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A Cascade Macrocyclisation-Transannulation Approach to Polycycle Constructions

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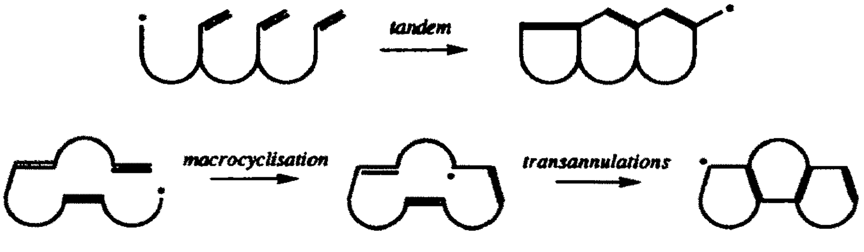
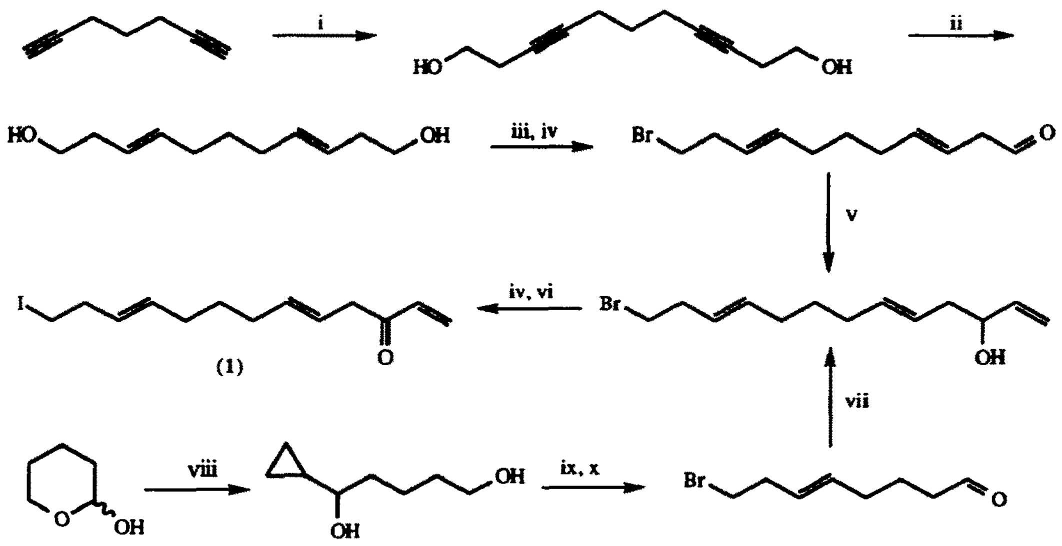
Abstract: Treatment of the iodotrienone **1** with Bu_3SnH-AIBN results in the formation of the angular 5,7,5-ring fused tricycle **6**, by way of a novel sequential 13-*endo*-trig macrocyclisation followed by two successive 5-*exo*-trig transannulation processes.

Studies of the tandem radical cyclisations of polyolefin substrates, especially those involving 5- and 6-*exo* modes of cyclisation, have provided synthetic chemistry with one of its most powerful methods for polycycle constructions in recent years (see Scheme 1).[1] In previous publications we have highlighted the genesis of an alternative approach to the synthesis of polycycles, using similar polyolefin substrates, but proceeding *via* a cascade macrocyclisation-transannulation protocol.[2] Furthermore, we have used this approach as a stratagem in the synthesis of linear 5,6-, 6,6- and 5,7-fused bicycles,[3] and also in an approach to the 8,6-(BC)-ring portion of the taxane ring system.[4] We have now investigated the scope for sequential radical macrocyclisation-tandem transannulation processes in the synthesis of tricyclic molecules from appropriate iodotriene precursor compounds according to Scheme 1, and in this *Letter* we describe the outcome of these preliminary studies.



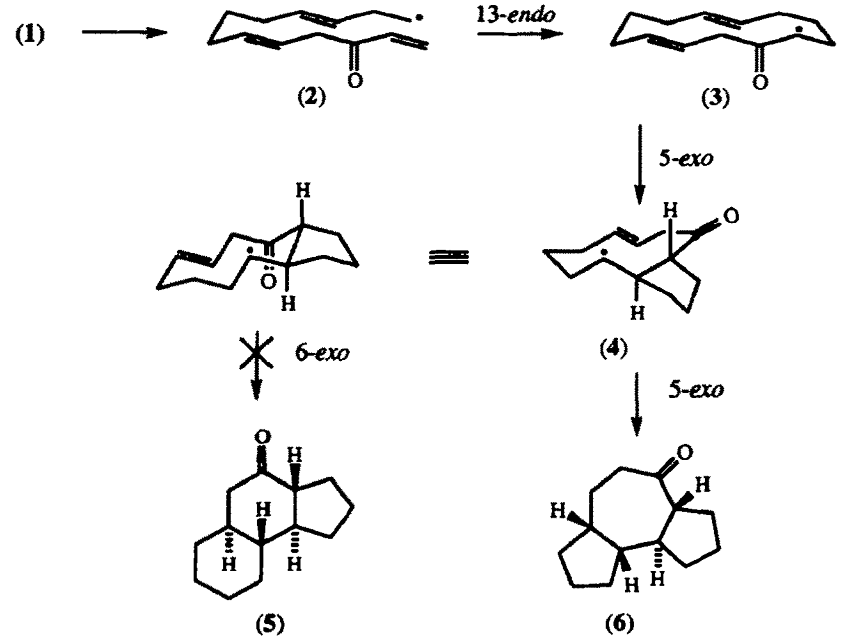
Scheme 1

We first examined the radical macrocyclisation-transannulation sequence involving the iodotrienone **1**, a substrate which could in principle lead to either of the angular ring fused tricycles **5** or **6**. The *E,E*-iodotrienone **1** was rapidly synthesised using two complementary routes which are summarised in Scheme 2.[5] A 3mM solution of **1** in dry degassed benzene was next heated under reflux in the presence of 1.1 equivalent of Bu_3SnH and a catalytic amount of AIBN for 0.5h. Work-up and chromatography led to the isolation of a single saturated ketone product in 55% yield. The compound displayed n.m.r. spectroscopic data which were consistent with the formation of a saturated tricyclic 6- or 7-ring ketone, but did not unambiguously distinguish between the 6,6,5-**5** and the 5,7,5-**6** ring fused tricycles. Accordingly, we prepared the crystalline 2,4-dinitrophenylhydrazone derivative (m.p. 184-186°C) of the product ketone and determined its X-ray crystal structure. This determination established unambiguously that the tricycle produced from the cascade radical cyclisation of **2** was the *cis-anti-trans* 5,7,5-ring fused tricyclic ketone **6** Figure 1.[6] The tricycle **6** is produced from **2** *via* a sequential 13-*endo*-trig macrocyclisation followed by two successive 5-*exo*-trig transannulation processes involving the radical intermediates **3** and **4**.

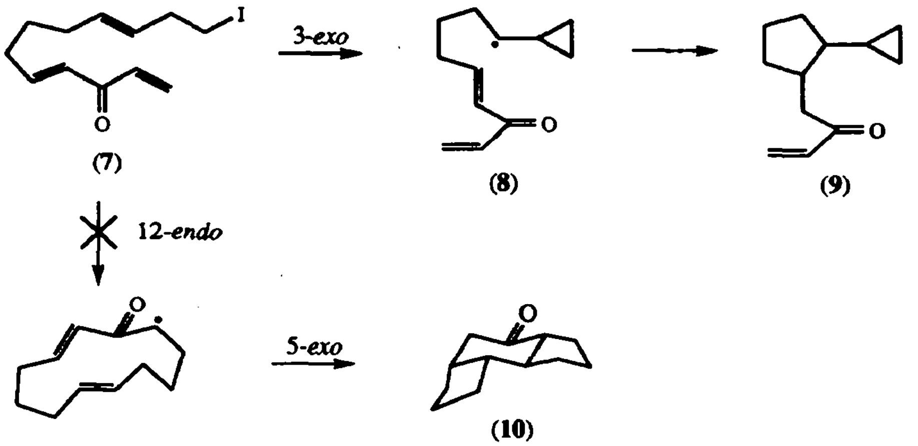


Reagents: i, NaNH$_2$, ethylene oxide (37%); ii, LiAlH$_4$, THF (98%); iii, NBS, PPh$_3$ (46%); iv, Dess-Martin periodinane (96%); v, CH$_2$=CHMgBr (56%); vi, NaI, Me$_2$CO (94%); vii, Ph$_3$P$^+$C$^-$HCH$_2$CH(O$^-$)CH=CH$_2$ (75%); viii, (cyclopropyl)-MgBr (81%); ix, ZnBr$_2$, HBr (aq.) (65%); x, PCC (77%).

Scheme 2

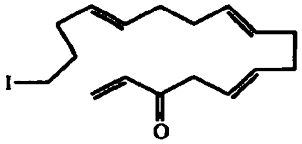


We next examined the radical cyclisation chemistry of the alkyl radical intermediate produced from the iodotrienone **7**,[7] with a view to the synthesis of the corresponding angular 5,6,5-ring fused tricycle **10**. To our surprise instead of leading to **10**, the radical cyclisation of **7** under similar conditions to those used to cyclise **1** to **5**, gave a 3:1 mixture of diastereoisomers of the cyclopropane-cyclopentane (**9**; 33%) in addition to recovered starting material (23%). The formation of **9** from **7** takes place by way of an initial and unusual, 3-*exo*-trig cyclisation,[8] wherein the equilibria are no doubt driven by a following and rapid 5-*exo*-trig cyclisation onto a reactive dienone electrophore, *viz* **8** → **9**.



(10)

Finally, we have examined the synthesis and the radical cyclisation chemistry of the all-*E*-iodotetraenone **11**, as a prelude to studying the synthesis of the steroid ring system according to the principles presented in Scheme 1. The all-*E*-iodotetraenone **11** was synthesised using a sequence similar to that described for the synthesis of **1**. Treatment of **11** with Bu_3SnH-AIBN resulted in a clean reaction but only to the isolation of the 17-ring product **12** of 17-*endo*-trig macrocyclisation; no evidence for the co-formation of polycyclic products resulting from subsequent radical transannulation reactions could be accrued from this first model study.



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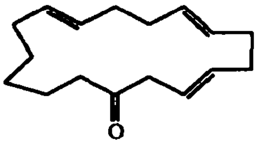

(12)

Further detailed studies are now in progress to build on these preliminary investigations for the rapid assembly of polycyclic systems based on cascade radical macrocyclisation-transannulation reactions.

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References

1. For bibliography see: Motherwell, W.B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, **1991**; Jasperse, C.P.; Curran, D.P.; Fevig, T.L. *Chem. Rev.*, **1991**, *91*, 1237.
2. 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**.
3. Pattenden, G.; Smithies, A.J.; Walter, D.S. *Tetrahedron Lett.*, preceeding publication.
4. Hitchcock, S.A.; Pattenden, G. *Tetrahedron Lett.*, **1992**, *33*, 4843 (corrigendum *Tetrahedron Lett.*, **1992**, *33*, 7448). For an example of a radical-mediated transannular strategy towards diterpenoid ring systems see: Myers, A.G.; Condroski, K.R. *J. Am. Chem. Soc.*, **1993**, *115*, 7926.
5. All new compounds showed satisfactory spectroscopic data together with mass spectrometry and/or microanalytical data.
6. Crystal data for 2,4-DNP derivative. Monoclinic, a = 9.622(3), b = 14.658(2), c = 13.494(2) Å, β = 106.05(2)°, u = 1828.91Å^3, z = 4, space group P2$_1$/a. R = 0.0764, R_w = 0.0524 for 597 observed reflections measured with Cu k_α radiation on an Enraf Nonius CAD4 diffractometer. Atomic coordinates, bond lengths, bond angles, thermal parameters and observed and calculated structure factors have been deposited at the Cambridge Crystallographic Data Centre.

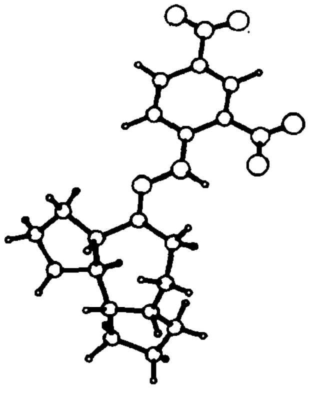

Figure 1. X-Ray Structure of 2,4-Dinitrophenylhydrazone Derivative of the Tricyclic Ketone (**6**)

7. Compounds **7** and **11** were prepared using synthetic sequences similar to those summarised in Scheme 2. See also reference 3.
8. For other examples see: Beckwith, A.J.L.; Ingold, K.U. in *Rearragements in Ground and Excited States*. Vol 1, Ed. de Mayo, P. Academic Press Inc., New York, **1980**; Montgomery, L.K.; Matt, J.W. *J. Am. Chem. Soc.*, **1967**, *89*, 3050; Montgomery, L.K.; Matt, J.W.; Webster, J.R. *J. Am. Chem. Soc.*, **1967**, *89*, 923; Cekovic, Z.; Saicic, R. *Tetrahedron Lett.*, **1990**, *31*, 6085.

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