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Microbial Reduction of α,α,α-Trifluoro-α'-sulfenylketones

Alberto Arnone, Giuditta Biagini, Rosanna Cardillo, Giuseppe Resnati*

C.N.R. - Centro Studio Sostanze Organiche Naturali, Dip. Chimica, Politecnico, 7 via Mancinelli, I-20131, Milano, ITALY;

Jean-Pierre Bégué, Daniele Bonnet-Delpon, Andrei Kornilov

BioCIS, C.N.R.S.-Facultè de Pharmacie, Rue J. B. Clement, 92296 Châtenay-Malabry, FRANCE

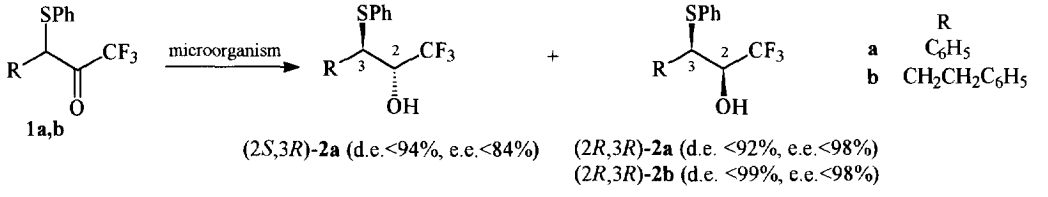
Abstract: Several microorganisms have been employed in the reduction of two α,α,α-trifluoro-α'-sulfenylketones. Some of them produce corresponding alcohols in high diastero- and enantioselection, the high conversion in a single enantiomer being secured by the racemization of starting ketones in the biotransformation conditions. Transformation of obtained sulfenyl-trifluoromethyl-alcohols into trifluoromethyl-epoxides is also described. Copyright © 1996 Elsevier Science Ltd

Chiral and non racemic trifluoromethyl substituted secondary alcohols are useful synthons for the preparation of a large variety of selectively fluorinated polyfunctional compounds.[1] Enzymatic resolution of an ester derivative[2] and asymmetric hydride reduction of a ketone moiety[3] are the most commonly employed approaches for the synthesis of optically active trifluoromethyl carbinols.

Here we present our preliminary results on an alternative methodology, namely the use of growing microorganisms for the diastereo- and enantioselective reduction of α,α,α-trifluoro-α'-phenylsulfenylketones **1a,b** (Scheme 1). These substrates have been chosen as the presence of the sulfenyl residue allows obtained alcohols **2** to be transformed into several other molecular arrays.[4] At the same time, this presence is a further challenge in the reduction process as diastereoisomeric mixtures of enantiomeric products can in general be formed.[5]

Ketones **1** have been prepared through regioselective opening of corresponding 1-trifluoromethyl-1-ethoxyepoxides[6] with sodium thiophenol.[7] A screening of several fungi, yeasts, and bacteria was first performed on trifluoroacetone derivative **1a**. In some cases the substrate was not biotrasformed by the

Scheme 1



(2*S*,3*R*)-**2a** (d.e.<94%, e.e.<84%) (2*R*,3*R*)-**2a** (d.e. <92%, e.e.<98%)
(2*R*,3*R*)-**2b** (d.e. <99%, e.e.<98%)

Table. Microbial transformations[a] of α,α,α-trifluoro-α'-sulfenylketones **1a,b**.

Run	Microorganism[b]	Substrate	Conversion (%)	*anti* (2*S*,3*R* : 2*R*,3*S*)	*syn* (2*R*,3*R* : 2*S*,3*S*)
1	*Rhodotorula glutinis* CBS 20	**1a**	84	7 (19 : 81)	93 (95 : 5)
2		**2a**		66	34
3	*Aspergillus niger* IPV 238	**1a**	74	36 (41 : 59)	64
4		**2a**		c	c
5	*Candida sake* CBS 159	**1a**	84	97 (92 : 8)	3
6		**1a**[d]	64	>98 (84 : 16)	<2
7		**1a**[d]	68	>98 (67 : 33)	<2
8		**1a**[d]	40	>98 (>98 : <2)	<2
9		**2a**	80	c	c
10	*Candida lipolytica* CBS 2074	**1a**	84	4 (61 : 39)	96 (>98 : <2)
11		**2a**		<2	>98(>98 : <2)
12	*Cladosporium cladosporioides* IPV 167	**1a**	76	64 (44 : 55)	36 (96 : 4)

(a) Each microorganism was grown for the given time (see onward) at 30 °C in shaken Erlenmeyer flasks (300 mL) containing the given culture medium (50 mL). The carbonyl compound, (in standard procedure 10 mg per flask) dissolved in ethanol (0.2 mL), was added to the grown culture and the incubation was continued for one further day. Each resulting mixture was extracted with ethyl acetate, combined organic phases were dried, evaporated under reduced pressure and the composition of the crude residue was determined by g.l.c. or hplc analyses. *Rhodotorula glutinis* and *Cladosporium cladosporioides* were grown for 2 days at 120 rev^{-1} on a medium containing glucose (20 g L^{-1}), malt extract (20 g L^{-1}), and peptone (5 g L^{-1}) in deionized water adjusted to pH 6.5; *Candida sake* and *Candida lipolytica* were grown for 2 days at 120 rev^{-1} on a medium containing glucose (30 g L^{-1}), yeast extract (10 g L^{-1}), and peptone (10 g L^{-1}) in deionized water and adjusted to pH 7.0; *Aspergillus niger* was grown for 2 days at 120 rev^{-1} on Czapex-Dox medium. (b) IPV: Istituto Patologia Vegetale (Università di Milano, Italy). (c) Ketone **1b** was transformed into products different from desired alcohol **2b**. (d) Growing medium: NH_4Cl (4 g L^{-1}), KH_2PO_4 (1 g L^{-1}), K_2HPO_4 (1 g L^{-1}), $MgSO_4$-$7H_2O$ (0.5 g L^{-1}), yeast extract (2 g L^{-1}), alcohol (methanol, ethanol, and *i*-propanol for runs 6, 7, and 8, respectively, 20 mL L^{-1}), tap water.

microorganism (*Streptomyces sp.* C-20, *Zymomonas mobilis* ATCC 29191, *Bacillus cereus* ATCC 10702), in other cases only minor amounts of the desired alcohols **2a** were produced, most of starting ketone **1a** being recovered unchanged (*Rhizoctonia solani* IPV A-19, *Geotrichum candidum* CBS 233.76).

Occasionally the ketone was converted into non identified products (*Phanerochaete chrysosporium* CBS 104.82). Five microorganisms gave satisfactory results and they are reported in the Table. A mixture of diastereoisomeric alcohols **2a** was obtained from the reduction of **1a** with *Aspergillus niger* and *Cladosporium cladosporioides*. However, both the *anti* and the *syn* isomers were formed with high selectivity when *Candida sake* and *Rhodotorula glutinis*, or *Candida lipolytica*, were used. With these three microorganisms, not only the diastereo-, but also the enantioselectivity of the reduction was high. In the enantiomeric mixture of *anti* alcohols **2a** formed with *Candida sake*, the isomer having the (2*S*,3*R*) absolute configuaration was greatly prevailing (run 5), and in the *syn* couple produced by *Candida*

lipolytica and *Rhodothorula glutinis* the (2*R*,3*R*) carbinol **2a** was present exclusively or predominantly (runs 1 and 10, respectively).[8, 9]

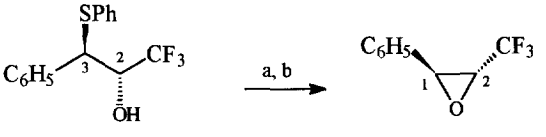
Under the adopted transformation conditions, a high conversion of the ketone substrate **1a** into the alcohol **2a** was observed in all cases. These chemical and stereochemical results can be reconciled only suggesting that the sulfenylated carbon of **1a** racemized through enolization during the biotransformation and one of the enantiomers is reduced preferentially or exclusively by the microorganism.

It has been reported that the use of modified cell growth conditions can induce characteristic secondary alcohol dehydrogenases leading to useful changes in the stereochemical course of reduction reactions.[10] We have therefore studied the reduction of ketone **1a** with cells grown with different carbon sources. When *n*-hexadecane and oleic acids were used, no conversion of the substrate to the desired alcohols **2a** was observed and when methanol, ethanol, and *i*-propanol were employed (runs 6 - 8) the biotransformation course was similar to that obtained under standard conditions. An improved diastero- and enatioselectivity were obtained with *i*-propanol, but the conversion was lower (40% after 24 h).

When above discussed microorganisms were tried for the reduction of ketone **1b**, a rather different patter of results was obtained. *Aspergillus niger* and *Candida sake* biotransfermed the substrate in products different from the desired alcohol **2b** and *Rhodothorula glutinis* showed a low diastereoseletion in the reduction process. Interestingly, *Candida lipolytica* gave exclusively the *syn* alcohol **2b** having the (2*R*,3*R*) absolute configuration with high conversion (Table, run 11).

α,α,α-Trifluoro-α'-sulfenyl alcohols **2** are versatile synthons. They have been transformed into trifluoromethyl substituted allylic alcohols,[11] but only one of the two stereocentres present in the molecule is preserved in this elaboration. Here we report how the reaction of the sulfenypropanol (2*S*,3*R*)-**2a** with trimethyloxonium fluoborate (dichloromethane/nitromethane, r.t.) gives an intermediate sulfonium salt which, on treatment with sodium hydride (DMF, 0 °C) affords the (1*S*,2*R*)-1-phenyl-3,3,3-trifluoro-1,2-epoxypropane (**3**) through intramolecular S_N2 elimination of phenylmethylsulfide (Scheme 2).[12] Both stereocentres of starting alcohol **2** are preserved in sulfur-free product **3**. To the best of our knowledge, very few methods are reported for the asymmetric synthesis of trifluoromethyl substituted epoxides asymmetrically substituted at both epoxide carbons.[13] The reported elaboration is a further proof of the effectiveness of sulfenyl alcohols **2** as chirons.

Scheme 2: a, trimethyloxonium fluorborate, r.t.; b, sodium hydride, 0 °C.



(2*S*,3*R*)-**2a** (1*S*,2*R*)-**3**

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References and Notes

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5. The microbial reduction of α'-bromo-α,α,α-trifluoroketones analogous to **1a,b** has also been studied due to the high synthetic versatility of the corresponding bromo-alcohols. However, in our hands while the carbonyl substrates disappeared from the cultural medium, no desired α'-bromo-α,α,α-trifluoroalcohols were recovered.
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7. Bégué, J.-P-; Bonnet-Delpon, D.; Kornilov, A. *Synthesis* in press.
8. Diastereoisomer and enantiomer ratio were established through g.c. (Megadex 5, dimethylpentyl-β-cyclodextrine, 25 m x 0.25 mm i.d., fused silica capillary, d_f 0.25 μm) and HPLC (Chiracel OD, Daicel Chemical Industries, LTD) analyses. The relative stereochemistries of phenylsulfenyl alcohols **2a,b** were assigned through comparison of their ^{1}H NMR signals with those of corresponding 4-methylphenylsulfenyl analogues (Bravo, P.; Frigerio, M.; Resnati, G. *Synthesis* **1988**, 955). Selected physical and spectral properties: (2*S*,3*R*)-**2a**: δ_H, 2.70 (1H, d, $J_{H,H}$ = 7.0 Hz, OH), 4.29 (1H, ddq, $J_{H,F}$ = 6.8 Hz, CHO), 4.53 (1H, d, $J_{H,H}$ = 3.2 Hz, CHS); δ_F, -76.00. (2*R*,3*R*)-**2a**: δ_H, 3.43 (1H, d, $J_{H,H}$ = 5.2 Hz, OH), 4.33 (1H, ddq, CHO), 4.39 (1H, d, $J_{H,H}$ = 7.3 Hz, CHS); δ_F, -76.40. $[\alpha]_D^{20}$ (c = 1.0, $CHCl_3$) -16.4. (2*S*,3*R*)-**2b**: δ_H, 2.81 (1H, d, $J_{H,H}$ = 5.3 Hz, OH), 3.35 (1H, ddd, $J_{H,H}$ = 2.6 Hz, CHS), 4.03 (1H, ddq, CHO); δ_F, -75.62. (2*R*,3*R*)-**2b**: δ_H, 3.30 (1H, ddd, $J_{H,H}$ = 6.0 Hz, CHS), 3.34 (1H, d, $J_{H,H}$ = 6.5 Hz, OH), 3.87 (1H, ddq, $J_{H,F}$ = 6.6 Hz, CHO); δ_F, -76.23. (1*S*,2*R*)-**3**: δ_H: 3.50 (1H, dq, $J_{H,H}$ = 21.8 Hz, $J_{H,F}$ = 5.3 Hz, $CHCF_3$), 4.12 (1H, d, CHPh); δ_F, -75.16.
9. The absolute configurations of alcohols **2a,b** were assigned by establishing the chirality of the hydroxylated carbons from the spectral properties of esters **4a,b** formed starting from (*R*)- and (*S*)-2-phenylpropionic acids (**3**) (Helmchen, G. *Tetrahedron Lett.* **1974**, 1527; Bravo, P.; Ganazzoli, F.; Resnati, G.; De Munari, S.; Albinati, A. *J. Chem. Res. (S)* **1988**, 216, *(M)* 1701). Ester (2*S*,3*R*,2'*R*)-**4a** (esterification of **2a** from *Candida sakè* with (*R*)-**3**): δ_H, 1.53 (3H, d, CH_3), 3.78 (1H, q, C*H*CH_3), 4.42 (1H, d, $J_{H,H}$ = 5.5 Hz, CHS), 5.69 (1H, dq, CHO). Ester (2*S*,3*R*,2'*S*)-**4a** (esterification of **2a** from *Candida sakè* with (*S*)-**3**): δ_H, 1.53 (3H, d, CH_3), 3.79 (1H, q, C*H*CH_3), 4.38 (1H, d, $J_{H,H}$ = 5.5 Hz, CHS), 5.70 (1H, dq, CHO). Ester (2*R*,3*R*,2'*R*)-**4a** (esterification of **2a** from *Candida lipolytica* with (*R*)-**3**): δ_H, 1.57 (3H, d, CH_3), 3.82 (1H, q, C*H*CH_3), 4.35 (1H, d, $J_{H,H}$ = 8.5 Hz, CHS), 5.73 (1H, dq, CHO). Ester (2*R*,3*R*,2'*S*)-**4a** (esterification of **2a** from *Candida lipolytica* with (*S*)-**3**): δ_H, 1.53 (3H, d, CH_3), 3.59 (1H, q, C*H*CH_3), 4.48 (1H, d, $J_{H,H}$ = 8.0 Hz, CHS), 5.78 (1H, dq, CHO). Ester (2*R*,3*R*,2'*R*)-**4b** (between **2b** from *Candida lipolytica* and (*R*)-**3**): δ_H, 1.51 (3H, d, CH_3), 3.20 (1H, ddd, CHS), 3.76 (1H, q, C*H*CH_3), 5.47 (1H, dq, $J_{H,H}$ = 5.2 Hz, CHO). Ester (2*R*,3*R*,2'*S*)-**4b** (between **2b** from *Candida lipolytica* and (*S*)-**3**): δ_H, 1.46 (3H, d, CH_3), 3.30 (1H, ddd, CHS), 3.55 (1H, q, C*H*CH_3), 5.45 (1H, dq, $J_{H,H}$ = 6.2 Hz, CHO).
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