# 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

### radical / cascade / macrocyclisation-transannulation / steroids

**Résumé** – Une nouvelle approche, permettant d'accéder aux stéroïdes possédant un noyau A aromatique et basée sur une cascade de macrocyclisations 13-*endo-trig/dig* suivies par une séquence de transannulations 5-*exo-trig* et 6-*exo-trig*, est présentée. Les synthèses du tétracycle *cis, anti, trans* 9 et du tétracycle *trans, syn* 13 à partir des précurseurs arylpolyèn(yne) *ortho*-substitués, 8 et 12 respectivement, représentent deux exemples. © 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 macrocyclisation 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

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Reagents and conditions; (i),  $CH_2=CH-CH_2OH$ ,  $nBu_4NHCl$ ,  $NaHCO_3$ ,  $Pd(OAc)_2$ , DMF, 50 °C, 82 %; (ii), KHMDS, Br'Ph\_3P<sup>+</sup>(CH\_2)\_3OTBS, THF, -78 °C, 85 %; (iii), DIBALH, DCM, -78 °C, 82 %; iv(), NCS, PPh\_3, DMF, 0 °C, 84 %; (v), DIBALH, DCM, -78 °C, 81 %; (vi), MnO\_2, DCM, rt, 82 %; (vii),  $CH_2=CHMgBr$ , THF, -78 °C, 88 %; (viii), BaMnO\_4, DCM, 25 °C, 92 %; ix, NaI, K<sub>2</sub>CO<sub>3</sub>, butan-2-one, 92 %.

Scheme 1.

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 Bu<sub>3</sub>SnH 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 vield 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 2), and the structure 9a with cis-anti-transstereochemistry was established for one of the isomers by X-ray crystallographic analysis [25]. When the synthetic sequence shown in scheme 1 was repeated, starting from ethyl 2-iodo-4-methoxy cinnamate, the corresponding 4-methoxyaryl iodotrienone was elaborated. When this derivative was treated with Bu<sub>3</sub>SnH-AIBN, work up and chromatography produced a similar yield of two diastereoisomeric tetracycles. Close inspection and compari-

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son 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 radicalmediated 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 Bu<sub>3</sub>SnH-AIBN under the same conditions to those used with the analogue 8b, work up and chromatography gave two crystalline tetracylic 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 cyclopentaphenathrenone 13 [25]. The trans-syn-cis steroidal structure 14 followed for the



#### Scheme 2.

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  $Bu_3SnH$ -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** respec-

tively, 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

- [1] Quellet L., Langois P., Deslongchamps P., Synlett (1997) 689.
- [2] Haruo Y., Sakamoto Y., Takahashi T., Synlett (1995) 231.
- [3] Pellissier H., Santelli M., Tetrahedron 52 (1996) 9093.
- [4] Ogasawara K., Sugahara T., Tetrahedron Lett. 37 (1996) 7403.
- [5] Grinsteiner T.J., Kishi Y., Tetrahedron Lett. 35 (1994) 8333 and references cited therein.
- [6] Corey E.J., Liu S., J. Am. Chem. Soc. 118 (1996) 8765.
- [7] Fish P.V., Johnson W.S., Jones G.S., Kullnig R.K., Tham F.S., J. Org. Chem. 59 (1994) 6150.
- [8] Batsanov A., Chen L., Gill G.B., Pattenden G., J. Chem. Soc., Perkin Trans. 1 (1996) 45 and references therein.

- [9] Handa S., Pattenden G., Li W.S., Chem. Commun. (1998) 311.
- [10] Boehm H.M., Handa S., Pattenden G., Roberts L., Blake A.J., Li W.S., J. Chem. Soc., Perkin Trans. 1 (2000) 3522.
- [11] Double P., Pattenden G., J. Chem. Soc., Perkin Trans. 1 (1998) 2005.
- [12] Roberts L., Pattenden G., J. Chem. Soc., Perkin Trans. 1 (1998) 863.
- [13] Handa S., Nair P.S., Pattenden G., Helv. Chim. Acta 83 (2000) 2629.
- [14] Handa S., Pattenden G., Contemporary Org. Synthesis 4 (1997) 196.
- [15] Caspar M.L., Wang X., Zoretic P.A., Tetrahedron Lett. 32 (1991) 4819.
- [16] Katouda W., Sakamoto Y., Takahashi T., Tomida S., Yamada H., Tetrahedron Lett. 36 (1995) 2273.

- [17] Ribeiro A.A., Shen Z., Wang M., Zoretic P.A., Tetrahedron Lett. 36 (1995) 2925.
- [18] Ribeiro A.A., Zhang Y., Zoretic P.A., Tetrahedron Lett. 36 (1995) 2929.
- [19] Curran D.P., Jahn U., Tetrahedron Lett. 36 (1995) 8921.
- [20] Chen Z., Zhang Y., Zoretic P.A., Tetrahedron Lett. 37 (1996) 7909.
- [21] Sakamoto Y., Takahashi T., Tomida S., Yamada H., J. Org. Chem. 62 (1997) 1912.
- [22] Fang H., Zoretic P.A., Tetrahedron Lett. 63 (1998) 7213.

- [23] Doi T., Takahashi T., Tomida S., Tetrahedron Lett. 40 (1999) 2363.
- [24] Ihara M., Katsumata A., Kuroyanagi J., Takasu K., Tetrahedron Lett. 40 (1999) 6277.
- [25] We thank Dr A J Blake of this School for this information, which will be published in the full paper.
- [26] Hitchcock S.A., Houldsworth S.J., Pattenden G., Pryde D.C., Thompson N.M., Blake A.J., J. Chem. Soc., Perkin Trans. 1 (1998) 3181.