimistic about the cyclisation from **14a** *via* **15** to **16**. Clearly there are many hidden stereoelectronic/energy features associated with the ease or otherwise of cascade radical-mediated macrocyclisation–transannulation processes from the precursors **2**, **5**, **6** and **11**–**14**, leading to the corresponding taxane ring systems. Nevertheless the model experiments described above have provided a basis for developing the cascade process **6**→**9** using a fully substituted chiral A-ring precursor[12] to access an advanced intermediate *en route* to Taxol; this programme is in progress.

As a corollary, we also examined the outcome of radical cyclisation from the *Z*- and *E*-isomers of the iodotrienone system **17**;[10] this system is complementary to the earlier-mentioned cascade **2**→**4**. Unfortunately, separate treatment of the *Z*- and *E*-isomers of **17** with Bu_3SnH–AIBN led to only the products of direct reduction of the carbon–iodine bonds in the substrate (65–92%); we obtained no evidence for the co-formation of the taxane ring system from these studies, *viz*. **18**→**19**.



Acknowledgements

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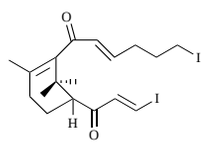
6 Satisfactory spectroscopic data together with microanalytical and/or mass spectrometric data were obtained for all new compounds.

7 Interestingly, treatment of the iododienynedione **6** with $(Me_3Si)_3$-SiH–AIBN produced the diiodide below (19%) in addition to the tricyclic system **9** (23%).



8 We thank Dr A. J. Blake of this Department for the X-ray structure determination which will be reported in the full paper.

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10 The synthesis of the precursors **12a**, **13a**, **14a** and **17** will be described in detail in a full paper.

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