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# An Exploration of the Scope for Radical-mediated Transannular Diels-Alder Reactions in Polycycle Synthesis

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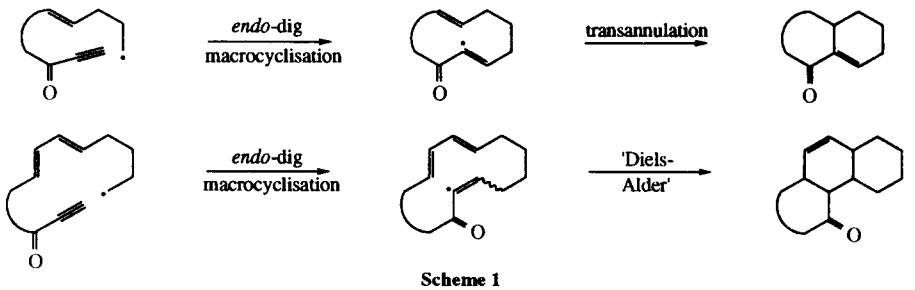
*Abstract*: Treatment of the iododienynone **4** with $Bu_3SnH$-AIBN results in the formation of the tricyclic enone **6** by way of radical-mediated macrocyclisation, to **5**, followed by transannular Diels-Alder reaction. By contrast, similar treatment of **8** produced the tetracycle **12** (70%) rather than the Diels-Alder product **9**, and the analogous system **13** gave rise to the novel tetracyclic diene-dione **18** presumably by way of the intermediates **14**, **16** and **17**. © 1997 Elsevier Science Ltd.

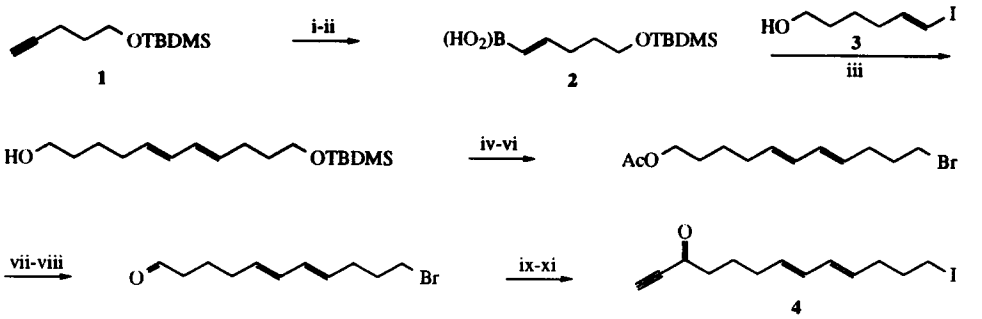
In previous studies directed towards the development of new approaches for the synthesis of polycyclic structures, we have demonstrated the considerable scope for a stratagem involving intramolecular macrocyclisation from alkyl radicals to conjugated ynone electrophores in concert with transannular vinyl radical cyclisation, leading to a range of unsaturated fused-ring systems (Scheme 1).[1] In an extension to these




**Scheme 1**

studies we have now examined the scope for similar 'cascade' cyclisations where the ynone substrate includes a conjugated 1,3-diene as acceptor for the vinyl radical intermediate resulting from the macrocyclisation, thereby offering the opportunity for polycycle ring construction *via* a radical-like transannular Diels-Alder reaction (Scheme 1).[2-4]

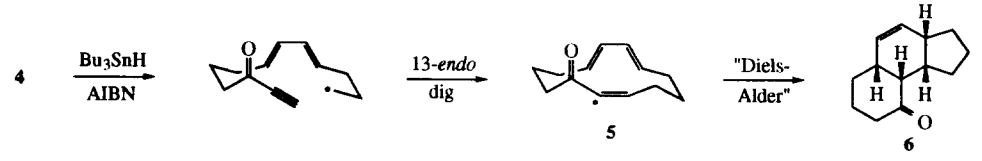
Thus, we first examined a synthesis of the iododienynone **4** with a view to exploring its cascade radical-mediated macrocyclisation-transannular Diels-Alder cyclisation to the tricyclic enone **6**. The iododienynone **4** was conveniently prepared as outlined in Scheme 2 starting from the known acetylene **1**[5] and vinyl iodide **3**,[6] and using a route which featured a Suzuki coupling[7] reaction between **3** and the boronic acid **2** to set up the conjugated *E,E*-1,3-diene unit in the target compound.[8] When a solution of **4** in benzene was treated with $Bu_3SnH$-AIBN at 80°C for 8 hr, work-up and chromatography led to the isolation of a single diastereomer of the expected tricyclic enone **6**, albeit in a disappointing 22% yield; the only other monomeric product isolated



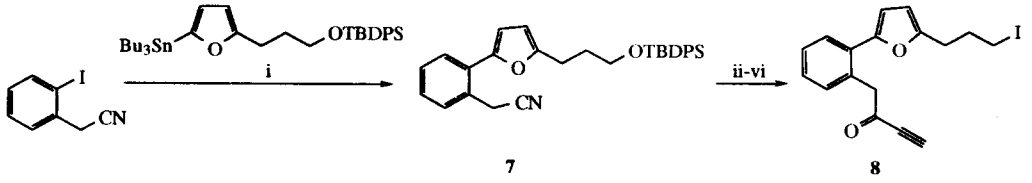

*Reagents*: i, Catecholborane, THF, reflux, 77%; ii, $H_2O$, 25°C, 87%; iii, $Pd(PPh_3)_4$, LiOH, THF, $H_2O$, 40°C, 82%; iv, $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, 0°C, 91%; v, TBAF, THF, 25°C, 79%; vi, $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0°C, 89%; vii, $K_2CO_3$, MeOH, 25°C, 97%; viii, Dess-Martin periodinane, $CH_2Cl_2$, 0°C, 89%; ix, HCCMgBr, THF, 25°C, 98%; x, Dess-Martin periodinane, $CH_2Cl_2$, 0°C, 82%; xi, NaI, $CH_3COCH_3$, 25°C, 99%.

**Scheme 2**

was that resulting from reduction of the carbon to iodide bond in **4**, which was obtained in 6% yield. The structure of the tricyclic enone **6** followed from comparison of its spectroscopic data with those of similar compounds prepared earlier by Roush *et al*,[4] and the *cis, syn, cis*-stereochemistry was assigned on the basis of detailed nOe studies with its pmr spectrum. It seems likely that **6** results from a normal (neutral) intramolecular Diels-Alder from the quenched vinyl radical intermediate **5**, rather than by way of a radical (6-*exo*-trig, then 5-*exo* trig) transannulation pathway; certainly this would account for the rather low conversion to **6**, with most of the product being uncharacterised oligomers.



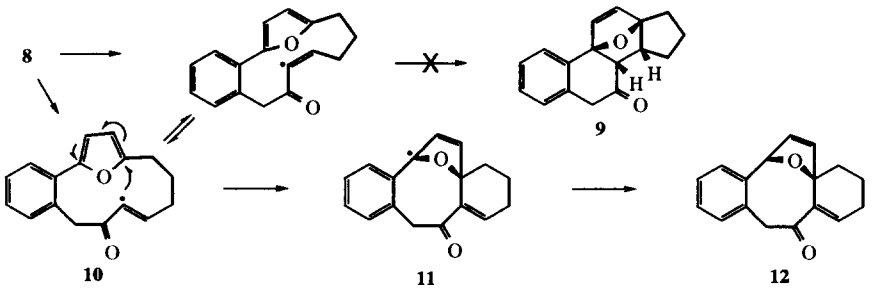

We next extended our study to a synthesis of the aryl furan-based iodoynone **8**, in anticipation that it would undergo tandem radical-mediated cyclisation to the steroidal analogue **9** (*cf* Scheme 1). Thus, the application of the ubiquitous Stille coupling protocol[9] quickly allowed the elaboration of the aryl furan **7** from



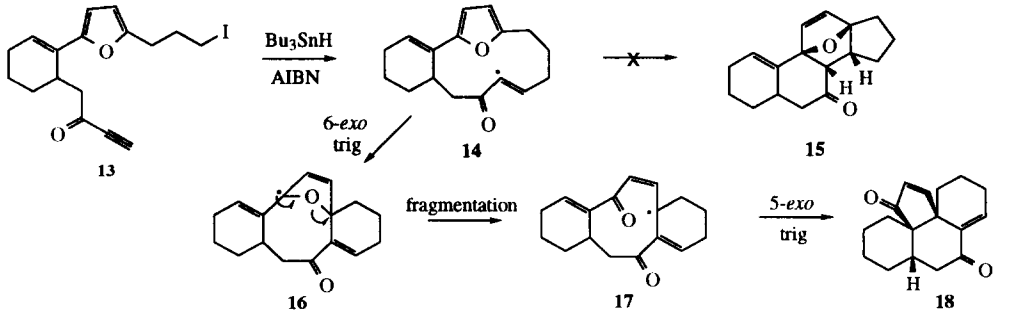

*Reagents*: i, $Pd(PPh_3)_2Cl_2$, THF, reflux, 89%; ii, TBAF, THF, 25°C, 75%; iii, $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0°C, 85%; iv, DIBAL-H, PhMe, 0°C; $H_2O$, MeOH, 25°C; HCCMgBr, THF, 25°C, 60%; v, Dess-Martin periodinane, $CH_2Cl_2$, 0°C, 50%; vi, NaI, $K_2CO_3$, $CH_3COCH_3$, 25°C, 77%.

**Scheme 3**

appropriate iodobenzene and furylstannane precursors, which was then smoothly converted into the target **8** by straightforward functional group manipulations (Scheme 3). When the furyliodoynone **8** was reacted with $Bu_3SnH$-AIBN, under similar conditions to those used to convert **4** into **6**, a single tetracyclic product was isolated in 70% yield. The spectroscopic data recorded for the product were not consistent with the steroidal system **9**, but instead they correlated with the tetracyclic ketone **12**.[8] The tetracycle **12** is produced from **8** *via* an initial 13-*endo* dig macrocyclisation, leading to **10**, followed by 6-*exo*-trig transannulation of the vinyl radical centre into C-2 of the furan moiety in **10**[10] accompanied by allylic radical migration, resulting in the benzyl radical **11** which then becomes quenched by H-abstraction.




The driving force for the formation of **12** from **8** no doubt has its origins in the stabilisation of the product radical centre in **11**, by the neighbouring benzene ring and the adjacent oxygen centre. To overcome the stabilising effect of the benzene ring in **8**, and drive a reaction towards a more useful steroidal system we examined finally a cascade radical macrocyclisation-transannular Diels-Alder approach to the more reduced system **15**, using the cyclohexene analogue **13** of **8** as precursor.[11] To our surprise, although treatment of **13** with $Bu_3SnH$-AIBN, led to the formation of a single tetracyclic structure in 40% yield, its spectroscopic data were not in accord with the hoped-for steroidal structure **15**. Instead, an X-ray analysis of the crystalline diol resulting from reduction of the tetracyclic dione product established unambigously that it had the unusual diene-dione structure **18**,[12] incorporating two contiguous quaternary carbon centres. The formation of the diene-dione **18** presumably results from an initial 13-*endo*-dig macrocyclisation of the radical produced from **13**, followed by 6-*exo*-trig transannular cyclisation of the vinyl radical intermediate **14** leading to **16** (*cf* **10**—› **11**).[10] Rather than being quenched by H-abstraction, this radical intermediate **16** then suffers fragmentation to **17**, which is nicely positioned to complete the tetracyclisation to **18** *via* a final 5-*exo*-trig transannulation involving the original cyclohexene double bond in the starting material.



The present results serve to emphasise, still further, the enormous scope provided by radical cascade reactions in the elaboration of novel and unusual polycycle constructs. The study also demonstrates the possibility, and the limitations, for what we have dubbed radical Diels-Alder reactions in synthesis, and also provides further examples of the use of furan-ring electrophores[10] in contemporary synthesis.

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11 The cyclohexenyl furan **13** was synthesised from appropiate furylstannane and cyclohexenol triflate precursors utilitising a Stille coupling reaction. Details will be elaborated in the full paper.

12 We thank Dr W.-S. Li and 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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