A cascade radical-mediated macrocyclisation–transannulation approach to oestrogen steroids

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Abstract – A new approach to ring A aromatic steroids, based on cascade 13-endo-trig/dig macrocyclisations followed by sequential 5-exo-trig and 6-exo-trig transannulations, exemplified in the syntheses of the cis,anti,trans tetracycle 9 and the trans,syn tetracycle 13 from the ortho-substituted aryl polyen(yne) precursors, 8 and 12 respectively, is described. © 2001 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

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Steroids are ubiquitous in nature, and an enormous variety of creative designs have been developed for their total synthesis [1–7]. In recent years we have illustrated the scope for cascades of 6-endo-trig radical cyclisation reactions from polyene acyl radical precursors in the synthesis of polycyclic systems including steroids [8–10], aza-steroids [11], spongianans [12], and even steroid-like heptacycles [13]. We now describe a new approach to ring A aromatic steroids, e.g. oestrone 1, whereby the B/C/D ring tricyclic system is elaborated by a radical-mediated macrocyclicisation in tandem with two radical transannulation reactions [14] from an appropriate ortho-substituted aryl polyene radical precursor, i.e. 2 [15–24].

In order to demonstrate the feasibility of this 13-endo-trig, 5-exo-trig, 6-exo-trig radical cascade, we first examined the iodotrienone system 8 with the expectation that the double enone electrophores in 8 would ‘drive’ the cascade of radical cyclisations in the anticipated sense. The iodotrienone 8 was synthesised from ethyl 2-iodocinnamate as shown in scheme 1. Thus, a
Heck reaction between the aryl iodide 3 and 2-propenol first led to the aldehyde 4 which then underwent a Wittig reaction to produce the Z-alkene 5a. Deprotection of the TBS ether 5a, followed by conversion of the resulting alcohol 5b into the corresponding chloride 5c, and a reduction–oxidation sequence next led to the cinnamaldehyde 6. Addition of vinylmagnesium bromide to 6, followed by oxidation of the resulting carbinol 7 to the dienone 8a and a Finkelstein reaction finally gave the iodotrienone precursor 8b.

When a solution of the iodotrienone 8b was treated with Bu3SnH and catalytic AIBN in degassed benzene over 6 h under high dilution conditions, followed by heating at reflux for 10 h, work-up and chromatography resulted in the separation of almost equal amounts of two crystalline isomeric steroidal products in a combined yield of 51%. NMR spectroscopic data for each of the products were consistent with the formation of tetracyclic ring systems resulting from the anticipated macrocyclisation-transannulation cascade, (viz scheme 1), and the structure 9a with cis-anti-trans-stereochemistry was established for one of the isomers by X-ray crystallographic analysis [25]. When the synthetic sequence shown in scheme 2 was repeated, starting from ethyl 2-iodo-4-methoxy cinnamate, the corresponding 4-methoxyaryl iodotrienone was elaborated. When this derivative was treated with Bu3SnH-AIBN, work up and chromatography produced a similar yield of two diastereoisomeric tetracycles. Close inspection and comparison of the NMR spectroscopic data for the major product resulting from this reaction, with the ketone 9a, showed that it had the same cis, anti, trans stereochemistry, i.e. 9b. However, at this stage we remained uncertain of the relative stereochemistry of the diastereoisomeric tetracycles, e.g. 10 and 11, formed in these two cascade radical-mediated cyclisations.

With the ultimate objective of developing a synthesis of oestrone 1, we next examined a synthesis of the iododienynone 12 corresponding to 8b, and its cascade radical-mediated triple cyclisation [26]. The dienynone 12 was synthesised in a similar manner to that used to elaborate 8b with the modification that ethynylmagnesium bromide was added to the aldehyde 6 instead of vinylmagnesium bromide. When a solution of the iododienynone 12 was treated with Bu3SnH-AIBN under the same conditions to those used with the analogue 8b, work up and chromatography gave two crystalline tetracyclic products in 40% and 20% yield. The structure of the major product, m.p. 95–97 °C, was established unambiguously by single crystal X-ray analysis as the trans, syn diastereoisomer of the anticipated cyclopentaphenathrene 13 [25]. The trans-syn-cis steroidal structure 14 followed for the
minor product of the 13-endo-dig, 5-exo-trig cyclisation of 12 from 1D NMR, COSY, HMQC and NOE difference experiments, and presumably results from in situ reduction of the major product 13 under the Bu3SnH-AIBN radical conditions.

Even with detailed NMR data available for the isomeric tetracycles 9, 10, 11, and 14, alongside X-ray data for 9a and 13 and molecular mechanics calculations, we are unable to distinguish between the two most likely stereochemistries, i.e. trans, anti, trans and cis,syn,trans, 10 and 11 respectively, for the other tetracyclic products produced from cascade radical cyclisation of the polyenes 8a and the 4-OMe derivative. Further studies are now in progress to address this issue and also to develop this method of polycycle constructions in other fused and steroid systems.

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References


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