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Enantioselective bioreduction of β-keto sulfones with the fungus *Curvularia lunata*

Vicente Gotor, Francisca Rebolledo* and Ramón Liz

Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, 33071 Oviedo, Spain

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Abstract—β-Keto sulfones bearing bulky groups are reduced with high enantioselectivities to the corresponding optically active β-hydroxy sulfones by the fungus *Curvularia lunata* CECT 2130; the cells can be re-used without loss of their catalytic activity.

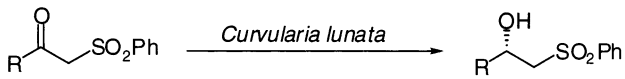
1. Introduction

Optically active β-hydroxy sulfones are of great utility in organic synthesis; they have been used in the preparation of many compounds, but find particular use in the synthesis of chiral, non-racemic lactones,[1] 2,5-disubstituted tetrahydrofurans,[2] and other β-hydroxy-α-substituted sulfones.[3] Recently, a compound of this class has proved its efficiency as a chiral controller in asymmetric Diels–Alder and alkylation reactions.[4]

One of the most useful strategies to access chiral, non-racemic β-hydroxy sulfones has been the baker's yeast mediated asymmetric reduction of β-keto sulfones.[5] However, a major factor in the enantioselectivity of these processes is the size of the substituents attached to the carbonyl group. Thus, with (phenylsulfonyl)-alkanones of the type **1** (see Table 1), the best reported result was obtained when the R substituent was a methyl group,[6] but with the larger pentyl[6b] and phenyl[7] substituents, the e.e.s of the resulting β-hydroxy sulfones were very low (10 and 15%, respectively).

Taking into account the importance of β-hydroxy sulfones, the limitations of the baker's yeast reduction and the availability of the starting β-keto sulfones, herein we investigate an alternative biocatalytic method for the enantioselective reduction of these compounds using whole cells of *Curvularia lunata* CECT 2130.[8] Our own results in the reduction of other prochiral ketones with this microorganism supported its selection.[9]

Table 1. Enantioselective reduction of β-keto sulfones



1a-1c (*S*)-**2a-2c**

Entry	Substrate[a]	R	t_R (h)	Product	Yield[b] (%)	E.e. (%)
1	**1a**	2-Furyl	7	(*S*)-**2a**	91	97
2	**1b**	Ph	10	(*S*)-**2b**	90	87
3	**1c**	n-C_5H_{11}	7	(*S*)-**2c**	92	92
4	**1a**[c]	2-Furyl	8	(*S*)-**2a**	91	97
5	**1a**	2-Furyl	24	(*S*)-**2a**	89	97

[a] 75–78 mg is always used, except in entry 5 (225 mg).
[b] Yield of crude, substantially pure material.
[c] Cells recycled from entry 1 reaction (without re-suspension in AcOEt; see experimental).

* Corresponding author.

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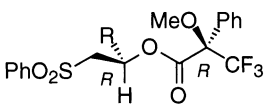
2. Results and discussion

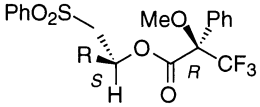
Reduction of the β-keto sulfones **1a**–**1c**[10] was carried out with resting cells of *C. lunata* as previously described,[9b] which involved suspending the mycelia in phosphate buffer (0.20 M, pH 6.0) in the presence of methanol (10 μL/mL of buffer).[11] As indicated in Table 1 (entries 1–3), the corresponding β-hydroxy sulfones **2a**–**2c** were obtained with high e.e.s, the best substrate being 1-(2-furyl)-2-(phenylsulfonyl)ethan-1-one **1a**, from which alcohol **2a** was obtained with an e.e. of 97%. In order to check if the mycelia retain their catalytic activity after the biotransformation, recovered cells from the reaction with **1a** were suspended in fresh phosphate buffer, and the same amount of **1a** added. After stirring for 8 hours, **2a** was obtained in the same yield and e.e. (entry 4). We have also demonstrated that these processes can be carried out with a higher substrate/biocatalyst ratio than other baker's yeast or *C. lunata* biotransformations. When the amount of **1a** is trebled (entry 5) a longer reaction time is necessary to complete the reduction, but **2a** is obtained in very good yield and with the same e.e. No efforts have previously been made to determine the optimum tolerance ratio (substrate mass/wet fungal biomass).

Enantiomeric excesses of (*S*)-**2a**–**2c** were determined by reaction with (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (MTPA-Cl),[12] with analysis of the resulting MTPA esters by ^{1}H and ^{19}F NMR. In all cases, two resolved signals were observed in the ^{19}F NMR spectra of the MTPA esters derived from (±)-**2a**–**2c**. In the case of (*S*)-**2a** obtained in the reactions of entries 1, 4 and 5, the ^{19}F NMR spectra indicated the presence of only one peak. A more accurate analysis by HPLC using a Chiralcel OD column showed an e.e. of 97%.[13]

The (*S*)-configuration for **2b** and **2c** was assigned by comparison of the signs of their specific rotations with those previously reported.[1d] The (*S*)-configuration for **2a** was assigned by means of Kelly's empirical method[14] as follows. In Table 2 the usual working models for the (*R*)-MTPA esters *l*- and *u*-**3a**–**3c** derived from (±)-**2a**–**2c** can be seen, as well as the δ values (^{1}H NMR) for their methoxy groups, and also their corresponding $\Delta\delta$ (*l*–*u*) values. The δ values for both diastereomers **3a** and **3b** were assigned taking into account that the 2-furyl and phenyl substituents shield the methoxy group in the *u*-diastereomers, but not in the *l*-diastereomers. In addition, in the (*R*)-MTPA ester derived from the product **2a** obtained with *C. lunata*, the methoxy signal appears at 3.38 ppm. Consequently, we deduced that the actual metabolite was (*S*)-**2a**. In the (*R*)-MTPA esters derived from the metabolite (*S*)-**2b**, the methoxy group resonates at 3.42 ppm, corroborating the assignation of **2a**. From these results it is evident that these *C. lunata* reductions obey Prelog's rule, the largest substituent being the phenylsulfonylmethyl in all cases.

Table 2. (*R*)-MTPA esters **3** derived from (±)-**2a**–**2c** and their methoxy signals (^{1}H NMR)





R	Ester	OMe, δ (ppm) *l*-**3**	OMe, δ (ppm) *u*-**3**	$\Delta\delta$ (*l*−*u*)
2-Furyl	**3a**	3.54	3.38	+0.16
Ph	**3b**	3.60	3.42	+0.18
n-C_5H_{11}	**3c**	3.59	3.50	+0.09

It should be pointed out that the $\Delta\delta$ values for esters **3a** (R = 2-furyl; +0.16 ppm) and **3b** (R = Ph; +0.18 ppm) are high when compared with those observed for the corresponding Mosher's esters derived from alkyl (hetero)aryl carbinols (ca. 0.09 ppm).[14] For esters **3c** [R = *n*-C_5H_{11} in place of (hetero)Ar; i.e. no shielding effect acts on the methoxy group in the *u* diastereomer], the $\Delta\delta$ value is only 0.09 ppm. From this one can conclude that the phenylsulfonylmethyl group exhibits a deshielding effect of about 0.09 ppm, which, acting in concert with the shielding one of the (hetero)aryl ring, leads to the high $\Delta\delta$ values observed for **3a** and **3b**. This phenylsulfonylmethyl group deshielding effect can be useful for the future assignment of other structurally related disubstituted carbinols.

3. Conclusion

In summary, we have developed a simple and efficient method for the enantioselective reduction of β-keto sulfones. The furan derivative is of special interest because, conveniently functionalised, it can be used for intramolecular Diels–Alder reactions.[16] Application of this methodology to the reduction of other β-keto sulfones and sulfoxides is currently in progress.

4. Experimental

The typical procedure used for these bioreductions is as follows. A loop of solid culture of *C. lunata*, from an agar plate, was sowed on 75 mL of a sterilised liquid medium[15] [composed of corn steep (Merck, 11928; 5 g), D-glucose (30 g), KH_2PO_4 (1 g), K_2HPO_4 (2 g), $NaNO_3$ (2 g), KCl (0.5 g), $MgSO_4{\cdot}7H_2O$ (0.5 g), $FeSO_4{\cdot}7H_2O$ (0.02 g) and distilled water (1 L)], in a 250 mL Erlenmeyer flask. After incubating for 72 hours (rotary shaker, 200 rpm, 28°C), cells (black filamentous mycelia) were harvested by filtration (3.5 g wet biomass), washed with 0.20 M phosphate buffer pH 6.0 (2×20 mL), and suspended in the same, fresh buffer (75 mL). To this cell suspension, compound **1** (75–78 mg) and methanol (750 μL) were added. Incubation (same conditions as above) was then carried out until the reaction was complete (TLC monitoring, chloroform:hexane:diethyl ether:methanol, 3:2:1:0.25), the cells were filtered again and washed with aqueous 0.8% NaCl (2×20 mL). The combined aqueous phases were continuously extracted with ethyl acetate (12–15 h).

Evaporation of the organic phase yields the corresponding, essentially pure compound **2**. A second fraction of product **2** (in some cases, up to 18% of the total yield) was obtained when the washed cells were re-suspended in ethyl acetate (50 mL) for 1–2 hours (incubation as above). Compound **2a** was purified by column chromatography (hexane:ethyl acetate, 5:2): mp 72–73°C, $[\alpha]_D^{22}$ +13.0 (*c* 0.98, $CHCl_3$) e.e. = 97%. ^1H NMR (200 MHz, $CDCl_3$) δ 7.95 (m, 2H), 7.75–7.50 (m, 3H), 7.30 (m, 1H), 6.32 (s, 2H), 5.30 (dt, J = 3.1 and 9.2 Hz, 1H), 3.70 (dd, J = 9.2 and 14.4 Hz, 1H), 3.55 (dd, J = 3.1 and 14.4 Hz, 1H), 3.50 (d, J = 3.1 Hz, 1H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.5 (C), 142.5 (CH), 139.0 (C), 134.0 (CH), 129.3 (CH), 127.9 (CH), 110.3 (CH), 107.3 (CH), 62.5 (CH), 60.4 (CH_2) ppm. MS (EI) m/z (%): 252 (M^+, <2), 234 (20), 110 (100). Compound (*S*)-**2b**[1d] was purified by column chromatography (hexane:diethyl ether:dichloromethane, 3.5:1:1): $[\alpha]_D^{20}$ +28.2 (*c* 0.83, $CHCl_3$) e.e. = 87%. Compound (*S*)-**2c**[1d] was purified by column chromatography (hexane:ethyl acetate, 8:1): $[\alpha]_D^{22}$ +13.0 (*c* 0.93, $CHCl_3$) e.e. = 92%.

Acknowledgements

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