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

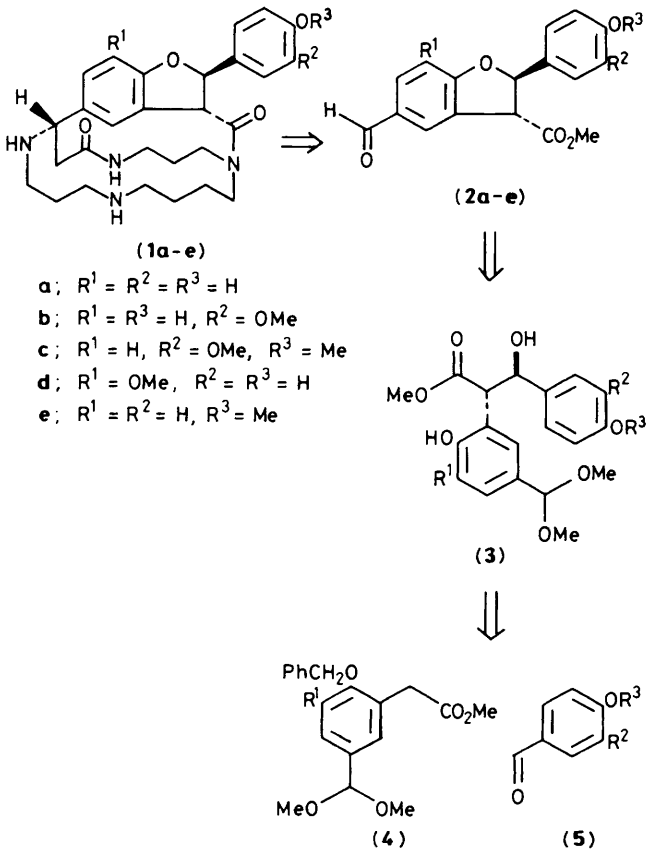
Raymond Baker,*[a]† Nigel G. Cooke,[a] Guy R. Humphrey,[a] Stanley H. B. Wright,[b] and Jordan Hirshfield[c]

[a] *Department of Chemistry, The University, Southampton SO9 5NH, U.K.*
[b] *Organic Chemistry Department, Merck Sharp & Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, U.K.*
[c] *Merck Sharpe & Dohme Research Laboratories, Rahway, New Jersey, U.S.A.*

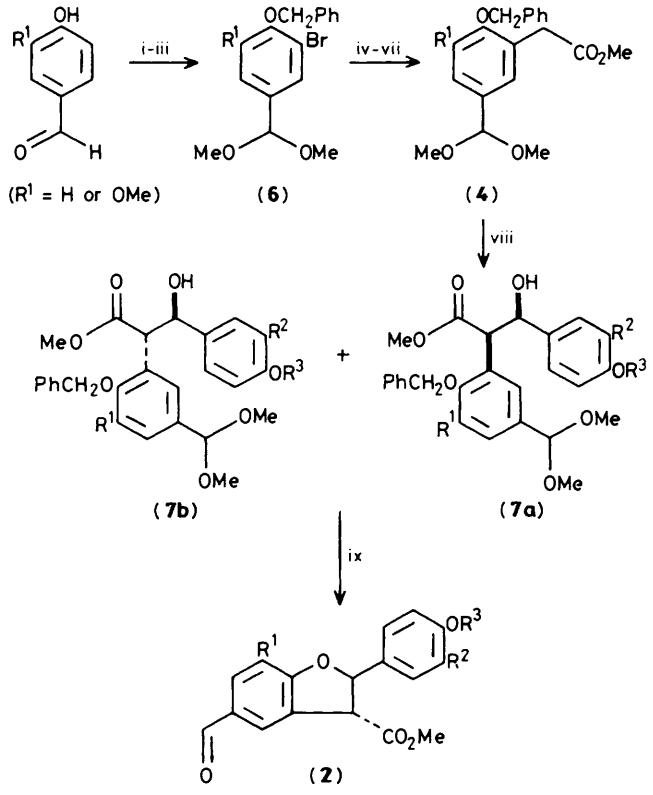
Syntheses of dihydrobenzofuran derivatives have involved formation of phenol subsituted β-hydroxy esters by an aldol reaction followed by Lewis-acid-catalysed intramolecular cyclisation as key steps; the use of chiral oxazolidinones in the aldol reaction has formed the basis of enantiospecific syntheses.

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.[1] Their structures and absolute configurations have been determined by Hikino *et al.*[2—5] and Hesse *et al.*,[6] 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_{16}–C_{17} fragment. In this communication we report the stereoselective syntheses of the dihydrobenzo[*b*]furans (**2**). It was expected that cyclisation of β-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.[7] We also report the use of chiral phenylacetylimides 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.[8]

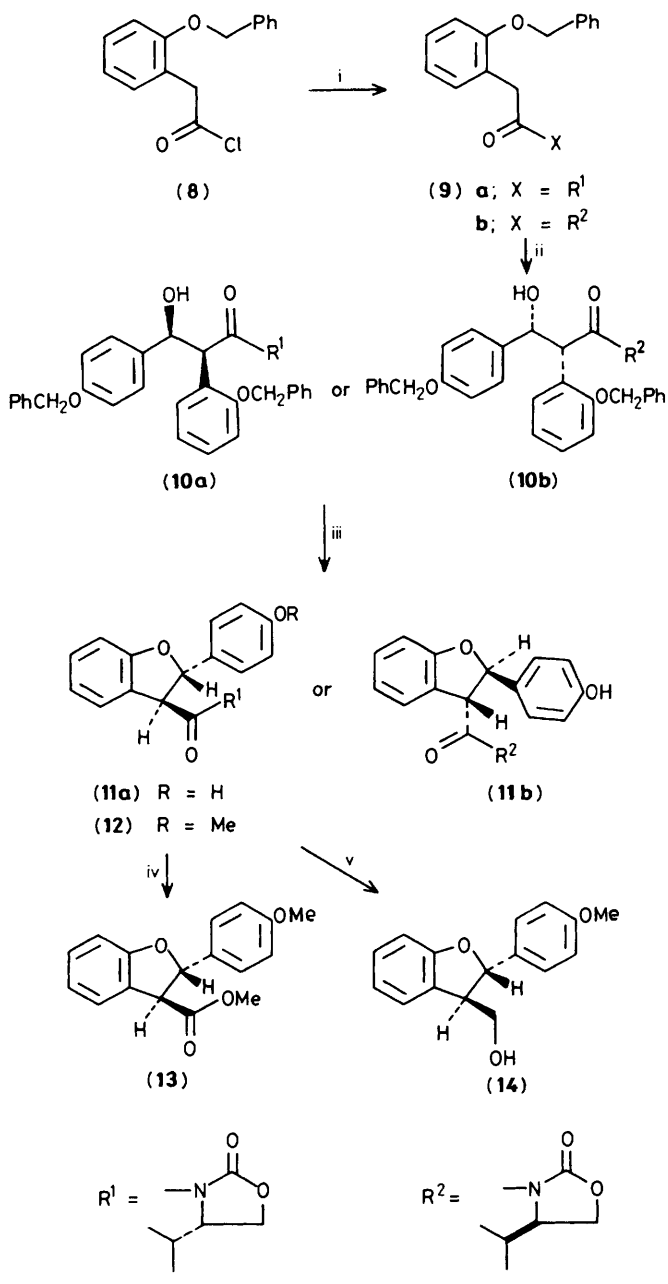
The five benzofuran segments required for the preparation of the ephedradines (**1a—d**) and *O*-methylorantine (**1e**) were prepared in the following way. The phenylacetic ester derivatives (**4**) were obtained in seven steps from *p*-hydroxy-



† *Present address:* Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K.



Scheme 1. *Reagents:* i, Br_2, $CHCl_3$, 40 °C, 2 h; ii, $PhCH_2Br$, K_2CO_3, DMF, 70 °C; iii, $CH(OMe)_3$, *p*-$CH_3C_6H_4SO_3H$, MeOH, reflux, 2 h; iv, Bu^nLi, ether, −70 °C, 30 min, dimethylformamide (DMF), −30 °C; v, $MeS(O)CH_2SMe$, Triton B, tetrahydrofuran (THF), reflux, 3 h; vi, HCl–MeOH, room temp., 2 d; vii, $HC(OMe)_3$, NH_4Cl, MeOH, reflux, 2 h; viii, $LiNPr^i_2$, ether, −70 °C, 1 h; (**5**), −70 °C, 2 h; ix, H_2, Pd–C, MeOH, room temp. 1—3 h; then CH_2Cl_2, room temp., $BF_3{\cdot}Et_2O$, 1—4 h.



Scheme 2. Reagents: i, (4*S*)- or (4*R*)-4-isopropyloxazolidin-2-one, Bu^nLi, −78 °C; then (**8**), THF, −78 °C; ii, 9BBN triflate, Pr^i_2NEt, CH_2Cl_2, 0 °C, 1 h; then 4-benzyloxybenzaldehyde, −70 °C, 1 h followed by room temp., 2 h; iii, H_2, Pd–C, MeOH, 1 atm., room temp., 2 h; then $BF_3{\cdot}Et_2O$; iv, NaOMe, MeOH, 0 °C; v, $LiAlH_4$, ether, 0 °C.

benzaldehyde or vanillin. Bromination[9] 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.*,[10] 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_H (360 MHz; $CDCl_3$) 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], according to the procedure of Evans *et al.*[11] in 95% yield (Scheme 2): (**9a**), colourless oil, $[\alpha]_D^{20}$ +58.4° (*c* 1.2 in $CHCl_3$); (**9b**), $[\alpha]_D^{20}$ −51.7° (*c* 2.5 in $CHCl_3$).

The enantioselective aldol reactions[11] 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^i_2NEt, CH_2Cl_2, 0 °C, 1 h). The aldol reactions were conducted with the (*Z*)-enolates and the aldehyde at −70 °C

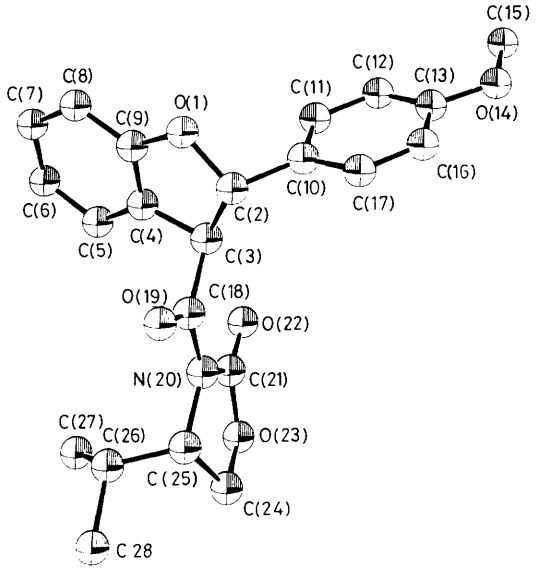


Figure 1. ORTEP diagram of (**12**).

for 1 h, followed by 2 h at room temperature. The reaction was worked up in the normal manner[12] to give the expected *erythro*-isomers (**10**), in 90–92% yield (enantiomeric excess >95%, as evidenced by 360 MHz ^{1}H and ^{13}C n.m.r.), as colourless glasses: (**10a**), $[\alpha]_D^{22}$ −88.7° (*c* 0.5 in $CHCl_3$); δ_H (360 MHz; $CDCl_3$) 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**), $[\alpha]_D^{22}$ +80.6° (*c* 0.36 in $CHCl_3$). Removal of the protecting groups from (**10a**) (H_2, 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[13] in essentially quantitative yield, as a colourless crystalline solid, m.p. 200—202 °C (from ether), $[\alpha]_D^{20}$ +388° (*c* 0.2 in $CHCl_3$); δ_H (360 MHz; $CDCl_3$) 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_2CO, K_2CO_3) gave the methyl ether (**12**), m.p. 149—150 °C, $[\alpha]_D^{20}$ +393° (*c* 0.5 in $CHCl_3$). 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*).‡ Similar treatment of the enantiomeric β-hydroxy imide (**10b**) gave, after Lewis-acid-catalysed cyclisation, the dihydrobenzo[*b*]-furan (**11b**), m.p. 200—201 °C (from ether), $[\alpha]_D^{20}$ −368° (*c* 0.3 in $CHCl_3$). 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**) {$[\alpha]_D^{22}$ +110° (*c* 0.3 in $CHCl_3$)} (NaOMe, MeOH, 0 °C) or the alcohol derivative (**14**) {$[\alpha]_D^{22}$ +39.4° (*c* 0.5 in $CHCl_3$)} ($LiAlH_4$, ether, 0 °C).

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‡ 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_α (λ = 1.5418 Å) radiation at 50 kV per 20 ma (ω 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^3 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 $\Sigma\omega(|F_o| - |F_c|)^2$ where $\omega = 1/\sigma(F)^2$ 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.