

## Stereoselective Synthesis of the Dihydrobenzo[*b*]furan Segments of the Ephedradine Alkaloids

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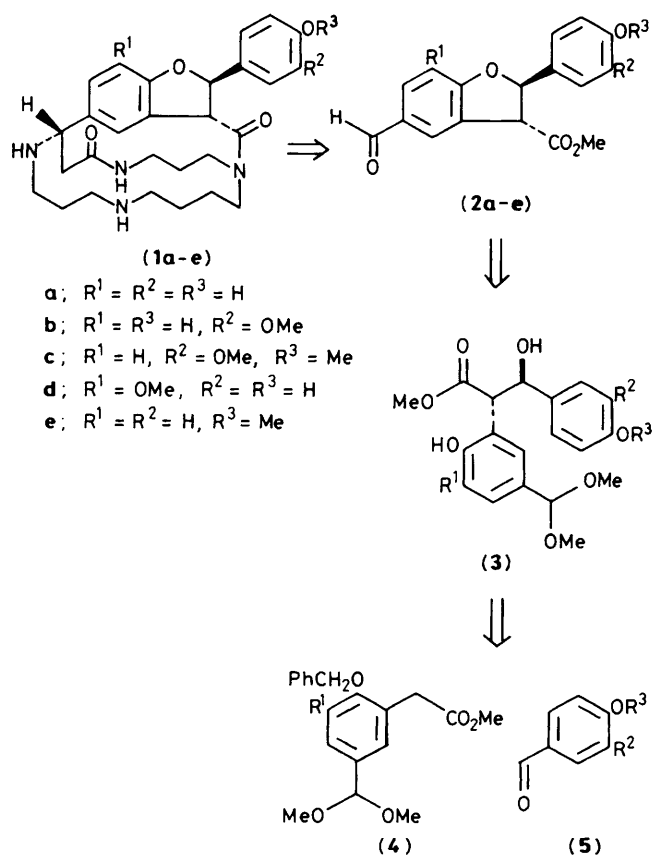
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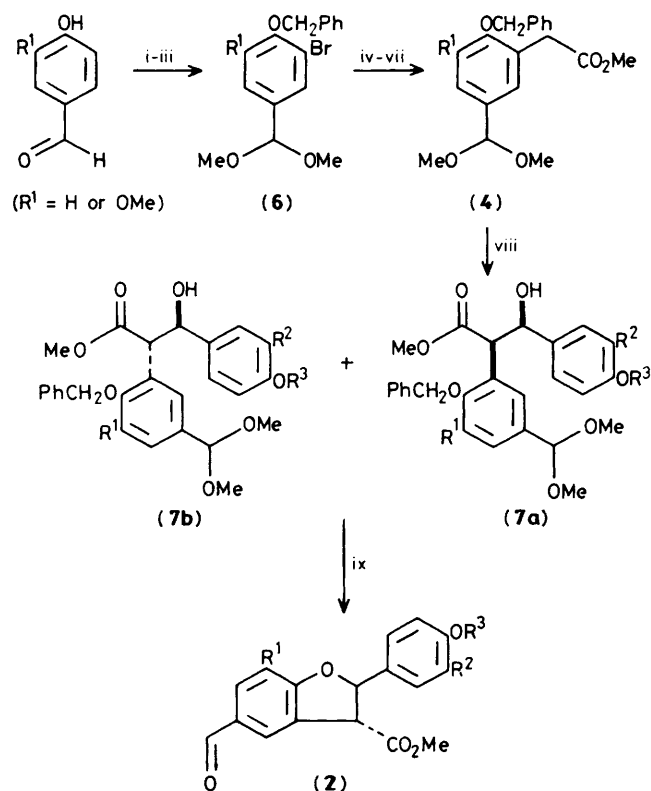
Syntheses of dihydrobenzofuran derivatives have involved formation of phenol substituted  $\beta$ -hydroxy esters by an aldol reaction followed by Lewis-acid-catalysed intramolecular cyclisation as key steps; the use of chiral oxazolidinones in the aldol reaction has formed the basis of enantiospecific syntheses.

The ephedradine alkaloids (**1a–d**), hypotensive agents from the crude drug 'mao-kon,' together with *O*-methylorantine (**1e**) are among the most complex of the macrocyclic polyamines.<sup>1</sup> Their structures and absolute configurations have been determined by Hikino *et al.*<sup>2–5</sup> and Hesse *et al.*,<sup>6</sup> and are characterised by a highly substituted dihydrobenzofuran unit which bridges a seventeen-membered lactam containing a spermine nucleus. Our retrosynthetic analysis divided the molecules into three segments, the dihydrobenzofuran derivatives (**2**), a spermine unit, and the C<sub>16</sub>–C<sub>17</sub> fragment. In this communication we report the stereoselective syntheses of the dihydrobenzo[*b*]furans (**2**). It was expected that cyclisation of  $\beta$ -hydroxy ester precursors (**3**) would afford the more thermodynamically stable *trans*-dihydrobenzofurans (**2**) and thus the key step was a simple aldol condensation between the phenylacetic ester derivatives (**4**) and the aldehydes (**5**). Only one previous report has appeared on the asymmetric synthesis of dihydrobenzofurans and this involved the oxidative dimerisation of coniferyl alcohol.<sup>7</sup> We also report the use of chiral phenylacetylides in the enantioselective syntheses of dihydrobenzo[*b*]furancarboxylic acid derivatives. The methodology described was pivotal to a projected enantiospecific approach to the ephedradine alkaloids and several other neolignan natural products.<sup>8</sup>

The five benzofuran segments required for the preparation of the ephedrines (**1a–d**) and *O*-methylorantine (**1e**) were prepared in the following way. The phenylacetic ester derivatives (**4**) were obtained in seven steps from *p*-hydroxy-



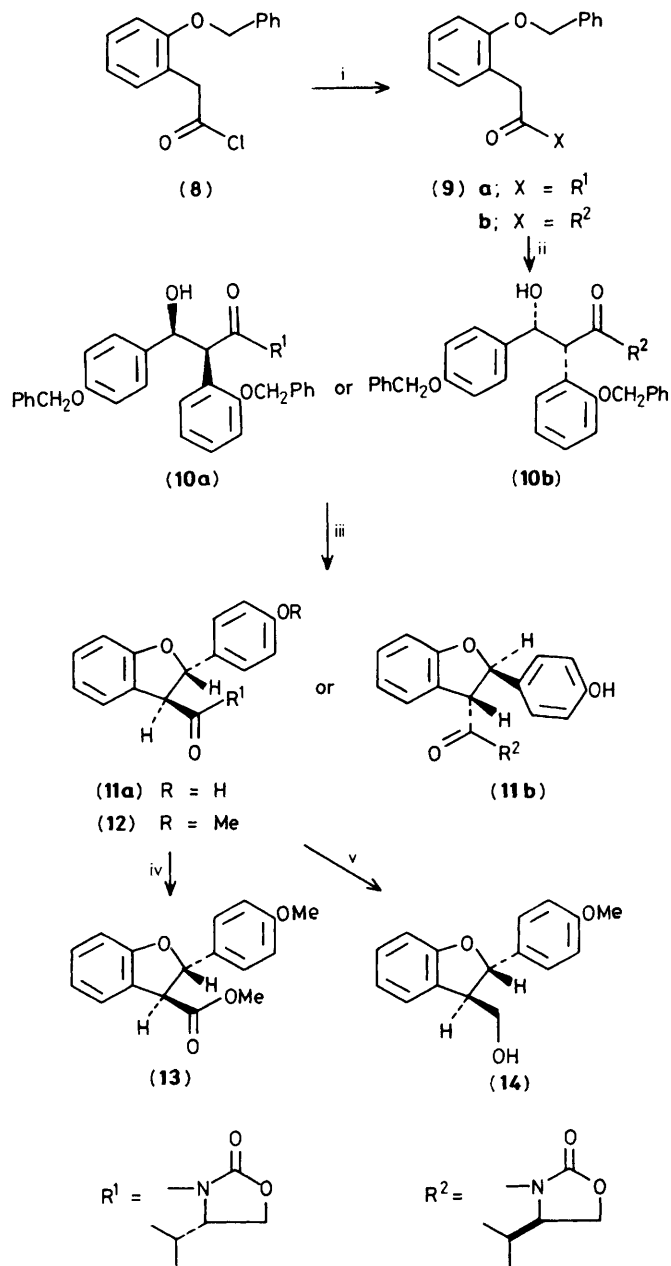
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**Scheme 1.** Reagents: i, Br<sub>2</sub>, CHCl<sub>3</sub>, 40 °C, 2 h; ii, PhCH<sub>2</sub>Br, K<sub>2</sub>CO<sub>3</sub>, DMF, 70 °C; iii, CH(OMe)<sub>3</sub>, *p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H, MeOH, reflux, 2 h; iv, Bu<sup>n</sup>Li, ether, −70 °C, 30 min, dimethylformamide (DMF), −30 °C; v, MeS(O)CH<sub>2</sub>SMe, Triton B, tetrahydrofuran (THF), reflux, 3 h; vi, HCl–MeOH, room temp., 2 d; vii, HC(OMe)<sub>3</sub>, NH<sub>4</sub>Cl, MeOH, reflux, 2 h; viii, LiNPr<sub>2</sub>, ether, −70 °C, 1 h; (5), −70 °C, 2 h; ix, H<sub>2</sub>, Pd–C, MeOH, room temp. 1–3 h; then CH<sub>2</sub>Cl<sub>2</sub>, room temp., BF<sub>3</sub>·Et<sub>2</sub>O, 1–4 h.

benzaldehyde or vanillin. Bromination<sup>9</sup> followed by protection of the phenolic hydroxy group (benzylation) and acetalisation gave the bromo acetals (6) in 85–87% yield. Formylation of (6) followed by homologation to the ester derivative (4), according to the procedure of Ogura *et al.*,<sup>10</sup> and reacetalisation gave the required ester substrates for the aldol reaction in 51–72% yield (Scheme 1). Treatment of the lithium enolates of the esters (4), in ether at −70 °C, with the aldehydes (5) gave the β-hydroxy esters (7) in 75–90% yield. The *threo*:*erythro* ratios varied from >95:5 to 75:25. Deprotection of the benzyl ethers (7) followed by treatment of methylene chloride solutions of the crude products with a catalytic quantity of boron trifluoride–ether complex gave exclusively the *trans*-dihydrobenzo[*b*]furans (2) in all cases, in 75–95% yield; *e.g.*, (2a) 95%, m.p. 146–148 °C, δ<sub>H</sub> (360 MHz; CDCl<sub>3</sub>) 3.84 (3H, s), 4.34 (1H, d, *J* 8 Hz), 6.23 (1H, d, *J* 8 Hz), 6.84 (2H, d, *J* 9 Hz), 6.98 (1H, d, *J* 8.5 Hz), 7.22 (2H, d, *J* 9 Hz), 7.80 (1H, d, *J* 8.5 Hz), 7.93 (1H, s), and 9.82 (1H, s).

Enantiospecific syntheses have also been developed by the application of enantioselective aldol reactions in the reaction sequence. The required chiral imides (9) were obtained by reaction of the acid chloride (8) with the lithio derivatives of the oxazolidinones [derived from (*S*)- and (*R*)-valine], accord-



**Scheme 2.** Reagents: i, (4*S*)- or (4*R*)-4-isopropylloxazolidin-2-one, Bu<sup>n</sup>Li, −78 °C; then (8), THF, −78 °C; ii, 9BBN triflate, Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h; then 4-benzyloxybenzaldehyde, −70 °C, 1 h followed by room temp., 2 h; iii, H<sub>2</sub>, Pd–C, MeOH, 1 atm., room temp., 2 h; then BF<sub>3</sub>·Et<sub>2</sub>O; iv, NaOMe, MeOH, 0 °C; v, LiAlH<sub>4</sub>, ether, 0 °C.

ing to the procedure of Evans *et al.*<sup>11</sup> in 95% yield (Scheme 2): (9a), colourless oil, [α]<sub>D</sub><sup>20</sup> +58.4° (*c* 1.2 in CHCl<sub>3</sub>); (9b), [α]<sub>D</sub><sup>20</sup> −51.7° (*c* 2.5 in CHCl<sub>3</sub>).

The enantioselective aldol reactions<sup>11</sup> were carried out between 4-benzyloxybenzaldehyde and the preformed 9-borabicyclo[3.3.1]nonane (9BBN) (*Z*)-enolates of the oxazolidinones (9) [(*Z*)-enolate formation: (9a) or (9b), 9BBN triflate, Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h). The aldol reactions were conducted with the (*Z*)-enolates and the aldehyde at −70 °C

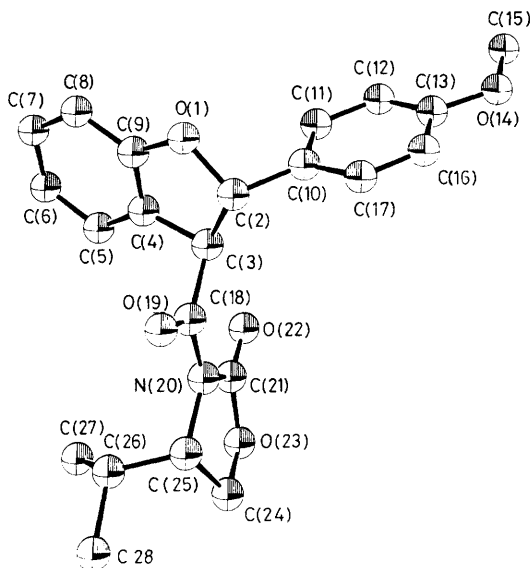


Figure 1. ORTEP diagram of (12).

for 1 h, followed by 2 h at room temperature. The reaction was worked up in the normal manner<sup>12</sup> to give the expected *erythro*-isomers (**10**), in 90–92% yield (enantiomeric excess >95%, as evidenced by 360 MHz <sup>1</sup>H and <sup>13</sup>C n.m.r.), as colourless glasses: (**10a**), [ $\alpha$ ]<sub>D</sub><sup>22</sup> –88.7° (c 0.5 in CHCl<sub>3</sub>);  $\delta_{\text{H}}$  (360 MHz; CDCl<sub>3</sub>) 0.54 (3H, d, *J* 6.6 Hz), 0.76 (3H, d, *J* 6.9 Hz), 2.23 (1H, m), 3.24 (1H, d, *J* 3.6 Hz), 3.92 (2H, m, including *J* 8.9 and 3.2 Hz), 4.25 (1H, ddd, *J* 8.9, 3.6, and 3.2 Hz), 4.81 (1H, d, *J* 12 Hz), 4.98 (1H, d, *J* 12 Hz), 4.97 (2H, s), 5.24 (1H, dd, *J* 6.6 and 3.6 Hz), 5.85 (1H, d, *J* 6.6 Hz), 6.77 (2H, d, *J* 7.5 Hz), 6.85 (1H, d, *J* 8.2 Hz), 6.93 (1H, t, *J* 7.3 Hz), 7.12 (2H, d, *J* 7.5 Hz), 7.19 (1H, t, *J* 8.1 Hz), 7.26 (1H, d, *J* 7.3 Hz), and 7.29–7.43 (10H, m); (**10b**), [ $\alpha$ ]<sub>D</sub><sup>22</sup> +80.6° (c 0.36 in CHCl<sub>3</sub>). Removal of the protecting groups from (**10a**) (H<sub>2</sub>, Pd–C, MeOH, 1 atm, room temp., 2 h) and treatment of a methylene chloride solution of the trihydroxy imide product with a catalytic quantity of boron trifluoride–ether complex gave the dihydrobenzo[*b*]furan (**11a**) as the single product<sup>13</sup> in essentially quantitative yield, as a colourless crystalline solid, m.p. 200–202 °C (from ether), [ $\alpha$ ]<sub>D</sub><sup>20</sup> +388° (c 0.2 in CHCl<sub>3</sub>);  $\delta_{\text{H}}$  (360 MHz; CDCl<sub>3</sub>) 0.87 (3H, d, *J* 6.9 Hz), 0.88 (3H, d, *J* 6.9 Hz), 2.27 (1H, d septet, *J* 6.9 and 4.2 Hz), 4.26 (1H, dd, *J* 8.9 and 3.3 Hz), 4.32 (1H, t, *J* 8.9 Hz), 4.51 (1H, m, including *J* 8.9, 4.2, and 3.3 Hz), 5.61 (1H, d, *J* 6.3 Hz), 6.18 (1H, d, *J* 6.3 Hz), 6.77 (2H, d, *J* 9 Hz), 6.89 (2H, m), and 7.20–7.35 (5H, m).

Methylation of (**11a**) (MeI, Me<sub>2</sub>CO, K<sub>2</sub>CO<sub>3</sub>) gave the methyl ether (**12**), m.p. 149–150 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> +393° (c 0.5 in CHCl<sub>3</sub>). The absolute stereochemistry of the methyl ether (**12**) was confirmed by single crystal X-ray analysis and is

shown clearly in Figure 1 to be (2'*S*,3'*S*,4*S*).<sup>‡</sup> Similar treatment of the enantiomeric  $\beta$ -hydroxy imide (**10b**) gave, after Lewis-acid-catalysed cyclisation, the dihydrobenzo[*b*]furan (**11b**), m.p. 200–201 °C (from ether), [ $\alpha$ ]<sub>D</sub><sup>20</sup> –368° (c 0.3 in CHCl<sub>3</sub>). The absolute configuration of (**11b**) was assigned as (2'*R*,3'*R*,4*R*) on the basis of its optical rotation. Removal of the chiral auxiliary group from the ether (**12**) was achieved, without detectable racemisation, to give either the carboxylic ester (**13**) {[ $\alpha$ ]<sub>D</sub><sup>22</sup> +110° (c 0.3 in CHCl<sub>3</sub>)} (NaOMe, MeOH, 0 °C) or the alcohol derivative (**14**) {[ $\alpha$ ]<sub>D</sub><sup>22</sup> +39.4° (c 0.5 in CHCl<sub>3</sub>)} (LiAlH<sub>4</sub>, ether, 0 °C).

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<sup>‡</sup> A crystal grown from methanol of dimensions 0.2 × 0.2 × 0.8 mm was mounted in air with epoxy resin at room temperature. Data were collected with a fully automated Enraf-Nonius CAD4 four-circle, kappa-geometry diffractometer, using Cu-K $\alpha$  ( $\lambda$  = 1.5418 Å) radiation at 50 kV per 20 ma ( $\omega$  scan). A total of 1571 symmetry-independent reflections were collected of which 1416 were considered observed at the level  $I \geq 3\sigma(I)$ . The unit cell parameters are  $a$  = 11.081(1),  $b$  = 30.088(8),  $c$  = 5.787(1) Å,  $\alpha$  =  $\beta$  =  $\gamma$  = 90°,  $U$  = 1929(1) Å<sup>3</sup> in the non-centrosymmetric, orthorhombic space group  $P2_12_12_1$  ( $Z$  = 4). The structure was solved by direct methods using the multiple tangent approach of MULTAN(1), a series of computer programs running on a PDP 11/60 computer. The solution was refined by full-matrix least-squares methods minimising the function  $\Sigma w(|F_o| - |F_c|)^2$  where  $w = 1/\sigma(F)^2$  to an unweighted residual index ( $R = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$ ) of 0.046. Non-hydrogen atoms were refined anisotropically; hydrogen atoms were assigned isotropic temperature factors equivalent to those of the atoms to which they are bound, and refined for positional parameter variation only. Initial hydrogen co-ordinates were calculated from idealised positions. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, see Notice to Authors, Issue No. 1.