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Enantioselective monoreduction of different 1,2-diaryl-1,2-diketones catalysed by lyophilised whole cells from *Pichia glucozyma*

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ABSTRACT

In this work we have studied the monoreduction of different 1,2-diaryl-ethanediones (benzils, **1**) with lyophilised whole cells from *Pichia glucozyma* CBS 5766, using the diphenyl compound (benzil, **1a**) as model substrate, and extended the enantioselective reduction to structurally different symmetric benzils for producing enantiomerically pure or enriched benzoins (α-hydroxyketones **2**) in high yields and very short reaction times. In order to study the regio- and stereoselectivity of this biocatalyst, we examined the reduction of diaryldiketones formed from different aryl moieties, to obtain symmetric and asymmetric crossed-benzoins. This methodology is conducted under very mild reaction conditions (aqueous media with small amounts of DMSO for solubilising the substrates, $T=28\,^{\circ}C$), therefore constituting a green alternative compared to other reported procedures for obtaining homochiral benzoins.

1. Introduction

Enantiomerically pure α-hydroxyketones are useful building blocks in the synthesis of different pharmaceuticals and fine chemicals, such as antitumoral antibiotics (Olivomycin A and Chromomycin A_3[1]), inhibitors of farnesyltransferase (Kurasoin A and B[2]), inhibitors of amiloid-β protein production[3] or antidepressant drugs (bupropion and its metabolites[4]). More concretely, benzoins (1,2-diaryl-2-hydroxyethanone structures, **2**, Scheme 1) are useful as urease inhibitors[5] or as building blocks for the synthesis of different heterocycles.[6] Homochiral benzoins can be obtained either chemically through benzoin condensation (catalysed by chiral thiazolium or triazolium salts,[7] chiral metallophosphites[8]) or enzymatically, through benzoin condensation starting from racemic benzoins and catalysed by several thiamine-diphosphate-dependent enzymes,[9] as well as by fungal deracemization[10] or dynamic kinetic resolution of racemic benzoins.[11]

Another enzymatic strategy arises via the enantioselective reduction of α-diketones catalysed by alcohol dehydrogenases. In fact, the use of these biocatalysts, mainly as whole cells, represents an attractive alternative to classical chemical synthesis, due to the mild and eco-friendly conditions of the reactions, conducted in aqueous media.[12] More concretely, biocatalytic reduction of benzil (1,2-diphenylethanedione **1a**, Scheme 1) to chiral benzoin **2a** (or related structures) has been described by using different microorganisms and operational conditions,[13] leading in some cases to the desired α-hydroxyketone and in other cases to the corresponding α-diol.[13b] In fact, this process was firstly reported with the most classical bio-reduction catalyst (baker's yeast, whole cells of *Saccharomyces cerevisiae*), although the reaction proceeded with no enantioselectivity.[13c] More recent studies with this same biocatalyst[13g] show the production of (*R*)-**2a** with 50% ee, while the use of organic cosolvents leaded to higher enantiopurity values.[13j]

Some other microorganisms have been also used for the bioreduction of benzils, always in a 'fresh cells' state, meaning with this term the straight use of the cells after the fermentation process; thus, the use of *Rhizopus oryzae* cells allowed good enantioselectivity, although at the expense of a low reaction rate and furnishing hydrobenzoin (1,2-diphenyl-1,2-ethanediol) as well.[13h] Cells from *Xanthomonas oryzae* and *Bacillus cereus* were shown to be selective and reduce **1a** only to **2a**, the first one yielding only (*R*)-**2a** also under low reaction rates,[13a] while the latest one shows a fair stereopreference towards (*S*)-**2a** production.[13e,f] In this case the enzyme responsible from this reaction (benzil reductase) from

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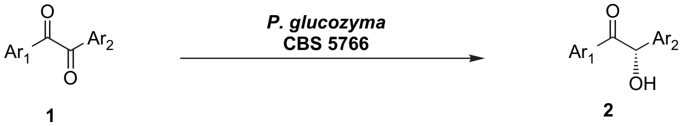


Ar^1 = Ar^2 = Ph	**1a**
Ar^1 = Ar^2 = 2-furanyl	**1b**
Ar^1 = Ar^2 = 3-furanyl	**1c**
Ar^1 = Ar^2 = 2-thienyl	**1d**
Ar^1 = Ar^2 = 3-thienyl	**1e**
Ar^1 = Ar^2 = 4-methoxyphenyl	**1f**
Ar^1 = Ar^2 = 4-methylphenyl	**1g**
Ar^1 = Ph, Ar^2 = 1-naphthyl	**1h**
Ar^1 = Ph, Ar^2 = 2-naphthyl	**1i**

Ar^1 = Ar^2 = Ph	**(*S*)-2a**
Ar^1 = Ar^2 = 2-furanyl	**(*S*)-2b**
Ar^1 = Ar^2 = 3-furanyl	**(*S*)-2c**
Ar^1 = Ar^2 = 2-thienyl	**(*R*)-2d**
Ar^1 = Ar^2 = 3-thienyl	**(*S*)-2e**
Ar^1 = Ar^2 = 4-methoxyphenyl	**(*S*)-2f**
Ar^1 = Ar^2 = 4-methylphenyl	**(*R*)-2g**
Ar^1 = Ph, Ar^2 = 1-naphthyl	**(*S*)-2h**
Ar^1 = 1-naphthyl, Ar^2 = Ph	**(*S*)-2h'**
Ar^1 = Ph, Ar^2 = 2-naphthyl	**(*S*)-2i**
Ar^1 = 2-naphthyl, Ar^2 = Ph	**(*S*)-2i'**

Scheme 1. Stereoselective reduction of 1,2-diaryl-ethanediones (**1**) to the corresponding benzoins (**2**).

B. cereus was isolated, characterised and over-expressed in *Escherichia coli*.[13e] Very recently, the use of fresh resting cells from *Aspergillus oryzae* and *Fusarium roseum* has been also described.[13k]

On the other hand, lyophilised cells from *Pichia glucozyma* have been described as easy-to-handle biocatalyst for stereoselective reduction of aromatic ketones.[14] In this work we have studied the reduction of **1a** with dry cells of *P. glucozyma* CBS 5766 and extended the stereoselective reduction to structurally different symmetric benzils for producing enantiomerically pure or enriched benzoins (Scheme 1) in high yields and very short times. In order to study the regio- and stereoselectivity of this biocatalyst, we examined the reduction of diaryldiketones formed from different aryl moieties, to obtain symmetric and asymmetric crossed-benzoins.

2. Results and discussion

Benzil (**1a**, Scheme 2) was used as the standard substrate to study the ability of different microorganisms towards the reduction of this kind of aromatic diketones. Among the lyophilised yeasts tested (*Pichia minuta* CBS 1708, *Pichia fermentans* DPVPG 2770, *P. glucozyma* CBS 5766, *Pichia etchellsii* CBS 2011, *Candida utilis* CBS 621 and *Kluyveromyces marxianus* CBS 397), best results were obtained with lyophilised cells from *P. glucozyma*.

Thus, lyophilised cells from *P. glucozyma* were suspended in a volume of phosphate buffer (pH 7.0, 0.1 M) to reach a biomass concentration of 10 g/L (dry cells). Substrate (42 mg) was dissolved in DMSO (1 mL) and the solution obtained was added to the biotransformation medium to reach a final concentration of substrate of 0.4 mg/mL.

Different concentrations of lyophilised cells were used, in order to find the best conditions to carry out the reduction of different diketones. The results are shown in Table 1; as can be seen, increasing the amount of catalyst from 10 to 20 g/L, both the yield and the ee value increased. The reason why the enantioselectivity is lower with lower amounts of lyophilised cells can be due to the higher concentration of substrate experienced by cells: it has been previously described that, in the presence of multiple dehydrogenases (as in a whole cell system) with different enantiopreferences, a direct correlation between substrate concentration and enantioselectivity can be observed.[15] This can be explained by the hypothesis that at higher substrate concentration all the occurring enzymes are active, while at lower concentrations only the ones with the higher affinity display their activity. As can be seen in Table 1 under the optimal conditions, adding 20 or 30 g/L of lyophilised cells to the medium, the reaction was complete after 3 h, yielding only (*S*)-**2a** as reaction product, with very high conversions (around 99%) and similar ee values (75%). The reduction of **1a** was carried out again and the reaction progress was followed, finding out that the highest conversion was reached after 2.5 h, not detecting any diol (hydrobenzoin, **3**).

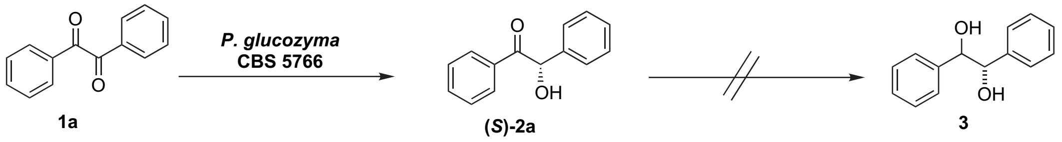
Table 1
Reduction of benzil (**1a**) catalysed by different concentrations of lyophilised cells of *P. glucozyma* CBS 5766

P. glucozyma CBS 5766 (lyophilised cells, g/L)	Reaction time (h)	Conversion (%)	ee (%) of (*S*)-2a
10	3	87	54
20	3	99	75
30	3	99	74

As detailed in Section 1, (*S*)-**2a** had been previously obtained by whole cells-catalysed reduction of **1a**, but after long reaction times (whole cells from *B. cereus*, 12 h,[13f] Baker's yeast dry cells, 72 h;[13g] *F. roseum* fresh cells, 24 h[13k]). Our new biocatalyst is able to reduce **1a** *in just 3 h* with high yields and enantiomeric excess. Furthermore, only minimum traces of the corresponding diol (hydrobenzoin) were observed when the reaction was allowed to reach 24 h. For the other microorganism recently described by Demir et al.,[13k] *Aspergillus oryzae* OUT5048 fresh cells, good enantioselectivity and yield in (*S*)-**2a** are obtained also after 3 h, but no indication of the amount of catalyst used in the bio-reduction of **1a** is presented, so no comparison can be drawn with our conditions.

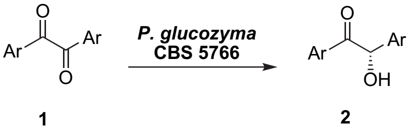
Therefore, 20 g/L of lyophilised cells of *P. glucozyma* were employed for further studying the asymmetric bio-reduction of different diaryldiketones into the corresponding benzoins (Table 2).

Some of the substrates employed in the biotransformation (shown in Table 2) such as benzil (**1a**) and 1,2-bis(4-



Scheme 2. Stereoselective reduction of benzil (**1a**) to the homochiral *S*-benzoin(*S*-**2a**) and hydrobenzoin (**3**).

Table 2
Substrates of the reduction catalysed by lyophilised cells of *P. glucozyma* CBS 5766



Substrate	Ar	Product	Reaction time	Conversion (%)	ee (%)
1a	Ph	(*S*)-**2a**	2.5 h	99	75
1b	2-Furanyl	(*S*)-**2b**	2.5 h	99	84
1c	3-Furanyl	(*S*)-**2c**	2.5 h	99	98
1d	2-Thienyl	(*R*)-**2d**	2.5 h	86	62
1e	3-Thienyl	(*S*)-**2e**	5 h	97	57
1f	4-Methoxyphenyl	(*S*)-**2f**	7 days	7	99
1g	4-Methylphenyl	(*R*)-**2g**	7 days	97	76

methylphenyl)ethane-1,2-dione (**1g**) are commercially available. On the other hand, 1,2-di(furan-2-yl)ethane-1,2-dione (**1b**), 1,2-di(furan-3-yl)ethane-1,2-dione (**1c**), 1,2-di(thiophen-2-yl)-ethane-1,2-dione (**1d**), 1,2-di(thiophen-3-yl)ethane-1,2-dione (**1e**) and 1,2-bis(4-methoxyphenyl)ethane-1,2-dione (**1f**) were synthesised by oxidation of the corresponding benzoins (1,2-di(furan-2-yl)-2-hydroxyethanone (**2b**), 1,2-di(furan-3-yl)-2-hydroxyethanone (**2c**), 2-hydroxy-1,2-di(thiophen-2-yl)ethanone (**2d**), 2-hydroxy-1,2-di(thiophen-3-yl)ethanone (**2e**) and 2-hydroxy-1,2-bis(4-methoxyphenyl)ethanone (**2f**)), following the protocol described by Corey and Suggs,[16] as described in Section 4. Previously, **2c**, **2d** and **2e** were synthesised following the procedure formerly described.[11a] Biotransformation products were purified by silica-gel chromatography and the optical rotations were measured. The absolute configurations of these products were assigned according to a correlation with data from the literature[9a,17] and by comparison of HPLC retention times with reference compounds.

The data depicted in Table 2 illustrate the conversions and ee values obtained. The reduction of aryl-substituted benzoin derivatives was different to non-substituted benzoins. In fact, for **1f**, only 7% conversion was reached after 2.5 h or longer reaction times. Poor conversion values for this substrate have been previously reported,[13g,k] showing how when the electron donating methoxy group is present in the *para* position the reduction proceeds more slowly. On the other hand, all reactions' products were assigned to be (*S*), except those ones coming from the reduction of **1d** and **1g**; in the first case, the stereorecognition is similar, but the absolute configuration is altered because of the preference of the sulfur atom. Nevertheless, the reduction of **1g** conducted to (*R*)-**2g**, the opposite enantiomer to the expected one, and once again this reaction was also slower than non-substituted benzoins: after 2.5 h, only 6% conversion was reached; the reaction was not complete until 7 days (97% conversion, 76% ee, Table 2). These results are anyway better than those described for the reduction of **1g** with Baker's yeast dry cells by Mahmoodi and Mohammadi[13g] (17% yield, 36% ee), although these authors did not observe any change in the stereorecognition for this substrate, due to the fact that with Baker's yeast all the reduction products are *R*. The change in stereobias for this substrate could be explained taking into account the possible presence of more than one alcohol dehydrogenase (ADH) with different enantioselectivity inside the cell, as has been described for several microorganisms.[18] If this is the case, for those substrates, which are reduced more slowly (**1f** and **1g**) it could be assumed that they are not recognised by ADH that catalyses the reduction of the compounds **1a**–**1e** (working very quickly on these substrates), so that after prolonged reaction time another ADH could start acting on them.

Five member heteroaryl moieties (**1b**–**e**) were quite well tolerated. Thus, (*S*)-**2c** was obtained in high yield and enantiomeric excess. Through lipase kinetic resolution of **2c**, (*S*)-**2c** is obtained in poor yields and enantiomeric excess, due to the spontaneous and quick oxidation that this substrate suffers at high temperatures.[9d] Nevertheless, by this methodology, (*S*)-**2c** can be isolated in very good yield and enantiopurity, by using very mild reaction conditions. In the literature it has been described how the antipode enantiomer, (*R*)-**2c**, can be obtained through benzoin condensation catalysed by BAL,[9d,19] so that these two biocatalytical approaches are complementary in the synthesis of both enantiomers of **2c**.

In order to test the potential of this biocatalyst, we decided to carry out the reduction of crossed-diaryldiketones, formed from non-identical aromatic moieties. The use of asymmetric α-hydroxyketones as substrates in lipase-metal combo catalysed dynamic kinetic resolution (DKR) is not possible, due to the fact that the intermediate diketone obtained in situ with the oxidising action of the ruthenium catalyst[11] would furnish a random mixture of the corresponding benzoins. Very recently we have described a methodology to get enantiopure acyloins,[20] through a 'hidden-acyloin' DKR employing lipase B from *Candida antarctica* (CAL-B); but this process is not applicable in the case of benzoins, because of the great size of the substrates, which would be too bulky for the CAL-B recognition. For this reason, regio- and stereoselective reduction of asymmetric diaryldiketones would constitute an elegant methodology to obtain enantiopure crossed-benzoins.

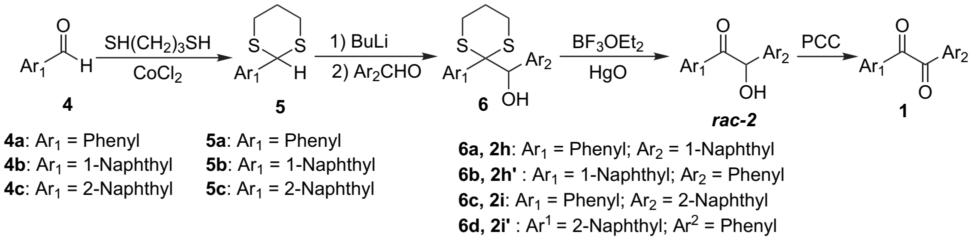
Crossed-diaryldiketone compounds were obtained by oxidation of the correspondent benzoins previously synthesised. It is well known that crossed-benzoins cannot be synthesised through the classical benzoin condensation procedure, due to the formation of four possible products in the reaction. Therefore we decided to use another methodology of α-hydroxycarbonyl compounds synthesis based on the use of 1,3-dithianes, as depicted in Scheme 3.

The results obtained in the reduction of these asymmetrical diaryldiketones are shown in Table 3.

The reduction of **1h** and **1i** could lead to two pairs of enantiomers (Scheme 4), so that all the possible compounds were previously synthesised in order to identify correctly the biotransformation products by HPLC and their UV absorption spectra, as described in Section 4.

Analysing the reduction products obtained from **1h**, (*S*)-**2h**′ was obtained after 20 h and just traces of (*S*)-**2h** could be detected.

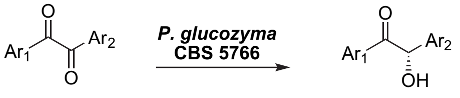
On the other hand, the reduction of **1i** led to two different products: (*R*)-**2i** and (*S*)-**2i**′. The biotransformation was carried out following the same procedure as the one described for the reduction of symmetric benzoins. After 24 h, the major product was



Scheme 3. Synthesis of diaryldiketones (**1**) from different aromatic aldehydes.

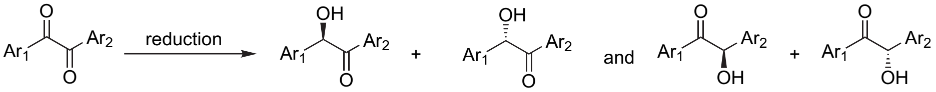
Table 3

Biocatalysed reduction of assymetrical diaryldiketones



1 **2**

Ar_1	Ar_2	Crossed benzoin	Benzil	Reduction products	Conversion (%)	ee (%)	Reaction time (h)
Phenyl	1-Naphthyl	*rac*-**2h**	**1h**	(*S*)-**2h**′/(*S*)-**2h**	76/4	91/99	20
1-Naphthyl	Phenyl	*rac*-**2h**′					
Phenyl	2-Naphthyl	*rac*-**2i**	**1i**	(*S*)-**2i**′/(*R*)-**2i**	63/28	53/99	20
2-Naphthyl	Phenyl	*rac*-**2i**′					



Scheme 4. Possible products of reduction of asymmetric 1,2-diaryl-1,2-ethanediones.

(*S*)-**2i**′ (63% yield) and the minor one (*R*)-**2i**. To understand this stereobias, it has to be considered that, as it has been described,[14] the reductions of different compounds catalysed by this microorganism generally follow the classical Prelog's rule[21] that predicts the stereochemistry of the obtained alcohol according to the relative size of substituents, through a delivery of the equivalent hydride from the *re* face, yielding the *S*-alcohol.

The mechanism of the reduction via alcohol dehydrogenases has been studied.[22] The enzyme, as well as a cofactor, requires a metal divalent cation (normally Zn^{2+}) to fix the substrate in the active site, through interaction with the carbonyl moiety of the substrate, placing the *re* side of the substrate ready to suffer the hydride transfer. Thus, we could assume that the dicarbonyl moiety of the molecule should be placed approximately in the same position to the carbonyl group of single ketones to interact with the Zn^{2+} cation, and therefore the delivery of the hydride should be carried out via the *re* side, as shown in a tentative Prelog model represented in Scheme 5. In the reduction of **1h**, both aromatic moieties (phenyl and 1-naphthyl) could be recognised both in the medium (**M**) and in the large (**L**) sites around the diketone structure, leading to a mixture of *S*-**2h**′ (major product, *right fitting*) and *S*-**2h** (minor product, *wrong fitting*), obtained through the hydride delivery via the *re* face. Nevertheless, the different geometry of the 2-naphthyl moiety must hamper the *wrong fitting*, fixing the *right fitting* and therefore allowing two different hydride transfers to both carbonyl groups via the *re* face, leading to a mixture of *S*-**2′i** and *R*-**2i**. For sure, it is clear that this is a tentative model, supposing planarity in the substrates geometry, which should be confirmed by more experimental data.

In fact, further experiments are being conducted in our laboratory to optimise this biocatalytic reduction, elucidate its full potential and apply it to a more broad range of substrates.

3. Conclusion

In this paper we present the bio-reduction of different aromatic diketones, as a clean methodology to obtain enantiomerically pure benzoins. The advantages of using lyophilised cells to catalyse the reduction of benzil and benzil derivatives in mild reaction conditions are shown reaching very high yields and enantiomeric excess, in less than 3 h in most cases. More important, not only stereoselective but also regioselective bio-reductions have been investigated. Significant developments have been done in the formation of asymmetric crossed-benzoins through the microbial reduction of aromatic diketones. This biocatalytic reduction protocol represents a potential useful tool for a green and sustainable synthesis of this kind of compounds.

4. Experimental

4.1. General

Benzil, 2-bis(4-methylphenyl)ethane-1,2-dione, benzoin, 1,2-di(furan-2-yl)-2-hydroxyethanone, 2-hydroxy-1,2-bis(4-methoxyphenyl)ethanone, 1-naphthaldehyde, 2-naphthaldehyde, 1,3-propanedithiol, 2-phenyl-1,3-dithiane, BF_3OEt_2 and PCC were purchased from Sigma Aldrich, and used as-received.

P. glucozyma was obtained from (Centraal Bureau voor Schimmelcultures, Utrecht, The Netherlands).

HPLC analyses were performed with a chiral column Chiracel OD-H (cellulose carbamate, 25 cm×0.46 cm i.d.) at room temperature using HPLC (mobile phase of *n*-hexane/2-propanol, 90/10 at a flow rate of 1 mL/min).

NMR spectra were recorded on a Bruker AC-250. Chemical shifts (δ) are reported in parts per million (ppm) relative to $CHCl_3$ (^1H: δ 7.27 ppm) and $CDCl_3$ (^{13}C: δ 77.0 ppm).

Column chromatography purifications were conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminium sheets precoated with silica gel; the spots were visualised under UV light (λ=254 nm).

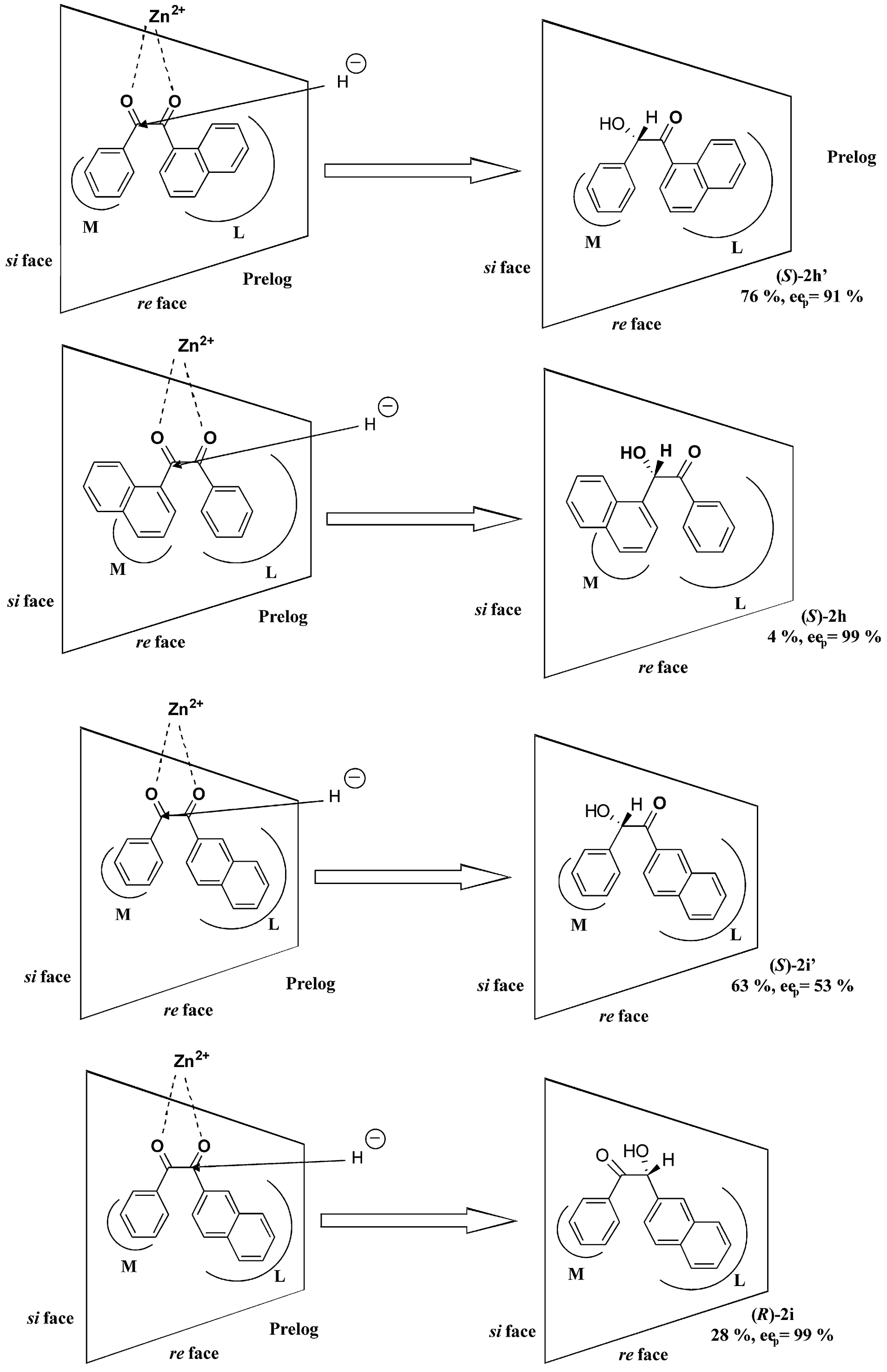
4.2. Microorganisms, media and culture conditions

P. glucozyma CBS 5766 was routinely cultured in 750 mL Erlenmeyer flasks with 100 mL of malt broth pH 6.0 for 48 h, at 27 °C on a rotary shaker set at 200 rpm.

Lyophilised cells were obtained from a culture performed in 3.0 L fermenters with 1.0 L of malt broth pH 6.0 for 48 h, at 27 °C and agitation speed 100 rpm. Fresh cells from submerged cultures were centrifuged and washed with 0.1 M phosphate buffer, pH 7.0; washed cells were lyophilised. The amounts of lyophilised cells obtained were in the range 8.1–8.3 g.

4.3. Biotransformation conditions

Reductions were carried out with a reaction volume of 10 mL with cells (200 mg, 20 g/L) resuspended in 0.1 M phosphate buffer with 5% glucose, pH 7.0. After 45 min of incubation, the substrate (0.02 mmol, 4.2 mg) dissolved in 0.1 mL of dimethylsulfoxide was



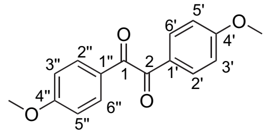
Scheme 5. Hypothetical application of Prelog's rule to the reduction of crossed 1,2-diaryl-1,2-ethanediones.

added and the incubation continued for 24 h under magnetical stirring at 28 °C.

4.4. General procedure for the synthesis of aromatic diketones (1b–f and 1h–i)

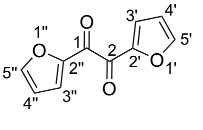
4.4.1. *Synthesis of 1,2-bis(4-methoxyphenyl)ethane-1,2-dione (**1f**)*[16]

Pyridinium chlorochromate (565 mg, 2.62 mmol) was suspended in 3.5 mL of CH_2Cl_2 in a 50 mL round bottom flask fitted with a reflux condenser. 2-Hydroxy-1,2-bis(4-methoxyphenyl)-ethanone (500 mg, 1.83 mmol) solved in 300 μL of CH_2Cl_2, was added and the mixture was stirred. The reaction progress was followed by TLC. After 6 h, 5 mL of ether was added and the supernatant decanted from the black residue. This solid was washed with ether (3×5 mL) and the combined organic solution was evaporated under vacuum. The resulting oil was purified by silica-gel column chromatography (CH_2Cl_2), collecting 300 mg (1.11 mmol) of yellow solid (60% yield). IR (film): 3000, 1648 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.64; H, 5.15.



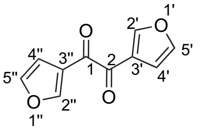
^1H NMR (250 MHz, $CDCl_3$): δ 4.01 (s, 6H, OCH_3), 7.24 (ddd, 4H, J=9.7, J=2.7, J=2.1 Hz, H-3′ and H-5′, H-3″ and H-5″), 8.09 (ddd, 4H, J=9.7, J=2.7, J=2.1 Hz, H-2′ and H-6′, H-2″ and H-6″). ^{13}C NMR (63 MHz, $CDCl_3$): δ 56.08 ($2CH_3$), 114.70 (C3′, C5′, C3″ and C5″), 132.82 (C2′, C6′, C2″ and C6″), 126.67 (C1′ and C1″), 165.27 (C4′ and C4″), 193.96 (C1 and C2).

*4.4.2. 1,2-Di(furan-2-yl)ethane-1,2-dione (**1b**)*



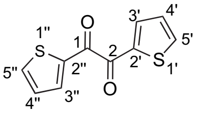
IR (CH_2Cl_2): 1643 cm^{-1}. Anal. Calcd for $C_{10}H_6O_4$: C, 63.16; H, 3.18. Found: C, 62.80; H, 3.00. ^1H NMR (250 MHz, $CDCl_3$): δ 6.58 (dd, 2H, J=3.7, J=1.7 Hz, H-4′ and H-4″), 7.59 (dd, 2H, J=3.7, J=0.7 Hz, H-3′ and H-3″), 7.72 (dd, 2H, J=1.7, J=0.7 Hz, H-5′ and H-5″). ^{13}C NMR (63 MHz, $CDCl_3$): δ 113.55 (C4′ and C4″), 125.26 (C3′ and C3″), 149.81 (C5′ and C5″), 149.87 (C2′ and C2″), 177.23 (C1 and C2).

*4.4.3. 1,2-Di(furan-3-yl)ethane-1,2-dione (**1c**)*



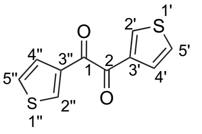
Anal. Calcd for $C_{10}H_6O_4$: C, 63.16; H, 3.18. Found: C, 62.50; H, 3.05. ^1H NMR (250 MHz, $CDCl_3$): δ 6.93 (d, 2H, J=1.51 Hz, H-4′ and H-4″), 7.49 (t, 2H, J=1.60 Hz, H-5′ and H-5″), 8.53 (s, 2H, H-2′ and H-2″). ^{13}C NMR (63 MHz, $CDCl_3$): δ 109.5 (C4′ and C4″), 123.35 (C3′ and C3″), 144.37 (C5′ and C5″), 152.30 (C2′ and C2″), 184.49 (C1 and C2).

*4.4.4. 1,2-Di(thiophen-2-yl)ethane-1,2-dione (**1d**) (64% yield)*



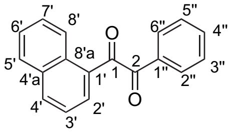
IR (CH_2Cl_2): 1652 cm^{-1}. Anal. Calcd for $C_{10}H_6O_2S_2$: C, 54.03; H, 2.72; S, 28.85. Found: C, 53.58; H, 2.60; S, 28.50. ^1H NMR (250 MHz, $CDCl_3$): δ 7.24 (dd, 2H, J=4.8, J=4.0 Hz, H-4′ and H-4″), 7.88 (dd, 2H, J=4.9, J=1.0 Hz, H-3′ and H-3″), 8.10 (dd, 2H, J=3.9, J=1.0 Hz, H-5′ and H-5″). ^{13}C NMR (63 MHz, $CDCl_3$): δ 129.14 (C4′ and C4″), 137.75 (C5′ and C5″), 137.99 (C3′ and C3″), 139.01 (C2′ and C2″), 182.86 (C1 and C2).

*4.4.5. 1,2-Di(thiophen-3-yl)ethane-1,2-dione (**1e**) (70% yield)*



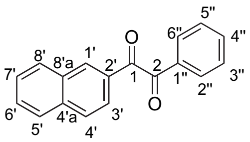
IR (CH_2Cl_2): 1636 cm^{-1}. Anal. Calcd for $C_{10}H_6O_2S_2$: C, 54.03; H, 2.72; S, 28.85. Found: C, 53.70; H, 2.50; S, 28.50. ^1H NMR (250 MHz, $CDCl_3$): δ 7.24 (dd, 2H, J=4.9, J=4 Hz, H-4′ and H-4″), 7.88 (dd, 2H, J=4.9, J=1.2 Hz, H-5′ and H-5″), 8.0 (dd, 2H, J=3.9, J=1.2 Hz, H-2′ and H-2″). ^{13}C NMR (63 MHz, $CDCl_3$): δ 128.14 (C4′ and C4″), 137.75 (C5′ and C5″), 138.0 (C2′ and C2″), 139.01 (C3′ and C3″), 182.87 (C1 and C2).

*4.4.6. 1-(Naphthalen-1-yl)-2-phenylethane-1,2-dione (**1h**)*



IR (film): 1654, 1660 cm^{-1}. Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65. Found: C, 82.40; H, 4.76. ^1H NMR (250 MHz, $CDCl_3$): δ 7.43 (m, 3H, H-3″, 4″and 5″), 7.56 (m, 2H, H-3′ and H-6′), 7.66 (m, 1H, H-7′), 7.85 (td, 2H, J=8.4, J=1.0 Hz, H-2″ and H-6″), 7.94 (m, 1H, H-5′), 7.97 (m, 1H, H-2′), 8.05 (d, 1H, J=8.1 Hz, H-4′), 9.24 (d, 1H, J=8.6 Hz, H-8′). ^{13}C NMR (63 MHz, $CDCl_3$): δ 124.87 (C8′), 126.37 and 127.57 (C3′ and C6′), 128.98 (C8′a), 129.24 (C5′), 129.49 (C2″ and C6″), 129.92 (C2′), 130.47 (C3″ and C5″), 131.35 (C4′a), 133.74 (C1″), 134.49 (C1′), 135.22 (C4′), 135.60 (C7′), 136.45 (C4″), 195.06 (C2), 197.62 (C1).

*4.4.7. 1-(Naphthalen-2-yl)-2-phenylethane-1,2-dione (**1i**)*

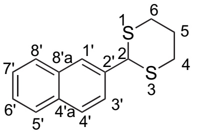


IR (film): 3087, 1667 cm^{-1}. Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65. Found: C, 82.00; H, 4.77. ^1H NMR (250 MHz, $CDCl_3$): δ 7.52 (m, 5H, H-Ph), 7.83 (m, 3H, H-4′, H-6′ and H-7′), 7.94 (m, 2H, H-5′ and H-8′), 8.03 (dd, 1H, J=8.6, J=1.7 Hz, H-3′), 8.33 (s, 1H, H-1′). ^{13}C NMR (63 MHz, $CDCl_3$): δ 124.06 (C3′), 127.64 (C7′), 128.40 (C5′), 129.50 (C4′), 129.64 (C6′), 130.01 and 130.38 (C2″ and C6″), 130.45 (C3″, C5″ and C-8′), 130.70 (C8′a), 132.70 (C4′a), 133.50 (C1″), 134.06 (C1′), 135.9 (C4″), 136.82 (C2′), 195.13 (C1 and C2).

4.5. General procedure for the synthesis of racemic crossed-benzoins (2h, 2h′, 2i and 2i′)

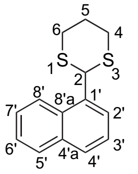
*4.5.1. Synthesis of 2-(naphthalen-2-yl)-1,3-dithiane (**5c**)*

1,3-Propanedithiol (602 μL, 6 mmol) was added to a solution of 2-naphthaldehyde (781 mg, 5 mmol) in acetonitrile (15 mL). $CoCl_2$ (30 mg, 5 mmol %) was added and the mixture was stirred at room temperature. After 15 h the solvent was evaporated under reduced pressure and the product was purified by column chromatography on silica gel, yielding 1.131 g (4.6 mmol, 92% yield). IR (film): 3055, 2924, 2885, 1505, 1278 cm^{-1}. Anal. Calcd for $C_{14}H_{14}S_2$: C, 68.25; H, 5.73; S, 26.03. Found: C, 68.10; H, 5.60; S, 25.85.



^1H NMR (250 MHz, $CDCl_3$): δ 2.01 (m, 1H, H-5), 2.24 (m, 1H, H-5), 2.98 (m, 2H, H-4 and H-6), 3.15 (m, 2H, H-4 and H-6), 5.37 (s, 1H, H-2), 7.52 (ddd, 2H, J=5.9, J=2.9, J=0.8 Hz, H-1′ and H-3′), 7.64 (dd, 1H, J=8.6, J=1.8, J=2.1 Hz, H-6′), 7.86 (m, 3H, H-4′, H-7′ and H-8′), 8.0 (d, 1H, J=1.4 Hz, H-5′). ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.58 (C5), 32.58 (C4 and C6), 51.99 (C2), 126.11 (C6′), 126.73 (C7′), 126.76 (C1′), 127.27 (C4′), 128.17 (C8′), 128.50 (C5′), 128.96 (C3′), 133.67 (C4′a), 133.72 (C8′a), 133.87 (C2′).

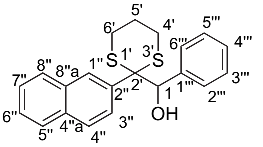
4.5.2. 2-(Naphthalen-1-yl)-1,3-dithiane (**5b**) (90% yield)



IR (film): 3049, 2930, 2888, 1506, 1417, 1272 cm^{-1}. Anal. Calcd for $C_{14}H_{14}S_2$: C, 68.25; H, 5.73; S, 26.03. Found: C, 68.07; H, 5.55; S, 25.90. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.03 (m, 2H, H-5) and 3.25 (m, 4H, H-4 and H-6), 5.96 (s, 1H, H-2), 7.56 (m, 3H, H-2′, H-3′ and H-6′), 7.87 (m, 3H, H-4′, H-5′ and H-7′), 8.34 (d, 1H, J=8.4 Hz, H-8′). ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.91 (C5), 33.20 (C4 and C6), 48.75 (C2), 123.70 (C2′), 126.01 (C8′), 126.28 (C6′), 126.61 (C7′), 126.75 (C4′), 129.38 (C3′), 129.46 (C5′), 130.59 (C8′a), 134.28 (C4′a), 135.34 (C1′).

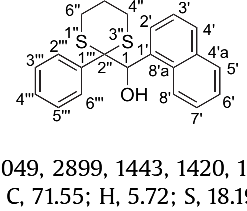
4.5.3. Synthesis of (2-(naphthalen-2-yl)-1,3-dithian-2-yl)phenylmethanol (**6d**)

Compound **5c** (522 mg, 2.12 mmol) was dissolved in 5 mL of anhydrous THF and BuLi (1.39 mL, 2.22 mmol) was added drop wise. The mixture was stirred at −78 °C for 1 h and then benzaldehyde (280 μL, 2.75 mmol) was added. The reaction was left to warm to room temperature. After 5 h, the reaction was quenched by addition of 5 mL of NH_4Cl 0.5 M. The organic phase was collected and dried with anhydrous $NaSO_4$. The solution was filtered and the solvent was evaporated. The product was purified by column chromatography (SiO_2, CH_2Cl_2), yielding 605 mg of a white solid (1.71 mmol, 81% yield). IR (film): 3453, 3055, 3020, 2904, 1502, 1450, 1277, 1188 cm^{-1}. Anal. Calcd for $C_{21}H_{20}OS_2$: C, 71.55; H, 5.72; S, 18.19. Found: C, 69.68; H, 5.70; S, 17.30.



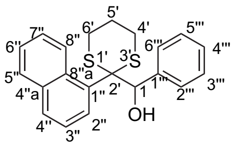
^{1}H NMR (250 MHz, $CDCl_3$): δ 1.86 (m, 2H, H-5′), 2.61 (m, 4H, H-4′ and H-6′), 5.01 (s, 1H, OH), 5.20 (s, 1H, H-1), 6.77 (m, 2H, H-2‴ and H-6‴), 7.08 (m, 3H, H-3‴, H-4‴ and H-5‴), 7.41 (m, 2H, H-1″ and H-3″), 7.71 (m, 4H, H-4″, H-6″, H-7″ and H-8″), 8.10 (d, 1H, J=0.7 Hz, H-5″). ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.17 (C5′), 27.50 and 27.75 (C4′ and C6′), 67.0 (C2′), 81.63 (C1), 126.50 (C6″), 126.94 (C7″), 126.51 (C1″), 126.94 (C4″), 127.76 (C2‴ and C6‴), 128.17 (C8″), 128.33 (C4‴), 128.64 (C5″), 128.90 (C3″), 131.03 (C3‴ and C5‴), 132.89 (C4″a), 133.50 (C8″a), 135.25 (C2″), 137.59 (C1‴).

4.5.4. Naphthalen-1-yl(2-phenyl-1,3-dithian-2-yl)methanol (**6a**) (80% yield)



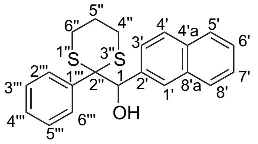
IR (film): 3480, 3049, 2899, 1443, 1420, 1061, 1272 cm^{-1}. Anal. Calcd for $C_{21}H_{20}OS_2$: C, 71.55; H, 5.72; S, 18.19. Found: C, 70.87; H, 5.65; S, 17.77. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.60 (m, 6H, H-4″, H-5″ and H-6″), 3.11 (d, 1H, J=3.7 Hz, H-1), 5.74 (d, 1H, J=3.7 Hz, H-OH), 7.18 (m, 7H, H-Ar), 7.64 (m, 5H, H-Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.27 (C5″), 27.64 (C6″), 27.91 (C4″), 68.10 (C2″), 68.40 (C1), 123.89 (C8′), 124.67 (C2′), 125.37 (C3′), 125.76 (C6′), 127.25 (C7′), 127.88 (C4‴), 128.56 (C3‴ and 5‴), 128.78 (C4′), 129.23 (C5′), 131.63 (C2‴ and 6‴), 132.30 (C8′a), 133.28 (C4′a), 134.15 (C1‴), 137.32 (C1′).

4.5.5. (2-(Naphthalen-1-yl)-1,3-dithian-2-yl)phenylmethanol (**6b**) (82% yield)



IR (film): 3056, 2923, 1587, 1454 cm^{-1}. Anal. Calcd for $C_{21}H_{20}OS_2$: C, 71.55; H, 5.72; S, 18.19. Found: C, 71.10; H, 5.66; S, 17.70. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.62 (m, 6H, H-4′, H-5′ and H-6′), 6.71 (d, 1H, J=3.2 Hz, H-1), 6.80 (d, 1H, J=3.2 Hz, OH), 6.98 (m, 5H, H-Ph), 7.19 (m, 1H, H-2″), 7.40 (m, 2H, H-6″ and H-3″), 7.69 (m, 1H, H-7″), 7.82 (m, 2H, H-4″ and H-5″), 9.05 (dd, 2H, J=3, J=2.1 Hz, H-8″). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.57 (C5′), 27.55 and 28.13 (C4′ and C6′), 66.90 (C2′), 78.16 (C1), 125.14 (C2″), 125.34 (C8″), 1265.78 (C6″), 127.30 (C7″), 127.59 (C4″), 127.99 (C3″), 128.22 (C2‴ and C6‴), 130.07 (C4‴), 130.39 (C3‴ and C5‴), 131.63 (C8″a), 132.10 (C5″), 133.87 (C4″a), 135.91 (C1″), 138.10 (C1‴).

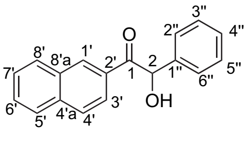
4.5.6. Naphthalen-2-yl(2-phenyl-1,3-dithian-2-yl)methanol (**6c**) (82% yield)



IR (film): 3500, 2986, 3020, 1500, 1141, 1159 cm^{-1}. Anal. Calcd for $C_{21}H_{20}OS_2$: C, 71.55; H, 5.72; S, 18.19. Found: C, 71.57; H, 5.68; S, 17.54. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.81 (m, 2H, H-5″), 2.60 (m, 4H, H-4″ and H-6″), 3.05 (s, 1H, OH), 5.06 (s, 1H, H-1), 6.80 (dd, 1H, J=8.5, J=1.7 Hz, H-Ar), 7.17 (m, 3H, H-Ar), 7.25 (s, 1H, H-Ar), 7.32 (m, 2H, H-Ar), 7.47 (m, 1H, H-Ar), 7.58 (m, 3H, H-Ar), 7.67 (m, 1H, H-Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.20 (C5″), 27.42 and 27.72 (C4″ and C6″), 67.05 (C2″), 81.53 (C1), 126.22 (C6′), 126.33 (C1′), 126.41 (C4‴), 126.77 (C7′), 127.94 (C4′), 128.07 (C5′ and C8′), 128.63 (C3′), 128.67 (C3‴ and C5‴), 131.04 (C2‴ and C6‴), 132.71 (C2′), 133.54 (C8′a), 135.19 (C4′a), 137.76 (C1‴).

4.5.7. Synthesis of 2-hydroxy-1-(naphthalen-2-yl)-2-phenylethanone (**2i′**)

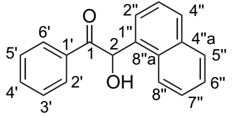
BF_3OEt_2 (389 μL, 3.1 mmol) was dissolved in 1 mL of THF/H_2O (85/15) and HgO (636 mg, 3.1 mmol) was added. This mixture was stirred at 0 °C for 5 min and a solution of **6d** (477 mg, 1.357 mmol) in 24 mL of THF/H_2O (85/15) was added. The reaction was stirred at room temperature under argon for 20 h. CH_2Cl_2 (25 mL) was added and the solution was filtered and washed with brine. The organic phase was collected and dried with anhydrous $NaSO_4$. CH_2Cl_2 was filtered and evaporated under reduced pressure. The product was purified by column chromatography (SiO_2, CH_2Cl_2) affording 301 mg of a white solid (1.15 mmol, 85% yield). IR (film): 3440, 3061, 3028, 1681 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 80.39; H, 5.24.



^{1}H NMR (250 MHz, $CDCl_3$): δ 5.22 (s, 1H, OH), 6.04 (s, 1H, H-2), 7.24 (m, 5H, H-Ph), 7.48 (qt, 2H, J=8.0, J=1.7 Hz, H-6′ and H-7′), 7.74

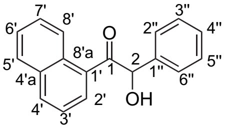
(m, 1H, H-8′), 7.77 (m, 1H, H-5′), 7.82 (dd, 1H, *J*=8.7, *J*=1.7 Hz, H-4′), 7.89 (dd, 1H, *J*=8.7, *J*=1.7 Hz, H-3′), 8.38 (s, 1H, H-1′). ^{13}C NMR (63 MHz, $CDCl_3$): δ 76.67 (C2), 124.67 (C3′), 127.43 (C7′), 128.19 (C4″), 129.04 (C5′), 129.06 (C6′ and C4′), 129.50 (C3″ and C5″), 129.60 (C8′), 130.16 (C2″ and C6″), 131.13 (C8′a), 131.83 (C1′), 132.62 (C4′a), 136.23 (C2′), 139.55 (C1″), 199.29 (C1). HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min): retention time: (*S*)-**2i′**=16.1 min, (*R*)-**2i′**=22.6 min. UV analysis: λ_{max}=210, 249, 288 nm.

*4.5.8. 2-Hydroxy-2-(naphthalen-1-yl)-1-phenylethanone (**2h**) (78% yield)*



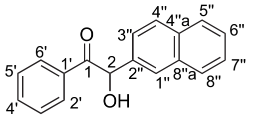
IR (film): 3459, 2911, 2840, 1683 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 81.78; H, 6.32. ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.45 (d, 1H, *J*=4.7 Hz, OH), 6.52 (d, 1H, *J*=4.4 Hz, H-2), 7.21 (m, 4H, H-Ar), 7.46 (m, 3H, H-Ar), 7.76 (m, 4H, H-Ar), 8.27 (d, 1H, *J*=8.4 Hz, H-8″). ^{13}C NMR (63 MHz, $CDCl_3$): δ 74.14 (C2), 123.71 (C8″), 125.86 (C6″), 126.61 (C7″), 127.26 (C2″), 127.59 (C4″ and C5″), 129.10 (C3″), 129.41 (C3′ and C5′), 129.99 (C2′ and C6′), 131.78 (C4′), 134.39 (C1″), 134.74 (C4″a), 135.60 (C1′), 136.96 (C8″a), 200.50 (C1). HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min): retention time: (*S*)-**2h**=14.8 min, (*R*)-**2h**=23.38 min. UV analysis: λ_{max}=223, 248 nm.

*4.5.9. 2-Hydroxy-1-(naphthalen-1-yl)-2-phenylethanone (**2h′**) (65% yield)*



IR (film): 3100, 3050, 2900, 2888, 1646 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 81.50; H, 5.24. ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.35 (s, 1H, OH), 6.52 (s, 1H, OH), 7.24 (m, 5H, H-Ph), 7.43 (m, 2H, H-3′ and H-6′), 7.66 (m, 1H, H-7′), 7.94 (m, 1H, H-5′), 7.97 (m, 1H, H-2′), 8.05 (d, 1H, *J*=8.1 Hz, H-4′), 9.24 (d, 1H, *J*=8.6 Hz, H-8′). ^{13}C NMR (63 MHz, $CDCl_3$): δ 77.81 (C2), 124.87 (C8′), 126.37 (C6′), 127.57 (C3′), 128.19 (C-4″), 128.98 (C8′a), 129.24 (C5′), 129.50 (C3″ and C5″), 129.92 (C2′), 130.16 (C2″ and C6″), 131.35 (C4′), 134.49 (C1′), 135.22 (C4′a), 135.60 (C7′), 139.55 (C1″), 195.06 (C1). HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min): retention time: (*S*)-**2h′**=16.0 min, (*R*)-**2h′**=23.1 min. UV analysis: λ_{max}=210, 249, 288 nm.

*4.5.10. 2-Hydroxy-2-(naphthalen-2-yl)-1-phenylethanone (**2i**) (87% yield)*



IR (film): 3453, 3052, 1677, 1077 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 80.26; H, 5.27. ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.05 (s, 1H, OH), 6.05 (s, 1H, H-2), 7.31 (m, 3H, H-Ar), 7.40 (m, 3H, H-Ar), 7.73 (m, 4H, H-Ar), 7.88 (m, 2H, H-Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ 76.76 (C2), 125.24 (C6″), 126.86 (C7″), 126.96 (C1″), 127.97 (C4″, and C8″), 128.15 (C3″ and C5″), 128.51 (C3′ and C5′), 129.16 (C2′ and C6′), 129.61 (C4″a), 133.60 (C4′), 133.83 (C8″a), 134.43 (C2″), 136.78 (C1′), 199.33 (C1). HPLC analysis (*n*-hexane/2-propanol, 90/10; flow 1 mL/min): retention time: (*S*)-**2i**=15.7 min, (*R*)-**2i**=20.93 min. UV analysis: λ_{max}=223, 248 nm.

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References and notes

1. Roush, W. R.; Briner, K.; Kessler, B. S.; Murphy, M.; Gustin, D. J. *J. Org. Chem.* **1996**, *61*, 6098–6099.
2. Uchida, R.; Shiomi, K.; Sunazuka, T.; Inokoshi, J.; Nishizawa, A.; Hirose, T.; Tanaka, H.; Iwai, Y.; Omura, S. *J. Antibiot.* **1996**, *49*, 886–889.
3. Wallace, O. B.; Smith, D. W.; Deshpande, M. S.; Polson, C.; Felsenstein, K. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1203–1206.
4. Fang, Q. K.; Han, Z.; Grover, P.; Kessler, D.; Senanayade, C. H.; Wald, S. A. *Tetrahedron: Asymmetry* **2002**, *11*, 3659–3663.
5. Tanaka, T.; Kawase, M.; Tani, S. *Bioorg. Med. Chem.* **2004**, *12*, 501–505.
6. (a) Wildemann, H.; Dunkelmann, P.; Muller, M.; Schmidt, B. *J. Org. Chem.* **2003**, *68*, 799–804; (b) Singh, M. S.; Singh, A. K. *Synthesis-Stuttgart* **2004**, *6*, 837–839.
7. Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743–1745.
8. Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070–3071.
9. (a) Demir, A. S.; Dünwald, T.; Iding, H.; Pohl, M.; Müller, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4769–4774; (b) Demir, A. S.; Sesenoglu, Ö.; Eren, E.; Hosrik, B.; Pohl, M.; Janzen, E.; Kolter, D.; Feldmann, R.; Dünkelmann, P.; Müller, M. *Adv. Synth. Catal.* **2002**, *344*, 96–103; (c) Dunkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M. *J. Am. Chem. Soc.* **2002**, *124*, 12084–12085; (d) Hischer, T.; Gocke, D.; Fernández, M.; Hoyos, P.; Alcántara, A. R.; Sinisterra, J. V.; Hartmeier, W.; Ansorge-Schumacher, M. B. *Tetrahedron* **2005**, *61*, 7378–7383; (e) Domínguez de María, P.; Stillger, T.; Pohl, M.; Wallert, S.; Drauz, K.; Gröger, H.; Trauthwein, H.; Liese, A. *J. Mol. Catal. B: Enzym.* **2006**, *38*, 43–47.
10. Demir, A. S.; Hamamci, H.; Sesenoglu, O.; Neslihanoglu, R.; Asikoglu, B.; Capanoglu, D. *Tetrahedron Lett.* **2002**, *43*, 6443–6449.
11. (a) Hoyos, P.; Fernández, M.; Sinisterra, J. V.; Alcántara, A. R. *J. Org. Chem.* **2006**, *71*, 7632–7637; (b) Hoyos, P.; Buthe, A.; Ansorge-Schumacher, M. B.; Sinisterra, J. V.; Alcántara, A. R. *J. Mol. Catal. B: Enzym.* **2008**, *52–53*, 133–139.
12. (a) Leonida, M. D. *Curr. Med. Chem.* **2001**, *8*, 345–369; (b) Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2659–2681; (c) de Wildeman, S. M. A.; Sonke, T.; Schoemaker, H. E.; May, O. *Acc. Chem. Res.* **2007**, *40*, 1260–1266; (d) Moore, J. C.; Pollard, D. J.; Kosjek, B.; Devine, P. N. *Acc. Chem. Res.* **2007**, *40*, 1412–1419.
13. (a) Konishi, J.; Ohta, H.; Tsuchihashi, G. *Chem. Lett.* **1985**, 1111–1112; (b) Buisson, D.; El Baba, S.; Azerad, R. *Tetrahedron Lett.* **1986**, *37*, 4453–4454; (c) Chênevert, R.; Thiboutot, S. *Chem. Lett.* **1988**, 1191–1192; (d) Allenmark, S.; Andersson, S. *Enzyme Microb. Technol.* **1989**, *11*, 177–179; (e) Maruyama, R.; Nishizawa, M.; Itoi, Y.; Ito, S.; Inoue, M. *J. Biotechnol.* **2001**, *75*, 630–633; (f) Saito, T.; Maruyama, R.; Ono, S.; Yasukawa, N.; Kodaira, K.; Nishizawa, M.; Ito, S.; Inoue, M. *Appl. Biochem. Biotechnol.* **2003**, *111*, 185–190; (g) Mahmoodi, N. O.; Mohammadi, H. G. *Monatsh. Chem.* **2003**, *134*, 1283–1288; (h) Demir, A. S.; Hamamci, H.; Ayhan, P.; Duygu, A. N.; Igdir, A. C.; Capanoglu, D. *Tetrahedron: Asymmetry* **2004**, *15*, 2579–2582; (i) Yadav, S. R.; Nainawat, A. K.; Kaushik, S.; Sharma, A.; Sharma, I. K. *Asian J. Exp. Sci.* **2005**, *19*, 135–141; (j) Mahmoodi, N.; Navrood, M. N. *Arkivoc* **2007**, *iii*, 37–45; (k) Demir, A. S.; Ayhan, P.; Demirtas, U.; Erkılıc, U. *J. Mol. Catal. B: Enzym.* **2008**, *55*, 164–168.
14. Molinari, F.; Gandolfi, R.; Villa, R.; Occhiato, E. G. *Tetrahedron: Asymmetry* **1999**, *10*, 3515–3520.
15. D'Arrigo, P.; Fuganti, C.; Pedrocchi Fantoni, G.; Servi, S. *Tetrahedron* **1998**, *5*, 15017–15026.
16. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647–2650.
17. Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217–1221.
18. (a) Besse, P.; Botte, J.; Fauve, A.; Veschambre, H. *Bioorg. Chem.* **1993**, *21*, 342–353; (b) Matsuda, T.; Harada, T.; Nakajima, N.; Nakamura, K. *Tetrahedron Lett.* **2000**, *41*, 4135–4138; (c) Matsuda, T.; Harada, T.; Nakajima, N.; Itoh, T.; Nakamura, K. *J. Org. Chem.* **2000**, *65*, 157–163.
19. Ansorge-Schumacher, M. B.; Greiner, L.; Schroeper, F.; Mirtschin, S.; Hischer, T. *Biotechnol. J.* **2006**, *1*, 564–568.
20. Bògar, K.; Hoyos-Vidal, P.; Alcántara-León, A. R.; Bäckwall, J. E. *Org. Lett.* **2007**, *9*, 3401–3404.
21. Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119–130.
22. (a) Sanghani, P. C.; Davis, W. I.; Zhai, L. M.; Robinson, H. *Biochemistry* **2006**, *45*, 4819–4830; (b) Yin, S. J.; Chou, C. F.; Lai, C. L.; Lee, S. L.; Han, C. L. *Chem.-Biol. Interact.* **2003**, *143*, 219–227; (c) Kim, K. J.; Howard, A. J. *Acta Crystallogr.* **2002**, *D58*, 1332–1334.