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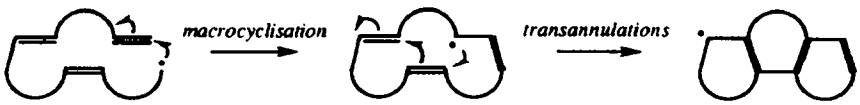
Sequential Radical Macrocyclisation-Transannulation Approach to Ring-fused Bicycles

Gerald Pattenden,* Allison J. Smithies and Daryl S. Walter

Department of Chemistry, The University, Nottingham NG7 2RD

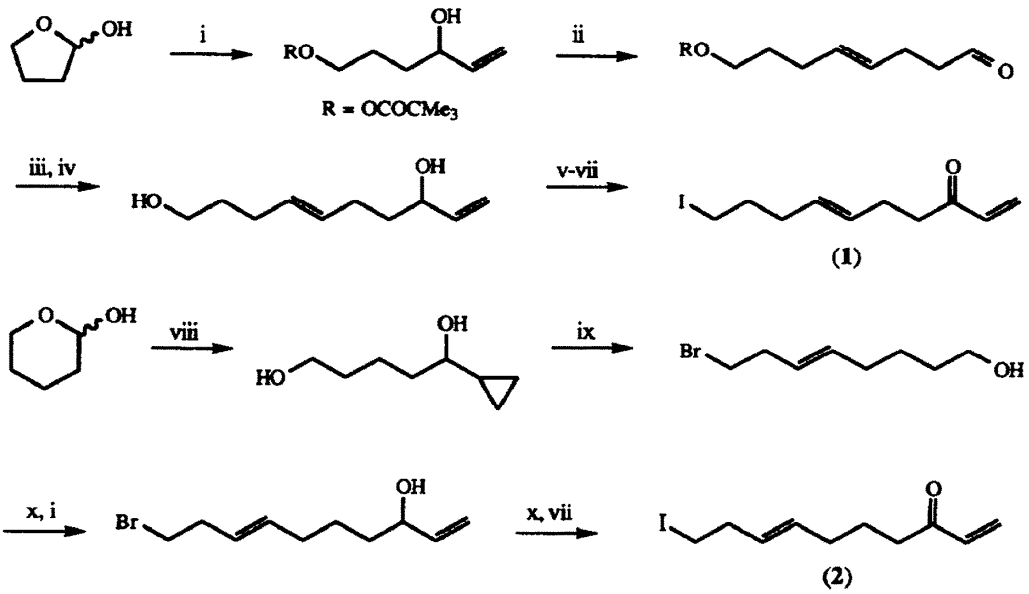
Abstract: The scope for tandem radical mediated macrocyclisation-transannulation processes (Scheme 1) in the elaboration of polycycles is illustrated with the facile syntheses of linear 5,6-, 6,6- and 5,7-ring fused carbobicycles, *viz* **7**, **8**, **11**, **13** from appropriate iododienone precursors, *viz* **1**, **2**, **12**, on treatment with Bu_3SnH-AIBN.

In earlier investigations we have developed facile syntheses of macrocyclic natural products, *e.g.* cembranes,[1] zearalenone,[2] based on intramolecular additions of allylic radicals to electron deficient alkenes. We have also described an approach to the taxane ring system using a 12-*endo* radical macrocyclisation of a functionalised ω-alkenyl alkyl iodide in tandem with a 8-*endo*/6-*exo* radical transannulation process.[3] The elaboration of ring-fused carbocycles based on sequential radical macrocyclisation-transannular processes would seem to offer a unique opportunity for the rapid, stereocontrolled synthesis of a wide range of highly functionalised polycyclic natural products, *e.g.* diterpenes, steroids, alkaloids, under mild conditions. With this aim in mind, we have investigated some general principles underlying the synthetic design presented in Scheme 1.[4] In this *Letter* we summarise the scope for tandem radical macrocyclisation-transannulation reactions as a stratagem in the synthesis of linear 5,5-, 5,6-, 5,7- and 6,6-ring fused carbocycles. In the accompanying communication we show how this overall strategy can be extended to the elaboration of tricyclic molecules from appropriate triene alkyl radical precursors.[5]



Scheme 1

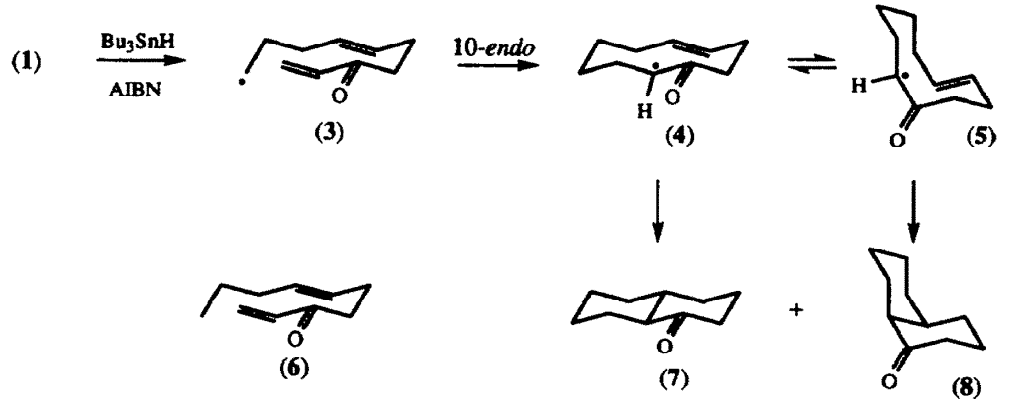
We began our investigations by first examining the tandem macrocyclisation-transannulation sequence involving the radical intermediate produced from the iododiene **1**, with a view to the synthesis of 1-decalone. Model studies, and earlier work, had demonstrated the need for an electron deficient alkene electrophore (*e.g.* conjugated enone) to promote macrocyclisations with nucleophilic carbon radicals,[6] and the iodide **1** (rather than the bromide) was selected because of its enhanced reactivity. Thus, the *E*-iododienone **1** was synthesised as summarised in Scheme 2[7]. When a 3mM solution of **1** in dry degassed benzene was heated in the presence of 1.1 equivalents of Bu_3SnH and a catalytic amount of AIBN for 0.5h, work up and chromatography, gave a 3:2 mixture of *trans*- and *cis*-isomers of 1-decalone, **7** and **8** respectively, in a combined 72% yield. The formation of **7** and **8** was accompanied by the product (**6**, ~10%) of reduction of the starting material, but we obtained no evidence for the co-formation of any cyclodecenone or alternative bicyclic products. Treatment of the 3:2 mixture of *cis* and *trans* 1-decalones with DBU (25°C, 24h) allowed the isolation of *trans*-1-decalone in essentially quantitative yield.[8]



Reagents: i, CH_2=CHMgCl, THF (53%), then $(CH_3)CCOCl$, CH_2Cl_2, pyridine (100%); ii, $Hg(OCOCF_3)_2$, CH_2=$CHOCH_2CH_3$ (68%), then sealed tube, 120° C, 13 h; iii, CH_2=CHMgCl, THF, (58%); iv, DIBAL, CH_2Cl_2, (82%); v, NBS, PPh_3, CH_2Cl_2, (53%); vi, Dess-Martin periodinane, CH_2Cl_2, (76%); vii, NaI, acetone, (100%); viii, cyclopropyl-MgBr, THF, (81%); ix, $ZnBr_2$, HBr (aq.), (65%); x, PCC, CH_2Cl_2, (80%).

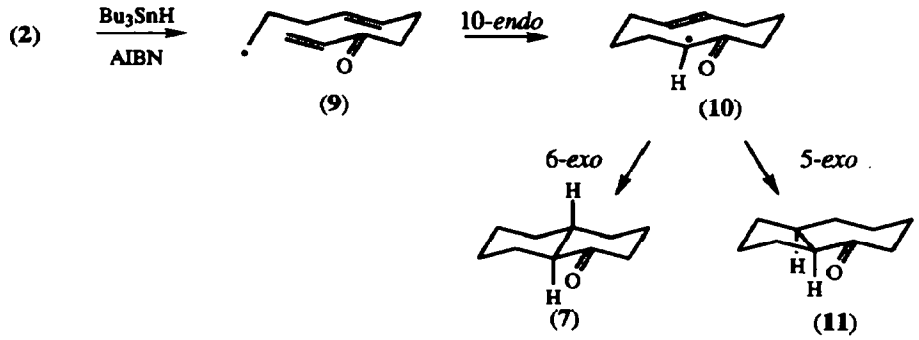
Scheme 2

We next examined the reaction between Bu_3SnH-AIBN and the positional isomer of **1**, *i.e.* **2**. To our initial surprise this 10-*endo* macrocyclisation-transannulation sequence led to a 1:1 mixture of *trans*-1-decalone **7** and *cis*-octahydroazulen-1-one **11**,[9] in a combined yield of 68%, resulting from competitive 6-*exo*/5-*exo* transannular cyclisation from the intermediate cyclodecenone radical **10**.

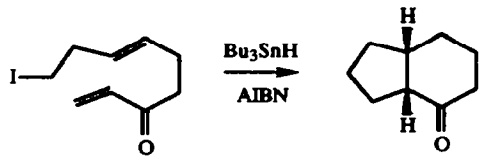


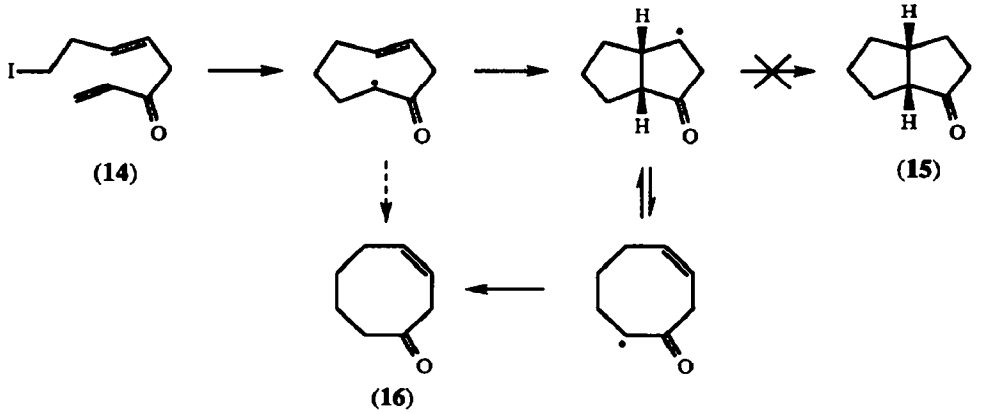
The differing reaction pathways followed by the radicals **3** and **9** produced from the iododienones **1** and **2** respectively, is interesting and they most likely have their origins in the conformational preferences of the 10-membered α-keto radical intermediates involved in the two cyclisations. Thus the *anti* α-keto radical **4**[10] derived from **3**, located in a chair-chair 10-membered intermediate should cyclise in an 6-*endo*/*exo* fashion leading to the *trans*-decalone **7**, whereas the same radical in a chair-boat-chair conformation, *viz* **5**, would be

expected to cyclise to the corresponding *cis*-decalone **8**. In neither of the conformations **4** and **5** should it be possible for the α-keto radical intermediates to undergo competing 5-*exo* cyclisations, and indeed no octahydroazulen-1-one product was observed from the tandem cyclisation of **3**; cyclisation of **4/5** *via* a *syn* α-keto radical would involve a significantly higher energy transition state, and is probably precluded. By contrast, transannular cyclisation of the *anti* α-keto radical **10** in the lowest energy chair-chair 10-ring conformation, should be facile in either a 5-*exo* or a 6-*exo* sense, with an equal probability of producing either a *cis* 7,5- or a *trans* 6,6-bicyclic product, as indeed we observe.



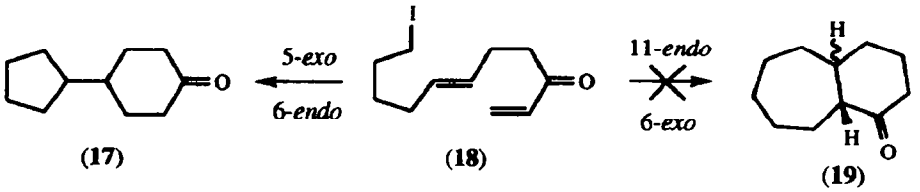
In further investigations of the scope for sequential radical macrocyclisation-transannulations in the construction of linear bicyclic systems we also examined the cyclisations of the iodo-dienones **12**, **14**, and **18**.[11] Interestingly, although the nonadienone **12** underwent tandem 9-*endo*-5-*exo* cyclisation producing the *cis*-tetralone **13** in reasonable yield (~50%), the corresponding *E*-octadienone **14** on treatment with Bu_3SnH-AIBN led to only the *Z*-cyclooctenone **16** (40%) together with recovered starting material. None of the expected bicyclo[3.3.0]octanone **15** was obtained in the reaction products. The formation of *Z*-cyclooctenone **16**[12] from *E*-**14** is interesting for a number of reasons, not least since it indicates that the transannulation step in this reaction, and presumably therefore some of the reactions mentioned earlier, can be reversible in favourable situations.





Finally, as if one needed further evidence of the propensity with which hexenyl radicals will undergo 5-

exo-trig cyclisation when given half a chance, treatment of the iododienone **18** with Bu_3Sn-AIBN led to the 4-cyclopentyl substituted cyclohexanone **17** in quantitative yield. None of the hoped for 7,6-bicyclic ketone **19** resulting from sequential 11-*endo*, 6-*exo* cyclisation was produced in this reaction.



(17) **(18)** **(19)**

Further studies are now in progress to extend these investigations to other carbon centred radicals[5] and to differing ring-sized polycycles, and also to delineate the parameters determining the efficacy of this new radical mediated macrocyclisation-transannulation approach to polycycle constructions.

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2. Hitchcock, S.A.; Pattenden, G. *Tetrahedron Lett.*, **1990**, *31*, 3641; Hitchcock, S.A.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1323.
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4. For some summary of earlier work see: Pattenden, G. 'Polycycle Constructions by Transition Metal Catalysed and Radical Mediated Processes' in *Organometallic Reagents in Organic Synthesis*, Academic Press, eds. J.H. Bateson and M.B. Mitchell, **1993**.
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7. All new compounds showed satisfactory spectroscopic data together with mass spectrometry and/or microanalytical data.
8. 1-Decalone showed the following c.m.r. data: *cis* δ(67.8MHz, $CDCl_3$) 23.1 (t), 23.5 (t), 24.5 (t), 25.2 (t), 28.9 (t), 29.1 (t), 39.1 (d), 40.6 (t), 50.7 (d), 212.9 (s); *trans* δ(67.8MHz, $CDCl_3$) 25.1 (t), 25.4 (t), 25.7 (t), 26.5 (t), 33.0 (t), 34.3 (t), 41.8 (t), 44.9 (d), 55.0 (d), 213.7 (s). These data compare favourably with those reported in 'Stereochemical Analysis of Alicyclic compounds by C-13 N.M.R. Spectroscopy', J.K. Whitesell and M.A. Minton, Chapman and Hall, **1987**, pp208 and 216.
9. *cis*-Perhydroazulene, c.m.r. data: δ(67.8MHz, $CDCl_3$) 24.4 (t), 25.4 (t), 26.2 (t), 27.7 (t), 32.5 (t), 35.2 (t), 40.4 (d), 43.2 (t), 54.6 (d), 212.5 (s); see: House, H.O.; Sayer, T.S.B.; Yau, C.-C. *J. Org. Chem.*, **1978**, *43*, 2153.
10. See: Broeker, J.L.; Houk, K.N. *J. Org. Chem.*, **1991**, *56*, 3651.
11. The iododienones **12**, **14**, and **16** were prepared using synthetic sequences similar to those summarised in Scheme 2 for the synthesis of the analogues **1** and **2**.
12. The cyclooctenone **16** showed n.m.r. spectroscopic data which were superimposable on those reported for an authentic sample; see: Bloodworth, A.J.; Courtneidge, J.L.; Curtis, R.J.; Spencer, M.D. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2951. . On standing, the β,γ-enone **16** was found to isomerise largely to the corresponding α,β-cyclooctenone.

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