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Preparation of chiral organochalcogeno-α-methylbenzyl alcohols via biocatalysis. The role of *Daucus carota* root

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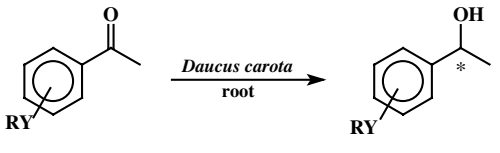
Abstract—A series of organochalcogeno acetophenones **3** has been submitted to the action of enzymes from *Daucus carota* root. Some of the chalcogeno ketones tested afforded the chiral organochalcogeno-α-methylbenzyl alcohols **4** in excellent enantiomeric excesses (>99%), under mild and environmentally friendly conditions. The stereoselectivity of the reduction is in accordance with Prelog's rule. Enzymatic kinetic resolution as alternative process was used to obtain the chiral *ortho*-organochalcogeno-α-methylbenzyl alcohols in excellent enantiomeric excess (>99%).

1. Introduction

Chiral organosulfur[1] and to a lesser extent chiral organoselenium[2] compounds have been prepared and found use in organic synthesis. In some cases the preparation of chiral auxiliaries starting from chiral substrates is time consuming and expensive, specially taking into account that very often the chiral group is lost in steps subsequent to the one they induce the formation of a stereogenic centre in the substrate. In the search for practical ways to generate selenium containing molecules bearing a stereogenic centre, we turned our attention to environmentally friendly biocatalytic methods.[3] These methods usually make use of isolated enzymes or microorganisms to prepare optically active compounds. In recent years plant cell cultures and whole plant cells have also been used for this purpose so performing synthetic transformations with high enantioselectivity.[4] Recently we disclosed our results on the reduction of substituted acetophenones,[5] including seleno acetophenones,[5c] using whole fungal cells. In this communication, we focused initially our attention on the potential of *Daucus carota* root (carrot) as biocatalyst.[4a,6] We were also interested in studying the behavior of selenium containing molecules towards biocatalytic conditions. The data concerning this type of reaction with organoselenium compounds available in the literature are very scarce, specially using whole cells of microorganisms or plant cells.[7] As far as we know this is the first attempt to perform a biotransformation in an organoselenium compound for preparative purposes using plant cells. In addition, in order to explore the potential of *D. carota* root we decided to evaluate also the bioreduction of organosulfur acetophenones to afford the corresponding chiral alcohols. The reaction is based on the utilization of carrot root as enzymatic source (alcohol dehydrogenase and their cofactors) to reduce the prochiral organochalcogeno acetophenones **3** to the chiral organochalcogeno-α-methylbenzyl alcohols **4** (Scheme 1).

Compounds **4** would present several potential uses. In the specific case of the organoseleno aryl alcohols **4a**–**f**,



3a-i

4a = *ortho*-MeSe **4f** = *para*-PhSe
4b = *meta*-MeSe **4g** = *ortho*-MeS
4c = *para*-MeSe **4h** = *meta*-MeS
4d = *ortho*-PhSe **4i** = *para*-MeS
4e = *meta*-PhSe

Scheme 1.

Keywords: *Daucus carota*; Selenium; Sulfur; Chiral alcohols; CAL-B.
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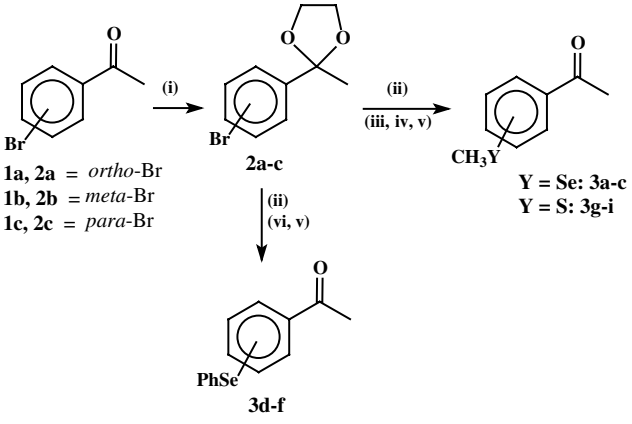
these compounds could find use as chiral derivatizing agents for the determination of enantiomeric excess of chiral carboxylic acids using ^{77}Se NMR techniques.[8] The potential use of compounds **4** as chiral ligands is supported by the existence of thio and seleno analogues of **4a**, **4d** and **4g** with use for this purpose.[9] Aryl sulfides couple with organometallic species under transition metal catalysis, leading to sulfur free products.[10] In this way, the thioaryl alcohols **4g–i** could be considered as chiral building blocks for the synthesis of compounds containing an aromatic core. Similar reactions with selenides were less investigated.[11] The availability of selenium containing chiral building blocks such as **4a–f** would stimulate more intensive research in this field.[12]

2. Synthesis of the organochalcogeno acetophenones

The organochalcogeno acetophenones **3a–i** were prepared from commercially available *ortho*-, *meta*- and *para*-bromoacetophenones as described in Scheme 2.

The ketone carbonyl group was protected according to the usual method.[13] Ketals **2a–c** in THF were treated with *t*-BuLi followed by addition of the appropriate elemental chalcogen and methyl iodide[14] or diphenyl diselenide to insert the organochalcogeno group. After hydrolysis of the ketal with an aqueous solution of 1 N hydrochloric acid, the desired methylseleno acetophenones **3a–c** and methylthio acetophenones **3g–i** were obtained in 27–30% overall yield, and the phenylseleno acetophenones **3d–f** in 55–60% overall yield.[15]

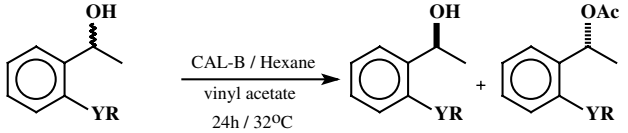


Scheme 2. Reagents and conditions: (i) C_6H_6, *p*-TsOH, ethylene glycol, reflux, 4 h; (ii) *t*-BuLi, THF, −76 °C, 30 min; (iii) selenium or sulfur powder, −76 °C → rt, 3 h; (iv) MeI, rt 15 min; (v) acetone/aq 1 N HCl, reflux, 2 h; (vi) PhSeSePh, THF, −76 °C → rt, 2 h.

In order to obtain the standards for chiral analysis correlation using gas chromatography, we prepared the stereoisomeric mixtures of organochalcogeno-α-methylbenzyl alcohols **4**. The chemical reduction of the organochalcogeno acetophenones **3a–i** was carried out using $NaBH_4$ in ethanol.[16]

3. Bioreduction of the organochalcogeno acetophenones

The bioreduction of the keto group was performed using fresh carrot roots as biocatalyst, obtained from a local market (Scheme 1). Initially, the reaction was carried out using a solution of the organochalcogeno ketones **3a–i** (20 mg) in ethanol (0.5 mL) with fresh carrot (10 g) in water (100 mL) and then incubation on an orbital shaker at 32 °C. The progress of the reaction was monitored by GC analysis. The results are summarized in Table 1. As can be observed, when *ortho*-methylseleno acetophenone (**3a**), *ortho*-phenylseleno acetophenone (**3d**) and *ortho*-methylthio acetophenone (**3g**) were treated with carrot roots under the bioreduction conditions employed, the chiral alcohols were not obtained, except for **4g** formed in low yield. The reaction was stopped after 3 days. A possible steric effect due to the organoselenium and methylthio groups at the *ortho*-



(*RS*)-**4a:** RY = MeSe
(*RS*)-**4d:** RY = PhSe
(*RS*)-**4g:** RY = MeS

Scheme 3.

Table 1. Reduction of organochalcogeno ketones **3a–i** using *D. carota* root into chiral organochalcogeno-α-methylbenzyl alcohols **4**

Entry	Chalcogeno ketone	Chalcogeno alcohol	Time (h)	Conversion (%)[a]	Ee (%)[b]	Configuration[c]
1	**3a** = *ortho*-MeSe	**4a**	72	n.c.	—	—
2	**3b** = *meta*-MeSe	**4b**	48	96	>99	(*S*)
3	**3c** = *para*-MeSe	**4c**	48	83	>99	(*S*)
4	**3d** = *ortho*-PhSe	**4d**	72	n.c.	—	—
5	**3e** = *meta*-PhSe	**4e**	72	95	>99	(*S*)
6	**3f** = *para*-PhSe	**4f**	72	72	>99	(*S*)
7	**3a** = *ortho*-MeS	**4g**	72	8	>99	(*S*)
8	**3b** = *meta*-MeS	**4h**	72	97	>99	(*S*)
9	**3c** = *para*-MeS	**4i**	72	95	>99	(*S*)

[a] Conversion determined by GC; n.c. = no conversion.
[b] Compounds **4a–i**: determined by chiral GC (column Chirasil-Dex CB-β-cyclodextrin 25 m × 0.25 mm).
[c] See Ref. 17.

Table 2. CAL-B catalyzed enantioselective acetylation of (*RS*)-*ortho*-organochalcogeno-α-methylbenzyl alcohols **4a**, **4d** and **4g**[21]

Entry	Compound	Conversion (%)[a]	4		5		E[d]
			Ee (%)[b]	Configuration[b]	Ee (%)[c]	Configuration[b]	
1	(*RS*)-**4a**	51	>99	(*S*)	97	(*R*)	>200
2	(*RS*)-**4d**	53	>99	(*S*)	88	(*R*)	81
3	(*RS*)-**4g**	50	>99	(*S*)	98	(*R*)	>200

[a] Deduced from the ee's of the substrate (ee_s) and the product (ee_p): $c = ee_s/(ee_s + ee_p)$.
[b] Determined by chiral GC, for absolute configuration, see Ref. 21.
[c] The ee value was determined after chemical conversion of the acetate to the corresponding alcohol.
[d] The enantiomeric ratio, E, was calculated according to Sih and coworkers.[22]

position to the keto group hinders the reduction (Table 1, entries 1, 4 and 7) even with extended reaction times.

In contrast, the *meta*- and *para*-organochalcogeno acetophenones (**3b**, **3c**, **3e**, **3f**, **3h** and **3i**) were reduced to the corresponding chiral organochalcogeno-α-methylbenzyl alcohols (**4b**, **4c**, **4e**, **4f**, **4h** and **4i**) with excellent enantioselectivity (ee > 99%) and high conversion. A preparative scale reduction was carried out affording the desired compounds in good isolated yields.[17] The enantiomeric excesses of the chiral organochalcogeno-α-methylbenzyl alcohols were determined by chiral GC analysis. The absolute configurations were attributed by chiral GC correlation with standards (*S*)-**4b**, (*S*)-**4c**, (*S*)-**4e**, (*S*)-**4f**, (*S*)-**4h** and(*S*)-**4i** prepared from (*S*)-3- and (*S*)-4-bromo-α-methylbenzyl alcohol.[18] The chiral organochalcogeno aryl alcohols obtained from reduction with *D. carota* root showed the same absolute configuration, independently from the organoseleno or methylthio substituent on the phenyl ring. In all these cases, the enantioselectivity is in accordance with Prelog's rule.[19]

In view of the inertness of the *ortho*-organochalcogeno acetophenones towards *D. carota* root, we attempted to obtain the enantiomerically pure *ortho*-organochalcogeno-α-methylbenzyl alcohols by means of an enzymatic kinetic resolution catalyzed by a lipase in organic media. *Candida antarctica* lipase B (Novozym 435, CAL-B) has been very effective in the enantioselective acetylation of secondary alcohols.[20] Based on these literature reports, we decided to use CAL-B to resolve the racemic mixtures of **4a**, **4d** and **4g** (Scheme 3, Table 2).

Under the reaction conditions of Scheme 3, the (*R*)-**4a**, **4d** and **4g** enantiomers reacted faster to give (*R*)-**5a**, **5d** and **5g** in high enantiomeric excess, leaving (*S*)-**4a**, **5d** and **5g** unreacted (Table 2).

The results in Table 2 show that the kinetic resolution of the (*RS*)-*ortho*-organochalcogeno-α-methylbenzyl alcohols is a good alternative to obtain these compounds enantiomerically pure. In addition, both enantiomers can be obtained in high enantiomeric purity what is interesting if we intend to use both as chiral auxiliaries.

In conclusion, it was shown that organoselenium compounds are compatible with the biocatalytic conditions employed, *meta*- and *para*-organoseleno acetophenones being reduced in high enantioselectivity by *D. carota* root. The inertness of the *ortho*-organochalcogeno acetophenones towards these conditions was overcome by using a kinetic enzymatic resolution of the corresponding alcohols to obtain them enantiomerically pure. A comparative study showed that the thio analogues have a similar behavior.

Presently the organoseleno aryl alcohols obtained in this work are being investigated as chiral derivatizing agents for the determination of the enantiomeric excess of chiral carboxylic acids.[23]

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15. All the new compounds synthesized were fully characterized. Selected spectral data: Compound **3c**: mp = 71 °C. IR (KBr) cm^{-1}: 2996, 2959, 2922, 1669, 1564, 1424, 1394, 1356, 1273, 1184, 1081, 955, 911, 812, 745, 589. ^1H NMR (300 MHz) δ (ppm): 7.85 (d, $J = 8.5$ Hz, 2H), 7.45 (d, $J = 8.5$ Hz, 2H), 2.59 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (75 MHz) δ (ppm): 197.3, 140.8, 134.4, 128.6, 128.5, 26.4, 6.7. MS: m/z (relative intensity) 214 (M^+, 74), 212 (37), 199 (100), 184 (21), 171 (15), 156 (14), 130 (3), 117 (6), 91 (61), 76 (13), 63 (13), 43 (50). Found: C, 50.75; H, 4.58. Calcd for $C_9H_{10}OSe$: C, 50.72; H, 4.73.
16. All the new compounds synthesized were fully characterized. Selected spectral data: Compound **4c**: IR (film) cm^{-1}: 3362, 2971, 2927, 2871, 1721, 1595, 1493, 1419, 1368, 1273, 1113, 1087, 900, 791, 581. ^1H NMR (500 MHz) δ (ppm): 7.40 (d, $J = 8.3$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 4.85 (q, $J = 6.3$ Hz, 1H), 2.34 (s, 3H), 1.47 (d, $J = 6.3$ Hz, 3H), 1.30 (s, 1H). ^{13}C NMR (125 MHz) δ (ppm): 143.9, 130.5, 130.4, 126.1, 70.0, 25.1, 7.3. MS: m/z (relative intensity) 216 (M^+, 57), 214 (29), 201 (71), 183 (5), 173 (10), 157 (44), 153 (10), 121 (4), 100 (20), 91 (28), 78 (56), 51 (22), 43 (100). Found: C, 50.51; H, 5.86. Calcd for $C_9H_{12}OSe$: C, 50.24; H, 5.62.
17. To increase the contact of the substrate with the biocatalyst, the external layer was removed and the rest was cut into small thin slices (5 mm). Preparative-scale reduction reaction: The reactions using 100 mg of the organochalcogeno ketones **3** in ethanol (2.5 mL) were performed in 1 L Erlenmeyer flasks containing freshly cut carrot roots (50 g), water (500 mL) at 32 °C on an orbital shaker (170 rpm). After the appropriate conversion time (Table 1), the mixture was filtered off and the carrot suspension was washed with ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (5×100 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was removed in vacuum and the residue was purified on a silica gel column using a mixture of hexane and ethyl acetate (4:1) as eluent to afford compounds **4**. 1-(Organylchalcogeno-phenyl)-ethanols **4b**: oil, yield = 86%, $[\alpha]_D^{26}$ −28.6° (*c* 1.5, $CHCl_3$), ee = 99%; **4c**: oil, yield = 74%, $[\alpha]_D^{26}$ −35.2° (*c* 1.25, $CHCl_3$), ee = 99%; **4e**: oil, yield = 60%, $[\alpha]_D^{26}$ −14.2° (*c* 2.4, $CHCl_3$), ee = 99%; **4f**: oil, yield = 52%, $[\alpha]_D^{26}$ −12.1° (*c* 1.5, $CHCl_3$), ee = 99%; **4h**: oil, yield = 66%, $[\alpha]_D^{23}$ −41.1° (*c* 0.71, $CHCl_3$), ee = 99%; **4i**: oil, yield = 60%, $[\alpha]_D^{23}$ −47.3° (*c* 0.57, $CHCl_3$), ee = 99%.
18. The (*S*)-3- and (*S*)-4-bromo-α-methylbenzyl alcohols were obtained by enzymatic kinetic resolution of the appropriate racemic mixture of *meta*- and *para*-bromo-α-methylbenzyl alcohols mediated by Novozym 435 (CAL-B) in *tert*-butyl methyl ether as the solvent and vinyl acetate as the acetyl donor. Further reaction of these chiral bromo precursors was carried out with *t*-BuLi followed by addition of the appropriate elemental chalcogen and methyl iodide or diphenyl diselenide to insert the organochalcogeno group. Andrade, L. H.; Omori, A. T.; Porto, A. L. M.; Comasseto, J. V., in press.
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21. General procedure: The enzyme (50 mg) was added to a solution of (*RS*)-*ortho*-organochalcogeno-α-methylbenzyl alcohols **4a**, **4d** or **4g** (0.20 mmol) and vinyl acetate (0.25 mL) in hexane (3 mL). The resulting mixture was stirred on an orbital shaker (170 rpm) at 32 °C. After 24 h the enzyme was filtered off and washed with dichloromethane (20 mL). The solvent was removed in vacuum and the residue was purified on a silica gel column using a mixture of hexane and ethyl acetate (4:1) as eluent to afford the alcohols **4** and their acetates **5** (Table 2). Compounds **4a**: oil, yield = 45%, $[\alpha]_D^{25}$ −42.4° (*c* 2.0, $CHCl_3$), ee = 99%; **4d**: oil, yield = 45%, $[\alpha]_D^{25}$ −63.5° (*c* 1.37, $CHCl_3$), ee = 99%; **4g**: oil, yield = 48%, $[\alpha]_D^{25}$ −68.3° (*c* 1.58, $CHCl_3$), ee = 99%; **5a**: oil, yield = 50%, $[\alpha]_D^{23}$ +44.7° (*c* 2.35, $CHCl_3$), ee = 97%; **5d**: oil, yield = 52%, $[\alpha]_D^{23}$ +43.2° (*c* 2.33, $CHCl_3$), ee = 88%; **5g**: oil, yield = 49%, $[\alpha]_D^{23}$ +41.3° (*c* 1.0, $CHCl_3$), ee = 98%. The chiral standards (*S*)-**4a**, (*S*)-**4d** and (*S*)-**4g** were prepared from (*S*)-1-phenylethanol using *ortho*-lithiation method with *n*-BuLi and TMEDA followed by addition of the appropriate elemental chalcogen and methyl iodide or diphenyl diselenide to insert the organochalcogeno group. Andrade, L. H.; Omori, A. T.; Porto, A. L. M.; Comasseto, J. V.; Cunha, R. L. O. R. Unpublished results.
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