Highly Regioselective 8-*endo*-Aryl Radical Cyclisation: a New Synthetic Route to Decahydrodibenzo-[*a,d*]- and -[*a,e*]-Cyclooctenols

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A highly regioselective 8-*endo-trig*-aryl radical cyclisation of the vinylcyclohexanols **2a–c** and allylcyclohexanols **6a–c** with tri-n-butyltin hydride provides decahydrodibenzo-[*a,e*]- and -[*a,d*]-cyclooctenols **3a–c** and **7a–c** respectively, in moderate to good yields.

Renewed recent interest in the synthesis of eight-membered carbocycles[1,2] has been stimulated by the potent pharmacological activity exhibited by a variety of naturally occurring compounds incorporating this ring system. Previously we have demonstrated exclusive 6-*endo-trig*- and 7-*endo-trig*-aryl radical cyclisations[3,4] in the tri-*n*-butyltin hydride (TBTH)-induced reactions in some 2-(*o*-bromobenzyl)-methylenecyclohexane and -vinylcyclohexanols leading to the respective *trans*-octahydroanthracenes[3] and *trans*-octahydro-2*H*-dibenzo[*a,d*]cycloheptenols,[4] through highly regioselective radical attack at the terminal olefinic carbon centre, in each case. We report here preliminary results revealing that such a strategy may be employed in eight-membered ring annulation leading to a simple route to some partially reduced dibenzo-[*a,d*]- and [*a,e*]-cyclooctenols.

The transformation of the vinylcyclohexanols **2a–c** to the *trans*-decahydrodibenzo[*a,e*]cyclooctenols **3a–c** is shown in Scheme 1. The cyclohexanols **2a**†, **b** and **c** were obtained as single diastereoisomers, in each case in excellent yields, by condensation with the easily accessible cyclohexanones **1a**,[4] **b**‡ and **c**‡ with vinylmagnesium bromide in THF followed by purification by chromatography on silica gel. The stereochemical homogeneity of each of these alcohols followed from ^{1}H NMR spectroscopy and the assigned stereostructure is based upon analogy.[5]

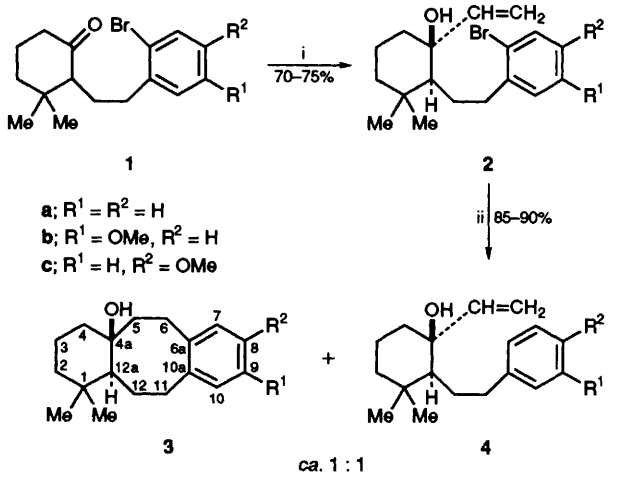
Radical cyclisation of each of the vinylcyclohexanols **2a–c** in refluxing benzene (0.007 mol dm^{-3} solution) for 6–7 h with TBTH (1.5 equiv.) and a catalytic amount of AIBN furnished a *ca.* 1:1 mixture (^{1}H NMR spectroscopy) of the tricyclic alcohols **3a–c** and the respective reduced products **4a–c**, after separation of the tin compounds by silica gel chromatography. Each of these mixtures was cleanly separated by chromatography on basic alumina affording the pure cyclised products **3a**, **b** and **c** in 40–45% yields. The assigned structures of the products resulting from the 8-*endo-trig* cyclisation were based upon spectroscopic data.

The scope of this 8-*endo-trig*-aryl radical cyclisation was further extended to the allylcyclohexanols **6a–c** (Scheme 2). The cyclohexanols were obtained as a single isomer in each case in excellent yield, by the Barbier reaction[6] of the cyclohexanones **5a**, **b** and **c** with allyl bromide. Again the stereochemical homogeneity of each of these alcohols was indicated by ^{1}H NMR spectroscopy and the assigned stereostructures are based upon analogy.[5] Radical cyclisation of the cyclohexanols **6a–c** in refluxing benzene with TBTH and a catalytic amount of AIBN under the same conditions as for **2**, afforded in each case a mixture (^{1}H NMR spectroscopy) of the respective tricyclic alcohols **7a–c** and the uncyclised reduced alcohols **8a–c** in over 90% yields, after silica gel chromatography. Separation of each of these mixtures by chromatography, as for **2**, gave the corresponding pure tricyclic alcohols **7a**, **b** and **c** in 60–65% yields. Again the structural assignments of these products are based on the spectroscopic data.

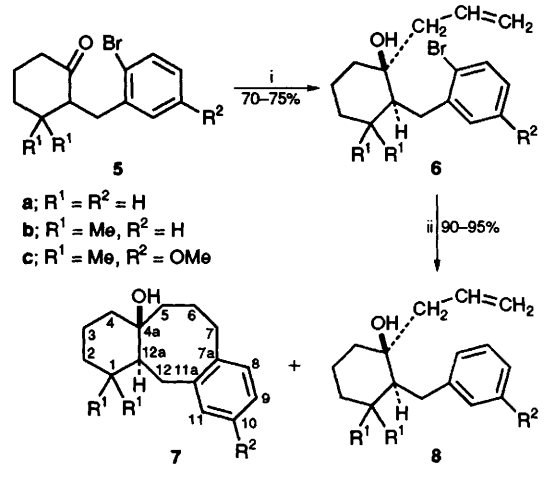
The relatively favourable disposition of the bond-forming carbon atoms in the intermediate oct-7-enyl aryl radicals, which are held in the rigid benzyl side chain and generated from the allylcyclohexanols **6a–c**, compared to that in the flexible 2-phenylethyl side chain formed from the vinylcyclohexanols **2a–c**, is clearly reflected in the substantially higher yields of the cyclisation products in the former substrates.

It is notable that besides efficient generation of the eight-membered carbocyclic ring by TBTH-mediated radical reactions, the present results provide the first experimental support to the theoretically predicted exclusive 8-*endo*-cyclisations in oct-7-enyl radicals.[7] The *endo-trig* aryl radical cyclisations developed for the synthesis of dibenzo-[*a,d*]- and -[*a,e*]-cyclooctene ring systems, if general in nature, will emerge as an important synthetic addition to eight-membered carbocyclic rings.

The CSIR New Delhi is gratefully acknowledged for financial support through grant no. 02(368)/92/EMR-II and for the award of Junior Research Fellowship to K. G., and Senior Research Fellowship to A. K. G. Dr A. K. Chakrav-



Scheme 1 *Reagents*: i, CH_2=$CHMgBr$, THF; ii, Bu_3^nSnH, AIBN, C_6H_6



Scheme 2 *Reagents*: i, CH_2=$CHCH_2Br$, Mg, THF; ii, Bu_3^nSnH, AIBN, C_6H_6

arty, Indian Institute of Chemical Biology, Calcutta, is thanked for some ^{13}C NMR spectra and their interpretations.

Received, 2nd November 1993; Com. 3/06557J

Footnotes

† Compounds described here are all racemates. Satisfactory elemental analyses were obtained for new compounds. Selected spectroscopic data; all ^1H NMR in $CDCl_3$ at 100 MH_z and ^{13}C NMR in $CDCl_3$ at 50 MHz unless stated otherwise, *J* in Hz: **3a**: ^1H NMR δ 0.66 (s, 3 H, CMe), 0.94 (s, 3 H, CMe), 1.01–2.08 (m, 11 H), 2.24–3.56 (m, 4 H, 2 $ArCH_2$) and 6.97–7.24 (m, 4 H, ArH). **3b**: ^1H NMR δ 0.66 (s, 3 H, CMe), 0.94 (s, 3 H, CMe), 1.02–2.10 (m, 11 H), 2.20–3.48 (m, 4 H, 2 $ArCH_2$), 3.77 (s, 3 H, ArOMe), 6.56 (d, *J* 2, 10-ArH), 6.66 (dd, *J* 8 and 2, 8-ArH) and 6.97 (d, *J* 8, 7-ArH); MS (EI) *m/z* 288 (M^+, 33%), 270 ($M^+ - H_2O$, 77), 255 (8), 201 (32), 185 (8), 160 (10) and 147 (100%). **3c**: ^1H NMR δ 0.66 (s, 3 H, CMe), 0.96 (s, 3 H, CMe), 1.02–2.10 (m, 11 H), 2.24–3.44 (m, 4 H, 2 $ArCH_2$), 3.77 (s, 3 H, ArOMe), 6.62 (d, *J* 2, 7-ArH) 6.73 (dd, J 8 and 2, 9-ArH) and 6.90 (d, *J* 8, 10-ArH).
7a: ^1H NMR δ 0.85–1.00 (m, 1 H), 1.12–2.15 (m, 13 H), 2.55–2.72 (m, 2 H, $ArCH_2$), 3.00–3.30 (m, 2 H, $ArCH_2$) and 7.15–7.35 (m, 4 H, ArH). **7b**: ^1H NMR (200 MHz), δ 0.75–1.00 (m, 1 H), 1.04 (s, 3 H, CMe), 1.15 (s, 3 H, CMe), 1.15–2.15 (m, 11 H), 2.50–2.70 (m, 2 H, $ArCH_2$), 2.80–3.20 (m, 2 H, $ArCH_2$) and 7.00–7.25 (m, 4 H, ArH), MS (EI) *m/z* 285 (M^+, 45%), 243 (M^+ – Me, 80), 240 ($M^+ - H_2O$, 100), 225 (33) and 212 (81); ^{13}C NMR δ 18.8 (C-3), 12.9 (β-methyl), 26.9, 29.7, 31.8 (C-12, C-6, C-7), 33.1 (α-methyl), 35.3 (C-1), 38.9 (C-5), 42.2 (C-2), 45.2 (C-4), 59.8 (C-12a), 74.7 (C-4a), 126.3, 126.4 (C-9, C-10), 128.8, 129.1 (C-8, C-11) and 140.0, 143.2 (C-7a, C-11a). **7c**: ^1H NMR (200 MHz), δ 0.70–0.98 (m, 1 H), 1.03 (s, 3 H, CMe), 1.14 (s, 3 H, CMe), 1.15–2.10 (m, 11 H), 2.45–2.65 (m, 2 H, $ArCH_2$), 2.80–3.10 (m, 2 H, $ArCH_2$), 3.80 (s, 3 H, ArOMe), 6.67 (dd, *J* 8 and 2, 9-ArH), 6.73 (d, *J* 2, 11-ArH) and 6.98 (d, *J* 8, 8-ArH); MS (EI) *m/z* 288 (M^+, 98%), 270 ($M^+ - H_2O$, 100), 255 (80), 242 (97), 227 (50), 199 (75), 173 (97) and 121 (95); ^{13}C NMR δ 18.3 (C-3), 21.9 (β-methyl), 27.0, 29.9, 30.9 (C-12, C-6, C-7), 33.1 (α-methyl), 35,3 (C-1), 39.0 (C-5), 42.2 (C-2), 45.2 (C-4), 55.4 (OMe), 59.7 (C-12a), 74.6 (C-4a), 111.2 (C-9), 115.0 (C-11), 129.6 (C-8), 132.3 (C-7a), 145.1 (C-11a) and 158.3 (C-10).
‡ These ketones were prepared by procedures identical to those described for the corresponding demethoxy analogue (ref 4).

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