Regio- and Chemo-selective Properties of Lipase from *Candida cylindracea*

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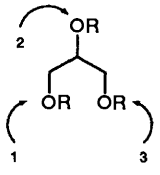
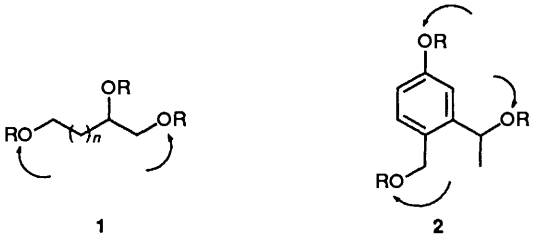
Lipase from *Candida cylindracea* allows discrimination between the two connectively non-equivalent hydroxy groups in primary diols or their esters *via* acylation–hydrolysis, with high regioselectivity. The same technique is used to distinguish between hydroxy groups of different nature in phenolic compounds.

Ester formation and hydrolysis deserves continuous attention in preparative organic chemistry mainly because of the involvement of such reactions in the protection–deprotection steps in syntheses of complex molecules. The manipulation of such compounds often requires special care in order to perform the operation in a chemo- and regio-selective manner. Accordingly there are numerous reports suggesting new mild and selective procedures to perform those transformations.[1] When considering mild and selective reagents one would first think of enzymes as ideal candidates. Indeed hydrolytic enzymes and particularly lipases are increasingly popular among organic chemists, especially since it has become common knowledge that they can act efficiently as catalysts in organic solvents,[2] and they are mainly employed in the preparation of chiral alcohols/esters in enantiomerically pure form *via* kinetic resolution of racemates in hydrolysis and interesterification procedures.[3] The natural activity of lipases is however concerned with the ability to perform selective acylation–deacylation of glycerol esters thereby displaying regio- and chemo-selective properties. In fact commercially available lipases of different origins are classified according to their 1,3- or

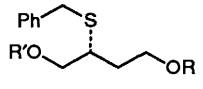


2-specificity in lipid hydrolysis as well as for their ability to recognise the acyl rest in mixed glycerol esters.[4] Recently[5] lipase regioselectivity has been shown to proceed with quite different properties in organic solvents than in water, in part due to the diminished rate of acyl group migration. Application of these enzymes to polyhydroxylated substrates are numerous and refer mainly to the carbohydrate field.[6] It is thus well recognised that the primary hydroxy group on C_6 of a hexose will be more reactive than secondary ones both in hydrolysis and acyl transfer reactions, while selective recognition among secondary hydroxy groups in the sugar moiety depends largely on the solvent used and the type of enzyme. Other synthetic applications are in steroid[7] and oligonucleotide chemistry[8] as well as isolated cases of hydrolysis in multifunctional substrates.[9] Although there are only a few examples of biotransformations involving lipases with phenols as substrates,[10] an unusually strong solvent effect has been observed recently in the regioselective recognition of the two phenolic ester groups in a dissymmetric derivative of hydroquinone.[11] We have turned our attention to some less studied problems in this field, namely the ability of hydrolytic enzymes to discriminate between hydroxy groups of similar reactivity in simple model polyhydroxylated compounds of type **1** or between different ones in phenols of type **2** (Scheme 1).

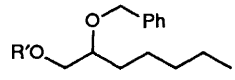


Scheme 1

The opportunity for this study occurred to us when we required the preparation of compound **3a** for determining the absolute configuration of a minor metabolite in the baker's yeast fermentation of benzyl mercaptan.[12] In the chemical esterification of the diol precursor there is no regioselectivity, and mono functionalisation requires tedious separation of isomers or protection–deprotection techniques. We therefore started investigating the ability of lipase from *Candida cylindracaea* (CCL) to discriminate between the two primary hydroxy groups in acylation reactions using vinyl acetate (VA) or isopropenyl acetate (IPA) in hexane. Table 1 summarises the product distribution in the acylation of diols **3a** and **4a**. Regioselectivity is appreciable only in the case of substrate **3a** when the reaction is stopped at 70% conversion. In this case the least hindered hydroxy ester **3b** predominates and no diacetate is formed. Surprisingly, the selectivity is much lessened in the case of substrate **4a** where the two extremities are differentiated by two more methylene groups. Lipase from CCL was better than other commercial preparations used in this context.[12]



3
a R = R' = H
b R = Ac, R' = H
c R = H, R' = Ac



4
a R = R' = H
b R = Ac, R' = H
c R = H, R' = Ac

In order to evaluate the steric effect on selectivity, we prepared 2-dibenzylamino substituted butane-1,4-diol and pentane-1,5-diol, **5** and **9** respectively (Scheme 2). We expected to see a much higher regioselectivity in this case, in connection with the increased differentiation of the two terminal primary hydroxy groups.[13] Indeed regioselectivity is now almost complete and the least hindered ester is obtained as prevalent or exclusive product. Table 2 shows the product distribution in the irreversible acylation of substrates **5** and **9**. The effect of the very bulky substituent is evident and is reflected in the more selective results with substrate **9**. Hexane is apparently the best solvent among the few apolar solvents compared (see Experimental section) while no great influence is to be assigned to the choice of the acylating agent between VA and IPA. When

Table 1 Product distribution in the acylation of compounds **3** and **4**[a]

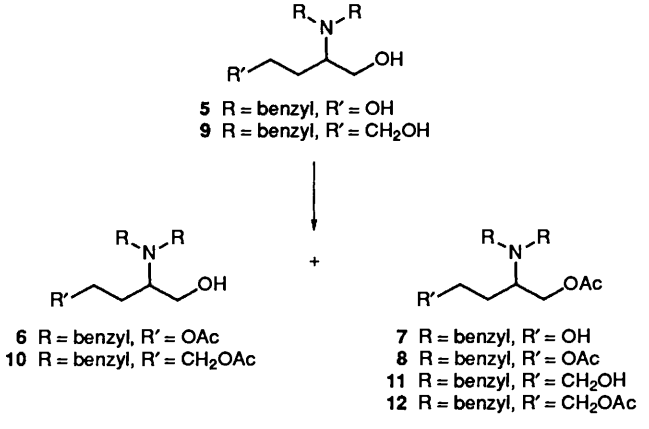
Substrate	Acyl donor	Solvent	Conversion (%)[b] (*t*/h)	Monoacetates, ratio **b**:**c**	Diacetate (%)	*T*/°C
3a	IPA	Hexane	70 (2)	9:1	0	0
3a	IPA	Hexane	100 (3)	9:1	30	0
3a	VA	Hexane	100 (2)	9:1	40	0
4a	VA	Hexane	90 (2)	85:15	60	0
4a	VA	CH_2Cl_2	50 (5)	7:3	1	25

[a] Reaction conditions: substrate (0.5 mmol), solvent (5 cm^3), acylating agent (1 cm^3), lipase (CCL, Sigma type VII, 1000 U) (50 mg). [b] Conversion was determined by gas chromatography.

Table 2 Product distribution in the acylation of compounds **5** and **9**[a]

Substrate	Lipase	Product ratio (%)	Conversion (%)[c] (*t*/h)
5	CCL	6 (93)	90 (2)
		7 (7)	
5	PPL	6 (96)	15 (24)
		7 (4)	
5	PFL	6 (82)	75 (24)
		7 (18)	
5	Rhizopus	6 (85)	20 (24)
		7 (15)	
9	CCL	10 (97)	90 (3)
		11 (3)	
9	CCL	10 (100)[b]	97 (24)
9	PPL	10 (97)	20 (24)
		11 (3)	
9	PFL	10 (90)	75 (24)
		11 (10)	
9	Rhizopus	10 (92)	20 (24)
		11 (8)	

[a] Reaction conditions: 0.5 mmol substrate, 1 cm^3 VA, 5 cm^3 hexane, 10^4 U of lipase. [b] IPA. [c] Conversions determined by gas chromatography. Difference to 100% corresponds to recovered diol.



Scheme 2

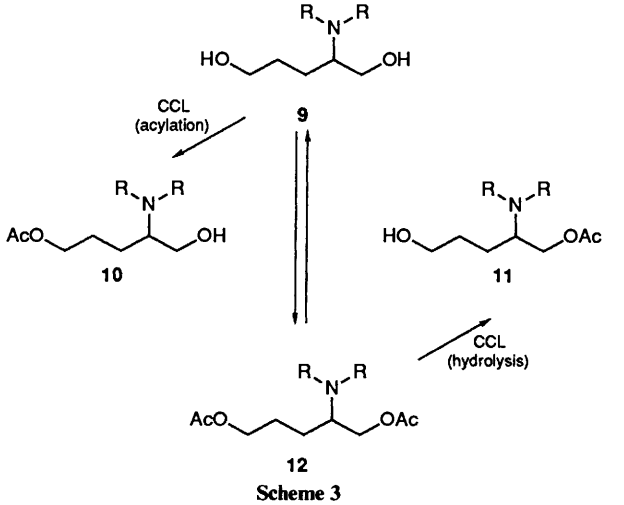
the hydrolysis of diacetates **8** and **12** in H_2O–MeCN is carried out, the hydroxy esters obtained are complementary to the one obtained in the esterification steps. In particular, **8** gives **6** and **7** in a 25:75 ratio, while from **12** the monoacetate **11** is obtained contaminated with less than 3% of the regioisomer. In this way, at least for compound **9**, the two isomeric hydroxy esters can be obtained in high yields and purity (Scheme 3).

The results obtained with substates of type **1** show the ability of lipase from *Candida cylindracea* to discriminate between chemically identical groups in the same molecule and that this ability is definitely dependent on the bulkiness of the groups on the α-carbon. One could say that the enzyme behaves like a bulky reagent. Better selectivity is obtained in the acylation rather than in the corresponding hydrolysis reaction which is

Table 3 Product distribution in the acylation of diols **13a**–**19a**[a]

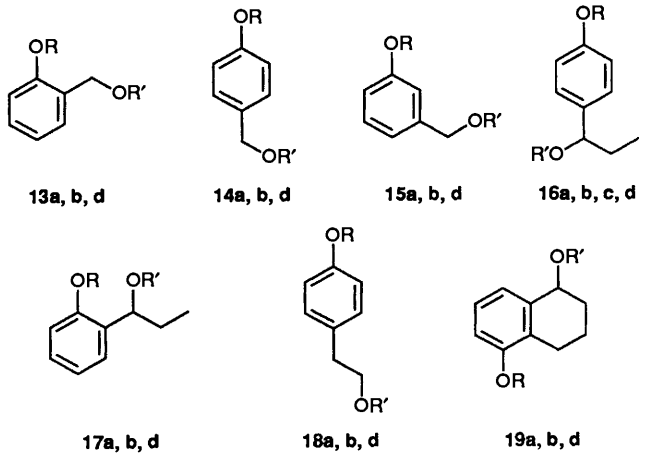
Substrate	Products (isolated yields, %)	Conversion (%) (*t*/h)
13a	**13b** (100)	100 (6)
14a	**14b** (100)	100 (4)
15a	**15b** (100)	100 (4)
18a	**18b** (100)	100 (4)
16a	**16c** (30)[b]	30 (24)
17a	—	
19a	**19b** (35)[c]	37 (24)
	19d (2)	

[a] 0.5 mmol substrate, 2 cm^3 VA, 4 cm^3 hexane, 100 mg CCL lipase. [b] Racemic. [c] 64% ee.



Scheme 3

also much slower. The substrates selected are not very soluble in hexane and the reaction is started as a suspension. Nevertheless the acylation goes to completion in a reasonable time and recovery of the products is complete. These observations suggest that the procedure is of preparative applicability. An alternative chemical esterification is not regioselective as proved by our experience and by analogous results reported in the literature.[14] We were then interested to investigate the chemoselective properties of CCL toward substrates containing, in the same molecule, chemically different hydroxy groups, *i.e.* primary, secondary and phenolic. Such a problem is often encountered in preparative organic chemistry and an enzymatic approach to it seemed interesting to us. We therefore selected some simple substrates bearing two chemically different hydroxy groups, to avoid difficult separation–identification in possible complex isomeric mixtures due to the presence of three OH groups. Scheme 4 shows the diols and diacetates derived from them that we tested for acylation and deacylation with CCL. The results of this investigation are reported in Table 3. In the esterification step the diols were suspended in a mixture of VA and hexane to which the enzyme preparation was added



a R = R' = H
b R = Ac, R' = Ac
c R = Ac, R' = H
d R = R' = Ac

Scheme 4

at room temp. and the mixture stirred for a few hours. In this acyl transfer reaction, the primary benzylic group was always esterified in the presence of free phenolic OH. The reaction is rather rapid and no trace of phenol ester is formed. The mono ester can be isolated quantitatively. When a secondary OH group is present in the molecule, reaction rates are much lower and different tendencies are observed in the three substrates tested. While diol **16a** gives the phenol ester **16c** in 30% yield, compound **17a** is not transformed at all. The tetraline derivative **19a** with some structural analogy with both **16a** and **17a** gives ester **19b** in 35% yield with no trace of the phenol ester. In all the cases observed, the difference in reactivity is so high that no mixture of products is observed. When displaying regioselective properties, lipases usually give complementary products in acylation–deacylation steps, since the positionally preferred alcohol for acylation, becomes also the favourite ester for hydrolysis as shown in the previous examples. This behaviour also applies to the recognition of enantiomers in the process of kinetic resolution of secondary alcohols and their esters as proved by many examples in the literature.[15] We expected therefore that the deacylation of the diacetates **13d–19d** would provide the corresponding mono phenol esters in a selective manner. This is not the case, and transesterification of diacetates (similar results were obtained with the dibutyrates) with CCL lipase to butanol shows that the phenol ester is in all cases much more reactive than the other esters giving, selectively, the free phenols as indicated in Table 4.

These results show that the use of lipases in acyl transfer reactions can be conveniently used in routine preparative chemistry to perform chemo- and regio-selective protection–deprotection steps in polyhydroxylated substrates, although from the data presented in this work and from that described in the literature,[7,9,10] it is not possible to predict reliably the course of the reaction and as for most enzymatic reactions every substrate has a peculiar behaviour. Substrates **3**, **5** and **9** were used in enantiomerically pure form, but the racemic mixtures behaved in the same way. Diol **4a** was racemic, but enantiomeric purity of the products obtained was not investigated. Compound **16c** obtained from **16a** was racemic, while **19b** from acylation of diol **19a** was obtained in 64% ee (absolute configuration not determined).

Experimental

General.—Compounds **14a** and **15a** were purchased from Fluka, compound **13a** was prepared by $LiAlH_4$ reduction from salicylic acid (C. Erba) once esterificated. $LiAlH_4$ reduction of 4-hydroxyphenyl acetate (Aldrich) gave **18a**, compounds **16a** and **17a** were obtained, by $NaBH_4$ reduction of the corresponding 4- and 2-hydroxypropiophenone (Fluka). Diacetate derivatives were prepared from the corresponding diols with acetic anhydride and pyridine. CCL lipase from SIGMA type VII, 1010 U/mg solid was used. Other lipases tested which proved to be less selective: *Rhizopus arrhizus*, *Mucor javanicus*, *Pseudomonas fluorescens* (from Fluka), *Psuedomonas sp.* type XII (from SIGMA). Throughout the Experimental section VA refers to vinyl acetate and IPA to isopropenyl acetate.

Table 4 Products obtained in the deacylation of diacetates **13d–19d**[a]

Substrate	Products (isolated yields, %)	Conversion (%) (*t*/h)
13d	**13b** (40)	50 (24)
	13a (10)	
14d	**14b** (100)	100 (4)
15d	**15b** (100)	100 (4)
18d	**18b** (100)	100 (3)
16d	**16b** (100)	100 (24)
17d	**17b** (60)	60 (48)
19d	**19b** (98)[b]	100 (72)
	19a (2)	

[a] 1.5 mmol substrate, 10 mmol butanol, 50 cm^3 n-hexane, 250 mg CCL lipase, 25 °C. [b] 250 mg of CCL added after the first 48 h.

2-Dibenzylaminopentane-1,5-diol **9**.—Glutamic acid (2 g, 15 mmol) was dissolved in absolute EtOH (50 cm^3) and HCl gas was passed through the solution for 30 min. The mixture was left at 25 °C for 24 h. After this time the solvent was evaporated at reduced pressure and the crude gummy oil was treated with a solution of KOH (0.84 g, 15 mmol) in EtOH (50 cm^3). This mixture was transferred into a three necked round bottomed flask and treated simultaneously, with vigorous stirring, with an ethanolic $PhCH_2Br$ solution (5 g, 30 mmol, 50 cm^3 of EtOH) and an ethanolic KOH solution (1.7 g, 30 mmol, 50 cm^3 of EtOH) which were added dropwise. After 16 h at 25 °C the reaction mixture was filtered and the solvent evaporated under reduced pressure. The crude oil was purified by chromatography (SiO_2, hexane–ethyl acetate, 9:1) to give diethyl *N,N*-dibenzylglutamate (3.6 g, 9.5 mmol, 63%) (Found: C, 72.1; H, 7.65; N, 3.6. Calc. for $C_{25}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65%). Reduction of the above compound with $LiAlH_4$ in anhydrous ether using standard conditions gave compound **9** (2.3 g, 7.6 mmol, 80%) oil; δ_H(250 MHz; $CDCl_3$) 1.22–1.38 (2 H, CH_2 m), 1.45–1.65 (3 H, CH_2, OH, m), 1.80–1.94 (1 H, OH, br), 2.77–2.89 (1 H, CH, m), 3.47 and 3.82 (4 H, $2CH_2$, AB system), 3.48–3.52 (2 H, CH_2, m), 3.66 (2 H, CH_2, t) and 7.20–7.40 (10 H, 2Ph, m) (Found: C, 76.2; H, 8.45; N, 4.65. Calc. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68%).

2-Dibenzylaminobutane-1,4-diol **5**.—Starting from aspartic acid and following the same sequence used for the preparation of compound **9**, diethyl *N,N*-dibenzylaspartate was obtained (Found: C, 71.5; H, 7.4; N, 3.8. Calc. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79%). Reduction of the above diester gave compound **5**; δ_H(250 MHz; $CDCl_3$) 1.40–1.54 (1 H, CH_2, m), 1.92–2.06 (1 H, CH_2, m), 2.20–2.80 (2 H, 2OH, br), 2.89–3.01 (1 H, CH, m), 3.42–3.80 (4 H, 2 × CH_2, m), 3.56 and 3.72 (4 H, $2CH_2$, AB system) and 7.18–7.38 (10 H, 2 × Ph, m) (Found: C, 75.8; H, 8.1; N, 4.9. Calc. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91%).

Gas Chromatographic Conditions for the Separation of the Derivatives of Compounds **5** *and* **9**.—Fused silica capillary

column (MEGA) 30 m × 0.25 i.d. coated with 0.25 μm of OV1. He, 0.8 bar, 80 °C 1 min, 20 °C/min, 200 °C 1 min, 5 °C/min, 230 °C 1 min, 2 °C/min, 250 °C. R_t 21.46 **9**, 22.37 **11**, 23.67 **10**, 24.22 **12**; 20.20 **5**, 20.72 **7**, 21.74 **6**, 22.44 **8**.

General Conditions for the Enzymatic Acylation of Compounds **5** *and* **9**.—Substrate (0.5 mmol), acylating agent (VA or IPA) (1 cm^3), solvent (hexane, toluene or dichloromethane) (5 cm^3) and lipase (100.000 U) were stirred at 300 rpm. The transformation products were recovered by dilution with ethyl acetate, filtration and evaporation of the solvent; the different products were separated when necessary by preparative TLC (SiO_2, hexane–ethyl acetate, 7:3). The mono acetate ratio was determined by GLC on the crude extract.

General Conditions for the Enzymatic Hydrolysis of Compounds **8** *and* **12**.—Substrate (0.5 mmol) was diluted in MeCN (3 cm^3) and water (3 cm^3) was added, CCL (0.2 g) was used for each run. The pH of the solution was kept at 7 with the aid of a Metrohm 655 Dosimat. After 24 h the mixture was extracted with ethyl acetate. The products were separated when necessary by preparative TLC (SiO_2, hexane–ethyl acetate, 8:2). The product distribution was determined by GLC on the crude extract.

General Conditions for the Enzymatic Acylation of Compounds **13a**, **14a**, **15a**, **16a**, **18a** *and* **19a**.—Substrates (0.5 mmol), vinyl acetate (2 cm^3), hexane (4 cm^3) and CCL (100 mg) were stirred at 300 rpm. The transformation products were recovered by dilution with ethyl acetate, filtration and evaporation of the solvent. When necessary purification and/or separation of the different compounds was performed by preparative TLC (SiO_2, hexane–ethyl acetate, 8:2). The mono acetate ratio was determined by ^1H NMR spectroscopy on the basis of the chemical shift of the benzylic protons, shifted downfield by 0.5–1.0 ppm when *O*-acetylated.

General Conditions for the Transesterification of **13d**, **14d**, **15d**, **16d**, **17d**, **18d** *and* **19d**.—Substrate (1.5 mmol), hexane (50 cm^3), BuOH (1 cm^3) and CCL (250 mg) were stirred at 500 rpm. For compound **19d** a second addition of CCL (250 mg) was made after 48 h. The solution was filtered and the solvent evaporated at reduced pressure. The crude extract was purified and separated when necessary by preparative TLC (SiO_2, hexane–ethyl acetate, 8:2). The product distribution was determined by ^1H NMR spectroscopy.

2-Dibenzylaminopentane-1,5-diyl diacetate **12**. δ_H(300 MHz; $CDCl_3$) 1.38–1.93 (4 H, 2 × CH_2, m), 2.01 (3 H, CH_3, s), 2.10 (3 H, CH_3, s), 2.80–2.91 (1 H, CH, m), 3.58 and 3.79 (4 H, 2 × CH_2, AB system), 3.94 (2 H, CH_2, t), 4.10 (1 H, CH_2, dd), 4.29 (1 H, CH_2, dd) and 7.20–7.40 (10 H, 2 × Ph, m) (Found: C, 72.0; H, 7.6; N, 3.65. Calc. for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65%).

4-Dibenzylamino-5-hydroxypentyl acetate **10**. δ_H(250 MHz; DMSO) 1.36–1.58 (2 H, CH_2, m), 1.95 (3 H, CH_3, s), 2.5 (covered by the DMSO signal) (1 H, CH, m), 3.26–3.49 (2 H, CH_2, m), 3.57 and 3.70 (4 H, 2 × CH_2, AB system), 3.83 (2 H, CH_2, t), 4.45 (1 H, OH, t) and 7.20–7.40 (10 H, 2 × Ph, m) (Found: C, 73.9; H, 8.0; N, 4.1. Calc. for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10%).

2-Dibenzylamino-5-hydroxypentyl acetate **11**. δ_H(250 MHz; DMSO) 1.20–1.70 (2 H, CH_2, m), 2.03 (3 H, CH_3, s), 2.70 (1 H, CH, m), 3.28 (2 H, CH_2, m), 3.56 and 3.65 (4 H, 2 × CH_2, AB system), 4.01 (1 H, CH_2, dd), 4.26 (1 H, CH_2, dd), 4.38 (1 H, OH, t) and 7.20–7.40 (10 H, 2 × Ph, m) (Found: C, 73.85; H, 8.0; N, 4.1. Calc. for $C_{21}H_{27}NO_3$: C, 73.89; H, 7.97; N, 4.10%).

2-Dibenzylaminobutan-1,4-diyl diacetate **8**. δ_H(300 MHz; $CDCl_3$) 1.54–1.78 (2 H, CH_2, m), 1.86 (3 H, CH_3, s), 2.10 (3 H, CH_3, s), 2.98–3.11 (1 H, CH, m), 3.57 and 3.81 (4 H, 2 × CH_2, AB system), 4.09–4.21 (3 H, 2 × CH_2, m), 4.34 (1 H, CH_2, dd) and 7.18–7.40 (10 H, 2 × Ph, m) (Found: C, 71.5; H, 7.4; N, 3.8. Calc. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79%).

3-Dibenzylamino-4-hydroxybutyl acetate **6**. δ_H(250 MHz; DMSO) 1.61–1.90 (2 H, CH_2, m), 1.82 (3 H, CH_3, s), 2.59–2.71 (1 H, CH, m), 3.41–3.54 (2 H, CH_2, m), 3.55 and 3.70 (4 H, 2 × CH_2, AB system), 3.96–4.09 (2 H, CH_2, m), 4.56 (1 H, OH, t) and 7.17–7.42 (10 H, 2 × Ph, m) (Found: C, 73.4; H, 7.7; N, 4.25. Calc. for $C_{20}H_{25}NO_3$; C, 73.37; H, 7.70; N, 4.28%).

2-Dibenzylamino-4-hydroxybutyl acetate **7**. δ_H(250 MHz; DMSO) 1.47 (1 H, CH_2, six lines), 1.80 (1 H, CH_2, six lines), 2.05 (3 H, CH_3, s), 2.82–2.94 (1 H, CH, m), 3.28–3.53 (2 H, CH_2, m), 3.62 (4 H, 2 × CH_2, s), 4.00 (1 H, CH_2, dd), 4.26 (1 H, CH_2, dd), 4.41 (1 H, OH, t) and 7.15–7.42 (10 H, 2 × Ph, m) (Found: C, 73.4; H, 7.7; N, 4.3. Calc. for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28%).

m-*Hydroxybenzyl acetate* **15b**. δ_H(250 MHz; $CDCl_3$) 2.10 (3 H, CH_3, s), 5.05 (2 H, CH_2, s), 6.38 (1 H, OH, s), 6.70–7.00 (3 H, Ph, m) and 7.21 (1 H, Ph, t) (Found: C, 65.0; H, 6.1. Calc. for $C_9H_{10}O_3$: C, 65.05; H, 6.07%).

m-*Acetoxybenzyl acetate* **15d**. δ_H(250 MHz; $CDCl_3$) 2.11 (3 H, CH_3, s) 2.29 (3 H, CH_3, s) 5.09 (2 H, CH_2, s), 6.99–7.12 (2 H, Ph, m), 7.23 (1 H, Ph, m) and 7.38 (1 H, Ph, t) (Found: C, 63.5; H, 5.75. Calc. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81%).

p-*Acetoxybenzyl acetate* **14d**. δ_H(250 MHz; $CDCl_3$) 2.10 (3 H, CH_3, s), 2.30 (3 H, CH_3, s), 5.09 (3 H, CH_2, s), 7.08 (2 H, Ph, m) and 7.37 (2 H, Ph, m) (Found: C, 63.45; H, 5.85. Calc. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81%).

p-*Hydroxybenzyl acetate* **14b**. δ_H(250 MHz; $CDCl_3$) 2.09 (3 H, CH_3, s), 5.03 (2 H, CH_2, s), 5.88 (1 H, OH, s), 6.83 (2 H, Ph, m) and 7.24 (2 H, Ph, m) (Found: C, 65.0; H, 6.05. Calc. for $C_9H_{10}O_3$: C, 65.05; H, 6.07%).

2-(p-*Hydroxyphenyl*)*ethanol* **18a**. δ_H(300 MHz; $CDCl_3$) 1.51 (1 H, OH, br), 2.80 (2 H, CH_2, t), 3.82 (2 H, CH_2, m), 5.0–5.2 (1 H, OH, br), 6.73 (2 H, Ph, m) and 7.06 (2 H, Ph, m) (Found: C, 69.6; H, 7.3. Calc. for $C_8H_{10}O_2$: C, 69.55; H, 7.30%).

2-(p-*Acetoxyphenyl*)*ethyl acetate* **18d**. δ_H(300 MHz; $CDCl_3$) 2.03 (3 H, CH_3, s), 2.28 (3 H, CH_3, s), 2.92 (2 H, CH_2, t), 4.26 (2 H, CH_2, t), 7.00 (2 H, Ph, m) and 7.20 (2 H, Ph, m) (Found: C, 64.8; H, 6.4. Calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%).

2-(p-*Hydroxyphenyl*)*ethyl acetate* **18b**. δ_H(300 MHz; $CDCl_3$) 2.05 (3 H, CH_3, s), 2.74 (2 H, CH_2, t), 4.24 (2 H, CH_2, t), 6.20–6.50 (1 H, OH, br), 6.78 (2 H, Ph, m) and 7.05 (2 H, Ph, m) (Found: C, 66.65; H, 6.75. Calc. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%).

1-(p-*Hydroxyphenyl*)*propan-1-ol* **16a**. δ_H(250 MHz; $CDCl_3$) 0.87 (3 H, CH_3, t), 1.61–1.89 (2 H, CH_2, m), 2.18 (1 H, OH, br), 4.52 (1 H, CH, t), 5.91 (1 H, OH, br), 6.78 (2 H, Ph, m) and 7.17 (2 H, Ph, m) (Found: C, 71.0; H, 8.0. Calc. for $C_9H_{12}O_2$: C, 71.03; H, 7.95%).

1-(p-*Acetoxyphenyl*)*propyl acetate* **16d**. δ_H(250 MHz; $CDCl_3$) 0.88 (3 H, CH_3, t), 1.70–2.00 (2 H, CH_2, m), 2.06 (3 H, CH_3, s), 2.27 (3 H, CH_3, s), 5.66 (1 H, CH, t), 7.07 (2 H, Ph, m) and 7.33 (2 H, Ph, m) (Found: C, 66.05; H, 6.85. Calc. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%).

1-(p-*Acetoxyphenyl*)*propan-1-ol* **16c**. δ_H(250 MHz; $CDCl_3$) 0.91 (3 H, CH_3, t), 1.62–1.89 (3 H, CH_2, OH, m), 2.30 (3 H, CH_3, s), 4.60 (1 H, CH, t), 7.05 (2 H, Ph, m) and 7.36 (2 H, Ph, m) (Found: C, 68.05; H, 7.3. Calc. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%).

1-(p-*Hydroxyphenyl*)*propyl acetate* **16b**. δ_H(250 MHz; $CDCl_3$) 0.87 (3 H, CH_3, t), 1.61–1.99 (2 H, CH_2, m), 2.06 (3 H, CH_3, s), 5.60 (1 H, CH, t), 5.80–5.99 (1 H, OH, br), 6.78 (2 H, Ph, m) and 7.17 (2 H, Ph, m) (Found: C, 68.05; H, 7.25. Calc. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%).

1-(o-*Hydroxyphenyl*)*methanol* **13a**. δ_H(250 MHz; $CDCl_3$) 2.29 (1 H, OH, t), 4.87 (2 H, CH_2, d), 6.79–6.89 (2 H, Ph, m), 7.03 (1 H, Ph, d) and 7.10–7.30 (2 H, Ph, OH, m) (Found: C, 67.7; H, 6.55. Calc. for $C_7H_8O_2$: C, 67.73; H, 6.50%).

o-*Hydroxybenzyl acetate* **13b**. δ_H(250 MHz; $CDCl_3$) 2.10 (3 H, CH_3, s), 5.12 (2 H, CH_2, s), 6.71–7.00 (2 H, Ph, m), 7.22–7.28 (2 H, Ph, m) and 7.82 (1 H, OH, s) (Found: C, 64.1; H, 6.05. Calc. for $C_9H_{10}O_3$: C, 65.05; H, 6.07%).

o-*Acetoxybenzyl acetate* **13d**. δ_H(250 MHz; $CDCl_3$) 2.06 (3 H, CH_3, s), 2.32 (3 H, CH_3, s), 5.09 (2 H, CH_2, s) and 7.12–7.51 (4 H, Ph, m) (Found: C, 63.5; H, 5.8. Calc. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81%).

5-*Hydroxy*-1,2,3,4-*tetrahydro*-1-*naphthyl acetate* **19b**. δ_H-(250 MHz; $CDCl_3$) 1.58–2.09 (4 H, 2 × CH_2, m), 2.08 (3 H, CH_3, s), 2.38–2.60 (1 H, CH_2, m), 2.72–2.81 (1 H, CH_2, m), 5.45 (1 H, OH, s), 5.98 (1 H, CH, m), 6.74 (1 H, Ph, d), 6.88 (1 H, Ph, d) and 7.07 (1 H, Ph, t) (Found: C, 69.95; H, 6.85. Calc. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84%).

1,2,3,4-*Tetrahydronaphthalene*-1,5-*diyl diacetate* **19d**. δ_H(250 MHz; $CDCl_3$) 1.69–2.01 (4 H, 2 × CH_2, m), 2.07 (3 H, CH_3, s), 2.31 (3 H, CH_3, s), 2.42–2.63 (1 H, CH_2, m), 2.64–2.80 (1 H, CH_2, m), 6.00 (1 H, CH, m), 6.98 (1 H, Ph, m) and 7.19 (2 H, Ph, m) (Found: C, 67.75; H, 6.5. Calc. for $C_{14}H_{18}O$: C, 67.73; H, 6.50%).

1-(o-*Hydroxyphenyl*)*propan*-1-*ol* **17a**. δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, CH_3, t), 1.86 (2 H, CH_2, m), 3.06 (1 H, OH, br), 4.71 (1 H, CH, t), 6.71–7.00 (3 H, Ph, m), 8.14 (1 H, Ph, m) and 9.05 (1 H, OH, s) (Found: C, 71.0; H, 8.0. Calc. for $C_9H_{12}O_2$: C, 71.03; H, 7.95%).

1-(o-*Acetoxyphenyl*)*propyl acetate* **17d**. δ_H(250 MHz; $CDCl_3$) 0.89 (3 H, CH_3, t), 1.62–2.00 (2 H, CH_2, m), 2.03 (3 H, CH_3, s), 2.34 (3 H, CH_3, s), 5.87 (1 H, CH, t) and 7.01–7.40 (4 H, Ph, m) (Found: C, 66.05; H, 6.9. Calc. for $C_{13}H_{16}O_4$: 66.09; H, 6.83%).

1-(o-*Hydroxyphenyl*)*propyl acetate* **17b**. δ_H(250 MHz; $CDCl_3$) 0.89 (3 H, CH_3, t), 1.70–2.00 (2 H, CH_2, m), 2.03 (3 H, CH_3, s), 5.85 (1 H, CH, t) and 7.20–7.40 (5 H, Ph, OH, m) (Found: C, 68.0; H, 7.3. Calc. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%).

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