A Highly Regioselective 6-*endo*-Aryl Radical Cyclisation: Stereocontrolled Synthesis of *trans*-Octahydroanthracenes

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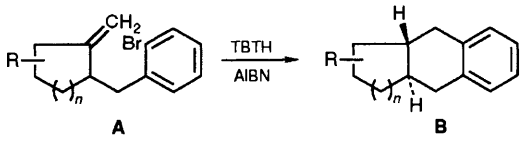
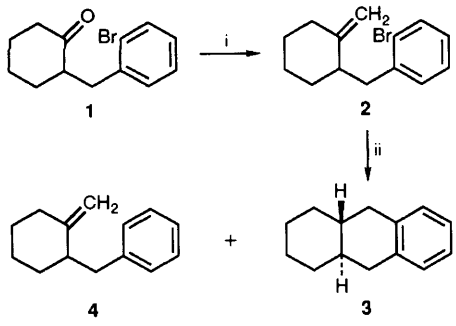
The sterocontrolled synthesis of *trans*-octahydroanthracenes **3**, **11** and **14** through implementation of an efficient and highly regioselective 6-*endo-trig*-aryl radical cyclisation of the respective 2-(*o*-bromobenzyl)-1-methylenecyclohexanes **2**, **10** and **13**, with tri-n-butyltin hydride is reported, along with a single crystal X-ray structure determination of **11**.

With only a few exceptions, 5-*exo-trig* radical cyclisations are generally preferred over 6-*endo-trig* ring closures in the intramolecular tri-n-butyltin hydride (TBTH) induced reactions in substituted hexenyl systems.[1] The use of TBTH mediated aryl radical cyclisations in the carbocyclic synthesis is considerably less wide spread than alkyl radical reactions. There are a limited number of recent reports[2,3] where aryl radicals having *ortho* cyclohexenyl ring substituents with an *endo* double bond in the 5,6- or 6,7-positions relative to the radical centre have been shown to give regioselective ring closures in the *exo*-mode leading to the five-membered carbocyclic[2] or the six-membered heterocyclic ring[2,3] annulated condensed cyclic compounds, respectively. An *ortho* isoquinoline ring incorporating a C-1 *exo*-methylene group at the 5,6-position relative to the aryl radical centre, however, has been reported [4] to give 6-*endo*-cyclisation exclusively, leading to six-membered condensed heterocyclic systems. We envisaged that a TBTH induced aryl radical in a substrate such as **A** would readily undergo 6-*endo* ring closure to **B** through the preferred attack at the least substituted[5] methylene carbon centre providing a simple general route to hexaannulated linear polycyclic systems. In this communication we present our preliminary results revealing that such a strategy may be



A **B**



Scheme 1 *Reagents*: i, $Ph_3P^+MeI^-$, *tert*-$C_5H_{11}O^-Na^+$ in toluene; ii, Bu^n_3SnH, AIBN, C_6H_6

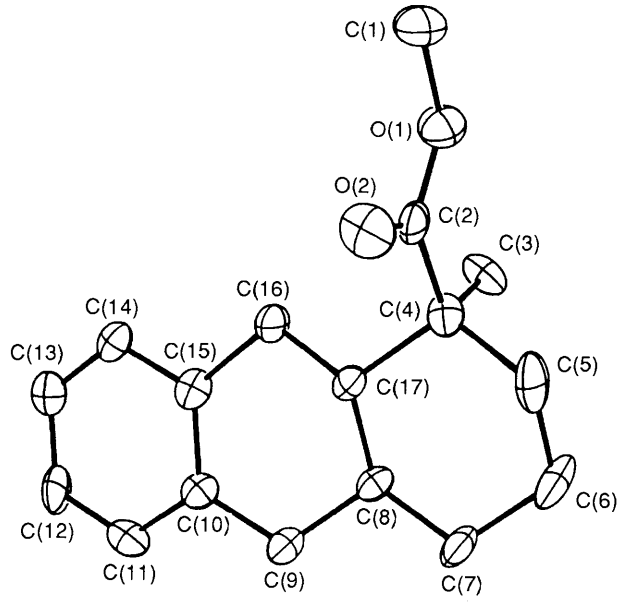


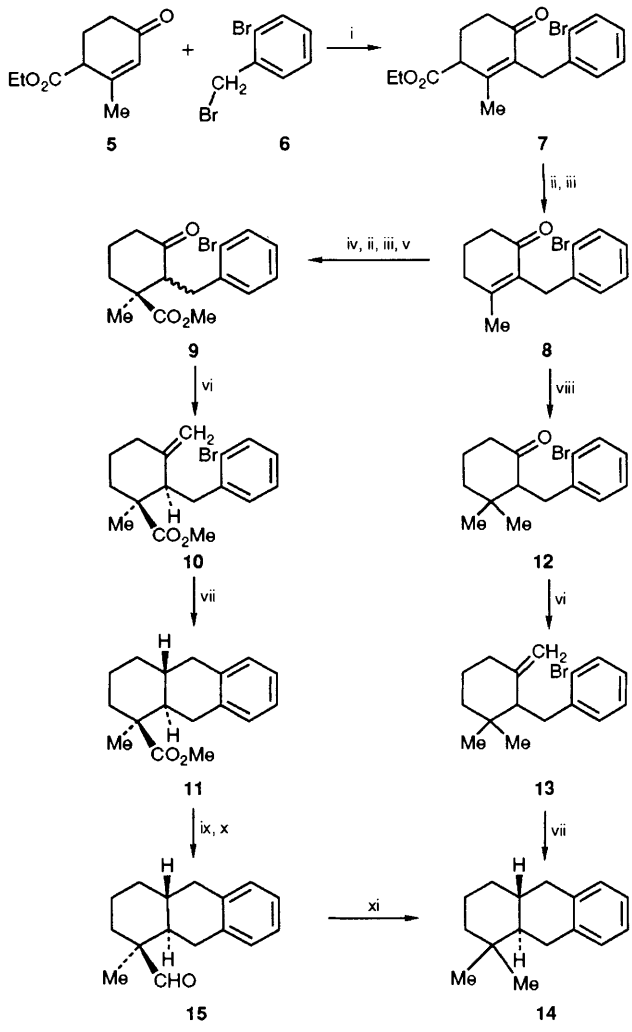
Fig. 1 ORTEP diagram of **11** with atom labelling. All hydrogen atoms have been omitted for clarity.

efficiently employed for highly stereocontrolled convergent synthesis of *trans*-octahydroanthracenes.

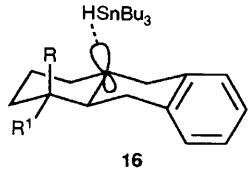
The alkene **2**,† obtained in 90% yield from the ketone **1**[6] by Wittig reaction under forcing conditions[7] (Scheme 1), on refluxing for 6 h in benzene (0.02 mol dm^{-3} solution) with TBTH (1.1 equiv.) and a catalytic amount of azoisobutyronitrile (AIBN) furnished a 9 : 1 mixture (GLC) of the known[8] *trans*-octahydroanthracene **3**‡ (m.p. 53 °C, lit.[8] m.p. 53.4–54.5 °C) and the reduced product **4** in 95% yield, after separation of the tin compound[9] by treatment with saturated aqueous KF followed by silica gel chromatography.

† Satisfactory elemental analyses were obtained for new compounds. ^1H NMR spectra in $CDCl_3$ solution were recorded at 200 MHz with $SiMe_4$ as internal standard. Selected ^1H NMR data **2**: δ 1.22–2.58 (m, 9H), 2.76 (dd, *J* 8.0 and 12.0 Hz, 1H), 3.12 (dd, *J* 4.0 and 12.0 Hz, 1H), 4.64 (bs, 1H), 4.74 (bs, 1H), 7.06–7.40 (m, 3H, ArH), 7.58 (dd, *J* 1.0 and 8.0 Hz, 1H). **10**: 1.45 (s, 3H, Me), 1.54–1.70 (m, 3H), 2.0–2.38 (m, 3H), 2.70–3.28 (m, 3H), 3.60 (s, 3H, –COOMe), 4.45 (bs, 1H), 4.72 (bs, 1H), 7.06–7.32 (m, 3H, ArH), 7.56 (d, *J* 8.0 Hz, 1H). **13**: 0.98 (s, 3H, Me), 1.06 (s, 3H, Me), 1.26–1.70 (m, 4H), 2.0–2.36 (m, 3H), 2.78 (t, *J* 12.0 Hz, 1H), 3.08 (dd, *J* 1.0 and 12.0 Hz, 1H), 4.20 (bs, 1H), 4.60 (bs, 1H), 7.0–7.26 (m, 3H, ArH), 7.55 (dd, *J* 1.0 and 8.0 Hz, 1H). **11**: 1.22 (s, 3H, Me), 1.62–2.15 (m, 8H), 2.48–2.92 (m, 4H), 3.68 (s, 3H, –COOMe), 7.0–7.10 (m, 4H, ArH). **14**: 0.80 (s, 3H, Me), 0.95 (s, 3H, Me), 1.08–1.96 (m, 8H), 2.34–2.90 (m, 4H), 7.12 (bs, 4H, ArH).

‡ Compounds described here are all racemates.



Scheme 2 *Reagents*: i, $Bu^tO^-K^+$, Bu^tOH; ii, KOH–H_2O–EtOH; iii, HCl 6 mol dm^{-3}; iv, KCN–H_2O–EtOH; v, CH_2N_2–Et_2O; vi, $Ph_3P^+MeI^-$, *tert*-$C_5H_{11}O^-Na^+$ in toluene; vii, Bu^n_3SnH, AIBN, C_6H_6; viii, $LiMe_2Cu$–BF_3·Et_2O–Et_2O; ix, $LiAlH_4$–Et_2O; x, PCC–CH_2Cl_2; xi, NH_2·NH_2·H_2O (99%) $(HOCH_2CH_2)_2O$, KOH



16

The *o*-bromobenzylcyclohexanones **9** and **12**, key intermediates for the alkenes **10** and **13**, were prepared[10,11] in good yields through the cyclohexenone **8**. The cyclohexenone **8** was obtained by alkylation[10,11] of Hagemann's ester **5** with the bromide **6** followed by alkaline hydrolytic decarboxylation of the alkylated product **7** (Scheme 2). The epimeric mixture of the enolizable keto-esters **9**[10] (*ca.* 1 : 1 mixture by GLC and ^1H NMR spectroscopy) on Wittig alkenation produced only the epimer **10** in 85–90% overall yield, by repeating the reaction twice with the recovered keto-esters. The assigned stereochemistry of the alkene **10** has been based upon the structure of its cyclisation product. Wittig reaction of the ketone **12** afforded the alkene **13** (92%).

The radical cyclisation of **10** in refluxing benzene with TBTH and a catalytic amount of AIBN under the same conditions as for **2**, afforded the *trans*-ester **11**, m.p. 92 °C in 85% yield as the only isolable product. An X-ray crystallography determination established the stereostructure of **11**

(Fig. 1)§ and the alkene **10**. Similarly, the radical cyclisation of the alkene **13** gave the *trans*-hydrocarbon **14** in 95% yield. The stereochemistry of **14** has been assigned by direct comparisons (GLC and ^{1}H NMR spectroscopy) with a sample prepared from the ester **11** through the sequence **15** → **14** (Scheme 2) using a standard reaction.[12] Unlike in the radical cyclisation of the alkene **2**, no reduced products could be detected in the ^{1}H NMR spectra of the crude reaction products from **10** and **13**, thereby clearly indicating the beneficial effect of the disubstitution at C-3 in the cyclohexane ring in the alkene substrates in the cyclisation reaction. The high stereoselectivity observed in the aryl radical cyclisations could be indicated by a preferred transition state, such as **16**.

In conclusion, a highly regioselective 6-*endo-trig*-aryl radical cyclisation[13] process developed in this work offers a stereocontrolled synthetic route to *trans*-hexaannulated condensed cyclic systems.

The CSIR, New Delhi, is gratefully acknowledged for the award of an SRF to S. P. and Mr S. Bhanja Choudhury of National Single Crystal X-Ray Diffraction Facility of the Department of Inorganic Chemistry of this Institute, for the ORTEP plot.

Received, 21st June 1991; Com. 1/03092B

§ *Crystal data* for compound **11**: $C_{17}H_{22}O_2$, $M = 258.4$, $a = 9.603(6)$, $b = 10.608(2)$, $c = 7.559(2)$ Å, $\alpha = 103.48(2)$, $\beta = 110.44(3)$, $\gamma = 83.22(4)°$, $U = 701$ Å^3. Space group $P\bar{1}$, $Z = 2$, $D_c = 1.22$ g cm^{-3}, μ(Cu-Kα) = 5.79 cm^{-1}. An Enraf-Nonius CAD-4 diffractometer employing graphite monochromated Cu-Kα radiation (λ = 1.54184 Å) in the ω-2θ scan mode was used to record 1442 reflections. Lorentz polarisation corrections were applied but absorption effects were ignored. The structure was solved by direct method (MULTAN 88) and refined by full-matrix least-squares analysis with anisotropic thermal parameters to non-hydrogen atoms, isotropic thermal parameters for hydrogen atoms. The final residuals for 906 reflections with $|F_o| \geq 4\sigma(|F_o|)$ were $R = 0.036$, $R_w = 0.040$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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