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TETRAHEDRON: *ASYMMETRY*

Enantioselective acylation of 2-hydroxymethyl-2,3-dihydrobenzofurans catalysed by lipase from *Pseudomonas cepacia* (Amano PS) and total stereoselective synthesis of (−)-(*R*)-MEM-protected arthrographol

S. Ramadas and G. L. David Krupadanam*

Department of Chemistry, Osmania University, Hyderabad 500 007, India

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Abstract

Lipase Amano PS catalysed acylation of (±)-2-hydroxymethyl-2,3-dihydrobenzofurans using vinyl acetate as the acyl donor in *n*-hexane gave (−)-(*R*)-2-acetoxymethyl-2,3-dihydrobenzofurans and (+)-(*S*)-2-hydroxymethyl-2,3-dihydrobenzofurans in high enantiomeric excess. (−)-(*R*)-Acetate **18j** is converted to (−)-(*R*)-MEM-protected arthrographol **22**. © 2000 Published by Elsevier Science Ltd.

1. Introduction

Substituted 2-hydroxymethyl-2,3-dihydrobenzofurans are an important class of naturally occurring oxygen heterocycles.[1–6] Natural dihydrobenzofurans are homochiral.[7–10] Enzymes have simplified the route to homochiral compounds which have value as drugs, synthetic intermediates and chiral auxiliaries.[11] Among the enzymes, lipases have been more extensively investigated as catalysts for either enantioselective acylation of racemic primary and secondary alcohols or enantioselective hydrolysis of racemic primary or secondary esters.[11]

(−)-(*R*)-Arthrographol **1** was almost simultaneously reported by two research groups, Pfefferle et al.[12] and Ayer et al.,[13] from *Aspergillus oryzae* and *Arthographis pinicola*, respectively. It was designated as (−)-(*R*)-asperfuran by Pfefferle et al., and (−)-(*R*)-arthrographol by Ayer et al. Compound **1** is reported to possess antifungal and chitin synthase inhibitor action.[12] Its structure was determined by ^{1}H NMR, ^{13}C NMR and MS spectral data and the absolute configuration was determined as (*R*) by CD spectra by correlation with (−)-(*R*)-tremetone **2**,

* Corresponding author. Tel: +91-40-7017336; fax: +91-40-3704926; e-mail: davidkrupa@hotmail.com

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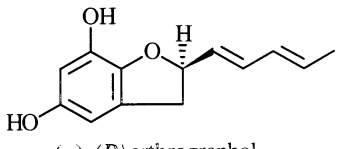
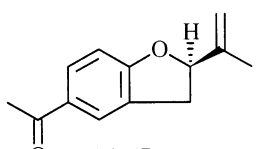
whose absolute configuration was determined by its degradation to (−)-(*R*)-malic acid.[14] The synthesis of (±)-arthrographol has been reported by Fujimoto et al.[15] Stereoselective synthesis of some chiral dihydrobenzofurans has been reported.[16–19] There are no reports in the literature of enzyme mediated resolution of 2-hydroxymethyl-2,3-dihydrobenzofurans.



(−)-(*R*)-arthrographol

1



(−)-(*R*)-tremetone

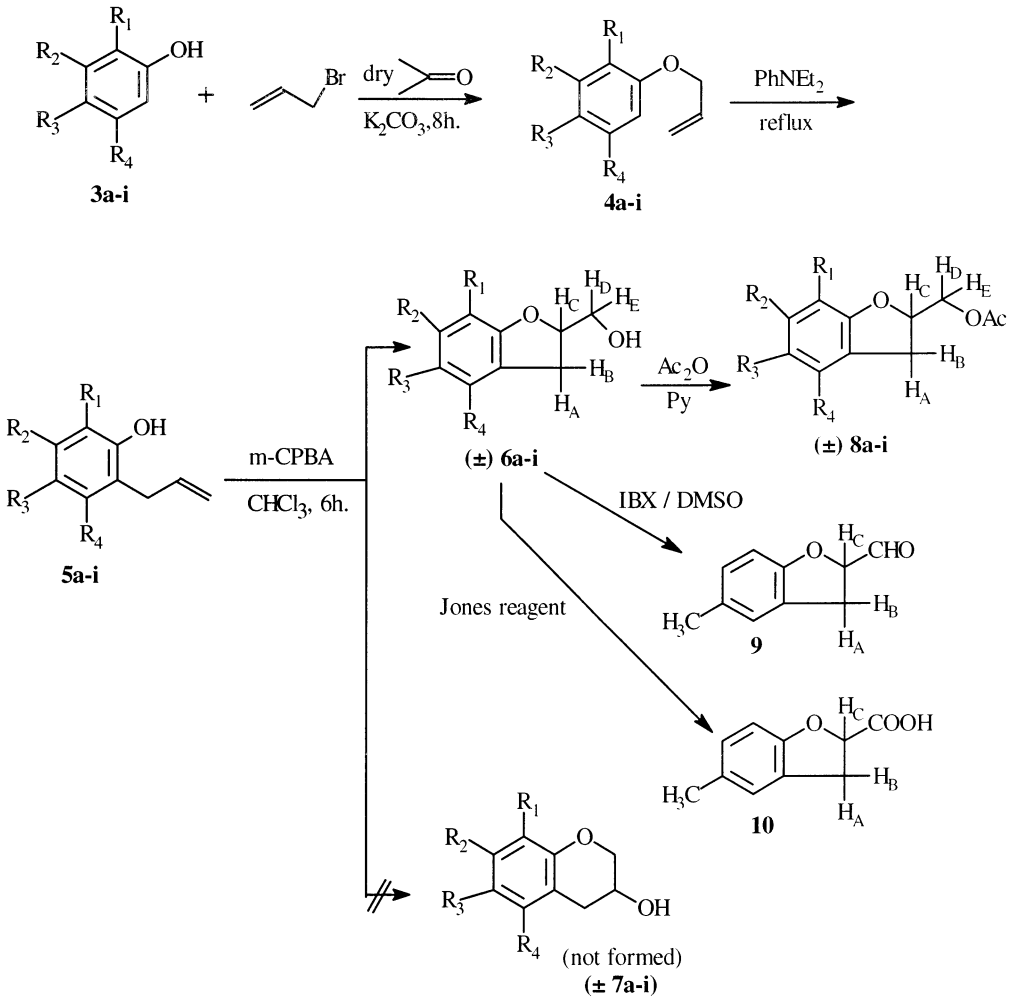
2

This paper reports the facile kinetic resolution by enantioselective acylation of unsubstituted and substituted (±)-2-hydroxymethyl-2,3-dihydrobenzofurans **6a–j** with the lipase from *Pseudomonas cepacia* (Amano PS) to give (−)-(*R*)-2-acetoxymethyl-2,3-dihydrobenzofurans **18a–j** and (+)-(*S*)-2-hydroxymethyl-2,3-dihydrobenzofurans **19a–j**. One of these compounds, (−)-(*R*)-5,7-dimethoxyethoxymethyloxy-2-acetoxymethyl-2,3-dihydrobenzofuran **18j**, which is obtained by the resolution of (±)-**6j**, is converted to (−)-(*R*)-MEM-protected arthrographol using reactions that do not affect the C-2 stereogenic centre.

2. Results and discussion

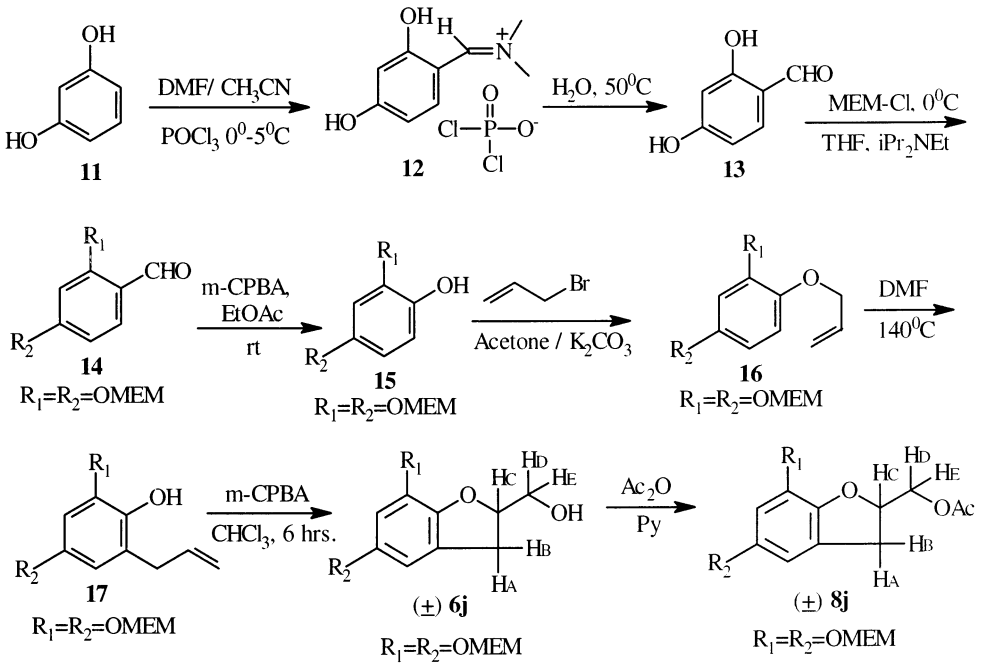
Phenols **3a–i** gave the corresponding *O*-allylethers **4a–i**[20,21] on reaction with allyl bromide in acetone–K_2CO_3. These gave the corresponding *O*-allylphenols **5a–i**[21,22] after a Claisen rearrangement in *N*,*N*-diethylaniline. Epoxidation of **5a–i** with *m*-CPBA followed by intramolecular epoxide opening by the phenolic hydroxyl gave the 2-hydroxymethyl-2,3-dihydrobenzofurans **6a–i** rather than the isomeric 3-hydroxychromans **7a–i**. The structure of the reaction products **6a–i** was proved by IBX/DMSO oxidation of **6a** to **9** and Jones oxidation of **6a** to **10** (Scheme 1).

In the ^{1}H NMR spectrum of **6a** the benzylic 3-CH_2 protons which are diastereotopic in nature appeared as an ABq×2. One of these methylene protons (H_A) appeared as a double doublet at δ 2.87 (J=16.0, 8.0 Hz) and the other (H_B) appeared as a double doublet at δ 3.08 (J=16.0, 10.0 Hz). The methylene protons of the CH_2OH group are also diastereotopic in nature and appeared as an ABq×2. One of these methylene protons (H_D) appeared as a double doublet at δ 3.60 (J=16.0, 6.0 Hz) and the other (H_E) appeared at δ 3.70 as a double doublet (J=16.0, 4.0 Hz). The methine proton (H_C) at the 2-position appeared as a complex multiplet at δ 4.75. The aromatic protons H-7 appeared at δ 6.52 as a doublet (J=10.0 Hz), H-6 at δ 6.78 as a double doublet (J=10.0, 2.0 Hz), and H-4 at δ 6.85 as a broad singlet. The CH_3 appeared at δ 2.20. The ^{13}C NMR spectrum of **6a** supported this structure. The CH_2OH appeared at δ 64.2, C-2 at δ 82.8 and the C-3 benzylic carbon appeared at δ 31.0. The aromatic carbons appeared at δ 129.3 (C-3a), 126.1 (C-5), 125.2 (C-4), 127.8 (C-6), 108.5 (C-7), 156.7 (C-7a) and 20.3 (CH_3), respectively. These values are in agreement with the values reported earlier for some natural dihydrobenzofurans.[3,12,23,24] Compound **6a** showed M at m/z 164 (85) and a base peak at 133 (100) due to the loss of CH_2OH from the molecular ion.



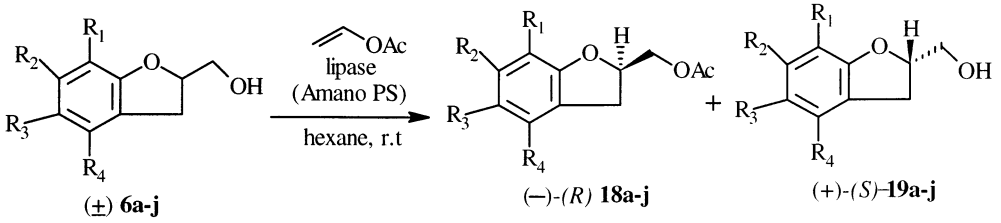
Scheme 1. (a) $R^1=R^2=R^4=H$, $R^3=CH_3$; (b) $R^1=R^2=R^3=R^4=H$; (c) $R^1=R^2=R^4=H$, $R^3=Cl$; (d) $R^1=R^2=R^4=H$, $R^3=OCH_3$; (e) $R^1=R^3=R^4=H$, $R^2=Cl$; (f) $R^1=R^2=R^3=H$, $R^4=Br$; (g) $R^1=R^2=R^3=H$, $R^4=CH_3$; (h) $R^2=R^3=R^4=H$, $R^1=Cl$; (i) $R^2=R^3=R^4=H$, $R^1=CH_3$

Alcohol (±)-**6j** was prepared from resorcinol **11** in six steps: (1) resorcinol in dry DMF/$POCl_3$ in CH_3CN gave **13**,[25] (2) treatment of 2,4-dihydroxybenzaldehyde **13** with MEM-Cl, $^iPr_2NEt$ gave 2,4-dimethoxyethoxymethyloxybenzaldehyde **14**, (3) Baeyer–Villiger oxidation with *m*-CPBA gave the MEM-protected phenol **15**, (4) allylation of **15** with allyl bromide in acetone K_2CO_3 gave the MEM-protected *O*-allylether **16**, (5) Claisen rearrangement of **16** with DMF at 140°C gave the MEM-protected *O*-allylphenol **17**, and (6) oxidative cyclisation of **17** with *m*-CPBA gave (±)-5,7-dimethoxyethoxymethyloxy-2-hydroxymethyl-2,3-dihydrobenzofuran **6j** (Scheme 2).



Scheme 2.

To monitor the enzyme mediated acylation of (±)-**6a–j** these compounds were acetylated with acetic anhydride and pyridine to give (±)-**8a–j**. *Pseudomonas cepacia* lipase (Amano PS) catalysed acylation of racemic 2-hydroxymethyl-2,3-dihydrobenzofurans (±)-**6a–j** was carried out with vinyl acetate as the acyl donor in *n*-hexane at rt and the progress of the reaction was monitored by TLC (Scheme 3). The reaction was terminated at or close to 50% conversion, the enzyme filtered off and the product containing 2-hydroxymethyl-2,3-dihydrobenzofuran and its acetate was separated by column chromatography on silica gel. The ee values of the product acetates **18a–j** and alcohols **19a–j** were determined by chiral HPLC (Table 1).



Scheme 3. (a) $R^1=R^2=R^4=H$, $R^3=CH_3$; (b) $R^1=R^2=R^3=R^4=H$; (c) $R^1=R^2=R^4=H$, $R^3=Cl$; (d) $R^1=R^2=R^4=H$, $R^3=OCH_3$; (e) $R^1=R^3=R^4=H$, $R^2=Cl$; (f) $R^1=R^2=R^3=H$, $R^4=Br$; (g) $R^1=R^2=R^3=H$, $R^4=CH_3$; (h) $R^2=R^3=R^4=H$, $R^1=Cl$; (i) $R^2=R^3=R^4=H$, $R^1=CH_3$; (j) $R^2=R^4=H$, $R^1=R^3=OMEM$

The resolved acetate **18a** showed a specific rotation of $[\alpha]_D=-19.21$ (*c* 1.0, $CHCl_3$). The CD spectrum of **18a** showed a negative Cotton effect with maxima at 237 nm ($\theta=-12.42\times10^{-3}$ deg cm^2 dmol^{-1}) and 287 nm ($\theta=-5.93\times10^{-3}$ deg cm^2 dmol^{-1}). The resolved alcohol **19a** showed a specific rotation $[\alpha]_D=+21.00$ (*c* 1.0, $CHCl_3$). The CD spectrum of **19a** showed a positive Cotton effect with maxima at 238 nm ($\theta=+18.52\times10^{-3}$ deg cm^2 dmol^{-1}) and 292 nm ($\theta=+6.74\times10^{-3}$ deg

Table 1

Entry	Substrate	Reaction time (h)	(−)-(*R*)-Acetates **18a–j**			(+)-(*S*)-Alcohols **19a–j**		
			Yield (%)	$[\alpha]_D$	% ee	Yield (%)	$[\alpha]_D$	% ee
1	(±)-**6a**	4	50	−19.2 (*c* 1.0, $CHCl_3$)	94.5	50	+21.0 (*c* 1.0, $CHCl_3$)	93.9
2	(±)-**6b**	3	50	−15.4 (*c* 0.5, $CHCl_3$)	59.5	50	+17.2 (*c* 0.5, $CHCl_3$)	81.8
3	(±)-**6c**	4	50	−21.1 (*c* 1.0, $CHCl_3$)	69.1	50	+18.45 (*c* 1.0, $CHCl_3$)	97.9
4	(±)-**6d**	3	50	−14.6 (*c* 0.5, $CHCl_3$)	95.5	50	+16.2 (*c* 1.0, $CHCl_3$)	67.6
5	(±)-**6e**	4	50	−20.15 (*c* 1.0, $CHCl_3$)	>99	50	+18.2 (*c* 1.0, $CHCl_3$)	>99
6	(±)-**6f**	3	50	−12.45 (*c* 0.5, $CHCl_3$)	>99	50	+21.3 (*c* 1.0, $CHCl_3$)	89.3
7	(±)-**6g**	5	50	−14.6 (*c* 0.5, $CHCl_3$)	51.5	50	+16.2 (*c* 1.0, $CHCl_3$)	25.2
8	(±)-**6h**	4	50	−21.2 (*c* 0.5, $CHCl_3$)	>99	50	+17.3 (*c* 0.5, $CHCl_3$)	93.8
9	(±)-**6i**	4	50	−22.1 (*c* 0.5, $CHCl_3$)	59.5	50	+15.5 (*c* 0.5, $CHCl_3$)	87.8
10	(±)-**6j**	12	50	−22.7 (*c* 1.05, $CHCl_3$)	93.4	50	+18.0 (*c* 1.0, $CHCl_3$)	81.1

$cm^2\ dmol^{-1}$). The CD spectra of **18a** and **19a** are shown in Fig. 1. The acetates **18b–j** showed negative Cotton effect bands similar to those of **18a** while the alcohols **19b–j** displayed positive Cotton effects similar to those of **19a** (Table 2). The resolved acetates **18a–j** are considered to be (*R*) while the 2-hydroxymethyl-2,3-dihydrobenzofurans **19a–j** are of (*S*) configuration. In this reaction the (*R*)-enantiomer was considered to be reactive and therefore underwent acetylation while the (*S*)-enantiomer was less reactive or unreactive.

3. Absolute configuration of the resolved acetates 18a–j and alcohols 19a–j

The active site model for the enantioselective acetylation of chiral primary alcohols without an oxygen atom attached directly to the asymmetric centre has been proposed by Alexandra et al.[26] According to this model the (*S*)-enantiomer is acylated selectively while the (*R*)-enantiomer is unreactive. However there is opposite stereoselectivity in the case of chiral primary alcohols with an oxygen atom attached directly to the stereogenic centre.[27–31] Alexandra et al.,[26] Carrea et al.,[27] Xie et al.,[28] Schieweek et al.,[29] and Kazlauskas[30,31] studied the kinetic resolution of chiral primary alcohols with an oxygen atom attached to the stereogenic centre using *Pseudomonas cepacia* lipase and observed that the (*R*)-enantiomer is selectively acetylated. This reversal was attributed to the hydrogen bonding between Tyr-29 and the substrate bearing oxygen at the stereocentre.[30,31]

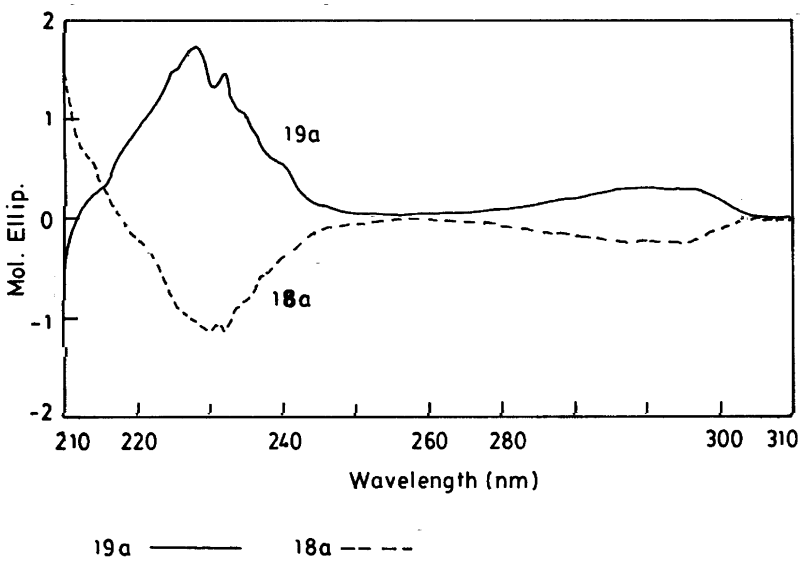


Figure 1. CD spectra of (–)-(*R*)-**18a** and (+)-(*S*)-**19a** in MeCN

In the case of enantioselective acetylation of chiral 2-hydroxymethyl-2,3-dihydrobenzofurans **6a–j**, which have an oxygen atom attached to the stereogenic centre, the (*R*)-enantiomer is reactive and the (*S*)-enantiomer is unreactive or less reactive, the products of the reaction are (–)-(*R*)-acetates **18a–j** and (+)-(*S*)-alcohols **19a–j**, which is in agreement with literature data.[27–31] Further proof that (*R*) is the reactive enantiomer is also provided by evidence in the following three sections, i.e. Section 3.1—molecular modelling studies, Section 3.2—comparison of the specific rotation of **18a–j** and **19a–j** with structurally similar compounds of known absolute configuration and a comparison of the CD data and CD curves of **18a–j** and **19a–j** with structurally similar compounds of known absolute configuration, and Section 3.3—transformation of (–)-(*R*)-5,7-dimethoxyethoxymethyloxy-2-acetoxymethyl-2,3-dihydrobenzofuran **18j** to (–)-(*R*)-MEM-protected arthrographol using reactions that do not change the configuration at C-2.

3.1. Molecular modelling studies

Docking studies were carried out on the lipase enzyme (pdb code: 3lip.pdb) with both enantiomers of 2-hydroxymethyl-2,3-dihydrobenzofuran using the *ligand fit* module of the CERIUS2 program suite. Initially, the ligand protein surface was searched for a possible active site with the default values of probe group radius of 1.3 Å that generated the grid. This generated the active site near to the Ser-87 as observed experimentally. This is followed by a Monto Carlo simulation of the ligand in the most possible active site near the Ser-87. This simulation generated a number of conformations of the ligand at the active site and this exercise was necessary because the bioactive conformation differed from the most stable conformation and there was a need to generate the bioactive conformation. Usually the best of the conformations generated was regarded as the bioactive conformation as a number of amino acid residues of the protein interact well with the ligand at the active site. This revealed that the orientation of the two enantiomers was different at the active site. In the (*R*)-isomer, the Ser-87 hydroxyl group was a distance of 2.64 Å from the hydroxyl of the ligand and this distance

Table 2
CD spectral data of **18a–j** and **19a–j**

Entry	Comp. no.	Acetates	θ (deg cm^2 dmol^{-1})	Comp. no.	Alcohols	θ (deg cm^2 dmol^{-1})
1	**18a**	(*R*)	(−) 237 nm, (−) 12.42×10^{-3} (−) 287 nm, (−) 5.93×10^{-3}	**19a**	(*S*)	(+) 238 nm, (+) 18.52×10^{-3} (+) 292 nm, (+) 6.74×10^{-3}
2	**18b**	(*R*)	(−) 227 nm, (−) 1.53×10^{-3} (−) 291 nm, (−) 0.57×10^{-3}	**19b**	(*S*)	(+) 230 nm, (+) 1.81×10^{-3} (+) 290 nm, (+) 0.35×10^{-3}
3	**18c**	(*R*)	(−) 230 nm, (−) 0.39×10^{-3} (−) 294 nm, (−) 0.50×10^{-3}	**19c**	(*S*)	(+) 231 nm, (+) 0.65×10^{-3} (+) 294 nm, (+) 0.31×10^{-3}
4	**18d**	(*R*)	(−) 230 nm, (−) 1.95×10^{-3} (−) 299 nm, (−) 0.95×10^{-3}	**19d**	(*S*)	(+) 231 nm, (+) 0.29×10^{-3} (+) 293 nm, (+) 0.20×10^{-3}
5	**18e**	(*R*)	(−) 233 nm, (−) 2.53×10^{-3} (−) 299 nm, (−) 2.00×10^{-3}	**19e**	(*S*)	(+) 230 nm, (+) 1.95×10^{-3} (+) 300 nm, (+) 2.14×10^{-3}
6	**18f**	(*R*)	(−) 235 nm, (−) 3.21×10^{-3} (−) 301 nm, (−) 1.75×10^{-3}	**19f**	(*S*)	(+) 225 nm, (+) 2.57×10^{-3} (+) 305 nm, (+) 2.32×10^{-3}
7	**18g**	(*R*)	(−) 235 nm, (−) 0.25×10^{-3} (−) 299 nm, (−) 0.18×10^{-3}	**19g**	(*S*)	(+) 238 nm, (+) 0.74×10^{-3} (+) 290 nm, (+) 0.25×10^{-3}
8	**18h**	(*R*)	(−) 235 nm, (−) 2.35×10^{-3} (−) 299 nm, (−) 1.52×10^{-3}	**19h**	(*S*)	(+) 220 nm, (+) 4.43×10^{-3} (+) 285 nm, (+) 3.26×10^{-3}
9	**18i**	(*R*)	(−) 231 nm, (−) 3.25×10^{-3} (−) 289 nm, (−) 2.17×10^{-3}	**19i**	(*S*)	(+) 239 nm, (+) 2.50×10^{-3} (+) 287 nm, (+) 2.20×10^{-3}
10	**18j**	(*R*)	(−) 229 nm, (+) 0.29×10^{-3} (−) 238 nm, (−) 0.28×10^{-3} (+) 280 nm, (+) 0.21×10^{-3}	**19j**	(*S*)	(+) 221 nm, (−) 0.95×10^{-3} (+) 230 nm, (+) 0.97×10^{-3} (−) 281 nm, (+) 0.35×10^{-3}

increased to 3.15 Å in the case of (*S*)-isomer. As the enzymatic action involved the interaction of serine at the active site, it was assumed that it played a significant role in the differentiation of the acylation reactivity between the two isomers and the more readily acylated (*R*)-isomer compared with the (*S*)-isomer. This observation was also in tune with the experimental observation.

3.2. Comparison of the sign and magnitude of the specific rotations and CD spectra of resolved acetates and alcohols with compounds of known absolute configuration

It is well known that for compounds which are structurally similar, similarity in sign and magnitude of the specific rotation and CD curves indicate a similarity in configuration at the stereogenic centre. (−)-(*R*)-Arthrographol **1**[12] and (−)-(*R*)-tremetone **2**[14] are structurally similar to the 2-hydroxymethyl-2,3-dihydrobenzofurans **6a–j**. The resolved acetates **18a–j** showed similar sign and magnitude of specific rotation as well as similar CD curves to those of (−)-(*R*)-arthrographol. Therefore the resolved acetates **18a–j** are of (*R*) absolute configuration by a comparison of their CD spectra and specific rotation with those of (−)-(*R*)-arthrographol and (−)-(*R*)-tremetone. The resolved alcohols **19a–j** which showed a (+) sign of specific rotation and the mirror image CD curve with respect to the resolved acetates **18a–j** are therefore of (*S*) absolute configuration (Table 3). The CD spectra of **18j** and **19j** are shown in Fig. 2.

Table 3
Specific rotation values and CD spectral data of resolved (−)-(*R*)-**18a** and (+)-(*S*)-**19a** compared with (−)-(*R*)-arthrographol **1**, (−)-(*R*)-tremetone **2**, **18j** and **19j** (see also Tables 1 and 2 for $[\alpha]_D$ and CD data)

Compound	$[\alpha]_D$	CD spectral data (nm)
(−)-(*R*)-Arthrographol **1**[12]	−20.1 (*c* 0.21, acetone)	(−) 232 nm ($\theta = -18.43 \times 10^{-3}$ deg cm^2 dmol^{-1}) (+) 260 nm ($\theta = +3.02 \times 10^{-3}$ deg cm^2 dmol^{-1}) (−) 305 nm ($\theta = -0.86 \times 10^{-3}$ deg cm^2 dmol^{-1})
(−)-(*R*)-Tremetone **2**[14]	−41.0 (*c* 1.0, $CHCl_3$)	
Resolved acetate **18a**	−19.2 (*c* 1.0, $CHCl_3$)	(−) 237 nm ($\theta = -12.42 \times 10^{-3}$ deg cm^2 dmol^{-1}) (−) 287 nm ($\theta = -5.93 \times 10^{-3}$ deg cm^2 dmol^{-1})
Resolved alcohol **19a**	+21.0 (*c* 1.0, $CHCl_3$)	(+) 238 nm ($\theta = +18.52 \times 10^{-3}$ deg cm^2 dmol^{-1}) (+) 292 nm ($\theta = +6.74 \times 10^{-3}$ deg cm^2 dmol^{-1})
Resolved acetate **18j**	−22.7 (*c* 0.5, $CHCl_3$)	(−) 229 nm ($\theta = +0.29 \times 10^{-3}$ deg cm^2 dmol^{-1}) (−) 238 nm ($\theta = -0.28 \times 10^{-3}$ deg cm^2 dmol^{-1}) (+) 280 nm ($\theta = +0.21 \times 10^{-3}$ deg cm^2 dmol^{-1})
Resolved alcohol **19j**	+18.0 (*c* 1.0, $CHCl_3$)	(+) 221 nm ($\theta = -0.95 \times 10^{-3}$ deg cm^2 dmol^{-1}) (+) 230 nm ($\theta = +0.97 \times 10^{-3}$ deg cm^2 dmol^{-1}) (−) 281 nm ($\theta = +0.35 \times 10^{-3}$ deg cm^2 dmol^{-1})

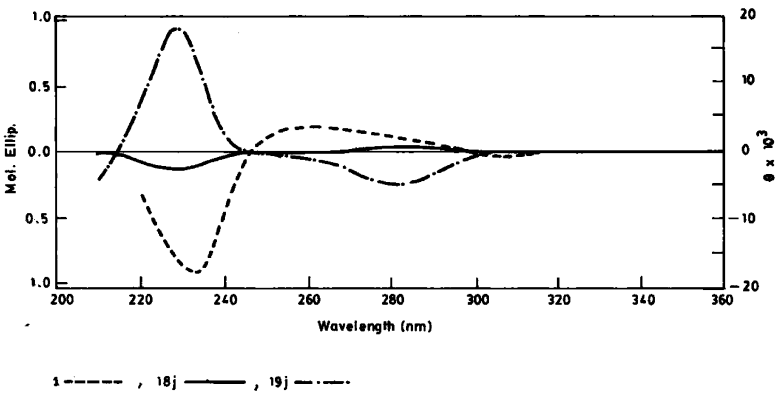
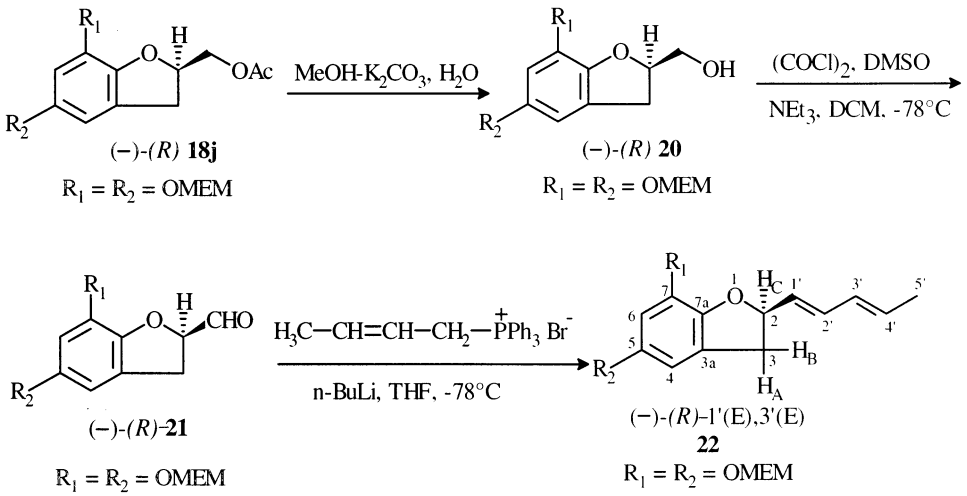


Figure 2. CD spectra of (−)-(*R*)-**18j** and (+)-(*S*)-**19j** in CH_3CN and the literature CD data of (−)-(*R*)-arthrographol **1**

*3.3. Additional proof that the absolute configuration of the resolved acetates is (*R*) is given by the conversion of one such resolved acetate, **18j**, to (−)-(*R*)-MEM-protected arthrographol **22***

Since the target molecule arthrographol **1** is of (*R*) configuration and is levorotatory with $[\alpha]_D = -20.9$ (*c* 0.21, acetone), acetate **18j** which had a specific rotation $[\alpha]_D = -22.66$ (*c* 0.5, $CHCl_3$) was used for this synthesis. The (−)-(*R*)-acetate **18j** was hydrolysed with MeOH–K_2CO_3 and H_2O to give (−)-(*R*)-alcohol **20**. Under these alkaline conditions the MEM ethers were not cleaved. (−)-(*R*)-Alcohol **20** was oxidised using Swern oxidation to the corresponding aldehyde **21**. The aldehyde **21** was used without isolation in the next step, i.e. a Wittig reaction. Crotyl triphenylphosphonium bromide was prepared by the reaction of crotyl bromide with triphenylphosphine and was added immediately to the aldehyde **21** in THF to give **22** (Scheme 4).



Scheme 4.

In the ^1H NMR spectrum of **22** the olefinic protons H-1′, H-2′, H-3′, H-4′ and the H-2 appeared as multiplets in the region δ 5.40–6.40. 5′-CH_3 appeared as a double doublet ($J = 6.0$, 1.0 Hz) at δ 1.80. The benzylic CH_2 protons appeared as an ABq×2. One of these methylene protons (H_A) appeared as a double doublet ($J = 16.0$, 8.0 Hz) at δ 2.92 and the other (H_B) appeared as a double doublet ($J = 16.0$, 6.0 Hz) at δ 3.32. The two OCH_2O protons appeared as singlets at δ 5.22 and 5.12 and the two OCH_2 protons appeared as multiplets at δ 3.52 and 3.80. The two OCH_3 protons appeared as a singlet at δ 3.32. The aromatic H-4 appeared at δ 6.55 as a doublet ($J = 2.0$ Hz) and H-6 appeared at δ 6.65 as a doublet ($J = 2.0$ Hz). In the ^{13}C NMR spectrum of **22** the olefinic carbons appeared at δ 127.5 (C-1′), 105.3 (C-2′), 126.9 (C-3′), 132.9 (C-4′) and the 5′-methyl group appeared at δ 18.2. The C-2 appeared at δ 79.3 and the C-3 benzylic carbon appeared at δ 38.9. The MEM group carbons appeared at δ 94.3 (C-5, OCH_2O), 94.9 (C-7, OCH_2O), 67.3 (C-5, OCH_2), 67.4 (C-7, OCH_2), 71.0 (C-5, CH_2O), 71.1 (C-7, CH_2O), and 59.2 (C-5, 7, OCH_3). The aromatic carbons appeared at δ 126.1 (C-3a), 108.1 (C-4), 151.9 (C-5), 132.0 (C-6), 141.2 (C-7) and 133.8 (C-7a). In the MS the molecular ion peak appeared at m/z 394 ($M^{\bullet+}$) (30) and the other fragment ions appeared at 89 (100) and 59 (98). Compound **22** showed a specific rotation $[\alpha]_D = -14.0$ (*c* 0.5, $CHCl_3$).

These studies show that in the kinetic resolution of (±)-2-hydroxymethyl-2,3-dihydrobenzofurans **6a**–**j** the (*R*)-enantiomer was acetylated selectively while the (*S*)-enantiomer was less reactive or unreactive and the resolved compounds were useful as homochiral synthetic intermediates.

4. Experimental

^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz, $CDCl_3$) spectra were recorded on a Varian Gemini 200 spectrometer and the chemical shifts are expressed in δ ppm. Optical rotations were measured on a JASCO J-20 polarimeter (cell size 50 mm) in $CHCl_3$. Mass spectra were recorded on VG micromass 7070-H and VG AUTOSPEC mass spectrometers. CD spectra were recorded on a JASCO J-715 spectropolarimeter. Progress of the acylation was monitored by TLC on silica gel ACME and column chromatography was carried out on finer than 200 mesh silica gel ACME.

The chiral HPLC of racemic (±)-**6a**–**j** was carried out on a Chiracel OD column (25×0.46 cm, Daicel, Japan) under the following conditions: flow rate 0.5 ml min^{-1}, 10% isopropanol in *n*-hexane as the eluent. The retention times (min) are (±)-**6a** 29.7 and 31.3, (±)-**6b** 11.8 and 13.1, (±)-**6c** 14.7 and 16.3, (±)-**6d** 19.1 and 20.3, (±)-**6e** 14.4 and 15.2, (±)-**6f** 24.3 and 26.0, (±)-**6g** 31.4 and 32.4, (±)-**6h** 24.6 and 26.1, (±)-**6i** 18.1 and 18.8, (±)-**6j** 26.5 and 27.8. The chiral HPLC of resolved alcohols **19a**–**j** was carried out on a Chiracel OD column (25×0.46 cm, Daicel, Japan) under the following conditions: flow rate 0.5 ml min^{-1}, 10% isopropanol in *n*-hexane as the eluent. The retention times (min) are (+)-**19a** 29.9 and 31.4, (+)-**19b** 11.9 and 13.4, (+)-**19c** 15.0 and 16.4, (+)-**19d** 19.5 and 20.6, (+)-**19e** 14.8, (+)-**19f** 25.0 and 26.1, (+)-**19g** 31.5 and 32.6, (+)-**19h** 24.7 and 26.9, (+)-**19i** 18.3 and 19.1, (+)-**19j** 27.2 and 28.5.

The chiral HPLC of racemic (±)-**8a**–**j** was carried out on a Chiracel OJ column (25×0.46 cm, Daicel, Japan) under the following conditions: flow rate 0.8 ml min^{-1}, 5% isopropanol in *n*-hexane as the eluent. The retention times (min) are (±)-**8a** 26 and 27.4, (±)-**8b** 13.0 and 15.1, (±)-**8c** 24.5 and 26.2, (±)-**8d** 21.5 and 22.8, (±)-**8e** 23.1 and 24.8, (±)-**8f** 15.2 and 16.4, (±)-**8g** 25.3 and 26.4, (±)-**8h** 18.0 and 19.5, (±)-**8i** 28.1 and 28.8, (±)-**8j** 18.6 and 19.8. The Chiral HPLC of resolved acetates **18a**–**j** was carried out on a Chiracel OJ column (25×0.46 cm, Daicel, Japan) under the following conditions: flow rate 0.8 ml min^{-1}, 5% isopropanol in *n*-hexane as the eluent. The retention times (min) are (–)-**18a** 26.5 and 27.8, (–)-**18b** 13.2 and 15.3, (–)-**18c** 25.1 and 26.5, (–)-**18d** 22.2 and 23.5, (–)-**18e** 23.4, (–)-**18f** 15.8, (–)-**18g** 25.8 and 26.7, (–)-**18h** 19.2, (–)-**18i** 28.5 and 29.2, (±)-**18j** 19.1 and 20.6.

*4.1. General procedure for the synthesis of (±)-2-hydroxymethyl-2,3-dihydrobenzofurans **6a**–**j***

4-Methyl-2-allylphenol **5a** (2.0 g, 13 mmol) and *m*-CPBA (2.2 g, 13 mmol) were dissolved in $CHCl_3$ (250 ml) and refluxed for 6 h on a water bath. After cooling to room temperature the separated *m*-chlorobenzoic acid (mp 157°C) was filtered. The filtrate was washed with aq. $NaHCO_3$ (2%) to remove traces of *m*-chlorobenzoic acid and then with water, dried and concentrated. The residue was chromatographed over silica gel by eluting with petroleum ether:ethyl acetate (9:1) and gave (±)-5-methyl-2-hydroxymethyl-2,3-dihydrobenzofuran **6a** as a colourless oil (1.5 g, 75% yield). UV (MeOH): 231 nm (log ε 3.8) and 287 nm (log ε 3.6). ^{1}H NMR: δ 2.20 (s, CH_3), 2.87 (dd, J=16.0, 8.0 Hz, CH_2-3, H_A), 3.08 (dd, J=16.0, 10.0 Hz,

CH_2-3, H_B), 3.60 (dd, $J=16.0$, 6.0 Hz, 2-CH_2–OH, H_D), 3.70 (dd, $J=16.0$, 4.0 Hz, 2-CH_2–OH, H_E), 4.75 (m, H-2, H_C), 6.52 (d, $J=10.0$ Hz, H-7), 6.78 (dd, $J=10.0$, 2.0 Hz, H-6), and 6.85 (bs, H-4). ^{13}C NMR: δ 20.3 (CH_3), 31.0 (C-3), 64.2 (CH_2OH), 82.8 (C-2), 108.5 (C-7), 125.2 (C-4), 126.1 (C-5), 127.8 (C-6), 129.3 (C-3a) and 156.7 (C-7a). FABMS: m/z (relative intensity) 164 ($M^{\bullet+}$, 85), 145 (45), 133 (100), 121 (25), 105 (70), 91 (45), 77 (40), 53 (15) and 43 (40). FABHRMS: Calc. $C_{10}H_{12}O_2$ ($M^{\bullet+}$) 164.083730, found: 164.083753.

4.1.1. (±)-2-Hydroxymethyl-2,3-dihydrobenzofuran ***6b***

UV (MeOH): 230 nm (log ε 3.7) and 280 nm (log ε 3.8). ^{1}H NMR: δ 2.55 (bs, OH), 2.98 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.20 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.70 (dd, $J=16.0$, 6.0 Hz, 2-CH_2–OH, H_D), 3.80 (dd, $J=16.0$, 4.0 Hz, 2-CH_2–OH, H_E), 4.85 (m, H-2, H_C), 6.78 (m, 2H, H-4, 7) and 7.10 (m, 2H, H-5, 6). ^{13}C NMR: δ 30.9 (C-3), 64.2 (CH_2OH), 82.8 (C-2), 109.0 (C-7), 120.2 (C-5), 124.6 (C-4), 126.2 (C-6), 127.6 (C-3a) and 158.8 (C-7a). FABMS: m/z (relative intensity) 150 ($M^{\bullet+}$, 40), 131 (40), 119 (50), 107 (20), 91 (100), 70 (20), 65 (20) and 39 (40). FABHRMS: Calc. $C_9H_{10}O_2$ ($M^{\bullet+}$) 150.068080, found: 150.068912.

4.1.2. (±)-5-Chloro-2-hydroxymethyl-2,3-dihydrobenzofuran ***6c***

UV (MeOH): 233 nm (log ε 3.6) and 284 nm (log ε 3.5). ^{1}H NMR: δ 2.13 (bs, OH), 3.04 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.22 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.72 (dd, $J=16.0$, 6.0 Hz, 2-CH_2–OH, H_D), 3.83 (dd, $J=16.0$, 4.0 Hz, 2-CH_2–OH, H_E), 4.92 (m, H-2, H_C), 6.68 (d, $J=10.0$ Hz, H-7), 7.05 (dd, $J=10.0$, 2.0 Hz, H-6) and 7.12 (d, $J=2.0$ Hz, H-4). ^{13}C NMR: δ 31.1 (C-3), 64.6 (CH_2OH), 82.9 (C-2), 109.2 (C-7), 120.5 (C-5), 124.9 (C-4), 126.4 (C-6), 127.9 (C-3a) and 159.0 (C-7a). MS: m/z (relative intensity) 184 ($M^{\bullet+}$, 80), 186 (M+2) (40), 165 (50), 153 (70), 141 (30), 125 (100), 89 (60), 77 (50), 63 (50), 51 (45) and 39 (40). FABHRMS: Calc. $C_9H_9ClO_2$ ($M^{\bullet+}$) 186.026157, found: 186.026253.

4.1.3. (±)-5-Methoxy-2-hydroxymethyl-2,3-dihydrobenzofuran ***6d***

UV (MeOH): 231 nm (log ε 3.5) and 299 nm (log ε 3.7). ^{1}H NMR: δ 2.05 (bs, OH), 2.98 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.32 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B, 3.73 (s, OCH_3), 3.75 (m, 2H, 2-CH_2–OH, H_D, H_E), 4.88 (m, H-2, H_C) and 6.70 (m, 3H, H-4, 6, 7). ^{13}C NMR: δ 31.1 (C-3), 54.3 (OCH_3), 64.6 (CH_2OH), 82.9 (C-2), 108.7 (C-7), 125.4 (C-5), 127.3 (C-6), 128.1 (C-4), 129.6 (C-3a) and 156.8 (C-7a). FABMS: m/z (relative intensity) 180 ($M^{\bullet+}$, 100), 149 (70), 136 (60), 121 (70), 91 (98). FABHRMS: Calc. $C_{10}H_{12}O_3$ ($M^{\bullet+}$) 180.078644, found: 180.079041.

4.1.4. (±)-6-Chloro-2-hydroxymethyl-2,3-dihydrobenzofuran ***6e***

UV (MeOH): 231 nm (log ε 3.6) and 278 nm (log ε 3.8). ^{1}H NMR: δ 2.36 (bs, OH), 2.97 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.18 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.78 (dd, $J=16.0$, 6.0 Hz, 2-CH_2–OH, H_D), 3.80 (dd, $J=16.0$, 4.0 Hz, 2-CH_2–OH, H_E), 4.90 (m, H-2, H_C), 6.72 (d, $J=2.0$ Hz, H-7), 6.78 (dd, $J=10.0$, 2.0 Hz, H-5) and 7.04 (d, $J=10.0$ Hz, H-4). ^{13}NMR: δ 30.7 (C-3), 64.4 (CH_2OH), 84.2 (C-2), 110.0 (C-7), 120.6 (C-5), 125.3 (C-4), 125.4 (C-6), 133.1 (C-3a) and 160.0 (C-7a). MS: m/z (relative intensity) 184 ($M^{\bullet+}$, 100), 186 (M+2) (40), 165 (50), 153 (70), 141 (40), 125 (80) and 89 (30). FABHRMS: Calc. $C_9H_9ClO_2$ ($M^{\bullet+}$) 186.035248, found: 186.035245.

4.1.5. (±)-4-Bromo-2-hydroxymethyl-2,3-dihydrobenzofuran ***6f***

UV (MeOH): 222 nm (log ε 3.7) and 285 nm (log ε 3.6). ^{1}H NMR: δ 1.95 (bs, OH), 3.04 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.25 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.73 (dd, $J=16.0$, 6.0 Hz,

2-CH_2–OH, H_D), 3.85 (dd, $J=16.0$, 4.0 Hz, 2-CH_2–OH, H_E), 4.93 (m, H-2, H_C), 6.45 (dd, $J=10.0$, 10.0 Hz, H-6), 7.13 (dd, $J=10.0$, 2.0 Hz, H-5), and 7.21 (dd, $J=10.0$, 2.0 Hz, H-7). ^{13}C NMR: δ 32.5 (C-3), 64.0 (CH_2OH), 82.4 (C-2), 107.8 (C-7), 118.8 (C-5), 123.1 (C-4), 127.5 (C-6), 129.1 (C-3a) and 159.2 (C-7a). MS: m/z (relative intensity) 228 ($M^{\bullet+}$, 40), 230 (M+2) (10), 209 (30), 197 (50), 118 (100), 89 (40), 77 (40), 51 (30) and 39 (25). FABHRMS: Calc. $C_9H_9BrO_2$ ($M^{\bullet+}$) 230.052019, found: 230.052015.

4.1.6. (±)-4-Methyl-2-hydroxymethyl-2,3-dihydrobenzofuran ***6g***

UV (MeOH): 228 nm (log ε 3.7) and 284 nm (log ε 3.6). ^1H NMR: δ 2.20 (s, CH_3), 2.86 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.08 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.65 (dd, $J=16.0$, 6.0 Hz, 2-CH_2–OH, H_D), 3.78 (dd, $J=16.0$, 4.0 Hz, 2-CH_2–OH, H_E), 4.81 (m, H-2, H_C), 6.50 (dd, $J=10.0$, 2.0 Hz, H-7), 6.58 (dd, $J=10.0$, 2.0 Hz, H-5) and 6.95 (dd, $J=10.0$, 10.0 Hz, H-6). ^{13}C NMR: δ 20.2 (CH_3), 31.9 (C-3), 64.2 (CH_2OH), 82.7 (C-2), 106.1 (C-7), 124.1 (C-5), 125.3 (C-4), 127.4 (C-6), 128.2 (C-3a) and 158.9 (C-7a). MS: m/z (relative intensity) 164 ($M^{\bullet+}$, 50), 145 (40), 133 (60), 121 (30), 105 (100) and 91 (70). FABHRMS: Calc. $C_{10}H_{12}O_2$ ($M^{\bullet+}$) 164.043723, found: 164.043763.

4.1.7. (±)-7-Chloro-2-hydroxymethyl-2,3-dihydrobenzofuran ***6h***

UV (MeOH): 225 nm (log ε 3.6) and 280 nm (log ε 3.8). ^1H NMR: δ 2.65 (bs, OH), 3.07 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.22 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.65 (dd, $J=16.0$, 6.0 Hz, 2-CH_2–OH, H_D), 3.82 (dd, $J=16.0$, 4.0 Hz, 2-CH_2–OH, H_E), 4.90 (m, H-2, H_C), 6.70 (m, H-5) and 6.97 (m, 2H, H-4, 6). ^{13}C NMR: δ 31.5 (C-3), 64.0 (CH_2OH), 83.8 (C-2), 114.4 (C-7), 123.0 (C-5), 127.9 (C-6), 128.3 (C-4), 128.4 (C-3a) and 154.9 (C-7a). FABMS: m/z (relative intensity) 184 M, 30 186 (M+2) (50), 184 (50), 165 (45), 153 (50), 141 (30), 125 (100), 112 (20), 105 (30) and 89 (70). FABHRMS: Calc. $C_9H_9ClO_2$ ($M^{\bullet+}$) 186.05 2430, found: 186.052453.

4.1.8. (±)-7-Methyl-2-hydroxymethyl-2,3-dihydrobenzofuran ***6i***

UV (MeOH): 223 nm (log ε 3.7) and 279 nm (log ε 3.6). ^1H NMR: δ 2.20 (s, CH_3), 3.03 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.22 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.73 (dd, $J=16.0$, 6.0 Hz, 2-CH_2–OH, H_D), 3.85 (dd, $J=16.0$, 4.0 Hz, 2-CH_2–OH, H_E), 4.87 (m, H-2, H_C), 6.73 (dd, $J=10.0$, 10.0 Hz, H-5), 6.90 (dd, $J=10.0$, 2.0 Hz, H-4) and 6.96 (dd, $J=10.0$, 2.0 Hz, H-6). ^{13}C NMR: δ 15.1 (CH_3), 31.5 (C-3), 64.7 (CH_2OH), 82.6 (C-2), 119.4 (C-7), 122.2 (C-5), 125.6 (C-4), 128.5 (C-6), 129.1 (C-3a) and 157.4 (C-7a). MS: m/z (relative intensity) 164 ($M^{\bullet+}$, 50), 145 (30), 133 (70), 121 (20), 105 (100) and 91 (50). FABHRMS: Calc. $C_{10}H_{12}O_2$ ($M^{\bullet+}$) 164.078762, found: 164.078793.

4.2. 5-Methyl-2,3-dihydrobenzofuran-2-carbaldehyde ***9***

THF (10 ml) was added to a solution of 2-iodoxybenzoic acid (0.50 g, 3 mmol) in dry DMSO (4 ml) **6a** (0.59 g, 3 mmol) and this solution was stirred for 1 h. The reaction was quenched by the addition of water, the precipitated solid was filtered, the filtrate was extracted with ethyl acetate and the combined extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent and purification of the crude product by column chromatography over silica gel by eluting with petroleum ether:ethyl acetate (8:2) afforded aldehyde **9** (0.4 g, 80% yield) as a colourless solid, mp 156°C. ^1H NMR: δ 2.30 (s, CH_3), 3.32 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.45 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 4.98 (m, H-2, H_C), 6.82 (d, $J=10.0$ Hz, H-7), 6.95 (m,

2H, H-4, 6) and 9.86 (s, CHO). EIMS: m/z (relative intensity) 162 ($M^{\bullet+}$) (40), 145 (18), 133 (75), 105 (100), 79 (30), 77 (40), 51 (30) and 39 (25).

4.3. 5-Methyl-2,3-dihydrobenzofuron-2-carboxylic acid **10**

A solution of chromium trioxide (1.5 g, 15 mmol) in water (5 ml) containing conc. H_2SO_4 (0.5 ml) was added over a 2 h period to a stirred solution of 5-methyl-2-hydroxymethyl-2,3-dihydrobenzofuran **6a** (1.0 g, 6 mmol) in acetone (5 ml) and this solution was then kept at 0°C for a further hour. The excess reagent was quenched with isopropanol, filtered and the filtrate was evaporated. The residue was dissolved in aq. $NaHCO_3$ solution, washed with ether and the aqueous layer was neutralised with dil. HCl, and then extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and concentrated. The residue was purified by chromatography over silica gel by eluting with petroleum ether:ethyl acetate (6:4) furnishing acid **10** (0.6 g, 60% yield), mp 176°C. ^{1}H NMR: δ 2.22 (s, CH_3), 3.32 (dd, $J=16.0$, 7.0 Hz, CH_2-3, H_A), 3.52 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 5.15 (dd, $J=10.0$, 7.0 Hz, H-2, H_C), 6.72 (d, $J=10.0$ Hz, H-7), 6.90 (m, 2H, H-4, 6) and 8.20 (bs, COOH). EIMS: m/z (relative intensity) 178 ($M^{\bullet+}$, 75), 133 (85), 105 (100), 77 (45) and 39 (45).

4.4. Synthesis of (±)-5,7-dimethoxyethoxymethyloxy-2-hydroxymethyl-2,3-dihydrobenzofuran **6j**

4.4.1. 2,4-Dihydroxybenzaldehyde **13**[25]

To a well cooled (0–5°C) solution of resorcinol **11** (22 g, 64 mmol) in acetonitrile (75 ml), dry DMF (6.3 g, 64 mmol) and freshly distilled dry $POCl_3$ (11.3 g, 73 mmol) were added with constant stirring at 0–5°C. The salt **12** that separated was filtered and was washed with cold acetonitrile. To this salt **12**, water (100 ml) was added and heated at 50°C for 0.5 h and then cooled. The solid that separated was filtered, washed with cold water, dried and chromatographed over silica gel by eluting with petroleum ether:ethyl acetate (1:1) to give 2,4-dihydroxybenzaldehyde **13** (21.5 g, 80% yield) as a white solid, mp 134°C (lit.[25] mp 134°C). UV (MeOH): 230 nm (log ε 3.5), 278 nm (log ε 3.7), 340 nm (log ε 3.4) and 347 nm (log ε 3.8). ^{1}H NMR (DMSO-d_6): δ 6.35 (d, $J=2.0$ Hz, H-2), 6.51 (dd, $J=8.0$, 2.0 Hz, H-5), 7.42 (d, $J=8.0$ Hz, H-6), 9.97 (s, CHO) and 10.44 and 11.28 (bs, OH-2, 4). ^{13}C NMR: δ 103.0 (C-3), 109.0 (C-5), 135.4 (C-6), 136.0 (C-1), 163.9 (C-2), 164.4 (C-4) and 194.6 (CHO). EIMS: m/z 138 ($M^{\bullet+}$) (80), 137 (98), 89 (10), 81 (15), 69 (18), 68 (5), 59 (30), 53 (10) and 38 (100).

4.4.2. 2,4-Dimethoxyethoxymethyloxybenzaldehyde **14**

N,*N*′-Diisopropylethylamine (23.0 g, 176.5 mmol) was added to a stirred solution of **13** (10.0 g, 72 mmol) in dry THF (100 ml), cooled to 0°C and methoxyethoxymethyl chloride (MEM-chloride) (22.0 g, 176.5 mmol) was added slowly and the solution was allowed to attain room temperature. After 2 h the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water followed by brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with petroleum ether:ethyl acetate 6:4) to give the MEM-protected derivative **14** (9.0 g, 90% yield) as a colourless oil. UV (MeOH): 209 nm (log ε 3.6), 225 nm (log ε 3.7), 273 nm (log ε 3.5) and 311 nm (log ε 3.6). ^{1}H NMR: δ 3.34 (s, $OCH_3\times2$), 3.65 (m, $OCH_2\times2$), 3.82 (m, $CH_2O\times2$), 5.30 (s, OCH_2O-4), 5.35 (s, OCH_2O-2), 6.75 (dd, $J=10.0$, 2.0 Hz, H-5), 6.85 (d, $J=2.0$ Hz, H-3), 7.78 (d, $J=10.0$ Hz, H-6) and 10.30 (s, CHO). ^{13}C NMR: δ 58.8

(C-2, 4, OCH_3), 68.0 (C-2, OCH_2), 68.1 (C-4, OCH_2), 71.3 (C-2, 4, CH_2O), 92.1 (C-2, 4, OCH_2O), 103.3 (C-3), 109.4 (C-5), 115.8 (C-1), 135.2 (C-6), 163.9 (C-4), 164.1 (C-2) and 188.1 (CHO). EIMS: m/z (relative intensity) 314 ($M^{\bullet+}$, 15), 225 (20), 165 (10) and 151 (12). Analysis found: C, 57.30; H, 7.03. $C_{15}H_{22}O_7$ requires: C, 57.32; H, 7.05%.

4.4.3. 2,4-Dimethoxyethoxymethyloxyphenol ***15***

Compound **14** (5.0 g, 16.5 mmol) was dissolved in dry ethyl acetate (50 ml) and *m*-CPBA (2.8 g, 16.5 mmol) was added and stirred for 24 h at rt and kept overnight. The separated *m*-chlorobenzoic acid (mp 157°C) was filtered. The filtrate was washed with aq. $NaHCO_3$ (2%) to remove traces of *m*-chlorobenzoic acid and then washed with water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with petroleum ether:ethyl acetate 1:1) to give phenol **15** (4.0 g, 80% yield) as a colourless oil. UV (MeOH): 201 nm (log ε 3.5), 224 nm (log ε 3.7) and 256 nm (log ε 3.6). ^{1}H NMR: δ 3.35 (s, $OCH_3\times2$), 3.55 (m, $OCH_2\times2$), 3.80 (m, $CH_2O\times2$), 5.12 (s, OCH_2O-4), 5.22 (s, OCH_2O-2), 6.58 (dd, $J=10.0$, 2.0 Hz, H-5), 6.80 (d, $J=2.0$ Hz, H-3), 6.77 (d, $J=10.0$ Hz, H-6) and 7.90 (s, OH). ^{13}C NMR: δ 58.3 (C-2, 4, OCH_3), 67.0 (C-2, OCH_2), 67.1 (C-4, OCH_2), 67.6 (C-2, CH_2O), 71.1 (C-4, CH_2O), 94.0 (C-4, OCH_2O), 94.7 (C-2, OCH_2O), 106.7 (C-3), 110.3 (C-5), 115.5 (C-6), 142.1 (C-1, OH), 144.8 (C-2) and 150.0 (C-4). EIMS: m/z (relative intensity) 302 ($M^{\bullet+}$, 10), 89 (80), 59 (100) and 45 (15). Analysis found: C, 55.60; H, 7.31. $C_{14}H_{22}O_7$ requires: C, 55.62; H, 7.33%.

4.4.4. 1-Allyloxy-2,4-dimethoxyethoxymethyloxybenzene ***16***

Compound **15** (3.75 g, 12 mmol) and allyl bromide (1.5 g, 12 mmol) were dissolved in dry acetone (150 ml) and refluxed over anhydrous K_2CO_3 (3.0 g) for 6 h on a water bath. The acetone was removed under reduced pressure and crushed ice was added to the residue. The resulting product was extracted with ether. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with petroleum ether:ethyl acetate 8:2) to give MEM-protected-1-allyoxybenzene **16** (3.15 g, 85% yield) as a colourless oil. UV (MeOH): 207 nm (log ε 3.6) and 282 nm (log ε 3.5). ^{1}H NMR: δ 3.32 (s, $OCH_3\times2$), 3.50 (m, $OCH_2\times2$), 3.80 (m, $CH_2O\times2$), 4.50 (d, $J=6.0$ Hz, OCH_2-1′), 5.12 (s, OCH_2O-4), 5.22 (s, OCH_2O-2), 5.25 (m, CH_2-3′), 6.00 (m, H-2′), 6.60 (dd, $J=10.0$, 2.0 Hz, H-5), 6.75 (d, $J=10.0$ Hz, H-6) and 6.84 (d, $J=2.0$ Hz, H-3). ^{13}C NMR: δ 58.4 (C-2, 4 $OCH_3\times2$), 67.1 (C-4, OCH_2), 67.2 (C-2, OCH_2), 69.5 (C-1′), 70.3 (C-2, 4, CH_2O), 94.3 (C-2, OCH_2O), 107.2 (C-3), 109.2 (C-5), 115.0 (C-6), 117.0 (C-3′), 133.3 (C-2′), 143.8 (C-1), 147.3 (C-2) and 151.6 (C-4). EIMS: m/z (relative intensity) 342 ($M^{\bullet+}$, 10), 89 (90) and 59 (100). Analysis found: C, 59.62; H, 7.63. $C_{17}H_{26}O_7$ requires: C, 59.64; H, 7.65%.

4.4.5. 2-Allyl-4,6-dimethoxyethoxymethyloxyphenol ***17***

Compound **16** (3.0 g, 8.5 mmol) was dissolved in *N*,*N*′-dimethylformamide (DMF, 6 ml) and refluxed for 10 h at 140°C in an oil bath. After cooling to room temperature the solution was poured onto crushed ice. The product was extracted with ethyl acetate, washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with petroleum ether:ethyl acetate 7:3) to give phenol derivative **17** (2.25 g, 75% yield) as a colourless oil. UV (MeOH): 204 nm (log ε 3.7) and 283 nm (log ε 3.6). ^{1}H NMR: δ 3.32 (s, OCH_3-6), 3.32 (d, $J=6.0$ Hz, CH_2-1′), 3.35 (s, OCH_3-4), 3.52 (m,

OCH_2×2), 3.80 (m, CH_2O×2), 5.00 (m, CH_2-3′), 5.10 (s, OCH_2O-6), 5.20 (s, OCH_2O-4), 5.95 (m, H-2′), 6.50 (d, $J=2.0$ Hz, H-5) and 6.65 (d, $J=2.0$ Hz, H-3). ^{13}C NMR: δ 34.1 (C-1′), 58.8 (C-4, 6, OCH_3), 67.4 (C-6, OCH_2), 68.5 (C-4, OCH_2), 71.5 (C-4, 6, CH_2O), 94.4 (C-6, OCH_2O), 95.7 (C-4, OCH_2O), 104.4 (C-5), 112.0 (C-3), 115.5 (C-3′), 127.0 (C-1), 136.3 (C-2′), 138.7 (C-2), 144.8 (C-6) and 150.1 (C-4). Analysis found: C, 59.60; H, 7.62. $C_{17}H_{26}O_7$ requires: C, 59.64; H, 7.65%.

4.4.6. (±)-5,7-Dimethoxyethoxymethyloxy-2-hydroxymethyl-2,3-dihydrobenzofuran ***6j***

Compound **17** (2.0 g, 5.5 mmol) and *m*-CPBA (1.0 g, 5.5 mmol) were dissolved in $CHCl_3$ (150 ml) and refluxed for 5 h on a water bath. After cooling to room temperature the separated *m*-chlorobenzoic acid was filtered. The filtrate was washed with aq. $NaHCO_3$ (2%) to remove traces of *m*-chlorobenzoic acid, then with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with petroleum ether:ethyl acetate 7:3) to give (±)-5,7-dimethoxyethoxymethyloxy-2-hydroxymethyl-2,3-dihydrobenzofuran **6j** (1.5 g, 75% yield). UV (MeOH): 218 nm (log ε 3.6), 232 nm (log ε 3.7) and 287 nm (log ε 3.5). ^{1}H NMR: δ 3.00 (dd, $J=16.0$, 6.0 Hz, CH_2-3, H_A), 3.20 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_B), 3.20 (m, 2-CH_2OH, H_D), 3.32 (s, OCH_3-7), 3.36 (s, OCH_3-5), 3.38 (m, 2-CH_2OH, H_E), 3.53 (m, OCH_2-5), 3.80 (m, 2H, OCH_2-7), 4.88 (m, H-2, H_C), 5.12 (s, CH_2O×2, OCH_2O-5), 5.25 (ABq×2, OCH_2O-7), 6.58 (d, $J=2.0$ Hz, H-4) and 6.62 (d, $J=2.0$ Hz, H-6). ^{13}C NMR: δ 38.3 (C-3), 61.5 (C-5, 7, OCH_3), 65.3 (C-2, OH), 72.6 (C-5, 7 CH_2O×2), 73.5 (C-5, 7 OCH_2), 83.7 (C-2), 94.1 (C-7, OCH_2O), 94.5 (C-5, OCH_2O), 125.7 (C-6), 126.0 (C-4), 131.4 (C-3a), 138.2 (C-7), 141.5 (C-7a) and 154.2 (C-5). EIMS: *m*/*z* (relative intensity 358 ($M^{\bullet+}$, 5), 130 (10), 89 (100) and 59 (98). Analysis found: C, 56.95; H, 7.30. $C_{17}H_{26}O_8$ requires: C, 56.97; H, 7.31%.

4.5. Acetylation of ***6a–j***

6a–j were acetylated with acetic anhydride/pyridine at rt for 6 h, the reaction mixture was poured into ice cold water, the compound was extracted with ethyl acetate, dried and concentrated to give **8a–j**

4.5.1. (±)-5-Methyl-2-acetoxymethyl-2,3-dihydrobenzofuran ***8a***

UV (MeOH): 226 nm (log ε 3.5) and 285 nm (log ε 3.4). ^{1}H NMR: δ 2.08 (s, OCOCH_3), 2.25 (s, CH_3), 2.98 (dd, $J=16.0$, 7.0 Hz, CH_2-3, H_A), 3.25 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 4.18 (dd, $J=16.0$, 6.0 Hz, CH_2O, H_D), 4.28 (dd, $J=16.0$, 4.0 Hz, CH_2O, H_E), 4.93 (m, H-2, H_C), 6.65 (d, $J=10.0$ Hz, H-7), 6.88 (dd, $J=10.0$, 2.0 Hz, H-6) and 6.92 (d, $J=2.0$ Hz, H-4). ^{13}C NMR: δ 20.6 (OCOCH_3, 5-CH_3), 32.1 (C-3), 65.8 (CH_2O), 79.9 (C-2), 109.0 (C-7), 130.0 (C-4), 128.4 (C-6), 129.9 (C-3a, C-5), 157.1 (C-7a) and 170.6 (C=O). FABMS: *m*/*z* (relative intensity) 206 ($M^{\bullet+}$, 30), 145 (100), 133 (30), 121 (15), 91 (15), 77 (20) and 43 (48). FABHRMS: Calc. $C_{12}H_{14}O_3$ ($M^{\bullet+}$) 206.094294, found: 206.095246.

4.5.2. (±)-2-Acetoxymethyl-2,3-dihydrobenzofuran ***8b***

UV (MeOH): 228 nm (log ε 3.5) and 279 nm (log ε 3.6). ^{1}H NMR: δ 2.08 (s, OCOCH_3), 2.95 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.30 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 4.18 (dd, $J=16.0$, 6.0 Hz, CH_2O, H_D), 4.30 (dd, $J=16.0$, 4.0 Hz, CH_2O, H_E), 4.95 (m, H-2, H_C), 6.80 (m, 2H, H-4, 7) and 7.10 (m, 2H, H-5, 6). ^{13}C NMR: δ 20.3 (OCOCH_3), 31.8 (C-3), 65.5 (CH_2O), 79.5 (C-2), 109.3 (C-7), 120.3 (C-5), 124.5 (C-4), 125.4 (C-6), 127.9 (C-3a, C-5), 159.0 (C-7a) and 169.9

(C=O). FABMS: m/z (relative intensity) 190 ($M^{\bullet+}$, 15), 131 (50), 119 (10), 91 (75), 65 (20), 51 (30) and 43 (100). FABHRMS: Calc. $C_{11}H_{12}O_3$ ($M^{\bullet+}$) 190.037222, found: 190.037236.

4.5.3. (±)-5-Chloro-2-acetoxymethyl-2,3-dihydrobenzofuran ***8c***

UV (MeOH): 232 nm (log ε 3.7) and 288 nm (log ε 3.5). ^{1}H NMR: δ 2.07 (s, OCOCH_3), 2.94 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.25 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 4.18 (dd, $J=16.0$, 6.0 Hz, CH_2O, H_D), 4.27 (dd, $J=16.0$, 4.0 Hz, CH_2O, H_E), 4.97 (m, H-2, H_C), 6.65 (d, $J=10.0$ Hz, H-7) and 7.05 (m, 2H, H-4, 6). ^{13}C NMR: δ 20.0 (OCOCH_3), 31.3 (C-3), 65.0 (CH_2O), 80.2 (C-2), 109.8 (C-7), 123.0 (C-5), 124.4 (C-4), 127.1 (C-6), 127.4 (C-3a), 157.4 (C-7a) and 170.0 (C=O). FABMS: m/z (relative intensity) 226 ($M^{\bullet+}$, 20), 228 (M+2) (10), 184 (15), 116 (100), 152 (15), 125 (50), 102 (10), 88 (50), 77 (30), 63 (45), and 44 (98). FABHRMS: Calc. $C_{11}H_{11}ClO_3$ ($M^{\bullet+}$) 226.039672, found: 226.039572.

4.5.4. (±)-5-Methoxy-2-acetoxymethyl-2,3-dihydrobenzofuran ***8d***

UV (MeOH): 225 nm (log ε 3.7) and 286 nm (log ε 3.6). ^{1}H NMR: δ 2.09 (s, OCOCH_3), 2.95 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.25 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.62 (m, 2H, CH_2O, H_D, H_E), 3.75 (s, OCH_3), 4.82 (m, H-2, H_C), 6.67 (m, 3H, H-4, 6, 7). ^{13}C NMR: δ 20.3 (OCOCH_3), 31.9 (C-3), 55.2 (OCH_3-5), 65.5 (C-CH_2O), 79.5 (C-2), 108.8 (C-7), 125.1 (C-4), 128.2 (C-3a, C-5), 128.7 (C-6), 156.9 (C-7a) and 169.8 (C=O). FABMS: m/z (relative intensity) 222 ($M^{\bullet+}$, 10), 207 (10), 146 (80), 131 (40), 115 (10), 106 (100), 91 (50), 77 (75) and 51 (40). FABHRMS: Calc. $C_{12}H_{14}O_4$ ($M^{\bullet+}$) 222.084337, found: 222.084351.

4.5.5. (±)-6-Chloro-2-acetoxymethyl-2,3-dihydrobenzofuran ***8e***

UV (MeOH): 220 nm (log ε 3.6) and 284 nm (log ε 3.5). ^{1}H NMR: δ 2.10 (s, OCOCH_3), 3.02 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.35 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 4.20 (dd, $J=16.0$, 6.0 Hz, CH_2O, H_D), 4.32 (dd, $J=10.0$, 4.0 Hz, CH_2O, H_E), 5.03 (m, H-2, H_C), 6.65 (d, $J=2.0$ Hz, H-7), 6.82 (dd, $J=10.0$, 2.0 Hz, H-5) and 7.03 (d, $J=10.0$ Hz, H-4). ^{13}C NMR: δ 20.5 (OCOCH_3), 32.6 (C-3), 65.2 (CH_2O), 80.5 (C-2), 115.1 (C-7), 121.4 (C-4), 122.9 (C-5), 127.5 (C-6), 128.5 (C-3a), 155.2 (C-7a) and 169.9 (C=O). FABMS: m/z (relative intensity) 226 ($M^{\bullet+}$, 10), 228 (M+2) (10), 166 (75), 165 (80), 153 (30), 131 (50), 125 (90), 102 (40), 88 (70), 77 (39), 63 (75), 44 (100) and 43 (50). FABHRMS: Calc. $C_{11}H_{11}ClO_3$ ($M^{\bullet+}$) 228.056136, found: 228.056124.

4.5.6. (±)-4-Bromo-2-acetoxymethyl-2,3-dihydrobenzofuran ***8f***

UV (MeOH): 249 nm (log ε 3.7) and 285 nm (log ε 3.6). ^{1}H NMR: δ 2.10 (s, OCOCH_3), 2.98 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.32 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 4.21 (dd, $J=16.0$, 6.0 Hz, CH_2O, H_D), 4.32 (dd, $J=16.0$, 4.0 Hz, CH_2O, H_E), 5.01 (m, H-2, H_C), 6.51 (dd, $J=10.0$, 10.0 Hz, H-6), 7.16 (dd, $J=10.0$, 2.0 Hz, H-5) and 7.32 (dd, $J=10.0$, 2.0 Hz, H-7). ^{13}C NMR: δ 20.2 (OCOCH_3), 33.1 (C-3), 65.1 (CH_2O), 79.2 (C-2), 108.0 (C-7), 118.6 (C-4), 123.1 (C-5), 126.9 (C-6), 129.3 (C-3a), 159.3 (C-7a) and 169.6 (C=O). FABMS: m/z (relative intensity) 270 ($M^{\bullet+}$, 10), 272 (M+2) (4), 211 (95), 131 (50), 118 (70), 102 (15), 88 (70), 77 (50), 63 (80) and 44 (100). FABHRMS: Calc. $C_{11}H_{11}BrO_3$ ($M^{\bullet+}$) 272.027145, found: 272.027136.

4.5.7. (±)-4-Methyl-2-acetoxymethyl-2,3-dihydrobenzofuran ***8g***

UV (MeOH): 229 nm (log ε 3.6) and 282 nm (log ε 3.5). ^{1}H NMR: δ 2.15 (s, OCOCH_3), 2.25 (s, CH_3), 2.85 (dd, $J=16.0$, 8.0 Hz, 1H, CH_2-3, H_A), 3.10 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.75 (dd, $J=16.0$, 6.0 Hz, CH_2O, H_D), 4.81 (dd, $J=16.0$, 4.0 Hz, CH_2O, H_E), 4.85 (m, H-2, H_C), 6.64 (dd, $J=10.0$, 2.0 Hz, H-7), 6.72 (dd, $J=10.0$, 2.0 Hz, H-5) and 6.85 (dd, $J=10.0$, 10.0 Hz,

H-6). ^{13}C NMR: δ 20.1 (OCO*CH*$_3$), 21.1 (CH_3), 31.7 (C-3), 64.2 (CH_2O), 77.6 (C-2), 109.6 (C-7), 123.0 (C-5), 124.5 (C-4), 126.1 (C-6), 129.2 (C-3a), 158.9 (C-7a) and 169.8 (C=O). FABMS: m/z (relative intensity) 206 ($M^{\bullet+}$, 10), 164 (70), 145 (50), 133 (70), 104 (100), 90 (40), 77 (50), 52 (15) and 40 (20). FABHRMS: Calc. $C_{12}H_{14}O_3$ ($M^{\bullet+}$) 206.065731, found: 206.065742.

4.5.8. (±)-7-Chloro-2-acetoxymethyl-2,3-dihydrobenzofuran ***8h***

UV (MeOH): 226 nm (log ε 3.5) and 280 nm (log ε 3.7). ^{1}H NMR: δ 2.08 (s, OCO*CH*$_3$), 3.05 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.35 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 4.24 (dd, $J=16.0$, 6.0 Hz, CH_2O, H_D), 4.31 (dd, $J=16.0$, 4.0 Hz, CH_2O, H_E), 5.05 (m, H-2, H_C), 6.75 (dd, $J=10.0$, 10.0 Hz, H-5), 7.00 (dd, $J=10.0$, 2.0 Hz, H-4) and 7.08 (dd, $J=10.0$, 2.0 Hz, H-6). ^{13}C NMR: δ 20.5 (OCO*CH*$_3$), 32.6 (C-3), 65.2 (CH_2O), 80.4 (C-2), 115.2 (C-7), 121.4 (C-4), 122.9 (C-5), 127.4 (C-6), 128.5 (C-3a), 155.2 (C-7a) and 170.0 (C=O). FABMS: m/z 226 (relative intensity) ($M^{\bullet+}$, 10), 228 (M+2) (5), 166 (95), 153 (20), 125 (80), 103 (50), 89 (70), 77 (40), 63 (70) and 43 (100). FABHRMS: Calc. $C_{11}H_{11}ClO_3$ ($M^{\bullet+}$) 228.082615, found: 228.082631.

4.5.9. (±)-7-Methyl-2-acetoxymethyl-2,3-dihydrobenzofuran ***8i***

UV (MeOH): 227 nm (log ε 3.6) and 278 nm (log ε 3.6). ^{1}H NMR: δ 2.20 (s, OCO*CH*$_3$), 2.40 (s, CH_3), 3.00 (dd, $J=16.0$, 8.0 Hz, CH_2-3, H_A), 3.20 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.70 (dd, $J=10.0$, 6.0 Hz, CH_2O, H_D), 3.82 (dd, $J=16.0$, 4.0 Hz, CH_2O, H_E), 4.85 (m, H-2, H_C), 6.88 (dd, $J=10.0$, 2.0 Hz, H-4), 6.72 (dd, $J=10.0$, 10.0 Hz, H-5), and 6.95 (dd, $J=10.0$, 2.0 Hz, H-6). ^{13}C NMR: δ 20.1 (CH_3), 20.8 (OCO*CH*$_3$), 31.4 (C-3), 64.5 (CH_2O), 82.5 (C-2), 119.2 (C-7), 120.2 (C-4), 122.1 (C-5), 126.6 (C-6), 129.0 (C-3a), 157.4 (C-7a) and 170.2 (C=O). FABMS: m/z (relative intensity) 206 ($M^{\bullet+}$, 10), 164 (50), 145 (45), 133 (50), 104 (100), 90 (40), 77 (45), 52 (10) and 40 (15). FABHRMS: Calc. $C_{12}H_{14}O_3$ ($M^{\bullet+}$) 206.074171, found: 206.074152.

4.5.10. (±)-5,7-Dimethoxyethoxymethyloxy-2-acetoxymethyl-2,3-dihydrobenzofuran ***8j***

UV (MeOH): 226 nm (log ε 3.6), 240 nm (log ε 3.8) and 285 nm (log ε 3.6). ^{1}H NMR: δ 2.06 (s, OCO*CH*$_3$), 2.95 (dd, $J=16.0$, 7.0 Hz, CH_2-3, H_A), 3.28 (dd, $J=16.0$, 10.0 Hz, CH_2-3, H_B), 3.40 (s, $OCH_3\times2$), 3.55 (m, $OCH_2\times2$), 3.80 (m, $CH_2O\times2$), 4.25 (m, 2H, 2-*CH*$_2$O, H_D, H_E), 4.98 (m, H-2, H_C), 5.14 (s, OCH_2O-5), 5.25 (s, OCH_2O-7), 6.60 (d, $J=2.0$ Hz, H-4), and 6.70 (d, $J=2.0$ Hz, H-6). ^{13}C NMR: δ 20.3 (OCO*CH*$_3$), 33.0 (C-3), 58.9 ($OCH_3\times2$), 65.6 (*CH*$_2$O), 67.5 (OCH_2-5), 67.8 (OCH_2-7), 71.5 (CH_2O-5), 71.6 (CH_2O-7), 80.5 (C-2), 94.4 (OCH_2O-5), 94.6 (OCH_2O-7), 104.7 (C-6), 106.9 (C-4), 131.1 (C-3a), 141.3 (C-7a), 152.2 (C-5) and 170.0 (C=O). EIMS: m/z (relative intensity) 400 ($M^{\bullet+}$, 5), 156 (10), 139 (12), 89 (75) and 59 (100). Analysis found: C, 56.97; H, 7.03. $C_{19}H_{28}O_9$ requires: C, 56.99; H, 7.05%.

4.6. General procedure for the lipase mediated enantioselective acylation of 2-hydroxymethyl-2,3-dihydrobenzofurans ***6a–j***

(±)-5-Methyl-2-hydroxymethyl-2,3-dihydrobenzofuran **6a** (0.5 g, 3 mmol) was dissolved in *n*-hexane (50 ml). Lipase Amano PS (500 mg) was added to this solution and the suspension was thermostated at rt. After a few minutes vinyl acetate (5 ml) was added and the reaction mixture was stirred using a magnetic stirrer and the progress of the reaction was monitored by TLC by comparing the amount of (±)-**6a** present with the amount of (±)-**8a**. After 50% conversion, the lipase was filtered off, the hexane was evaporated and the resulting gum was chromatographed on silica gel by eluting with petroleum ether:ethyl acetate (7:3, v/v) to give acetate **18a** and alcohol **19a**. Similarly, (±)-**6b–j** gave (−)-(*R*)-acetates **18b–j** and (+)-(*S*)-alcohols **19b–j** after lipase mediated

kinetic resolution. The chemical yield, $[\alpha]_D$ and % ee of **18a–j** and **19a–j** are given in Table 1. The CD spectral data are given in Table 2.

*4.7. Synthesis of (–)-(R)-MEM-protected arthrographol **22** from (–)-**18j***

*4.7.1. (–)-(R)-5,7-Dimethoxyethoxymethyloxy-2-hydroxymethyl-2,3-dihydrobenzofuran **20***

Acetate **18j** (1.5 g, 4 mmol) in methanol (10 ml) was hydrolysed by K_2CO_3–MeOH (0.42 g, 3.0 mmol) in water (three drops) and stirring at rt for 30 min. The reaction mixture was extracted with ethyl acetate dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography by eluting with petroleum ether:ethyl acetate (8:2) to give (–)-(*R*)-alcohol **20** as a colourless oil (1.3 g, 90% yield). UV (MeOH): 205 nm (log ε 3.6) and 283 nm (log ε 3.6). ^{1}H NMR: δ 2.50 (s, bs, OH), 3.00 (dd, J=16.0, 6.0 Hz, CH_2-3, H_A), 3.60 (m, 2-CH_2–OH, H_D), 3.30 (dd, J=16.0, 8.0 Hz, CH_2-3, H_B), 3.32 (s, OCH_3-7), 3.36 (s, OCH_3-5), 3.70 (m, 2-CH_2–OH, H_E), 3.53 (m, OCH_2-5), 3.80 (m, OCH_2-7), 4.88 (m, H-2, H_C), 5.14 (ABq, OCH_2O-5), 5.12 (s, CH_2O×2), 5.25 (ABq, OCH_2O-7), 6.58 (d, J=2.0 Hz, H-4) and 6.62 (d, J=2.0 Hz, H-6). $[\alpha]_D$=–20.83 (*c* 1.31, $CHCl_3$).

*4.7.2. Oxidation of **20**: formation of (–)-(R)-5,7-dimethoxyethoxymethyloxy-2,3-dihydrobenzofuran-2-carbaldehyde **21***

A solution of oxalyl chloride (0.53 g, 4 mmol) in dry DCM (20 ml) was cooled at −78°C under nitrogen atmosphere and then anhydrous DMSO (0.32 g, 4 mmol) was added dropwise. After stirring for 10 min at −78°C, a solution of (–)-(*R*)-**20** (1.35 g, 4 mmol) in dry DCM (5 ml) was introduced to the reaction mixture via a syringe. The resultant white suspension was stirred at −78°C for 1 h and then quenched with triethylamine (0.42 g, 4 mmol) at the same temperature, then allowed to attain room temperature, poured over crushed ice, and the organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were washed with water, brine and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford (–)-(*R*)-**21** as a syrup in 85% yield. The compound was used immediately in the next step without further characterisation.

*4.7.3. Synthesis of (–)-(R)-MEM-protected arthrographol **22***

n-Butyllithium (0.11 ml of a 2.5 M solution of hexane) was added to a suspension of crotyl triphenylphosphonium bromide (0.5 g, 2 mmol) in dry THF (10 ml) at 0°C to give an orange-red solution of the phosphonyl anion. The solution was cooled to −78°C and a solution of the aldehyde **21** (0.5 g, 2 mmol) in THF (2 ml) was added dropwise. The mixture was stirred at −78°C for 2 h, then warmed to room temperature and quenched with water. The solution was transferred to a separatory funnel, diluted with water and extracted with DCM. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with petroleum ether:ethyl acetate 7:3) to give (–)-(*R*)-MEM-protected arthrographol **22** (0.44 g, 89% yield). UV (MeOH): 226 nm (log ε 4.0) and 292 nm (log ε 3.5). ^{1}H NMR: δ 1.80 (dd, J=6.0, 1.0 Hz, CH_3-5′), 2.92 (dd, J=16.0, 8.0 Hz, H-3, H_A), 3.32 (dd, J=16.0, 6.0 Hz, H-3, H_B), 3.32 (s, H-5, 7, OCH_3), 3.52 (m, OCH_2-5), 3.80 (m, OCH_2-7), 5.12 (s, OCH_2O-5), 5.22 (s, OCH_2O-7), 5.40–6.40 (m, fourolefinic protons, H-1′, 2′, 3′, 4′ and H-2), 6.55 (d, J=2.0 Hz, H-4), 6.65 (d, J=2.0 Hz, H-6). ^{13}C NMR: δ 18.2 (C-5′, CH_3), δ 38.9 (C-3), δ 59.2 (C-5, 7 OCH_3×2), 67.3 (C-5, OCH_2), 67.4 (C-7, CH_2O), 71.0 (C-5, CH_2O), 71.1 (C-7, CH_2O), 79.3 (C-2), 94.3 (C-5, OCH_2O), 94.9 (C-7, OCH_2O), 105.3 (C-2′), 108.1 (C-4),

126.9 (C-3′), 127.5 (C-1′), 126.1 (C-3a), 133.8 (C-7a), 131.0 (C-4′), 132.0 (C-6), 141.2 (C-7) and 151.9 (C-5). EIMS: m/z (relative intensity) 394 ($M^{\bullet+}$, 30) 89 (100) and 59 (98). HREIMS: Calc. $C_{21}H_{30}O_7$ ($M^{\bullet+}$) 394.199154, found: 394.199124. $[\alpha]_D = -14.0$ (c 0.5, $CHCl_3$).

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References

1. Nascimento, I. R.; Lopes, L. M. X. *Phytochemistry* **1999**, *52*, 345.
2. Benevides, P. J. C.; Sartorelli, P.; Kato, M. J. *Phytochemistry* **1999**, *52*, 339.
3. Ishii, H.; Ishikawa, T. *Tetrahedron Lett*. **1982**, *23*, 4245.
4. Bohlmann, F.; Scheidges, C.; Zdero, C.; King, R. M.; Robinson, H. *Phytochemistry* **1984**, *23*, 1109.
5. Lau, C. K.; Belanger, P. C.; Dufresne, C.; Scheigetz, J.; Therien, M.; Fitzsimmons, B.; Young, R. N.; Ford Hutchinson, A. W.; Riendeau, D.; Denis, D.; Guay, J.; Charleson, C.; Piechuta, H.; McFarlance, C. S.; Leechiu, S. H.; Eline, D.; Alvaro, R. F.; Miwa, C.; Walsh, J. L. *J. Med. Chem*. **1992**, *35*, 1299.
6. Hellberg, M. R.; Namil, A.; Delgado, P.; David, K. C.; Kessler, T. L.; Graff, G.; Haggard, K. S.; Nixon, J. C. *J. Med. Chem*. **1999**, *42*, 267.
7. Pieters, L.; Bryne, T. D.; Claeys, M.; Vlietinck, A. *J. Nat. Prod*. **1993**, *56*, 899.
8. Cokerill, G. S.; Levett, P. C.; Whiting, D. A. *J. Chem. Soc., Perkin Trans I* **1995**, 1103.
9. Jarvis, B. B.; Pena, N. B.; Comezoglu, S. N.; Madhusudhana Rao, M. *Phytochemistry* **1986**, *25*, 533.
10. Achenbach, H.; Utz, W.; Usubillaga, A.; Rodriguez, H. A. *Phytochemistry* **1991**, *30*, 3753.
11. Roberts, S. M.; Wiggins, K.; Lasy, K; Phythian, S. *Preparation Biotransformations of Whole Cell and Isolation Enzymes in Organic Synthesis*; John Wiley & Sons: New York, 1993.
12. Pfefferle, W.; Anke, H.; Bross, M.; Steffan, B. *J. Antibiot*. **1990**, *43*, 648.
13. Ayer, W. A.; Nozawa, K. *Can. J. Micro. Biol*. **1990**, *36*, 83.
14. Bonner, W. A.; Burke, N. I.; Fleck, W. E.; Hill, R. K.; Joyle, J. A.; Sjoberg, B.; Zalkow, J. H. *Tetrahedron* **1964**, *20*, 1419.
15. Miyake, M.; Fujimoto, Y. *Chem. Lett*. **1993**, 1683.
16. Smith, A. B.; Sestelo, J. P.; Dormer, P. G. *J. Am. Chem. Soc*. **1995**, *117*, 10755.
17. Hosokawa, T; Vno, T.; Insi, S.; Murahashi, S. *J. Am. Chem. Soc*. **1981**, *103*, 2318.
18. Russell, M. G. N.; Baker, R.; Ball, R. G.; Thomas S. R.; Tsou, N. N.; Castro, J. L. *J. Chem. Soc., Perkin Trans I* **2000**, 893.
19. Vozumi, Y.; Kyoto, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem*. **1999**, *64*, 1620.
20. White, W. N.; Gwgnn, D.; Pokrouskaya, I. E.; Fife, W. *J. Am. Chem. Soc*. **1958**, *80*, 3271.
21. Savenholm, V.; Parker, V. D. *J. Chem. Soc., Perkiin Trans II* **1974**, 169.
22. Lasek, W.; Makosza, M. *Synthesis* **1993**, 780.
23. Weerawarna, S. A.; Biswas, M. G.; Nelson, W. L. *J. Heterocyclic Chem*. **1991**, *28*, 1395.
24. Ayer, W. A.; Craw, P. A. *Can. J. Chem*. **1991**, *69*, 1909.
25. Mendelson, W. L.; Hayden, S. *Synth. Commun*. **1996**, *26*, 603.
26. Weissfloch, A. N. E.; Kazlauskas, R. *J. Org. Chem*. **1995**, *60*, 6959.
27. Carrea, G.; Amici, M. D.; Micheli, C. D.; Liverani, P.; Carnielli, M.; Riva, S. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1063.
28. Xie, Z. F.; Suemune, H.; Sakai, K. *Tetrahedron*: *Asymmetry* **1993**, *4*, 973.
29. Schieweek, F.; Altenbach, H. J. *Tetrahedron*: *Asymmetry* **1998**, *9*, 403.
30. Kazlauskas, R. J. *Curr. Opin. Chem. Biol*. **2000**, *4*, 81.
31. Tuomi, W. V.; Kazlauskas, R. J. *J. Org. Chem*. **1999**, *64*, 2638.