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Tetrahedron Letters 45 (2004) 4027–4030
Tetrahedron Letters

A new total synthesis of (±)-oestrone

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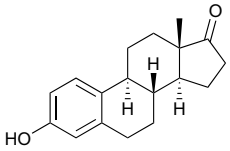
Received 12 March 2004; accepted 26 March 2004

Abstract—A conceptually new total synthesis of oestrone, based on a novel cascade of radical cyclisations from the iodo aryl vinylcyclopropane **2**, via **10**, **15**, **16** and **17**, leading to the intermediate *trans*,*anti*,*trans*-oestradiol derivative **11** in one step, is described. Oxidation of **11**, followed by demethylation of the resulting aryl methyl ether **18** then gives (±)-oestrone **1**.

The female sex hormone oestrone **1** occupies a special place in the history of natural products and in the development of modern medicinal chemistry. It was the first natural steroid hormone to be obtained in pure form (1929) and it was the first 'real' steroid[1] to be synthesised totally (1948).[2] Furthermore, oestrone served as an invaluable precursor to the commercially important 19-norsteroids, which were first offered as oral contraceptives over 50 years ago. Since these early beginnings a variety of strategies have been developed for the total synthesis of oestrone and nonaromatic steroids. Prominent amongst these methods have been those based on the ubiquitous Diels–Alder reaction[3] and on biomimetic electrophilic polyene cyclisations.[4]



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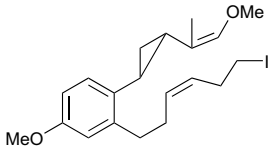

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Over several years we have examined the scope for a range of cascade radical-mediated reactions in the synthesis of polycyclic ring systems,[5] including steroids.[6] We have now extended these investigations and examined a conceptually new synthetic approach to oestrone **1** in which the B/C/D ring system in the steroid is produced in a cascade radical-mediated macrocyclisation and successive transannulation reactions from a substituted aryl vinylcyclopropane precursor, viz. **2**.

Thus, building on earlier investigations[7] and model studies,[8] the iodovinylcyclopropane **2** was synthesised starting from 2-iodo-4-methoxy benzaldehyde **3**[9] as summarised in Scheme 1. A Wadsworth–Emmons reaction between **3** and the appropriate phosphonate carbanion first led to the *E*-iodocinnamate **4**, which was then converted into the substituted arylpropanal **5** using a Heck reaction with prop-2-en-1-ol, in 87% yield. A Wittig reaction between **5** and triphenyl(*tert*-butylsilyloxy)propyltriphenylphosphonium iodide in the presence of potassium bis-(trimethylsilyl)amide at −78 °C was stereo-selective and next gave the *Z*-alkene **6a** in 92% yield. Reduction of **6a** using DIBAL-H, followed by Simmons–Smith cyclopropanation of the resulting allylic alcohol **6b** then gave the *trans* cyclopropylmethanol **7** in 70% yield. Oxidation of **7** with PDC led to the corresponding aldehyde **8a** in which a two-step sequence, was converted into the *trans* cyclopropylmethyl ketone **8b**. Treatment of **8b** with the carbanion derived from methoxymethyldiphenylphosphine oxide and LDA at −78 °C proceeded smoothly and gave the enol ether **9** as a 1:1 mixture of *Z*- and *E*-isomers in 90% yield. Finally, deprotection of the silyl ether **9** and iodination of the resulting alcohol gave the iodovinylcyclopropane **2**.

When a solution of the iodovinylcyclopropane **2** in dry degassed toluene was heated under reflux and treated with Bu_3SnH–AIBN via syringe pump over 8 h, a remarkable regio- and stereo-selective sequence of radical cyclisations ensued, leading to the *trans*,*anti*,*trans*-oestradiol derivative **11** in 12–15% yield. The steroid was obtained as a mixture of C17–OMe epimers and

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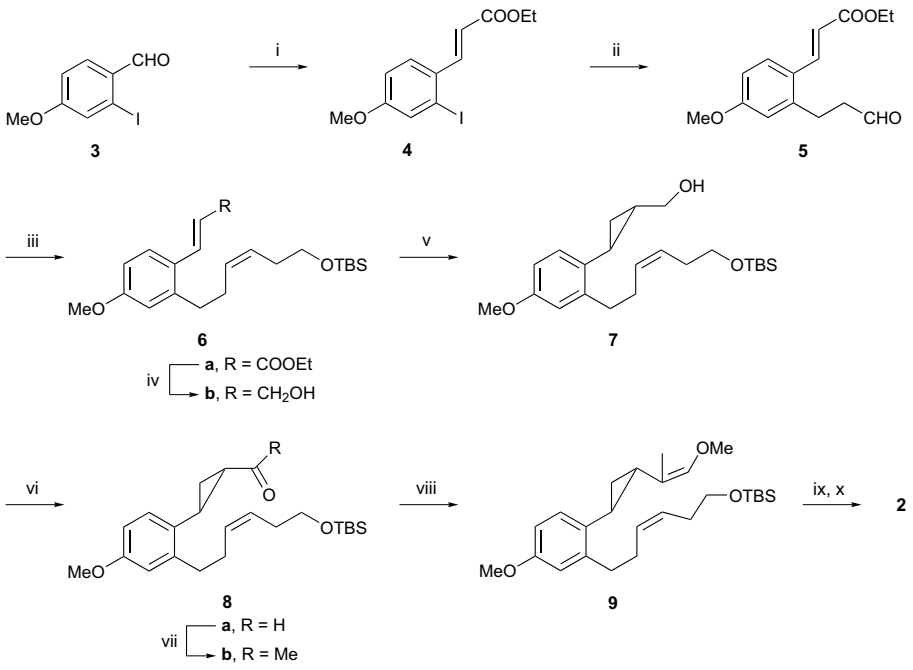
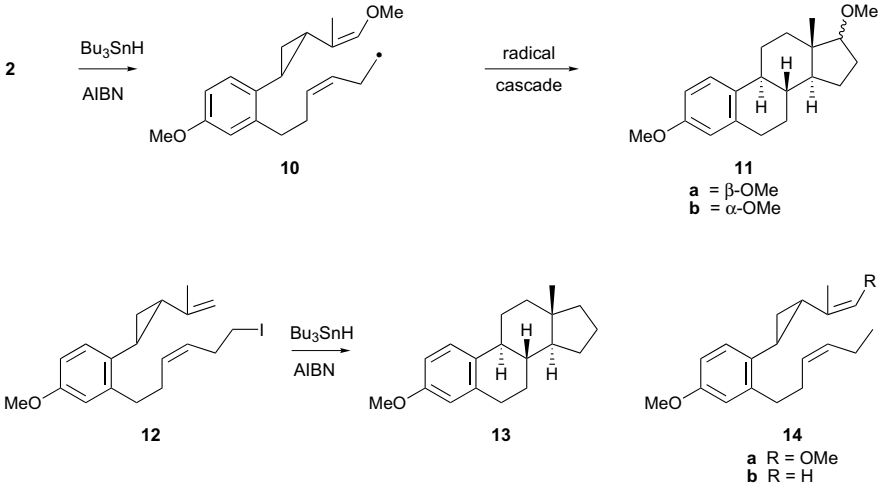
doi:10.1016/j.tetlet.2004.03.166



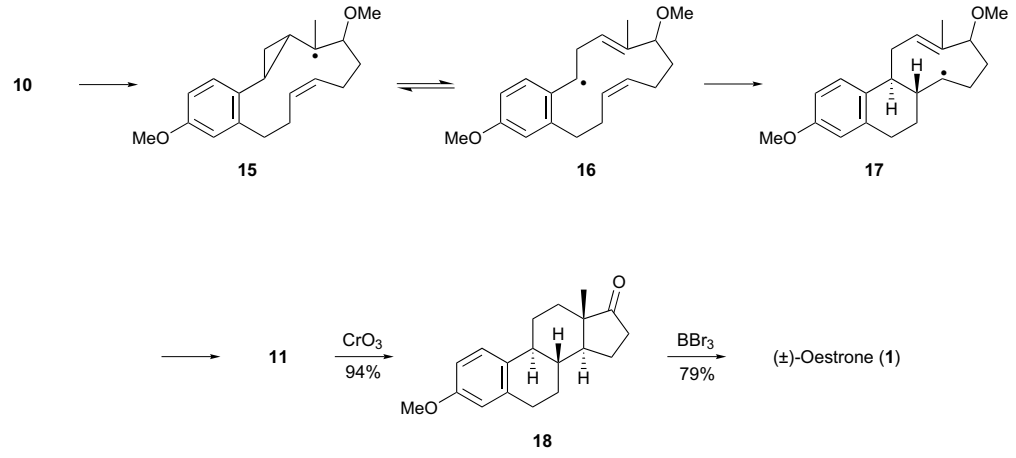
Scheme 1. Reagents and conditions: (i) $EtO_2CCH_2PO(OEt)_2$, BuLi, THF, 72%; (ii) $CH_2{=}CHCH_2OH$, $Pd(OAc)_2$, *n*-Bu_4*n*Cl, DMF, 87%; (iii) $IPh_3P(CH_2)_3OTBS$, KHMDS, THF, 92%; (iv) DIBAL-H, DCM, 82%; (v) Et_2Zn, CH_2I_2, 70%; (vi) PDC, 84%; (vii) MeMgBr followed by Dess–Martin periodinane, 86%; (viii) $MeOCH_2POPh_2$, LDA, THF; then NaH, THF, 90%; (ix) TBAF, THF, 98%; (x) I_2, imidazole, PPh_3, 80%.

crystallisation from acetonitrile–hexane gave colourless crystals of the known β-OMe epimer **11a**, mp 160–161 °C (lit.[10] mp 161–163 °C) whose NMR spectroscopic data were identical with those described in the literature. The major product obtained from treatment of **2** with Bu_3SnH–AIBN was **14a** (52%), which results from direct reduction of the carbon-to-iodide in the starting material. In contemporaneous studies, the iodovinylcyclopropane **12** lacking a terminal (enol ether) methoxy substituent was shown to undergo an identical sequence of regio- and stereo-selective radical cyclisations, when treated with Bu_3SnH–AIBN in refluxing benzene, leading to the oestrane **13** (15%), together with the reduction product **14b** (20%). The *trans*,*anti*,*trans* oestrane **13** showed ^{13}C NMR spectroscopic data which were identical with those reported in the literature for this compound.[11]

Several attempts were made to increase the yield of the oestradiol derivative **11** using alternative radical forming reagents and conditions, including Bu_3GeH–AIBN, SmI_2–DMPU $(Bu_3Sn)_2$-*hv*, $(Me_3Si)_3SiH$–AIBN, vitamin B_{12} and other Co(III) compounds with Zn or NaHg, in different solvents under varying thermal conditions. However, in none of these cases were we able to increase the yield of **11** beyond 15%, and the major product was always **14a** (40–50%).[12] The cascade of radical reactions between **2** and **11** involves four successive C → C bond forming reactions, that is (i) a 12-*endo trig* macrocyclisation of **10** leading to **15**; (ii) cyclopropylmethyl to



but-2-enyl carbon radical equilibration of **15** to **16**; (iii) 6-*exo trig* transannulation to **17**; (iv) 5-*exo trig* transannulation of **17**, followed by H-quench to **11**. Since the product of reduction of **2**, that is **14a**, is obtained in 52% yield, each of the radical reactions between **2** and **11** therefore proceeds in an average yield of ca. 65%. Whether or not the radical intermediate **10** becomes quenched by H-abstraction in an intramolecular sense or as a consequence of stereo-electronic features peculiar to the substrate **2**, or combinations of these possibilities, is unclear at this time.



The synthesis of oestrone **1** from the methyl ether **11** was smoothly accomplished by oxidation to **18** (94%) using chromium trioxide in acetone, followed by demethylation of **18** with BBr_3 in THF (79%). The synthetic (±)-oestrone **1** showed physical and spectroscopic properties identical with those described in the literature.[13]

Acknowledgements

We thank Paul Wiedenau and Stuart McCulloch for their earlier contributions to this study, and AstraZeneca for financial support.

References and notes

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