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Enzymatic kinetic resolution of organochalcogenides in supercritical CO_2

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ABSTRACT

1-(Phenylthio)-, 1-(phenylseleno)- and 1-(phenyltelluro)-propan-2-ol were efficiently resolved by CAL-B in sc-CO_2.

1. Introduction

Supercritical carbon dioxide (sc-CO_2) has been employed in recent years as an alternative solvent for a number of purposes in the context of Green Chemistry, since it is cheap, non-toxic and can be easily recycled.[1] Among the applications of sc-CO_2 as an alternative green solvent, is its use in biocatalysis.[2] It has been observed that pressure and temperature have deep influence in the efficiency of biotransformations in this solvent.[2] However, to date there is no way to predict enzyme activity and enantioselectivity in sc-CO_2. In this way, a careful screening for the optimal reaction conditions for a biotransformation in sc-CO_2 must be established for each specific substrate/enzyme system.

The enzymatic kinetic resolution of alcohols[3] and amines[4] containing chalcogen groups in their structures, especially Se and Te, has been investigated in our group in the last years.[5] The importance of organic compounds containing sulfur,[6] selenium[7] and tellurium[8] in organic synthesis, and the role played by compounds of these elements in biological systems[9] make the preparation of enantiomerically pure organochalcogen compounds under environmentally benign conditions a challenge for the chemists dedicated to the field.

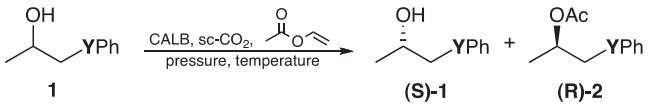
In view of the facts commented above, we decided to investigate the enzymatic kinetic resolution of hydroxychalcogenides in sc-CO_2. As far as we know, this is the first time that sc-CO_2 is used for this purpose.

2. Results and discussion

The three hydroxychalcogenides shown in Scheme 1 were prepared by opening racemic propylene oxide with phenylchalcogenolate anions, according to previously described procedures.[3] The β-hydroxychalcogenides were then submitted to enzymatic kinetic resolution using vinyl acetate as the acetate transfer agent and CAL-B as the enzyme. The commercially available supported enzyme CAL-B was chosen because of the superior results obtained by us with this enzyme in prior enzymatic kinetic resolution of hydroxychalcogenides in conventional solvents.[3,5]

Optimization of the reaction conditions, that is, pressure, temperature, amount of enzyme and reaction time, in order to obtain the maximal enantiomeric excess for the products, was performed using a Doehlert experimental design,[10] with **1a** as a model compound. A set of 21 experiments resulted, which are presented in Table 1.

The data obtained in the Doehlert experimental design were analyzed using Analysis of Variance (ANOVA)[11] and Response Surface Methodology (RSM),[12] using the software Statistica 9 (Statsoft, USA).[13] The experimental data were adjusted to a polynomial regression model (Eq. 1), where *Y* is the response, that is, enantio-



1 (S)-1 (R)-2

Y = S (**1a**), Se (**1b**) and Te (**1c**) **Y** = S (**2a**), Se (**2b**) and Te (**2c**)

Scheme 1. Enzymatic kinetic resolution of β-hydroxychalcogenides in sc-CO_2.

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Table 1
Experiments performed according to the Doehlert experimental design aiming the enzymatic kinetic resolution of **1a** by CAL-B in sc-CO_2

Planned experiments					Experimental results					
Entry	Time (h)	Pressure (bar)	Temp (°C)	CAL-B (mg)	(*S*)-**1a**[a] yield (%)	(*R*)-**2a**[a] yield (%)	(*S*)-**1a**[b] ee (%)	(*R*)-**2a**[b] ee (%)	*c*	*E*
1	3	150.0	36.7	200	43	42	91.1	93.9	51	75
2	5	150.0	36.7	200	43	36	85.2	96.1	53	47
3	4	250.0	36.7	200	33	43	92.3	96.9	51	100
4	4	217.1	36.7	200	33	31	91.3	97.3	52	89
5	4	217.1	38.3	300	45	39	90.1	92.7	51	64
6	1	150.0	36.7	200	39	43	93.5	96.7	51	115
7	2	50.0	36.7	200	–	–	–	–	–	–
8	2	116.6	30.0	200	42	45	94.9	90.1	49	120
9	2	116.6	35.0	100	36	46	95.4	91.7	49	128
10	4	50.0	36.7	200	–	–	–	–	–	–
11	4	116.6	30.0	200	43	45	90.5	92.7	51	64
12	4	116.6	35.0	100	41	37	94.3	79.5	46	78
13	2	250.0	36.7	200	36	45	95	88.4	48	114
14	3	217.1	30.0	200	32	33	95.3	97.9	51	179
15	3	217.1	35.0	100	41	48	96.8	96.7	50	193
16	2	183.8	43.4	200	43	49	91.3	83.7	48	56
17	3	83.3	43.4	200	31	42	58.8	33.9	37	5.4
18	3	150.0	41.7	100	36	46	94.5	96.9	51	136
19	2	183.8	38.3	300	43	42	90.1	91.7	51	62
20	3	83.3	38.3	300	33	49	66.0	38.7	37	7.1
21	3	150.0	31.7	300	40	47	91.7	98.1	52	110

[a] Isolated yield after flash silica gel column chromatography. Compound **1a** (1 mmol), vinyl acetate (1 mL). Maximum yield in each case: 50%. The absolute configurations were attributed by comparison with literature data.[3,17]
[b] Enantiomeric excess determined by chiral high efficiency liquid chromatography.

Pressure (bar)	**Temperature** (°C)	**Time** (min.)	**Enzyme** (mg)
231.7	37	163	100

Chart 1. Optimal reaction conditions for the enzymatic kinetic resolution of **1a** by CAL-B in sc-CO_2.

meric excess (ee); β_i, β_{ij} and β_{ii} are the regression coefficients; X_i and X_j are the experimental variables (time, temperature, pressure, and CAL-B amount) and ε is the residual. The resulting polynomial was used to construct a Response Surface, to which were applied the Lagrangian criteria,[14] allowing the determination of the optimal reaction conditions for a maximum ee. This optimum can be any point inside the experimental domain, not necessarily a tested one. The optimal parameters are shown in Chart 1. It is worth mentioning that no reaction was observed for conditions were the carbon dioxide was not supercritical (entries 7 and 10 of Table 1).

$$Y = \beta_0 + \beta_i X_i + \beta_{ij} X_i X_j + \beta_{ii} X_i^2 + \varepsilon \quad (1)$$

These optimum conditions were employed in the enzymatic kinetic resolution reaction (Scheme 1) for compounds **1a, b**, and **c**, leading to the results shown in Chart 2.[15]

The high ee and *E* values (Chart 2) obtained for the enzymatic kinetic resolution reaction (Scheme 1) for the β-hydroxy sulfide **1a** using the determined optimum parameters (Chart 1), indicate a good agreement between the predicted and the obtained ee for this transformation ($ee_{predicted}$ = 97.3%, $ee_{obtained}$ = 96.6%). Good results, that is, high ee and *E* values, were also obtained when these conditions were applied for the same reaction for the selenide **1b** and the telluride **1c** (Chart 2), showing that the process can be applied to organochalcogenides in general.

In conclusion, the enzymatic kinetic resolution of β-hydroxychalcogenides promoted by CAL-B in sc-CO_2 is an efficient method to obtain these compounds in enantiomerically enriched form under environmentally friendly conditions. In view of the recent use of enantiomerically-enriched organotellurides in the enantioselective synthesis of biologically active compounds,[16] the method described in this Letter is under investigation to produce enantiomerically-enriched tellurides in a large scale.

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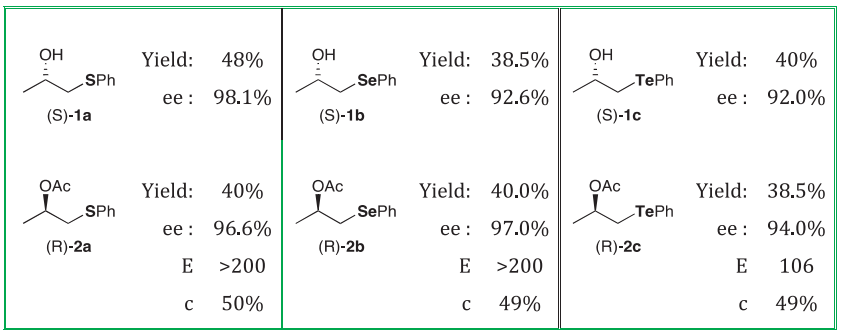

Chart 2. Enzymatic kinetic resolution of **1a**, **b**, **c** using the optimum parameters shown in Chart 1.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.073.

Reference and notes

1. (a) Rayner, C. M. *Org. Process. Res. Dev.* **2006**, *11*, 121–132; (b) Leitner, W. *Acc. Chem. Res.* **2002**, *35*, 746–756; (c) Beckman, E. J. *J. Supercrit. Fluids* **2004**, *28*, 121–191.
2. Hobbs, H. R.; Thomas, N. R. T. *Chem. Rev.* **2007**, *107*, 2786–2820.
3. (a) Costa, C. E.; Clososki, G. C.; Barchesi, H. B.; Zanotto, S. P.; Nascimento, M. G.; Comasseto, J. V. *Tetrahedron: Asymmetry* **2004**, *15*, 3945–3954; (b) Dos Santos, A. A.; Costa, C. E.; Princival, J. L.; Comasseto, J. V. *Tetrahedron: Asymmetry* **2006**, *17*, 2252–2259; (c) Da Costa, C. E. Biotransformações na obtenção de hidróxi-selenetos e hidróxi-teluretos quirais. São Paulo, 2007. PhD Thesis, Instituto de Química-Universidade de São Paulo.
4. (a) Andrade, L. H.; Silva, A. V. *Tetrahedron: Asymmetry* **2008**, *19*, 1175–1181; (b) Andrade, L. H.; Silva, A. V.; Pedrozo, E. C. *Tetrahedron Lett.* **2009**, *50*, 4331–4334.
5. For a review see: Comasseto, J. V.; Gariani, R. A. *Tetrahedron* **2009**, *65*, 8447–8459.
6. See for example: Pellissier, H. *Tetrahedron* **2007**, *63*, 1297–1330.
7. Back, T. G. *Organoselenium Chemistry*; Oxford University Press: Oxford, UK, 1999.
8. Petragnani, N.; Stefani, H. A. *Tellurium in Organic Synthesis*, second ed.; Elsevier: Amsterdam, 2007.
9. The biological importance of sulfur compounds deserves comments. Selenium is an essential trace element, which is present in important enzymes of mammalians. Several non-natural compounds of selenium and tellurium mimic the activity of one of these enzymes, the gluthatione peroxidase. See for example: Alberto, E. E.; Nascimento, V.; Braga, A. L. *J. Braz. Chem. Soc.* **2010**, *21*, 2032–2041. The study of the biological activity of organic compounds of tellurium is considered an emerging research area: Ba, L. A.; Döring, M.; Jamier, V.; Jacob, C. *Org. Biomol. Chem.*, **2010**, *8*, 4203–4216.
10. Doehlert, D. H.; Klee, V. L. *Discrete Mathematics* **1972**, *2*, 309–334. For details see Supplementary data.
11. Bereton, Richard. G. *Applied Chemometrics for Scientists*, First edition; John Wiley and Sons: Chichester, 2007.
12. Goupy, Jacques.; Creighton, Lee. *Introduction to Design of Experiments with JMP® Examples*, Third Edition; SAS Institute Inc: Cary, NC, 2007.
13. Brandvik, P. J. *Chemometr. Intell. Lab. Syst.* **1998**, *42*, 51–61.
14. Güler, Osman. *Foundations of Optimization*; First edition: Springer, 2010.
15. *General procedure for the enzymatic kinetic resolution*: To a 100 mL steel reactor (Thar®) were added the appropriate 1-(phenylchalcogene)propan-2-ol (1 mmol) and CAL-B (100 mg). The supported enzyme was involved by a porous metallic membrane fixed in the extremity of the stirring rod. The CO_2 was introduced into the reactor until the desired pressure was reached, when the adequate temperature was adjusted to reach the supercritical point. After that, vinyl acetate (1 mL) was introduced into the system by means of a high-pressure valve equipped with a loop (500 μL). The mixture was stirred (330 rpm) for 163 min and then CO_2 was allowed to evaporate, the product being collected in a glass trap. The residue was then separated by flash column chromatography in silica gel eluting with hexane/ethyl acetate (4:1).
Compound (S)-**1a**: (CAS = 67253-47-8), yellow oil, yield = 80.6 mg (48%); $[\alpha]_D^{21}$+55.6° (*c* 1.0, $CHCl_3$), ee = 98.1%; Lit. [17] $[\alpha]_D^{20}$+60.6° (*c* 1.0, $CHCl_3$). Spectral data in accordance with those of the literature.[17] *Compound (R)*-**2a**: (CAS = 136656-71-8), yellow oil, yield = 33.6 mg (40%); $[\alpha]_D^{21}$+1.0° (*c* 1.0, $CHCl_3$), ee = 96.6%; Lit. [17] $[\alpha]_D^{20}$+0.5° (*c* 1.0, $CHCl_3$) Spectral data in accordance with those of the literature.[17] *Compound (S)*-**1b**: (CAS = 70678-11-4), yellow oil, yield = 82.7 mg (38.5%); $[\alpha]_D^{21}$+49.1° (*c* 1.0, $CHCl_3$), ee = 92.5%; Lit. [3a] $[\alpha]_D^{21}$+56° (*c* 1.0, CH_2Cl_2), ee = >99%. Spectral data in accordance with those of the literature.[3a] *Compound (R)*-**2b**: (CAS = 834882-67-6), yellow oil, yield = 102.8 mg (40%); $[\alpha]_D^{21}$+13.0° (*c* 1.0, $CHCl_3$), ee = 97.0%; Lit. [3a] $[\alpha]_D^{21}$ −7° (*c* 1.0, CH_2Cl_2), ee = >99%. Spectral data in accordance with those of the literature.[3a] *Compound (S)*-**1c**: (CAS = 926647-66-7), yellow oil, yield = 105.4 mg (40.0%); $[\alpha]_D^{22}$-35.5° (*c* 1.0, CH_2Cl_2), ee = 92.0%; Lit. [3b] $[\alpha]_D^{28}$+5° (*c* 1.0, CH_2Cl_2), ee = >99%. Spectral data in accordance with those of the literature.[3b] *Compound (R)*-**2c**: (CAS = 926648-04-6), yellow oil, yield = 117.6 mg (38.5%); $[\alpha]_D^{22}$ −6.1° (*c* 1.0, CH_2Cl_2), ee = 94.0%; Lit. [3b] $[\alpha]_D^{28}$ −6° (*c* 1.0, CH_2Cl_2), ee = >99%. Spectral data in accordance with those of the literature.[3b]
16. Ferrarini, R. S.; Dos Santos, A. A.; Comasseto, J. V. *Tetrahedron Lett.* **2010**, *51*, 6843–6846. and corrigendum: *Tetrahedron Lett.* **2011**, *52*, 2001.
17. Goergens, U.; Schneider, M. P. *J. Chem. Soc. Chem. Commun.* **1991**, 1064–1066.