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Cascade Radical Cyclisations with Vinylcyclopropane Electrophores

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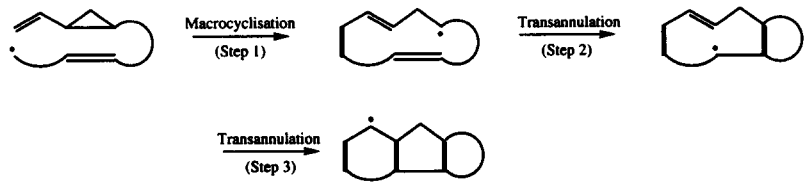
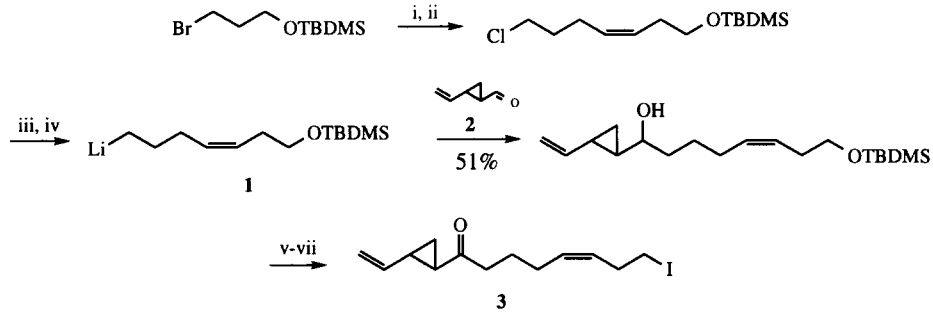
Abstract: Treatment of the polyene iodide **3**, containing a vinylcyclopropane electrophore, with *tris*-(trimethylsilyl)silane (TTMSS)-AIBN gave **6** and **7** (2:1, 65%) resulting from a radical cascade 13-*endo* macrocyclisation followed by successive 6-*exo*/5-*exo* transannular cyclisations. In a similar manner, the iodo vinylcyclopropane **12a** underwent triple cyclisation to a mixture of diastereoisomers of the oestrone analogue **14** (~ 16%), but the vinylcyclopropyl ester **9a** gave only the product **11** of macrocyclisation on treatment with TTMSS-AIBN. © 1997 Published by Elsevier Science Ltd.

Cascade radical-mediated cyclisations of polyolefin substrates have emerged as a very powerful method for the construction of complex ring-fused systems.[1] In earlier publications we have highlighted the scope for the stereoselective synthesis of various bicyclic and tricyclic carbo- and hetero-cyclic systems using a cascade macrocyclisation-transannular cyclisation strategy from acyclic precursors.[2] Hitherto in our studies, and in the complementary studies from other laboratories,[3] electron deficient alkenes and alkynes have proven to be the most effective radical-acceptor groups (*ie* electrophores) in the aforementioned macrocyclisations; this is due to the very favourable FMO interactions of such π-systems with nucleophilic carbon radical donors.[4] With a view to extending the range of polycyclic assemblies that could be accessible *via* cascade macrocyclisation-transannular cyclisation protocols we have examined the utility of alternative electrophores in these reactions. Cyclopropane-containing electrophores were attractive to us because of the similarity between the chemistries of the cyclopropane and alkene bonds.[5] In addition, the release of strain resulting from radical-induced cyclopropane ring opening would drive the macrocyclisation reaction in the desired direction irreversibly and the cyclopropane ring, with one additional carbon centre, would feature as a novel *umpolung* of the alkene unit in these cascade cyclisations. In this *Letter* we describe our preliminary observations in this area utilising the conjugated vinylcyclopropane unit, in the dual role as starter electrophore (step 1) and precursor to the terminating electrophore (step 3), in cascade macrocyclisation-transannulation reactions (Scheme 1).



Scheme 1

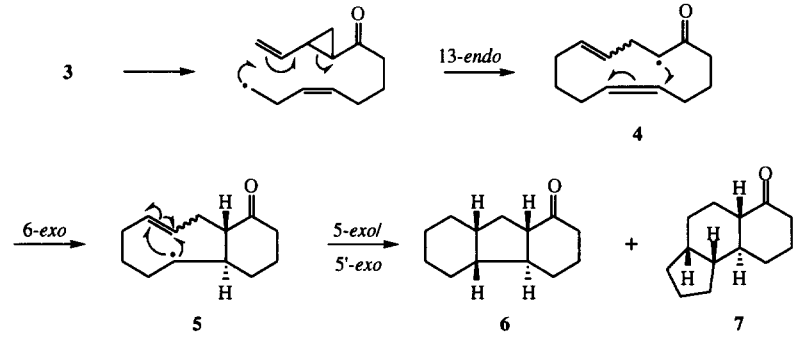
Thus, we first synthesised the iodoalkene - substituted conjugated vinylcyclopropyl ketone **3** using the addition of the organolithium reagent **1** to the cyclopropane aldehyde **2** as a key step (Scheme 2).[6] Addition of a solution of *tris*-(trimethylsilyl)silane (TTMSS)[7] and AIBN in dry benzene, *via* a syringe pump over 14h, to a stirred solution of the iodide **3** in benzene under reflux, followed by work-up, led to a 2:1 mixture (~65%) of tricyclic ketone products which were separated and purified by chromatography. Analysis of the NMR data for the two products,[8] together with an unambiguous synthesis of the tricyclic ketone **7**,[9] demonstrated that the major and minor products resulting from treatment of the iodide **3** with TTMSS-AIBN corresponded to structures **6** and **7** respectively. The *trans, anti, cis* stereochemistry assigned to the minor product **7** is based on analogy with structurally similar compounds produced by similar routes,[9] whereas the stereochemistry displayed in structure **6** is tentative at this time.



Reagents: i, PPh_3, Δ 110°C, 90%; ii, $(Me_3Si)_2NK$ then $Cl(CH_2)_3CHO$, 0°-25°C, 57%; iii, NaI, MeCOEt, 100°C, 95%; iv, tBuLi, -78°C; v, PDC-SiO_2, CH_2Cl_2,77%; vi, HOAc-THF-H_2O, 85%; vii, I_2-PPh_3, Im, 85%.

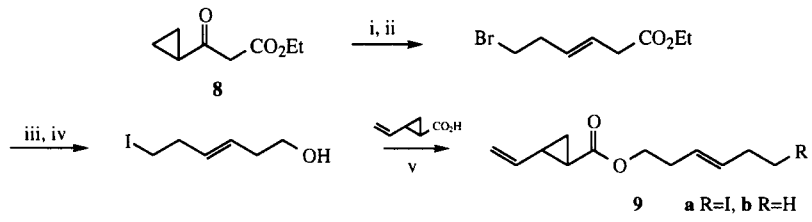
Scheme 2

The tricycles **6** and **7** are produced from **3** *via* 13-*endo*-trig radical macrocyclisation leading to the tridecadienone radical intermediate **4**, followed by 6-*exo*-trig transannulation giving **5**. Competitive 5-*exo*-trig transannular cyclisations from **5** then produce the observed products **6** and **7** (Scheme 3).



Scheme 3

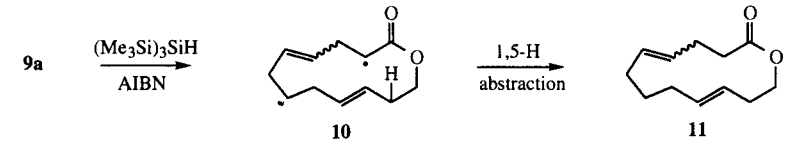
We next examined the outcome of treatment of the ester **9a**, corresponding to the iodo vinylcyclopropane **3**, with TTMSS-AIBN. The ester **9a** was synthesised from the known cyclopropyl substituted β-keto ester **8**[10] as shown in Scheme 4. When a solution of the ester **9a** in benzene was heated under reflux with TTMSS in the presence of AIBN for 21h, we obtained no evidence for the formation of any tricyclic lactone products analogous to **6** and **7**. Instead, in addition to the product **9b** of straightforward carbon-iodide bond reduction in **9a** (~18%)



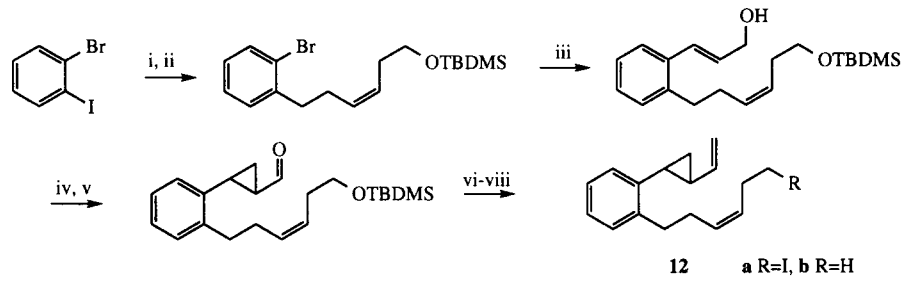
Reagents: i, $NaBH_4$-EtOH, 69%; ii, HBr, $ZnBr_2$, 75%; iii, $LiAlH_4$-Et_2O, 77%; iv, NaI, MeCOMe, 88%; v, DCC, DMAP, 76%.

Scheme 4

the only product produced was the macrocyclic dienone **11** (26%) resulting from 13-*endo*-trig macrocyclisation and hydrogen atom radical quench. Indeed Macromodel studies[11] reveal a significantly higher transition state energy for transannulation from **10** in comparison with **5**, allowing competitive 1,5-hydrogen abstraction in the radical propagator **10** to dominate.



Encouraged by the outcome of cascade radical cyclisation of **3** to **5/6**, we were drawn to investigate the radical-mediated macrocyclisation-double transannular cyclisation of the disubstituted benzene derivative **12a** with a view to synthesis of the oestrone analogue **14**. The benzene derivative **12a** was elaborated from 2-

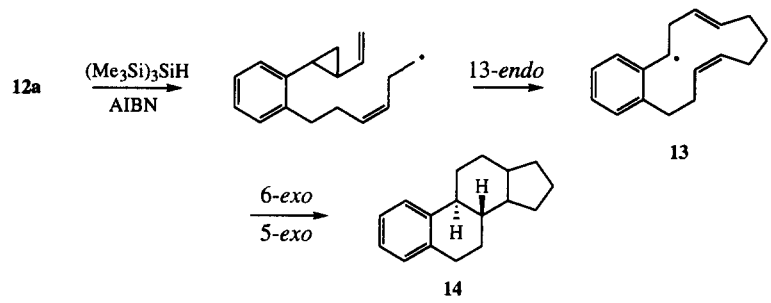


Reagents: i, ⌇OH, $Pd(OAc)_2$, Bu_4NCl, 85%; ii, $Ph_3P^+CH_2CH_2CH_2OSiMe_2Bu^t\ Br^-$, $(Me_3Si)_2NK$, 82%; iii, HO⌇$SnBu_3$, $Pd(OAc)_2$, Ph_3As, 40%; iv, Et_2Zn, CH_2I_2, 70%; v, PCC-SiO_2, NaOAc, 67%; vi, $MePPh_3^+\ Br^-$, $KOBu^t$, 74%; vii, AcOH, THF, H_2O, 95%; viii, I_2, PPh_3, Im, 71%.

Scheme 5

bromoiodo benzene as shown in Scheme 5, and featured sequential intermolecular Heck and Stille sp^2-sp^2 coupling reactions. When the iodo vinylcyclopropane **12a** was treated with TTMSS-AIBN under identical conditions to those which produced **5/6** from **3**, it underwent sequential triple cyclisation producing one major and two minor diastereomers of the tetracycle **14** in a combined yield of 16%; the only other product isolated, and not unexpectedly,[12] was the hydrocarbon **12b** (18%) resulting from reduction of the iodide **12a**.

The above results demonstrate that the vinylcyclopropane electrophore has scope in certain radical cascade polycycle constructions provided attention is given to the juxtaposition of additional alkene and other functionality in the tether separating the radical donor from the electrophore. Additional work is now in progress to evaluate other cyclopropane ring-containing electrophores in radical-mediated synthetic processes.



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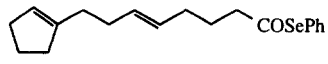
6 All new compounds displayed satisfactory spectroscopic data together with microanalytical and/or mass spectrometric data.

7 For the use of TTMSS as a non-toxic alternative to tin hydrides in radical reactions see: Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681. Ballestri, M.; Chatgilialoglu, C.; Clark, K.B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678. Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

8 Structures were assigned on the basis of NMR data from DQF-COSY, homodecoupling and NOE experiments.

9 The tricyclic ketone **7** was produced from the radical cyclisation of the diene selenyl ester shown below, using similar chemistry to that already published for the homologous (6,6,6-fused) tricyclic system; see Ligong, C.; Gill, G.B.; Pattenden, G.; Simonian, H. *J. Chem. Soc., Perkin Trans.1* **1996**, 31.



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12 Cyclisation studies of related systems carried out in our laboratory and molecular modelling studies [11] suggest that the first transannular cyclisation from **13** is sterically hindered by the rigidity of the fused benzene ring in the intermediate.

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