*Journal of Organometallic Chemistry*, 379 (1989) 81–88
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands
JOM 20327

# Stereoselective synthesis of *cis*-1,3-disubstituted 1,3-dihydroisobenzofurans via arenechromium tricarbonyl methodology

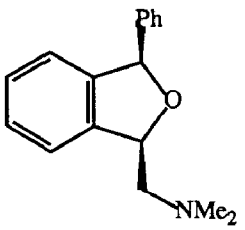
**Steven J. Coote, Stephen G. Davies *,**
*The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY (U.K.)*
**David Middlemiss and Alan Naylor**
*Glaxo Group Research, Ware, Herts, SG12 0DJ (U.K.)*
(Received July 23rd, 1989)

## Abstract

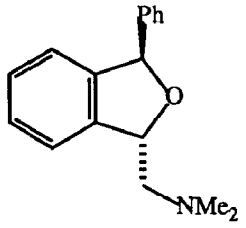
Phthalanchromium tricarbonyl is converted by t-butyllithium and alkyl halides completely stereoselectively into the corresponding *exo*-1-methyl, ethyl and benzyl derivatives. Double methylation of phthalanchromium tricarbonyl generates completely stereoselectively *exo-cis*-1,3-dimethylphthalanchromium tricarbonyl, from which *cis*-1,3-dimethylphthalan is liberated on oxidation. In contrast, double methylation of phthalan itself produces a 40/60 mixture of *cis*- and *trans*-1,3-dimethylphthalan.

## Introduction

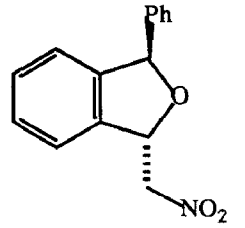
Substituted 1,3-dihydroisobenzofurans (phthalans) are of interest owing to their spectroscopic and pharmacological properties [1,2]. Saxena has shown that both the *cis*- and *trans*-isomers of 1-*N*,*N*-dimethylaminomethyl-3-phenylphthalan (**1** and **2**) exhibit antihistaminic activity [3]. The individual diastereoisomers **1** and **2** were obtained following separation of their nitro precursors by fractional recrystallisation; the stereochemical assignments were established by a single crystal X-ray study of the *trans*-isomer **3** of the precursor [4].




**1**



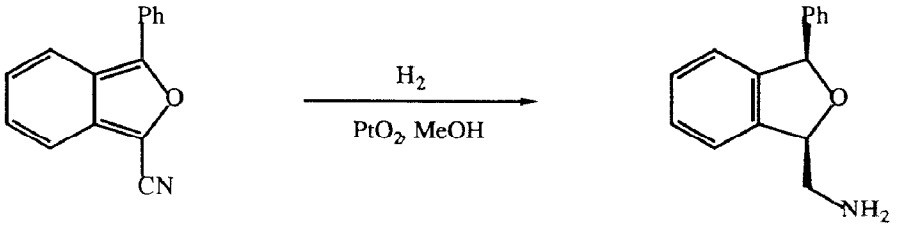

**2**




**3**

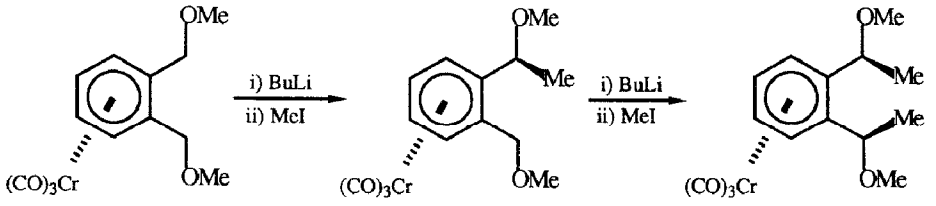
0022-328X/89/$03.50 

A stereoselective synthesis of *cis*-1,3-disubstituted phthalans has been reported, and involves the hydrogenation of 1-cyano-3-phenylisobenzofuran (**4**), which yields only the *cis*-isomer **5** [4].

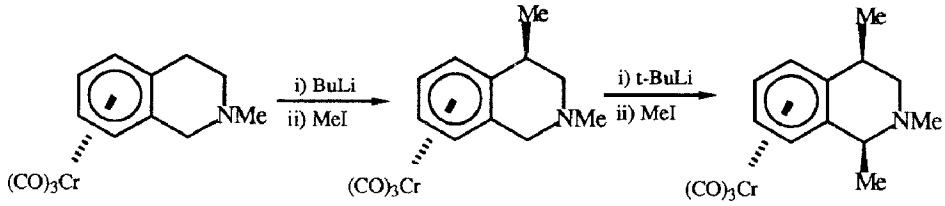



**4** **5**

We have previously demonstrated the utility of the chromium tricarbonyl moiety for promoting stereoselective benzylic alkylations [5–7]. Thus, double benzylic methylation of the dimethyl-*o*-xylenediyl ether complex **6** gave completely stereoselectively the *meso*-derivative **7** [6]. Furthermore, double methylation of the tetrahydroisoquinoline complex **8** gave completely stereoselectively the *exo-cis*-1,4-dimethyl derivative **9** [7].




**6** **7**

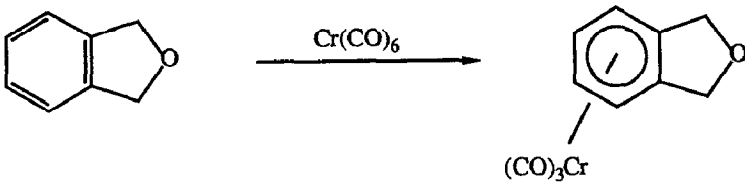



**8** **9**

We describe below the application of chromium tricarbonyl methodology to the synthesis of *cis*-1,3-disubstituted phthalans.

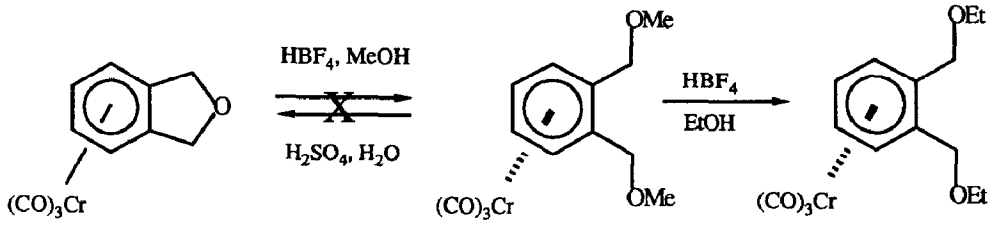
## Results and discussion

Thermolysis of chromium hexacarbonyl with phthalan (**10**) under standard conditions [8] gave phthalanchromium tricarbonyl (**11**).




10 11

Treatment of the dimethyl ether complex **6** with aqueous acid produced none of **11** despite ready formation of the benzylic carbonium ion, as evidenced by the trans-etherification of **6** to **12** in acidic ethanol. Furthermore, complex **11** was inert towards acidic methanol, none of complex **6** being detected. The absence of interconversion of **6** and **11** under acidic conditions may be rationalised in stereo-electronic terms. Cyclisation of the chromium tricarbonyl stabilised benzylic carbonium ion [9] derived from **6** would involve an unfavourable 5-*endo-trig* [10] process, while the carbon–oxygen bonds in **11** are unable to adopt the required, antiperiplanar to chromium, conformation for carbonium ion formation.



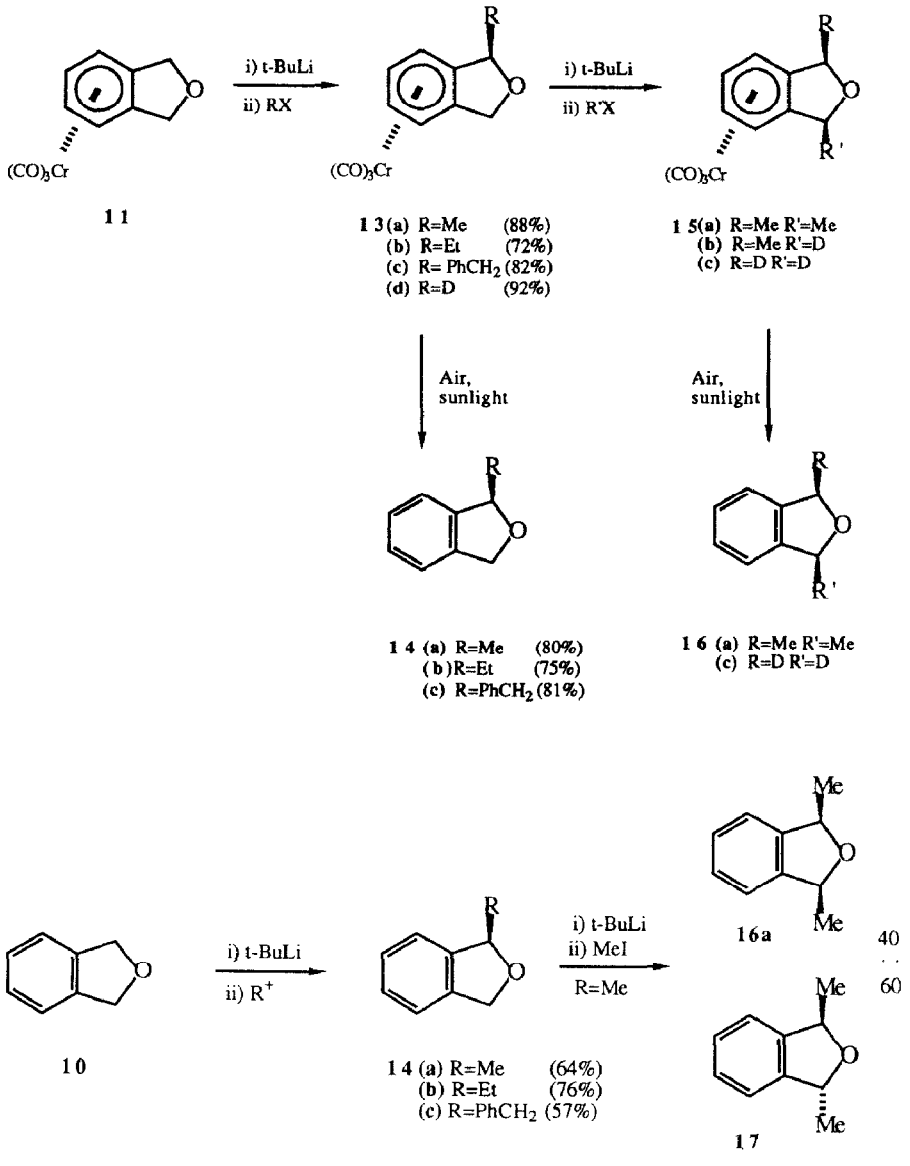

11 6 12

Treatment of **11** with t-butyllithium at −78°C and subsequent addition of methyl iodide gave *exo*-1-methylphthalanchromium tricarbonyl (**13a**) completely stereoselectively in 88% isolated yield. The structure of **13a** was established from its $^1$H NMR spectrum, the *exo* stereochemistry being assigned by analogy [5–7]. Similarly, ethylation, benzylation and deuteriation of **11** were also completely stereoselective, giving **13b, 13c** and **13d** respectively. Exposure of diethyl ether solutions of complexes **13a–c** to air and sunlight liberated the corresponding 1-alkylphthalans **14a–c** [1,11].

Sequential treatment of complex **13a** with t-butyllithium and methyl iodide gave, completely stereoselectively, *exo-cis*-1,3-dimethylphthalanchromium tricarbonyl (**15a**) as the sole product (91% isolated yield). The structure of **15a** followed from its $^1$H NMR spectrum, the equivalence of the methyl and benzylic protons confirming the expected *cis* stereochemistry. Oxidative decomplexation of **15a** gave *cis*-1,3-dimethylphthalan (**16a**) [12,13]. Similarly, deuteriation of **13a** with t-butyllithium and deuteriomethanol gave **15b** containing > 90% deuterium in the 3-*exo* position, and none in the 3-*endo* position according to $^2$H NMR spectroscopy.

Deuteriation of **13d** gave stereoselectively **15c** containing 1.65 deuterium equivalents. This is consistent with a kinetic isotope effect of ca. 2 for the removal of the 3-*exo* proton compared with that of the 1-*exo* deuteron in **13d**. Decomplexation of **15c** gave **16c**.

Direct alkylation of phthalan **10** may also be achieved, although deprotonation proved to be considerably slower than for the complex **11**. Thus exposure of **10** to




t-butyllithium at −78 °C for 6 h gave, after addition of the appropriate alkyl halide, 1-alkylphthalans **14a–c** in good yields. Treatment of 1-methylphthalan (**14a**) with t-butyllithium followed by methyl iodide gave a 40/60 mixture of *cis*- and *trans*-1,3-dimethylphthalan (**16a** and **17**, respectively) with the expected *trans*-isomer predominating [14].

## Experimental

All preparations, purification, and reactions of tricarbonyl($\eta^6$-arene)chromium(0) complexes were performed under nitrogen by standard vacuum line techniques.

THF was distilled from sodium benzophenone ketyl under nitrogen. Dibutyl ether was dried over sodium and distilled prior to use. t-Butyllithium was used as a 2.62 *M* solution in pentane. Both IR and $^2$H NMR spectra were obtained as chloroform solutions. The $^1$H and $^{13}$C NMR spectra were recorded with [$^2$H]chloroform solutions at 300 MHz and 62.9 MHz respectively.

*Tricarbonyl(η$^6$-1,3-dihydroisobenzofuran)chromium(0)* ***(11)***

A deoxygenated mixture of 1,3-dihydroisobenzofuran (1.50 g, 12.5 mmol) and hexacarbonylchromium (3.0 g, 13.6 mmol) in dibutyl ether (40 ml) and THF (4 ml) was heated under reflux under nitrogen a (16 h). The cooled solution was filtered and evaporated. The residue was subjected to column chromatography ($Al_2O_3$ Grade V, $Et_2O$) and gave a single fraction as a yellow solid. Recrystallisation from $Et_2O$/hexane gave the *title compound* as yellow needles (2.04 g, 64%), $\nu_{max.}$ 1970 and 1890 cm$^{-1}$ (C=O); δ(H) 5.53–5.25 (4H, m, aromatic protons), 4.93, 4.88 (4H, AB system $J_{AB}$ 10.8 Hz, ArC$H_2$); *m/z* 256 (*M*$^+$) (Found: C, 51.4; H, 3.2. $C_{11}H_8CrO_4$ calc: C, 51.6; H, 3.15%).

*Tricarbonyl(η$^6$-exo-1-methyl-1,3-dihydroisobenzofuran)chromium(0)* ***(13a)***

To a stirred solution of tricarbonyl(η$^6$-1,3-dihydroisobenzofuran)chromium(0) (**11**) (0.163 g, 0.64 mmol) in THF (20 ml) at −78°C was added t-butyllithium (0.25 ml, 0.66 mmol), and the resulting red solution stirred (−78°C, 1.75 h). Methyl iodide (1 ml, 16.1 mmol) was added and stirring continued −78°C, 2 h). After addition of methanol (1 ml) the mixture was warmed and evaporated. Column chromatography ($Al_2O_3$ Grade V, $Et_2O$) gave a single fraction as a yellow oil (0.151 g, 88%). Crystallisation from n-pentane (−20°C) gave the *title compound* as fine yellow needles, $\nu_{max.}$ 1970, 1880 cm$^{-1}$ (C=O) and 1250 cm$^{-1}$ (C–O); δ(H) 5.52–5.23 (4H, m, aromatic protons), 5.16 (1H, dq, *J* 1.7 and 6.5 Hz, ArC*H*$CH_3$), 4.98, 4.87 (2H, ABX system, $J_{AB}$ 12.3, $J_{AX}$ 1.7 Hz, ArC$H_2$O), 1.44 (3H, d, *J* 6.6 Hz, CHC$H_3$); *m/z* 270 (*M*$^+$) (Found: 53.0; H, 3.7. $C_{12}H_{10}CrO_4$ calc: C, 53.3; H, 3.7%).

*Tricarbonyl(η$^6$-exo-1-ethyl-1,3-dihydroisobenzofuran)chromium(0)* ***(13b)***

Alkylation as above with ethyl iodide as the electrophile gave the *title compound* as a yellow oil (72%), $\nu_{max.}$ 1960 and 1890 cm$^{-1}$ (C=O); δ(H) 5.51–5.22 (4H, m, aromatic protons), 4.99 (1H, m, ArC*H*Et), 4.97, 4.87 (2H, AB system, $J_{AB}$ 11.4 Hz, ArC$H_2$O), 1.74 (2H, m, $CH_3CH_2$), 1.00 (3H, t, *J* 7. Hz, $CH_2CH_3$); *m/z* 284 (*M*$^+$) (Found: *M*$^+$, 284.0143. $C_{13}H_{12}CrO_4$ calc: *M*, 284.0141).

*Tricarbonyl(η$^6$-exo-1-benzyl-1,3-dihydroisobenzofuran)chromium(0)* ***(13c)***

Alkylation as above with benzyl bromide as the electrophile gave the *title compound* as a yellow oil (82%), $\nu_{max.}$ 1970 and 1880 cm$^{-1}$ (C=O); δ(H) 7.38–7.15 (5H, m, uncomplexed aromatic protons), 5.42–5.07 (5H, m, complexed aromatic protons and ArC*H*$CH_2$Ph), 4.80 (2H, br s, ArC$H_2$O), 3.49, 3.11 (2H, ABX system, $J_{AB}$ 14.0, $J_{AX}$ 7.0, $J_{BX}$ 5.9 Hz, PhC$H_2$CH); *m/z* 346 (*M*$^+$) (Found: *M*$^+$, 346.0293. $C_{18}H_{14}CrO_4$ calc: *M*, 346.0297).

*Tricarbonyl(η$^6$-exo-1-deuterio-1,3-dihydroisobenzofuran)chromium(0)* ***(13d)***

Reaction as above with deuteriomethanol as the electrophile gave the *title compound* as a yellow oil (92%), δ(H) 5.53–5.24 (4H, m, aromatic protons),

5.95–5.85 (3H, m, ArC$H_2$OC$H$D); δ(D) 4.93 (1D, br s, ArCH$D$); *m/z* 257 ($M^+$).

*Tricarbonyl(η⁶-exo-1,3-dihydroisobenzofuran)chromium(0) (**15a**)*

A solution of tricarbonyl(η⁶-*exo*-1-methyl-1,3-dihydroisobenzofuran)chromium(0) (**13a**) (0.124 g, 0.46 mmol) in THF (20 ml) at −78 °C was treated with t-butyllithium (0.2 ml, 0.52 mmol) in the above fashion and quenched with methyl iodide to give, after chromatography, a yellow oil that solidified on standing (0.118 g, 91%). Recystallisation from $Et_2O$/pentane afforded the *title compound* as yellow plates, $\nu_{max.}$ 1970 and 1880 $cm^{-1}$ (C=O); δ(H) 5.46–5.25 (4H, m, aromatic protons), 5.13 (2H, q, *J* 6.5 Hz, ArC$H$C$H_3$), 1.49 (6H, d, *J* 6.5 Hz, ArCHC$H_3$); *m/z* 284 ($M^+$) (Found: C, 55.0; H, 4.1. $C_{13}H_{12}CrO_4$ calc: C, 54.9; H, 4.3%).

*Tricarbonyl(η⁶-exo-1-methyl-3-deuterio-1,3-dihydroisobenzofuran)chromium(0) (**15b**)*

Reaction as above with deuteriomethanol as the electrophile gave the *title compound* as a yellow oil (93%), δ(H) 5.53–5.23 (4H, m, aromatic protons), 5.14 (1H, q, *J* 6.5 Hz, ArC$H$C$H_3$), 4.82 (1H, br s, ArCHD), 1.43 (3H, d, *J* 6.5 Hz, ArCHC$H_3$); Δ(D) 5.53 (1D, br s, ArCH$D$); *m/z* 271 ($M^+$). Integration of the molecular ion peak ($M^+$ 271) with respect to that of complex **13a** revealed ca. 95% deuterium incorporation.

*Tricarbonyl(η⁶-exo-1,3-dideuterio-1,3-dihydroisobenzofuran)chromium(0) (**15c**)*

A solution of tricarbonyl(η⁶-*exo*-1-deuterio-1,3-dihydroisobenzofuran)chromium(0) (**13d**) (0.028 g, 0.11 mmol) in THF (15 ml) at −78 °C was metallated with t-butyllithium (0.07 ml, 0.18 mmol), and the mixture then treated with deuteriomethanol. Column chromatography ($Al_2O_3$ Grade V, $Et_2O$) gave the *title compound* as a yellow solid (0.026 g, 92%), δ(H) 5.53–5.25 (4H, m, aromatic protons), 4.86 (2H, br s, ArC$H$D); δ(D) 4.93 (2D, br s, ArCH$D$); *m/z* 258 ($M^+$). Integration of the $^1$H NMR signals of the *endo* benzylic protons with respect to those for the *exo* benzylic protons of complex **13d** revealed ca. 82% deuterium incorporation consistent with a kinetic isotope effect of ca. 2 for the preferential removal of the 3-*exo* proton over the 1-*exo*-deuteron in complex **13d**.

*General procedure of the decomplexation of the complexes **13a–c**, **15a** and **15c***

A solution of the relevant tricarbonylchromium complex **13a–c**, **15a** or **15c** in $Et_2O$ (20 mg $ml^{-1}$) was allowed to stand in air and sunlight until the yellow solution became colourless. Filtration (Celite) and evaporation gave the crude decomplexed 1,3-dihydroisobenzofurans as colourless oils. Owing to the ready autoxidation of these compounds [11], further purification (where necessary) was achieved by cup distillation under reduced pressure.

*1-Methyl-1,3-dihydroisobenzofuran (**14a**) [1,11,13].* δ(H) 7.32–7.16 (4H, aromatic protons), 5.34 (1H, dq, *J* 6.4 and 1.8 Hz, ArC$H$C$H_3$), 5.15, 5.06 (2H, ABX system, $J_{AB}$ 12.2, $J_{AX}$ 2.2, $J_{BX}$ 1.7 Hz, ArC$H_2$O), 1.52 (3H, d, *J* 6.1 Hz, ArCHC$H_3$); *m/z* ($M^+ - 1$).

*1-Ethyl-1,3-dihydroisobenzofuran (**14b**).* $\nu_{max.}$ 1260 $cm^{-1}$ (C–o); δ(H) 7.29–7.16 (4H, m, aromatic protons), 5.22 (1H, br s, ArC$H$Et), 5.14, 5.08 (2H, ABX system, $J_{AB}$ 12.1, $J_{AX}$ 2.5, $J_{BX}$ 1.3 Hz, ArC$H_2$O), 1.99–1.71 (2H, m, C$H_2$CH$_3$), 0.99 (3H, t, *J* 7.4 Hz, CH$_2$C$H_3$); δ(C) 141.97, 139.65, 127.29, 127.14, 121.14, 120.90, 85.02, 72.59, 29.01, 9.16; *m/z* 147 ($M^+ - 1$) (Found: C, 80.95; H, 9.6. $C_{10}H_{12}O$ calc: C, 81.0; H, 8.2%).

*1-Benzyl-1,3-dihydroisobenzofuran (**14c**).* $\nu_{max.}$ 1255 $cm^{-1}$ (C–O); δ(H) 7.43–7.05 (9H, m, aromatic protons), 5.55 (1H, br s, ArC*H*$CH_2$Ph), 5.09 (2H, br s, ArC$H_2$O), 5.14 (2H, m, PhC$H_2$CH); δ(C) 141.47, 139.43, 137.72, 129.52, 128.31, 128.17, 128.05, 127.34, 126.87, 126.17, 121.40, 120.76, 84.32, 72.34, 42.68; *m/z* 209 ($M^+ - 1$) (Found: C, 85.8; H, 7.1. $C_{15}H_{14}O$ calc: C, 85.7; H, 6.7%).

*cis-1,3-Dimethyl-1,3-dihydroisobenzofuran (**16a**) [12,13].* δ(H) 7.30–7.13 (4H, m, aromatic protons), 5.23 (2H, q, *J* 6.2 Hz, ArC*H*$CH_3$), 1.54 (6H, d, *J* 6.3 Hz, ArCHC$H_3$); *m/z* 147 ($M^+ - 1$).

*cis-1,3-Dideuterio-1,3-dihydroisobenzofuran (**16c**).* δ(H) 7.32–7.30 (4H, br s, aromatic protons), 5.16 (2H, br s, ArC*H*D).

*General procedure for the alkylation of 1,3-dihydroisobenzofuran (**10**)*

A stirred solution of 1,3-dihydroisobenzofuran (**10**) (1.44 g, 11.9 mmol) in THF (30 ml) at −78 °C under nitrogen was treated with t-butyllithium (4.8 ml, 12.6 mmol), to give a red colouration that darkened with time. The mixture was stirred (−78 °C, 6 h) and treated with methyl iodide (2 ml, 32.1 mmol), resulting in immediate discharge of the colour. Stirring was continued (−78 °C, 1.6 h), methanol (10 ml) was added, and the solution stirred (20 °C, 12 h). The solvent was removed, water (40 ml) added and the aqueous layer extracted ($Et_2O$, 3 × 40 ml). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give 1-methyl-1,3-dihydroisobenzofuran (**14a**) as a pale brown oil that darkened upon prolonged exposure to air (1.02 g, 64%) [13]. Use of ethyl iodide as the electrophile yielded 1-ethyl-1,3-dihydroisobenzofuran (**14b**) as a colourless oil (76%), while that of benzyl bromide afforded 1-benzyl-1,3-dihydroisobenzofuran (**14c**) (57%).

*Methylation of 1-methyl-1,3-dihydroisobenzofuran (**14a**)*

A stirred solution of 1-methyl-1,3-dihydroisobenzofuran (**14a**) (0.129 g, 0.96 mmol) in THF (10 ml) at −78 °C under nitrogen was treated with t-butyllithium (0.4 ml, 1.05 mmol). The mixture was stirred (−78 °C, 4.3 h) and treated with methyl iodide (0.5 ml, 8.05 mmol), resulting in discharge of the colour. Stirring was continued (−78 °C, 1 h) and the reaction quenched by the addition of methanol (5 ml). The solution was stirred (20 °C, 12 h) and concentrated, and water (15 ml), was added. The aqueous layer was extracted ($Et_2O$, 3 × 10 ml) and the combined extracts were dried ($MgSO_4$). Filtration and evaporation gave a pale yellow oil (0.105 g, 74%). The $^1H$ NMR spectrum of the product revealed the presence of both *cis-* and *trans*-1,3-dimethyl-1,3-dihydroisobenzofuran (**16a** and **17** respectively) [12,13] in the ratio 1/1.4. δ(H) (*trans* **17**) 7.30–7.14 (4H, m, aromatic protons), 5.41 (2H, q, *J* 5.7 Hz, ArC*H*$CH_3$), 1.48 (3H, d, *J* 6.2 Hz, ArCHC$H_3$); *m/z* 166 ($M^+ + 18$).

**Acknowledgements**

We thank Glaxo Group Research for a studentship (to SJC).

**References**

1 M. Barfield, R.J. Spear and S. Sternhell, J. Am. Chem. Soc., 97 (1975) 5160.
2 R.R. Fraser and R.N. Renaud, Can. J. Chem., 49 (1971) 755.

3 S. Ram, A.K. Saxena, P.C. Jain and G.K. Patnaik, Ind. J. Chem., 23B (1984) 1261.
4 F.J. Petracek, N. Sugisaka, M.W. Klohs, R.G. Parker, J. Bordner and J.D. Roberts, Tetrahedron Lett., 10 (1970) 707.
5 J. Blagg, S.J. Coote, S.G. Davies, and B.E. Mobbs, J. Chem. Soc., Perkin Trans. 1, (1986) 2257.
6 J. Blagg, S.G. Davies, N.J. Holman, C.A. Laughton and B.E. Mobbs, J. Chem. Soc., Perkin Trans. 1, (1986) 1581.
7 J. Blagg, S.J. Coote, S.G. Davies, D. Middlemiss and A. Naylor, J. Chem. Soc., Perkin Trans. 1, (1987) 689. S.J. Coote, S.G. Davies and K.H. Sutton, ibid., (1988) 1481.
8 C.A.L. Mahaffy and P.L. Pauson, Inorg. Synth., 19 (1979) 154.
9 Asymmetric Synthesis via Chiral Transition Metal Auxiliaries. S.G. Davies, G. Bashiardes, R.P. Beckett, S.J. Coote, I.M. Dordor-Hedgecock, C.L. Goodfellow, G.L. Gravatt, J.P. McNally and M. Whittaker, Phil. Trans. R. Soc. Lond. A, 326 (1988) 619.
10 J.E. Baldwin, J. Chem. Soc., Chem. Commun., (1976) 734.
11 A. Reiche and M. Schultz, Justus Liebigs Ann. Chem., 653 (1962) 32.
12 F. Nelken and H. Simonis, Chem. Ber., 41 (1908) 986.
13 E. Berner, Acta Chem. Scand., 36B (1982) 729.
14 D. Tobia and B. Rickborn, J. Org. Chem., 51 (1986) 3849; J.G. Smith and R.T. Wikman, J. Chem. Soc., Chem. Commun., (1983) 1448.