Anionic Fries Rearrangements of Esters of *ortho*-Iodobenzyl Alcohols: Rapid Routes to Oestrone Methyl Ether and Its 9β Epimer, and Aryl Naphthalide Lignans

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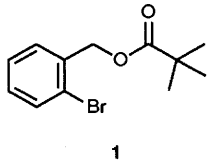
A fast, general, low-temperature rearrangement of *ortho*-iodobenzyl esters, triggered by lithium–iodine exchange, leads to isobenzofurans which are intercepted *in situ* by inter and intramolecular Diels–Alder (IMDA) reactions to produce a variety of carbocycles including natural lignans and steroids.

The metal–halogen exchange-initiated intramolecular cycliacylation and cyclialkylation of aromatic halides bearing appropriate electrophilic centres is a useful method for the preparation of carbocycles and heterocycles.[1] Documented examples of successful exchange-initiated cyclizations of bromo- or iodo-carbonyl substrates, which are potentially enolizable by the initially generated nucleophilic centre, however, are relatively scarce.[2] Our recent investigations into anionic variants of the Fries rearrangement as applied to regiospecific xanthone[3] and acridone[4] synthesis, coupled with a recent disclosure[5] concerning the exchange-initiated conversion of the non-enolizable bromopivaloate **1** to the hydroxyphthalan **2** (R = Bu^t), prompted us to enquire as to whether such a homologous Fries rearrangement might be generally applicable to substrates such as **3** in which the acid derived R substituent possessed potentially acidic and/or reactive (but subsequently useful) functional groups. Success in such a manoeuvre would require a rate of lithium–iodine exchage in **3** not only rapid enough to supersede the rate of competitive deprotonation by the alkyllithium reagent but also a rate of subsequent 5-*exo*-trig cyclization to hydroxyphthalans **2** which would preempt the intervention of any kinetically favoured deprotonation alternatives. We now report the development of this as a general approach to substituted hydroxyphthalans **2**, known precursors to isobenzofurans, useful in brief preparations of many natural products.[6] Condensation of 2-iodobenzyl alcohol with 4-pentenoic acid 1,3-dicyclohexylcarbodiimide [(DCC), 4-dimethylaminopyridine (DMAP), CH_2Cl_2] afforded benzyl ester **3a** (91%). Treatment of a 0.07 mol dm^{-3} solution of **3a** in THF–Et_2O–hexanes (4 : 1 : 1) with one equivalent of LiBu at −100 °C followed by immediate quenching with ammonium chloride and work-up afforded



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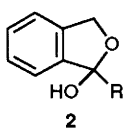

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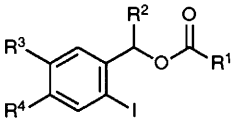
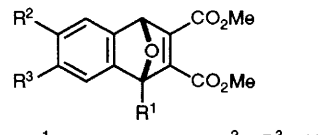
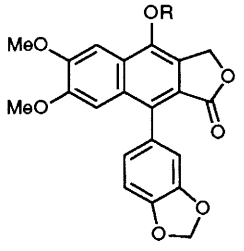


3a; $R^1 = (CH_2)_2CH{=}CH_2$, $R^2 = R^3 = R^4 = H$
b; R^1 = 3,4-(methylenedioxy)phenyl, $R^2 = H$, $R^3 = R^4 = OMe$
c; $R^1 = (CH_2)_3C{\equiv}CH$, $R^2 = R^3 = R^4 = H$
d; $R^1 = (CH_2)_3C{\equiv}CTMS$, $R^2 = R^3 = R^4 = H$
e; $R^1 = (CH_2)_4CH{=}CH_2$, $R^2 = R^3 = R^4 = H$
f; $R^1 = Ph$, $R^2 (CH_2)_3CH{=}CH_2$, $R^3 = R^4 = OMe$
g; $R^1 = Et$, $R^2 = (CH_2)_3CH{=}CH_2$, $R^3 = R^4 = OMe$
h; $R^1 = Me$, $R^2 = (CH_2)_3CH{=}CH_2$, $R^3 = R^4 = OMe$
i; $R^1 = CH_2OCH_2CH{=}CH_2$, $R^2 = R^3 = R^4 = H$



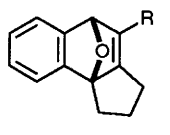
4a; $R^1 = (CH_2)_2CH{=}CH_2$, $R^2 = R^3 = H$
b; R^1 = 3,4-(methylenedioxy)phenyl, $R_2 = R^3 = OMe$



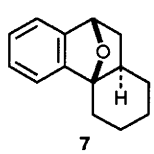
5a; R = H
b; R = Me

crude material devoid of any aromatic iodine. Treatment of this crude product with dimethyl acetylene dicarboxylate (cat. HOAc, 100 °C, 30 min) furnished intermolecular Diels–Alder adduct **4a**[7] in 60% yield. Similar treatment of ester **3b**[8] resulted in the formation of **4b** (42% overall from **3b**), which had previously been prepared[9] and regiospecifically converted into the arylnaphthalide lignans diphyllin **5a** and justicidin A **5b**.[9,10]

Of particular interest in the current study was the possibility of incorporating into esters **3** a tethered dienophilic residue for subsequent use in intramolecular Diels–Alder processes. Individual exposure of esters **3c** and **d** to the usual rearrangement conditions followed by refluxing of the crude rearrangement products in benzene (cat. HOAc, 16 h) afforded adducts **6a** (34%) and **6b** (38%) in comparable yield. Thus, protonation of the aryllithium by the free acetylenic hydrogen does not appear to be a significant process. Similarly, ethylenic esters **3e–g** afforded the *exo*[11] adduct **7**[7] (80%), **8a** (64%) and **8b** (72%), respectively, of which only the latter readily aromatized to the naphthalene **9** on leaving to stand at 25 °C. Presumably the higher overall yields observed for these ethylenic-derived adducts over the acetylenic counterparts **6a** and **b** is a consequence of more favourable orbital overlap between the transient IBFs and the ethylenic dienophiles, an idea supported by molecular models. The flexibility of the overall process is obvious in that the dienophilic residue for the IMDA reaction can be tethered to the acyl portion (as in **3c** and **d**) or the alcohol portion (as in **3f** and **g**) of the starting iodobenzyl ester. The latter starting materials were prepared by addition of the Grignard reagent derived from 5-bromopentene to 2-iodo-4,5-dimethoxybenzaldehyde[8] followed by esterification of the resulting secondary alcohol. It is interesting that the rearrangement/Diels–Alder process of acetate **3h** and allyloxyacetate **3i** did not lead to either the isolation of **8c** or **10**, respectively. The higher kinetic acidity of the methyl



6a; R = H
b; R = TMS



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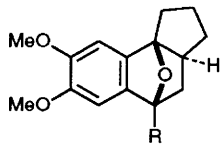
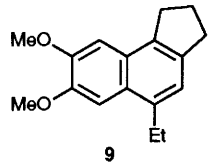


8a; R = Ph
b; R = Et
c; R = Me



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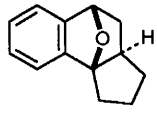

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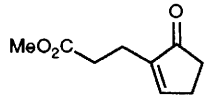

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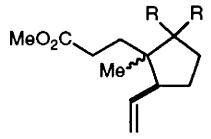
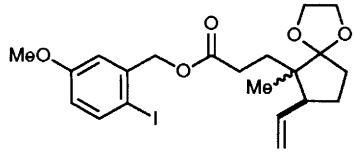
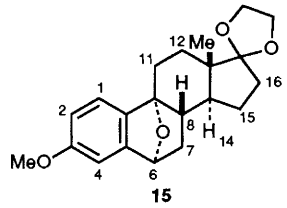


12a; R + R = O, β-Me
b; R + R = O, α-Me
13a; R + R = OCH_2CH_2O, β-Me
b; R + R = OCH_2CH_2O, α-Me



14a; β-Me
b; α-Me



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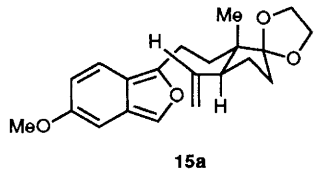
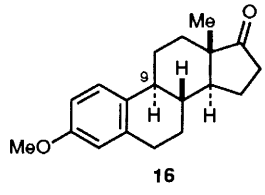


15a



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group **3h** and the oxymethylene group **3i** are probably responsible for the outcome—the recovery of the deiodinated starting materials.

The synthetic utility of the rearrangement–IMDA sequence is demonstrated here by a rapid total synthesis of (±)-oestrone methyl ether, a synthetic target of several previous IMDA approaches employing *o*-quinodimethanes.[12] Pauson–Khand reaction[13] of methyl pent-4-ynoate with $Co_2(CO)_8$ and ethylene [65 °C, 150 psi (psi = 6.9 kPa) 6 h, toluene] afforded **11** (29%). Conjugate addition of vinylmagnesium bromide (cat. CuI, Me_2S, THF, −60 °C) followed by enolate trapping (MeI, HMPA, −40 °C) afforded **12a** and **b**, (71%, 2:1 diastereoselectivity) in which the major diastereoisomer **12a** possessed the two larger vicinal groups in a *trans* relationship.[14] Ketalization of the mixture **12a**, **b** (ethylene glycol, TsOH, benzene, reflux) afforded the separable diastereoisomers **13a** and **b**. Transesterification of separated **13a** and **b** (NaOH–MeOH, then DCC, DMAP, 2-iodo-3-methoxybenzyl alcohol)† provided **14a** and **b**. Exposure of **14a** to the standard rearrangement–IMDA sequence afforded a single crystalline

† Prepared in 42% yield by iodination (Ag_2SO_4, CH_2Cl_2, I_2, 25 °C, 5 h) of 3-methoxy benzyl alcohol.

adduct **15**‡ in 27% yield by the favoured transition state **15a** involving a pseudo-chair-like C ring and *exo*-β-face delivery[12a] of the dienophile. The production of significant amounts of 3-methoxybenzyl alcohol (presumably formed *via* ester cleavage) during the rearrangement step accounted for the bulk of the material balance. This tendency for ester cleavage had not been observed in any of our prior experiments but attempted conversion of **14b** to the corresponding C-14 epimer of **15** failed completely for the same reason. Hydrogenolysis of **15** (AcOH, 50 psi, 3 h, 10% Pd/C) followed directly by deketalization (AcOH, THF, H_2O, heat) afforded in 60% total yield a 1 : 2 mixture of (±)-oestrone methyl ether **16** and its C-9 epimer as estimated by 500 MHz ^1H NMR spectroscopy in comparison with an authentic sample of **16**. We have not been able to separate the C-9 epimers, even by reverse-phase chromatography. The epimeric mixture results from partial inversion of configuration at C-9 during reductive removal of the oxygen bridge in **15**. Although this was not unexpected,[15] hydrogenolysis of a similar bridged intermediate had been reported[11] to proceed with complete retention of configuration at C-9. More examples of the rearrangement–IMDA sequence, especially with nitrogen-containing dienophiles, are being sought and modifications designed to forestall the ester cleavage and improve stereocontrol at C-9 during hydrogenolysis are contemplated. Results of these investigations will be reported elsewhere.

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‡ *Selected spectroscopic data* for **15**: m.p. 145–146 °C (Et_2O–hexane); ^1H NMR (250 MHz, $CDCl_3$): δ 0.95 (s, 3H, Me), 1.19–2.52 (m, 12H, 2 H-16, 2 H-15, 2 H-7, 2 H-11, 2 H-12, H-8, H-14), 3.78 (s, 3H, OMe), 3.81–3.96 (m, 4H, ketal CH_2CH_2), 5.24 (d, *J* 5.0, Hz 1H, H-6), 6.65 (dd, *J* 8.0 Hz, 2.2, 1H, H-2), 6.78 (d, *J* 2.2 Hz, 1H, H-4), 7.02 (d, *J* 8.0 Hz, 1H, H-1); MS (EI) *m/z* 342 (14, M^+), 174 (81), 123 (12), 99 (100), 86 (15), 55 (4), 40 (28); HRMS (EI) Calc. for $C_{21}H_{26}O_4$: 342.1832. Found: 342.1826.

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