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Two step synthesis of C_2 symmetric 2,6-diarylalkyloxybenzaldehydes — a Mitsunobu approach

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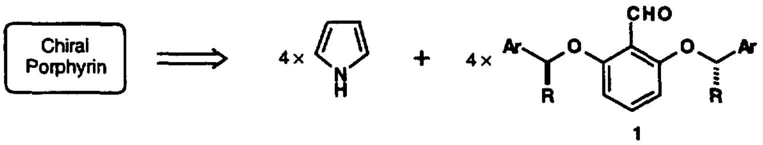
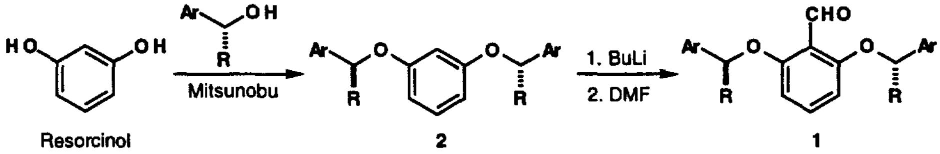
Abstract: A simple two step method for the synthesis of three novel C_2 symmetric 2,6-diarylalkyloxybenzaldehydes is described. Starting from resorcinol, the route involves double Mitsunobu reaction with chiral alcohols followed by regiospecific lithiation and formylation. © 1997 Elsevier Science Ltd

Introduction

The design and synthesis of novel chiral catalysts for asymmetric oxidation processes continues to be an important and active area of research.[1–3] In particular, there is still a need to develop enzyme-like porphyrin catalysts capable of epoxidising unfunctionalised alkenes with high enantioselectivities.[2] With this in mind, we are currently investigating the preparation of chiral metalloporphyrins in which the tetra-pyrrolic macrocycle is derived from the one-pot[4] condensation of pyrrole and the previously unknown C_2 symmetric 2,6-diarylalkyloxybenzaldehydes **1**. Aldehydes **1** were selected for a number of reasons. First of all, the stereogenic centres in the metalloporphyrin catalysts prepared from **1** would be close to the reacting metal centre. Secondly, the C_2 symmetry of aldehydes **1** avoids the formation of atropisomeric mixtures during the porphyrin synthesis. Finally, we imagined that aldehydes **1** could be synthesised in just a few steps from readily available starting materials.





This paper is concerned with the preparation of aldehydes **1** using the route outlined above. We proposed to prepare diethers **2** via double Mitsunobu[5] substitution of resorcinol with commercially available chiral alcohols. Then, regioselective lithiation of **2** *ortho* to both arylalkyloxy groups followed by formylation (in a similar manner to that described by Townsend in his total synthesis of Averufin)[6] should generate the required aldehydes **1**. Herein, we report the successful implementation of this route with the synthesis of three C_2 symmetric 2,6-diarylalkyloxybenzaldehydes.

Results and discussion

In order to test the viability of our proposed route, we prepared the known[7,8] and achiral 2,6-dibenzyloxybenzaldehyde **4**. Thus, resorcinol was reacted with two equivalents of benzyl alcohol under standard Mitsunobu conditions to give diether **3** in 53% yield.[9] Lithiation of **3** was accomplished by

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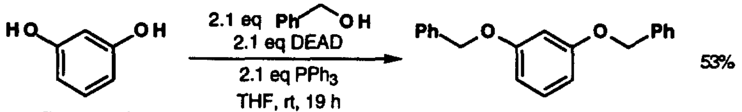
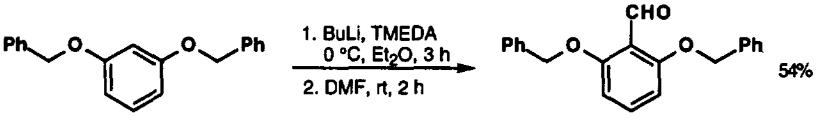
treatment with n-butyllithium-TMEDA in diethyl ether at 0°C (Townsend's conditions[6]) and subsequent formylation with DMF at room temperature generated a single aldehyde in 54% yield which was identical (by ^{1}H NMR spectroscopy) to aldehyde **4** reported previously by Nagata[7] and Lindsey.[8] As expected,[6,10] lithiation had indeed occurred regiospecifically *ortho* to *both* benzyloxy groups.



Resorcinol

3



3

4

This two step preparation of aldehyde **4** is an improvement on the previously published syntheses. For example, Lindsey's two step route uses the very expensive 2,6-dimethoxybenzaldehyde as starting material and Nagata's four step synthesis from 2,6-dihydroxybenzoic acid is somewhat lengthy and time consuming.[7,8] In contrast, our two step route from inexpensive[11] resorcinol is particularly attractive.

We then turned our attention to the preparation of the required chiral aldehydes **1**. The results of our synthetic studies are shown in Table 1. Double Mitsunobu substitution of resorcinol with each of (*R*)-1-phenylethan-1-ol, (*S*)-1-phenylbutan-1-ol and (*S*)-1-indanol generated diethers (*S*,*S*)-**5**, (*R*,*R*)-**7** and (*R*,*R*)-**9** in moderate yields after chromatography. Longer reaction times (48–72 hours) were needed with these sterically more hindered alcohols than with benzyl alcohol and, in some cases, we observed the formation of alkene products which presumably acounts for the lower yields.[12] In all cases, only one diastereoisomer of the diether products was isolated after chromatography and we believe that they have ≥96% enantiomeric excess as the stereospecificity of the Mitsunobu reaction is well documented.[5] In addition, any erosion of stereochemical integrity would have been detected by the formation of small amounts of *meso*-diethers and we did not observe this.[13]

The conversion of the diethers into the corresponding 2,6-diarylalkyloxybenzaldehydes **1** proceeded uneventfully and in reasonable yields upon lithiation and formylation. In the preparation of aldehyde (*R*,*R*)-**8** (entry 2), the yield was particularly good. As with the reaction of dibenzyl ether **3**, only one aldehyde was observed in each case. Comparison of their ^{1}H and ^{13}C NMR spectra with that of dibenzyl aldehyde **4** indicated that formylation had occurred as expected *ortho* to both alkylaryloxy groups.

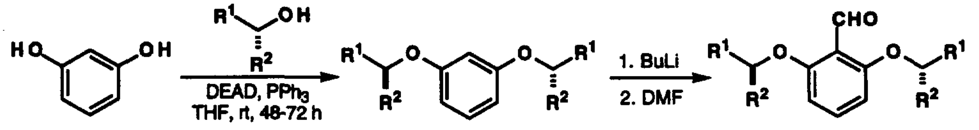
In summary, we have described a short, convenient and general method for the synthesis of a novel class of C_2 symmetric 1,3-diarylalkyloxybenzenes **2** and 2,6-diarylalkyloxybenzaldehydes **1**. Our approach is illustrated with the preparation of three new diethers and three new aldehydes. Diethers **2** may prove to be useful chiral ligands whilst aldehydes **1** could have potential applications as chiral auxiliaries. In addition, we are exploring the conversion of aldehydes (*S*,*S*)-**6**, (*R*,*R*)-**8** and (*R*,*R*)-**10** into chiral metalloporphyrins for use in asymmetric catalysis and the results will be presented in due course.

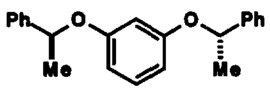
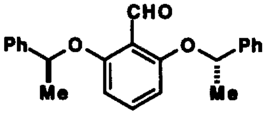
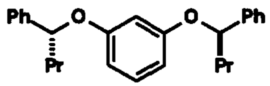
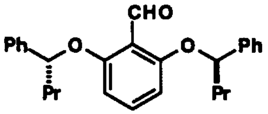
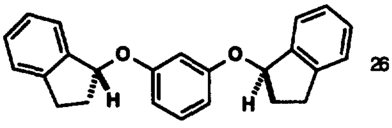
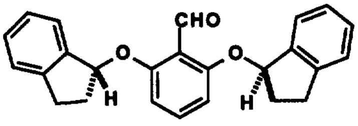
Experimental section

General

Et$_2$O and THF were freshly distilled from sodium-benzophenone ketyl. All reactions were carried out under oxygen-free nitrogen using oven-dried glassware. Thin layer chromatography was carried out on commercially available Merck 5554 aluminium-backed silica plates and column chromatography was carried out using Kieselgel 60. Proton and carbon NMR spectra were recorded on a Jeol EX-

Table 1. Two step synthesis of C_2 symmetric 2,6-diarylalkyloxybenzaldehydes



Entry	*Mitsunobu Step*		*Formylation Step*	
	1,3-Diarylalkyloxybenzene	Yield (%)[a]	2,6-Diarylalkyloxybenzaldehyde	Yield (%)[a]
1	 (*S,S*)-5	32	 (*S,S*)-6	38[b]
2	 (*R,R*)-7	28	 (*R,R*)-8	75[c]
3	 (*R,R*)-9	26	 (*R,R*)-10	30[d]

[a] After purification by column chromatography; [b] $[\alpha]_D^{20}$ +251.6 (*c* 1.16 in $CHCl_3$);
[c] $[\alpha]_D^{20}$ −223.2 (*c* 1.06 in $CHCl_3$); [d] $[\alpha]_D^{20}$ +92.2 (*c* 1.34 in $CHCl_3$).

270 (270 MHz) instrument using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield of tetramethylsilane. Carbon NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT experiments. Infra red spectra were recorded on a Perkin–Elmer Paragon 1000 FT IR spectrometer. Chemical ionisation and high resolution mass spectra were recorded on a Fisons Analytical (VG) Autospec spectrometer. Optical rotations were recorded on a Jasco DIP-370 polarimeter (using sodium D line; 589 nm) and $[\alpha]_D{}^{20}$ are given in units of 10^{-1} deg cm^2 g^{-1}.

General procedure for Mitsunobu reactions

Diethyl azodicarboxylate (3.75 mmol) was added dropwise to a stirred solution of triphenylphosphine (3.75 mmol) in THF (20 cm^3) under nitrogen at 0°C. After 5 min., the reaction mixture turned yellow–orange and, after being allowed to warm to room temperature, resorcinol (1.8 mmol) was added followed by addition of the chiral alcohol (3.75 mmol). The resulting solution was stirred at room temperature for the desired length of time (19–72 h) and then the solvent was evaporated under reduced pressure. Trituration with Et_2O (10 cm^3) gave a fine white precipitate which was removed by filtration. Then, the filtrate was evaporated under reduced pressure to give the crude product which was purified by chromatography on silica with hexane–methyl acetate as eluent.

1,3-Dibenzyloxybenzene 3

Using the general procedure, a 53% yield of the title compound was obtained after 19 h at room temperature as needles, m.p. 72–73°C (from hexane) (lit.[14] 60–64°C); ν_{max}(Nujol)/cm^{-1} 1284 and

1177; δ_H(270 MHz; $CDCl_3$) 7.4–7.3 (10 H, m, 2×Ph), 7.19 (1 H, t, *J* 8.1, H^5), 6.63 (1 H, t, *J* 2.1, H^2), 6.60 (2 H, dd, *J* 8.1 and 2.1, H^4 and H^6) and 5.04 (4 H, s, 2×CH_2); δ_C(67.9 MHz; $CDCl_3$) 160.0, 136.9, 129.9, 128.6, 128.0, 127.5, 107.4, 102.2 and 70.0 (2×CH_2); *m/z* 290 (15%, M$^+$) and 91 (100, $PhCH_2$).

(−)-(S,S)-1,3-Di-(1-phenylethyloxy)benzene 5

Using the general procedure, a 32% yield of the title compound was obtained after 48 h at room temperature as a pale yellow oil, $[\alpha]_D^{20}$−8.19 (*c* 0.97 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1280, 1176 and 1148; δ_H(270 MHz; $CDCl_3$) 7.4–7.3 (10 H, m, 2×Ph), 6.96 (1 H, t, *J* 8.1, H^5), 6.41–6.38 (3 H, m, H^2, H^4 and H^6), 5.15 (2 H, q, *J* 6.6, 2×PhC*H*Me) and 1.56 (6 H, d, *J* 6.6, 2×Me); δ_C(67.9 MHz; $CDCl_3$) 159.0, 129.5, 128.5, 127.3, 125.4, 108.4, 104.0, 75.9 (2×Ph*C*HMe) and 24.4 (2×Me); *m/z* 318 (3%, M$^+$), 214 (7, M–PhCHMe) and 105 (100, PhCHMe) (Found: M$^+$, 318.1624. $C_{22}H_{22}O_2$ requires *M*, 318.1620).

*(+)-(*R,R*)-1,3-Di-(1-phenylbutyloxy)benzene 7*

Using the general procedure, a 28% yield of the title compound was obtained after 64 h at room temperature as a white solid, m.p. 53–55°C (from hexane); $[\alpha]_D^{20}$+20.1 (*c* 1.13 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 1285, 1187 and 1145; δ_H(270 MHz; $CDCl_3$) 7.4–7.2 (10 H, m, 2×Ph), 6.94 (1 H, t, *J* 8.7, H^5), 6.36 (2 H, dd, *J* 6.5 and 2.4, H^4 and H^6), 6.34 (1 H, d, *J* 2.4, H^2), 4.92 (2 H, dd, *J* 7.9 and 5.2, 2×PhC*H*CH_2), 2.0–1.3 (8 H, m, 2×CH_2CH_2) and 0.90 (6 H, t, *J* 7.3, 2×Me); δ_C(67.9 MHz; $CDCl_3$) 159.4, 142.3, 129.4, 128.4, 127.3, 125.9, 108.3, 104.0, 79.9 (2×Ph*C*HCH_2), 40.8 (2×CH_2), 18.9 (2×CH_2) and 13.9 (2×Me); *m/z* 374 (44%, M$^+$), 242 (7, M–PhCH$(CH_2)_2$Me) and 91 (100) (Found: M$^+$, 374.2253. $C_{26}H_{30}O_2$ requires *M*, 374.2245).

*(−)-(*R,R*)-1,3-Di-(indan-1-yloxy)benzene 9*

Using the general procedure, a 26% yield of the title compound was obtained after 72 h at room temperature as a pale yellow oil, $[\alpha]_D^{20}$−6.7 (*c* 1.14 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 1282, 1173 and 1143; δ_H(270 MHz; $CDCl_3$) 7.4–7.0 (9 H, m, H^5 and 2×Ar), 6.59 (2 H, m, H^4 and H^6), 6.56 (1 H, d, *J* 2.4, H^2), 5.6 (2 H, dd, *J* 6.5 and 4.3, 2×ArCH) and 3.1–2.0 (8 H, m, 2×CH_2CH_2); δ_C(67.9 MHz; $CDCl_3$) 159.7, 144.0, 141.8, 129.9, 128.8, 126.7, 125.3, 124.9, 108.0, 103.8, 81.4 (2×ArCH), 32.3 (2×CH_2) and 30.2 (2×CH_2); *m/z* 342 (1%, M$^+$), 226 (3, M–indanyl) and 117 (100) (Found: M$^+$, 342.1627. $C_{24}H_{22}O_2$ requires *M*, 342.1620).

General procedure for formylation reactions

n-Butyllithium (2.25 M solution in hexane, 1.52 mmol) was added dropwise over 15 min. to a stirred solution of the the chiral diether (1.38 mmol) and TMEDA (1.54 mmol) in Et_2O (10 cm^3) under nitrogen at 0°C. After 3 h, the reaction mixture was allowed to warm to room temperature and DMF (2.74 mmol) was added dropwise. After a further 2 h at room temperature, the reaction mixture was poured into water (10 cm^3) and extracted with Et_2O (2×20 cm^3). The combined organic extracts were washed with saturated ammonium chloride solution (20 cm^3) and then with water (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by chromatography on silica with hexane–methyl acetate as eluent gave the aldehydes.

2,6-Dibenzyloxybenzaldehyde 4

Using the general procedure, a 54% yield of the known[7,8] title compound was obtained as a pale yellow oil, δ_H(270 MHz; $CDCl_3$) 10.64 (1 H, s, CHO), 7.5–7.2 (11 H, m, H^4 and 2×Ph), 6.60 (2 H, d, *J* 8.4, H^3 and H^5) and 5.15 (4 H, s, 2×CH_2); *m/z* 318 (1%, M$^+$), 290 (2, M–CO), 227 (6, M–$PhCH_2$), 210 (15) and 91 (100, $PhCH_2$).

*(+)-(S,S)-2,6-Di-(1-phenylethyloxy)benzaldehyde **6***

Using the general procedure, a 38% yield of the title compound was obtained as a pale yellow oil, $[\alpha]_D^{20}$+251.6 (*c* 1.16 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 2853, 2762 and 1686 (C=O); δ_H(270 MHz; $CDCl_3$) 10.74 (1 H, s, CHO), 7.4–7.2 (10 H, m, 2×Ph), 7.04 (1 H, t, *J* 8.4, H^4), 6.31 (2 H, d, *J* 8.4, H^3 and H^5), 5.34 (2 H, q, *J* 6.4, 2×PhC*H*Me) and 1.65 (6 H, d, *J* 6.4, 2×Me); δ_C(67.9 MHz; $CDCl_3$) 189.5 (C=O), 160.3, 142.6, 135.0, 128.7, 127.6, 125.5, 115.9, 106.6, 77.0 (2×Ph*C*HMe) and 24.4 (2×Me); *m/z* 346 (1%, M^+), 242 (3, M–PhCHMe) and 105 (100, PhCHMe) (Found: M^+, 346.1554. $C_{23}H_{22}O_3$ requires *M*, 346.1569).

*(−)-(R,R)-2,6-Di-(1-phenylbutyloxy)benzaldehyde **8***

Using the general procedure, a 75% yield of the title compound was obtained as a yellow oil, $[\alpha]_D^{20}$−223.2 (*c* 1.06 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2866, 2779 and 1690 (C=O); δ_H(270 MHz; $CDCl_3$) 10.78 (1 H, s, CHO), 7.4–7.2 (10 H, m, 2×Ph), 6.99 (1 H, t, *J* 8.7, H^4), 6.25 (2 H, d, *J* 8.7, H^3 and H^5), 5.15 (2 H, dd, *J* 7.5 and 5.2, 2×PhC*H*CH_2), 2.1–2.0 (2 H, m, 2×CH_AH_B), 1.9–1.7 (2 H, m, 2×CH_AH_B), 1.6–1.3 (4 H, m, 2×CH_2) and 0.93 (6 H, t, *J* 7.3, 2×Me); δ_C(67.9 MHz; $CDCl_3$) 189.3 (C=O), 160.5, 141.5, 134.9, 128.6, 127.5, 125.9, 115.0, 106.2, 80.6 (2×Ph*C*HCH_2), 40.6 (2×CH_2), 18.8 (2×CH_2) and 13.9 (2×Me); *m/z* 402 (23%, M^+), 374 (5, M–CO), 227 (21, M–$(CH_2)_2$Me) and 91 (100) (Found: M^+, 402.2199. $C_{27}H_{30}O_3$ requires *M*, 402.2194).

*(+)-(R,R)-2,6-Di-(indan-1-yloxy)benzaldehyde **10***

Using the general procedure, a 30% yield of the title compound was obtained as a green–yellow oil, $[\alpha]_D^{20}$+92.2 (*c* 1.34 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 2844, 2773 and 1690 (C=O); δ_H(270 MHz; $CDCl_3$) 10.38 (1 H, s, CHO), 7.5 (1 H, d, *J* 8.4, H^4), 7.4–7.0 (8 H, m, 2×Ar), 6.81 (2 H, d, *J* 8.4, H^3 and H^5), 5.82 (2 H, dd, *J* 6.4 and 4.9, 2×C*H*CH_2), 3.16 (2 H, ddd, *J* 16.1, 8.7 and 4.9, 2×ArCH_AH_B), 2.94 (2 H, ddd, *J* 16.1, 8.7 and 6.4, 2×ArCH_AH_B), 2.64 (2 H, m, 2×CH_AH_BCH) and 2.38 (2 H, m, 2×CH_AH_BCH); δ_C(67.9 MHz; $CDCl_3$) 189.3 (C=O), 161.1, 143.7, 141.2, 135.1, 128.9, 126.7, 125.3, 124.9, 118.0, 107.3, 83.2 (2×CHO), 32.8 (2×CH_2) and 30.2 (2×CH_2); *m/z* 382 (5%, M^+), 354 (2, M–CO) and 117 (100) (Found: M^+, 370.1572. $C_{25}H_{22}O_3$ requires *M*, 3470.1569).

Acknowledgements

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9. Lindsey has described the use of a triple Mitsunobu reaction with 2,4,6-trihydroxybenzaldehyde and benzyl alcohol in the preparation of a related aldehyde (see Wagner *et al.*[8]).

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11. Current Aldrich Chemical Company Limited prices: Resorcinol, £15.80 per 100 g; 2,6-dihydroxybenzoic acid, £35.10 per 100 g; 2,6-dimethoxybenzaldehyde, £200.30 per 100 g.
12. Benzyl alcohol cannot of course undergo elimination.
13. The Mitsunobu reactions presented in Table 1 have been repeated using *racemic* chiral alcohols. In each case, a 1:1 mixture of racemic C_2 symmetric and *meso*-diethers were formed in essentially the same yields as those reported in the Table. The diasteroisomeric diethers co-eluted during chromatography but had visibly different ^{1}H and ^{13}C NMR spectra. Thus, if any *meso*-diethers had been formed during the Mitsunobu reactions with the enantiomerically enriched alcohols, we would have detected them. From this, we believe that the diethers and aldehydes described in this paper have ≥96% ee (the detection limits of NMR spectroscopy).
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