

Stereoselective Bioreduction of Telluro-acetophenones to Optically Active Hydroxy Tellurides

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Abstract: Organotellurium compounds exhibit a broad range of useful applications in organic synthesis, materials science and medicinal chemistry fields. Despite their increasing applicability, the synthesis of enantiomerically pure organotellurium compounds remains nowadays scarcely reported in the literature. Herein, the chemical synthesis and biocatalyzed reductions of a set of telluro-acetophenones using both (*R*) and (*S*)-selective alcohol dehydrogenases (ADHs) is described for the first time, obtaining enantiomerically enriched hydroxy tellurides with excellent selectivities under very mild reaction conditions. On the one hand, enantiopure *para*-substituted (*S*)-hydroxy tellurides were obtained using the Ras-ADH (77-95% conversion) and ADH-A (52-75%), the ADH-A leading to the enantiopure (*S*)-hydroxy tellurides substituted at the *meta*-position (69-75%). On the other hand, the evl-1.1.200 displayed high selectivity towards the preparation of optically active alcohols with substitutions at the *para*-position of the aromatic ring (60-68% conversion and 92-97% ee), while the Lb-ADH led to the best results when reducing bulky ketones at the *meta*-position (79-82% conversion and 88-99% ee).

Introduction

The chemistry of tellurium (Te) has experienced great progress in recent decades¹ presenting Te-containing compounds as versatile reagents and synthons for many synthetic purposes, including carbon-carbon bond formation reactions,² and a variety of functional group interconversions.³ Organotellurium substances also have important and useful applications in materials science,⁴ as well as displaying remarkable pharmacological profiles⁵ with a broad range of biological activities.⁶

Despite their synthetic and biological importance, especially when considering their chiral versions, few efforts have been focused on the synthesis of enantiomerically pure organotellurium compounds. In contrast to the more deeply studied organoselenium analogues,⁷ robust and straightforward routes towards optically active organotellurium compounds remain nowadays scarcely reported in the literature. To the best of our knowledge, their asymmetric syntheses are limited to the enzymatic kinetic resolutions (EKR) of aliphatic,⁸ vinyl-,⁹ and β -

hydroxy¹⁰ organotellurides successfully applied as chiral building blocks (Figure 1) and the development of non stereoselective approaches when starting from optically active precursors of the desired organotellurium compounds used as antioxidant agents, and precursors of enzymatic inhibitors and antitumor agents (Figure 1).¹¹

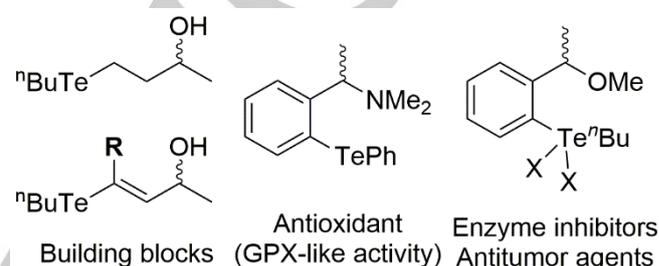


Figure 1. Representative (chiral) Te-containing compounds with synthetic applications and biological properties.

Nowadays, biocatalysis is a consolidated technology in organic synthesis mainly due to the high level of stereoselectivity displayed by enzymes under mild reaction conditions and the wide number of existing enzymes able to catalyze multiple transformations.¹² Among asymmetric biotransformations, the stereoselective reduction of carbonyl compounds catalyzed by alcohol dehydrogenases (ADHs, E.C.1.1.1.1, also known as ketoreductases or carbonyl reductases) provides an elegant manner to produce optically active alcohols by using purified or whole-cell enzyme forms.¹³ Interestingly, the versatility of ADHs has been widely demonstrated for the stereoselective reduction of a broad range of prochiral carbonyl compounds, including β -nitroketones,¹⁴ β -keto amides¹⁵ or ketones containing halogens,¹⁶ sulfur,¹⁷ boron¹⁸ and others functionalities.¹⁹

Hence, we have focused in the chemical synthesis and later development of ADH-catalyzed bioreductions of a set of telluro-acetophenones using both (*R*)- and (*S*)-selective ADHs, which could lead us to the development of a straightforward strategy towards enantiomerically enriched hydroxy tellurides under very mild reaction conditions in aqueous medium.

Results and Discussion

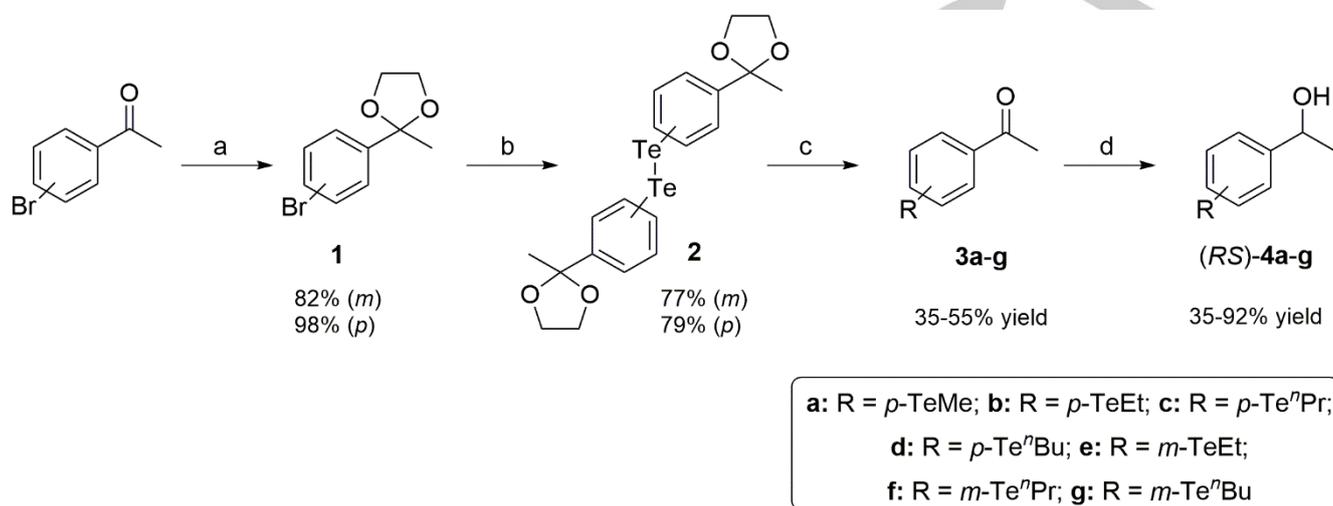
A series of prochiral telluro-acetophenones **3a-g** bearing variable alkyl aliphatic chains (R= Me, Et, ⁿPr and ⁿBu, Scheme 1) straight linked to the Te atom in *meta* and *para* positions was chemically synthesized according to adapted protocols to the ones described in the literature for structurally similar organotellurium compounds.²⁰ Firstly, commercially available 3'- and 4'-bromoacetophenone were converted into the corresponding acetals **1** using ethylene glycol with 98% (*meta*) and 82% (*para*) isolated yields. Subsequently, the acetals were employed as precursors for Grignard reagents to provide ditellurides **2** in 77%

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(*meta*) and 79% (*para*) isolated yields after the oxidative step.²⁰ Finally, sodium borohydride was used for the Te-Te bond cleavage, followed by alkylation and deprotection sequential steps led to telluroketones **3a-g** in yields ranging from 35% to 55%. By using this strategy five novel telluro-acetophenones containing methyl (**3a**), ethyl (**3b** and **3e**) and *n*-propyl (**3c** and **3f**) rests linked to Te atom were synthesized besides of already known TeⁿBu

ones (**3d** and **3g**). For analytical purposes, racemic hydroxy tellurides **4a-g** were prepared in 35-92% yields by chemical reduction of ketones **3a-g** with sodium borohydride in methanol. Thus, efficient analytical separations were developed using the gas chromatography (GC) technique, before carrying out the stereoselective reductive biotransformations using a variety of made in house and commercially available ADHs.



Scheme 1. Synthetic route for telluro-acetophenones **3a-g** and the corresponding racemic hydroxy tellurides **4a-g**. Reaction conditions: a) Ethylene glycol, *p*-TsOH, toluene, reflux, 24 h (82-98% yield). b) i. Mg, THF, reflux, 3 h; ii. Te, r.t., overnight; iii. H₂O, atmosphere, 1 h (77-79% yield). c) i. RX (R = Me, Et, ^{*n*}Pr, ^{*n*}Bu; X = Br or I), NaBH₄, MeOH, THF, 0 °C to r.t., 10 min; ii. *p*-TsOH, acetone, reflux, 1.5 h (35-55% yield). d) NaBH₄, MeOH, 0 °C to r.t., 2 h (35-92% yield).

Next, the bioreductions of telluro-acetophenones **3a-g** were investigated (Table 1) under previously established conditions.²¹ As biocatalysts, lyophilized cells of *Escherichia coli* (*E. coli*) overexpressing ADH from *Ralstonia* species (Ras-ADH),²² *Lactobacillus brevis* (Lb-ADH),²³ *Sphingobium yanoikuyae* (Sy-ADH),²⁴ *Thermoanaerobacter ethanolicus* (Tes-ADH),²⁵ *Thermoanaerobacter species* (ADH-T),²⁶ *Rhodococcus ruber* (ADH-A)²⁷ and the commercially available evo 1.1.200²⁸ were assayed.

Satisfyingly five out of the seven ADHs were able to catalyze the enantioselective bioreduction of telluroketones **3a-g** to the desired optically active hydroxy tellurides **4a-g**, attaining depending on the enzyme choice moderate to excellent selectivities towards the production of (*R*)-alcohols (58->99% *ee*), while remarkably the synthesis of enantiopure (*S*)-alcohols **4a-g** was possible using the appropriate enzyme (Table 1).

Regarding bioreductive reactions of *para*-substituted telluroketones **3a-d** they were achieved in good to excellent extension using the Ras-ADH (77-95% conversion, entry 1) and the ADH-A (52-75% conversion, entry 6), obtaining in all cases the (*S*)-hydroxy tellurides in enantiomerically pure form, meanwhile the Sy-ADH (entry 3) led to modest activity and selectivity values. Interestingly for the Ras-ADH, increasing the alkyl length chain linked to Te atom from ethyl (**3b**, R = *p*-TeEt) to butyl (**3d**, R = *p*-Te^{*n*}Bu) a decrease in the conversion rates from 95 to 77% was observed (entry 1). An interesting trend was also

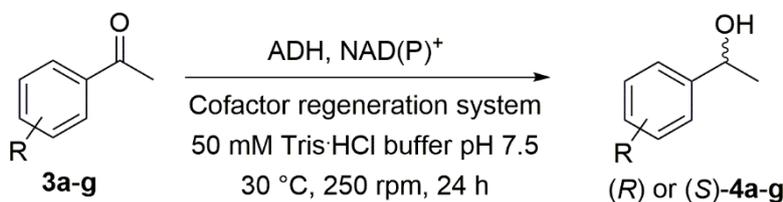
observed when changing the aromatic pattern substitution from *para* to *meta* position, resulting in a significant decrease in activity for the Ras-ADH in the bioreduction of **3e-g** (40-54% conversion and 72-86% *ee*, entry 1), while the ADH-A demonstrated its versatility by producing the enantiopure (*S*)-alcohols in 69-75% conversion (entry 6).

When anti-Prelog enzymes such as the Lb-ADH (entry 2) and the commercially available evo-1.1.200 (entry 7) were employed, the Lb-ADH acted with a moderate to excellent selectivity towards *para*-substituted acetophenones (57->99% *ee*), reaching a complete selectivity when the bulkier substrate **3d** was considered obtaining the corresponding butyl derivative **4d** in enantiopure form. A similar trend was observed with the evo-1.1.200 (51-60% conversion and 58-84% *ee*), however a notable difference between both enzymes was noticed when facing the *meta*-substituted ketones **3e-g**. In fact, a significant decrease in activity was observed with the Lb-ADH, while high selectivities and moderate conversions were reached with the evo-1.1.200 (60-68% conversion and 92-97% *ee*) for the production of (*R*)-**4e-g**.

Finally, a semi-preparative scale ADH-catalysed reduction was carried out employing 100 mg of telluro-acetophenone **3b** (R = *p*-TeEt) employing Ras-ADH as biocatalyst. After 24 h, the conversion rate reached 84%, obtaining the optically active hydroxy telluride (*S*)-(-)-**4b** with 42% of isolated yield and >99% *ee* ($[\alpha]_D^{20} = -10.2$ ($c = 2.0$, CHCl₃)) after silica gel column

purification, demonstrating the robustness of the bioreduction process.

Table 1. Bioreduction of telluro-acetophenones **3a-g** catalyzed by alcohol dehydrogenases (ADHs)



Entry	Alcohol dehydrogenase	4a (R = <i>p</i> -TeMe)		4b (R = <i>p</i> -TeEt)		4c (R = <i>p</i> -Te ^{<i>i</i>} Pr)		4d (R = <i>p</i> -Te ^{<i>t</i>} Bu)		4e (R = <i>m</i> -TeEt)		4f (R = <i>m</i> -Te ^{<i>i</i>} Pr)		4g (R = <i>m</i> -Te ^{<i>t</i>} Bu)	
		c [%] ^a	ee [%] ^b	c [%] ^a	ee [%] ^b	c [%] ^a	ee [%] ^b	c [%] ^a	ee [%] ^b	c [%] ^a	ee [%] ^b	c [%] ^a	ee [%] ^b	c [%] ^a	ee [%] ^b
1	<i>E. coli</i> /Ras-ADH	92	>99 (S)	95	>99 (S)	88	>99 (S)	77	>99 (S)	54	77 (S)	48	72 (S)	40	86 (S)
2	<i>E. coli</i> /Lb-ADH	44	57 (R)	69	84 (R)	79	88 (R)	82	>99 (R)	32	97 (R)	13	n.d.	7	n.d.
3	<i>E. coli</i> /Sy-ADH	56	46 (S)	62	52 (S)	54	63 (S)	67	95 (S)	68	58 (S)	58	80 (S)	56	71 (S)
4	<i>E. coli</i> /TeS-ADH	<5	n.d.	17	n.d.	13	n.d.	<5	n.d.	9	n.d.	<5	n.d.	<5	n.d.
5	<i>E. coli</i> /ADH-T	<5	n.d.	19	n.d.	22	n.d.	<5	n.d.	8	n.d.	<5	n.d.	<5	n.d.
6	<i>E. coli</i> /ADH-A	52	>99 (S)	69	>99 (S)	72	>99 (S)	75	>99 (S)	75	>99 (S)	75	>99 (S)	69	>99 (S)
7	evo-1.1.200	60	58 (R)	53	67 (R)	51	73 (R)	52	84 (R)	68	97 (R)	64	96 (R)	60	92 (R)

^a Conversion values were determined by GC. ^b Enantiomeric excess values were determined by GC after removed the alkyl-tellurium moiety ("TeR") with ^tBuLi. Absolute configurations appear in brackets. n.d. not determined due to the low conversion rates.

Conclusions

In summary, a series of telluro-acetophenones, including five novel ones, has been successfully reduced to the corresponding optically active hydroxy tellurides employing ADH-catalyzed bioreduction processes. For the production of enantiopure *para*-substituted (S)-hydroxy tellurides, the best results were obtained using the Ras-ADH and ADH-A, the latest being also capable to give access to the enantiopure (S)-hydroxy tellurides when the substitution was present at the *meta*-position. In a complementary approach, the Lb-ADH and the evo-1.1.200 allowed the preparation of the (R)-alcohols displaying the best selectivities with the Lb-ADH in the bioreduction of the most bulkier substrates, while the evo-1.1.200 demonstrated its potential in the preparation of optically alcohols with substitutions at the *para*-position of the aromatic ring.

Overall, this is the first report of ADHs-catalyzed reduction of Te-containing carbonyl substrates, demonstrating that the biocatalytic reduction of prochiral telluroketones mediated by ADHs is an efficient and powerful approach to produce optically

active hydroxy tellurides, being possible the isolation of the (S)- or (R)-enantiomers depending on the enzyme of choice.

Experimental Section

Chemical reagents for the synthesis of ketones **3a-g** and alcohols **4a-g** were purchased from Sigma-Aldrich. For the bioreduction experiments, D-glucose, NADH and NADPH were also acquired from Sigma-Aldrich, while glucose dehydrogenase (GDH-105) was obtained from Codexis Inc. and evo-1.1.200 from Evoxx Technologies GmbH. Made in house ADHs were overexpressed in *E. coli*: *Ralstonia* species (Ras-ADH), *Sphingobium yanoikuyae* (Sy-ADH), *Thermoanaerobacter* species (ADH-T), *Lactobacillus brevis* (Lb-ADH), *Thermoanaerobacter ethanolicus* (TeS-ADH) and *Rhodococcus ruber* (ADH-A).

Nuclear magnetic resonance (NMR) spectra (¹H and ¹³C) were recorded on a Bruker AV300 MHz spectrometer. ¹²⁵Te NMR spectra were recorded on a Bruker Avance III at 9.4 T (400.13 MHz for ¹H NMR and 126.24 for ¹²⁵Te NMR) and the chemical shifts for ¹²⁵Te NMR were registered relative to an external standard diphenyl ditelluride (Ph₂Te) at δ = 422 ppm. All chemical shifts (δ) are given in parts per million (ppm). Gas chromatography (GC) analyses were performed on an Agilent HP6890 GC chromatograph equipped with FID detector. Conversion rates measurements were performed on non-chiral GC column DB-1701 (30 m

x 0.25 mm, 0.25 μm), while for the enantiomeric excess values determination chiral GC column Chirasil β -Dex (25 m x 0.25 mm, 0.25 μm) were required. Melting points were measured in a Stuart apparatus SMP3 (Bibby Sterilin, Staffordshire, UK) introducing the samples in open capillary tubes and the measurements are uncorrected. Optical rotation measurement was performed at 590 nm on Autopol IV Automatic polarimeter (Rudolph Research Analytical, Hackettstown, NJ, USA). Thin-layer chromatography (TLC) analyses were conducted with Merck Silica Gel 60 F254 precoated plates and visualized with UV, potassium permanganate and vanillin stain. Column chromatographies were performed using silica gel 60 (230-240 mesh).

General procedures for the chemical synthesis of ketones 3a-g and alcohols 4a-g

Acetalization of 3'- and 4'-bromoacetophenones²⁰

A mixture of the corresponding bromoacetophenone (5.98 g, 25.0 mmol), ethylene glycol (15 mL, 250.0 mmol), *p*-TsOH (0.25 mg, 1.50 mmol) and anhydrous toluene (150 mL) was stirred and heated under reflux for 24 h. Water formed during the reaction (about 0.5 mL) was removed using a Dean-Stark trap. The reaction mixture was cooled and extracted with ethyl acetate (3 x 50 mL), and the combined organic phase sequentially washed with a NaHCO₃ saturated aqueous solution (30 mL), water (30 mL) and brine (30 mL). The resulting organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure, affording the corresponding dioxolanes 1.

2-(4-Bromophenyl)-2-methyl-1,3-dioxolane. White crystals, 82%. *R_f* (20% EtOAc/hexane): 0.64; ¹H NMR (CDCl₃, 300.13 MHz): δ = 1.63 (s, 3H), 3.71–3.78 (m, 2H), 4.00–4.07 (m, 2H), 7.35 (dd, 2H, ³*J*_{H,H} = 8.7 Hz, ⁴*J*_{H,H} = 1.9 Hz), 7.46 (dd, 2H, ³*J*_{H,H} = 8.7 Hz and ⁴*J*_{H,H} = 1.9 Hz) ppm.

2-(3-Bromophenyl)-2-methyl-1,3-dioxolane. Colorless oil, 98%. *R_f* (20% EtOAc/hexane): 0.61. ¹H NMR (CDCl₃, 300.13 MHz): δ = 1.62 (s, 3H), 3.70–3.78 (m, 2H), 3.99–4.08 (m, 2H), 7.20 (t, 1H, ³*J*_{H,H} = 7.8 Hz), 7.41–7.46 (m, 2H), 7.63–7.65 (m, 1H) ppm.

Synthesis of diaryl ditellurides 2²⁰

A suspension of magnesium (0.53 g, 22.0 mmol) in anhydrous THF (40 mL) was added to a solution of the corresponding 2-(bromophenyl)-2-methyl-1,3-dioxolane (**1**, 4.86 g, 20.0 mmol) in anhydrous THF (10 mL) under nitrogen atmosphere. The mixture was refluxed for 3 h and after this time, the reaction was left to warm until room temperature. At this point, elemental tellurium (20.0 mmol) was added in one-portion and kept under stirring overnight. The solution was cooled to 0 °C and water (30 mL) was added dropwise. The crude reaction was filtered through a celite pad and washed exhaustively with CH₂Cl₂ (3 x 50 mL). The resulting organic phase was finally washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure, isolating the corresponding diaryl ditellurides **2** in satisfactory purity to be used in the next step without further purification.

1,2-bis[4-(2-Methyl-1,3-dioxolan-2-yl)phenyl]ditellane. Red powder, 77%. Mp: 139–141 °C. *R_f* (20% EtOAc/hexane): 0.33. ¹H NMR (CDCl₃, 300.13 MHz): δ = 1.63 (s, 3H), 3.76–3.77 (m, 2H), 4.02–4.03 (m, 2H), 7.30 (dd, 2H, ³*J*_{H,H} = 8.4, ⁴*J*_{H,H} = 1.8), 7.77 (dd, 2H, ³*J*_{H,H} = 8.4 Hz, ⁴*J*_{H,H} = 1.8 Hz); ¹³C NMR (CDCl₃, 75.5 MHz): δ = 27.6, 64.5, 107.2, 108.5, 125.2, 126.3, 128.2, 137.3, 143.6 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 408 ppm.

1,2-bis[3-(2-Methyl-1,3-dioxolan-2-yl)phenyl]ditellane. Red powder, 79%. Mp: 140–143 °C. *R_f* (20% EtOAc/hexane): 0.41. ¹H NMR (CDCl₃,

300.13 MHz): δ = 1.64 (s, 3H), 3.72–3.82 (m, 2H), 4.00–4.10 (m, 2H), 7.18 (t, 1H, ³*J*_{H,H} = 7.6), 7.34 (t, 1H, ³*J*_{H,H} = 8.0 Hz), 7.76 (d, 1H, ³*J*_{H,H} = 7.6 Hz), 7.97 (s, 1H) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 27.5, 64.4, 107.8, 108.3, 125.2, 129.1, 134.2, 137.0, 144.2 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 426 ppm.

Synthesis of telluroketones 3a-g

MeOH (2 mL) was added dropwise to a suspension of the corresponding diacetal ditelluride **2** (0.58 mg, 1.0 mmol), the corresponding alkyl halide (3.0 mmol) and NaBH₄ (0.11 g, 3 mmol) in anhydrous THF (5 mL) under nitrogen atmosphere at 0 °C. The mixture was left to warm until room temperature and stirred for 1 h. After this period unreacted hydride excess was destroyed adding an aqueous NH₄Cl saturated solution (5 mL). The mixture was extracted with CH₂Cl₂ (3 x 15 mL), combining the organic layers that were next washed with brine (15 mL). The resulting organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was dissolved in acetone (15 mL) and *p*-TsOH (0.15 mmol) was added. The mixture was refluxed for 4 h, and after this time, the solvent was removed under reduced pressure and the reaction crude purified by column chromatography on silica gel (20% EtOAc/hexane), affording the corresponding organotellurium ketones **3a-g**.

1-[4-(Methyltellanyl)phenyl]ethanone (3a). Yellow powder, 35%. *R_f* (20% EtOAc/hexane): 0.43. IR (NaCl): ν = 1217, 1366, 1580, 1670, 1738, 2971 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 2.25 (s, 3H), 2.56 (s, 3H), 7.64 (dd, 2H, ³*J*_{H,H} = 8.6 Hz, ⁴*J*_{H,H} = 2.0 Hz), 7.75 (dd, 2H, ³*J*_{H,H} = 8.6 Hz, ⁴*J*_{H,H} = 2.0 Hz) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = -16.3, 26.6, 121.6, 128.6, 135.2, 135.8, 197.7 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 343 ppm.

1-[4-(Ethyltellanyl)phenyl]ethanone (3b). Pale yellow oil, 55%. *R_f* (20% EtOAc/hexane): 0.68. IR (NaCl): ν = 1263, 1580, 1674, 2816, 2916, 2954 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 1.69 (t, 3H, ³*J*_{H,H} = 7.6 Hz), 2.57 (s, 3H), 2.96 (q, 2H, ³*J*_{H,H} = 7.6 Hz), 7.74 (m, 4H) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 0.9, 17.3, 26.6, 120.7, 128.7, 136.0, 136.0, 197.8 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 541 ppm.

1-[4-(Propyltellanyl)phenyl]ethanone (3c). Yellow oil, 53%. *R_f* (20% EtOAc/hexane): 0.46. IR (NaCl): ν = 1262, 1589, 1675, 2867, 2925, 2956 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 0.99 (t, 3H, ³*J*_{H,H} = 7.2 Hz), 1.85 (sext, 2H, ³*J*_{H,H} = 7.3 Hz), 2.55 (s, 3H), 2.94 (t, 3H, ³*J*_{H,H} = 7.3 Hz), 7.71 (m, 4H) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 11.5, 16.7, 25.1, 26.5, 120.9, 128.5, 135.9, 136.8, 197.7 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 470 ppm.

1-[4-(Butyltellanyl)phenyl]ethanone (3d). Pale yellow oil, 45%. *R_f* (20% EtOAc/hexane): 0.74. IR (NaCl): ν = 1261, 1580, 1676, 2869, 2925, 2954 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 0.91 (t, 3H, ³*J*_{H,H} = 7.4 Hz), 1.37–1.42 (m, 2H), 1.76–1.86 (m, 2H), 2.57 (s, 3H), 2.97 (t, 3H, ³*J*_{H,H} = 7.4 Hz), 7.72 (m, 4H) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 8.8, 13.5, 25.2, 26.6, 33.8, 121.0, 128.6, 135.9, 136.7, 197.8 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 477 ppm.

1-[3-(Ethyltellanyl)phenyl]ethanone (3e). Pale yellow oil, 46%. *R_f* (20% EtOAc/hexane): 0.63. IR (NaCl): ν = 1249, 1562, 1679, 2860, 2917, 2953 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 1.63 (t, 3H, ³*J*_{H,H} = 7.6 Hz), 2.56 (s, 3H), 2.89 (q, 2H, ³*J*_{H,H} = 7.6 Hz), 7.27–7.28 (m, 1H), 7.80–7.93 (m, 1H), 8.26 (s, 1H) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 1.0, 17.4, 26.7, 112.2, 127.5, 129.2, 137.6, 137.9, 142.6, 197.6 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 551 ppm.

1-[3-(Propyltellanyl)phenyl]ethanone (3f). Yellow oil, 43%. *R_f* (20% EtOAc/hexane): 0.46. IR (NaCl): ν = 1249, 1561, 1680, 2867, 2925, 2956

cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 0.98 (t, 3H, ³J_{H,H} = 7.3 Hz), 1.82 (sext, 2H, ³J_{H,H} = 7.4 Hz), 2.58 (s, 3H), 2.93 (t, 3H, ³J_{H,H} = 7.4 Hz), 7.27 (t, 1H, ³J_{H,H} = 7.7 Hz), 7.81–7.89 (m, 2H), 8.27 (t, ⁴J_{H,H} = 1.7 Hz, 1H) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 11.8, 16.7, 25.1, 26.7, 112.4, 127.5, 129.2, 137.7, 137.9, 142.6, 197.7 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 479 ppm.

1-[3-(Butyltellanyl)phenyl]ethanone (3g). Pale yellow oil, 49%. *R_f* (20% EtOAc/hexane): 0.75. IR (NaCl): ν = 1249, 1562, 1681, 2869, 2925, 2955 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 0.89 (t, 3H, ³J_{H,H} = 7.3 Hz), 1.36–1.43 (m, 2H), 1.73–1.81 (m, 2H), 2.58 (s, 3H), 2.94 (t, 2H, ³J_{H,H} = 7.6 Hz), 7.26–7.31 (m, 1H), 7.84–7.86 (m, 2H), 8.27 (s, 1H) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 9.0, 13.5, 25.1, 26.7, 33.9, 112.5, 127.5, 129.3, 137.8, 142.6, 197.7 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 485 ppm.

Synthesis of racemic alkyltellurium-1-phenylethanols 4a-g

NaBH₄ (0.57 mg, 1.5 mmol) was added in portions to a solution of the corresponding telluroketone **3a-g** (1 mmol) in dry MeOH (2 mL) under nitrogen atmosphere and 0 °C. The mixture was left to warm until room temperature and stirred for 1 h. Unreacted hydride excess was destroyed adding an aqueous NH₄Cl saturated solution (2 mL), and then MeOH was evaporated in a rotary evaporator under reduced pressure. The mixture was extracted with CH₂Cl₂ (3 x 10 mL), combining the organic layers that were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (20% EtOAc/hexane), affording the corresponding racemic hydroxy tellurides **4a-g** employed later for analytical purposes.

1-[4-(Methyltellanyl)phenyl]ethanol (4a). Pale yellow oil, 75%. *R_f* (20% EtOAc/hexane): 0.36; IR (NaCl): ν = 1086, 1111, 1396, 2925, 2970, 3370 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 1.47 (d, 3H, ³J_{H,H} = 6.3 Hz), 2.00 (brs, 1H), 2.19 (s, 3H), 4.85 (q, 1H, ³J_{H,H} = 6.3 Hz), 7.22 (dd, 2H, ³J_{H,H} = 7.9 Hz, ⁴J_{H,H} = 1.8 Hz), 7.62 (dd, 2H, ³J_{H,H} = 7.9 Hz, ⁴J_{H,H} = 1.8 Hz) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = -16.4, 25.3, 70.1, 111.1, 126.4, 137.0, 145.2 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 326 ppm.

1-[4-(Ethyltellanyl)phenyl]ethanol (4b). Pale yellow oil, 92%. *R_f* (20% EtOAc/hexane): 0.36; IR (NaCl): ν = 750, 968, 1009, 2970, 3324 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 1.48 (d, 3H, ³J_{H,H} = 6.5 Hz), 1.65 (t, 2H, ³J_{H,H} = 6.5 Hz), 1.92 (brs, 1H), 2.87 (q, 2H, ³J_{H,H} = 7.6 Hz), 4.87 (q, 1H, ³J_{H,H} = 7.6 Hz), 7.23 (dd, 2H, ³J_{H,H} = 8.0 Hz, ⁴J_{H,H} = 1.9 Hz), 7.70 (dd, 2H, ³J_{H,H} = 8.0 Hz, ⁴J_{H,H} = 1.9 Hz) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 0.7, 17.5, 25.3, 70.2, 110.4, 126.4, 138.7, 145.4 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 527 ppm.

1-[4-(Propyltellanyl)phenyl]ethanol (4c). Yellow oil, 70%. *R_f* (20% EtOAc/hexane): 0.45; IR (NaCl): ν = 750, 764, 1274, 2959, 3324 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 0.99 (t, 3H, ³J_{H,H} = 7.2 Hz), 1.47 (d, 3H, ³J_{H,H} = 6.5 Hz), 1.80 (sext, 2H, ³J_{H,H} = 7.2 Hz), 1.93 (brs, OH), 2.88 (t, 2H, ³J_{H,H} = 7.2 Hz), 4.86 (q, 1H, ³J_{H,H} = 6.5 Hz), 7.21 (dd, 2H, ³J_{H,H} = 8.2 Hz, ⁴J_{H,H} = 1.9 Hz), 7.68 (dd, 2H, ³J_{H,H} = 8.2 Hz, ⁴J_{H,H} = 1.9 Hz) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 11.4, 16.7, 25.2, 25.3, 70.2, 110.5, 126.4, 138.6, 145.4 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 454 ppm.

1-[4-(Butyltellanyl)phenyl]ethanol (4d). Pale yellow oil, 89%. *R_f* (10% EtOAc/hexane): 0.22; IR (NaCl): ν = 764, 1010, 1261, 2959, 3336 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 0.91 (t, 3H, ³J_{H,H} = 7.2 Hz), 1.35–1.47 (m, 2H), 1.73 (d, 3H, ³J_{H,H} = 6.5), 1.78–1.80 (m, 2H), 2.01 (brs, OH), 2.89 (t, 2H, ³J_{H,H} = 7.5 Hz), 4.85 (q, 1H, ³J_{H,H} = 6.5 Hz), 7.19 (dd, 2H, ³J_{H,H} = 8.3 Hz, ⁴J_{H,H} = 1.8 Hz), 7.68 (dd, 2H, ³J_{H,H} = 8.3 Hz, ⁴J_{H,H} = 1.8 Hz) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 8.6, 13.5, 25.2, 25.3, 34.0, 70.2, 110.6, 126.3, 138.5, 145.3 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 461 ppm.

1-[3-(Ethyltellanyl)phenyl]ethanol (4e). Pale yellow oil, 89%. *R_f* (20% EtOAc/hexane): 0.38; IR (NaCl): ν = 697, 764, 1275, 2969, 3324 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 1.48 (d, 3H, ³J_{H,H} = 6.5 Hz), 1.66 (t, 2H, ³J_{H,H} = 7.6 Hz), 2.89 (q, 2H, ³J_{H,H} = 7.6 Hz), 4.84 (q, 1H, ³J_{H,H} = 6.5 Hz), 7.16–7.21 (m, 1H), 7.26–7.29 (m, 1H), 7.59–7.62 (m, 1H), 7.72 (s, 1H) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 1.2, 17.3, 25.3, 70.2, 112.0, 124.8, 129.3, 135.4, 137.4, 146.8 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 534 ppm.

1-[3-(Propyltellanyl)phenyl]ethanol (4f). Yellow oil, 79%. *R_f* (20% EtOAc/hexane): 0.50. IR (NaCl): ν = 697, 764, 1267, 2959, 3323 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 0.99 (t, 3H, ³J_{H,H} = 7.4 Hz), 1.48 (d, 3H, ³J_{H,H} = 6.5), 1.82 (sext, 2H, ³J_{H,H} = 7.4 Hz), 1.94 (brs, OH), 2.90 (t, 2H, ³J_{H,H} = 7.4 Hz), 4.84 (q, 1H, ³J_{H,H} = 6.5 Hz), 7.15–7.20 (m, 1H), 7.28–7.29 (m, 1H), 7.58–7.61 (m, 1H), 7.72 (s, 1H) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 11.4, 16.8, 25.2, 25.3, 70.2, 112.0, 124.7, 129.3, 135.3, 137.2, 146.7 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 469 ppm.

1-[3-(Butyltellanyl)phenyl]ethanol (4g). Pale yellow oil, 35%. *R_f* (20% EtOAc/hexane): 0.56. IR (NaCl): ν = 698, 1064, 1267, 2956, 3334 cm⁻¹. ¹H NMR (CDCl₃, 300.13 MHz): δ = 0.90 (t, 3H, ³J_{H,H} = 7.3 Hz), 1.38–1.41 (m, 2H), 1.47 (d, 3H, ³J_{H,H} = 6.3 Hz), 1.76–1.79 (m, 2H), 2.04 (brs, 1H), 2.91 (t, 2H, ³J_{H,H} = 7.7 Hz), 4.83 (q, 1H, ³J_{H,H} = 6.3 Hz), 7.17 (t, 2H, ³J_{H,H} = 7.4 Hz), 7.36–7.61 (m, 1H), 7.70 (s, 1H) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 8.6, 13.5, 25.2, 25.3, 34.0, 70.1, 124.7, 129.3, 135.2, 137.2, 146.7 ppm; ¹²⁵Te NMR (126.2 MHz): δ = 462 ppm.

Bioreduction experiments

ADH-catalyzed reduction experiments were performed in aqueous medium (50 mmol L⁻¹ Tris.HCl buffer pH 7.5) using a small quantity of dimethylsulfoxide (DMSO, 2.5% v/v) as cosolvent aiming the solubilization of telluroketones in aqueous media, all of them containing catalytic amounts of NAD⁺ or NADP⁺ (10 mmol L⁻¹) depending on the enzyme cofactor dependency at 30 °C for 24 h. For cofactor regeneration purposes, the usual substrate-coupled method was employed, in which 2-propanol (iPrOH, 5% v/v) acted as co-substrate and co-solvent, except for Ras-ADH that used the enzyme-coupled approach with glucose and glucose dehydrogenase.

Bioreduction mediated by *E. coli*/Ras-ADH

Lyophilized cells of *E. coli*/Ras-ADH (12 mg), DMSO (15 μL, 2.5% v/v), 1 mmol L⁻¹ NADP⁺ (60 μL of a 10 mmol L⁻¹ stock solution), 50 mmol L⁻¹ glucose (60 μL of a 500 mmol L⁻¹ stock solution) and glucose dehydrogenase (10 U) were added into an Eppendorf tube containing telluroketones **3a-g** (25 mmol L⁻¹) in a 50 mmol L⁻¹ Tris.HCl buffer pH 7.5 (420 μL). The reaction was shaken at 30 °C and 250 rpm for 24 h, and after this time, the mixture was extracted with ethyl acetate (3 x 500 μL). The organic layers were separated by centrifugation (2 min, 5700 rpm), combined and finally dried over Na₂SO₄. An aliquot was taken to inject in the GC for the measurement of conversion and enantiomeric excess values.

Bioreduction mediated by *E. coli*/Lb-ADH

Lyophilized cells of *E. coli*/Lb-ADH (12 mg), iPrOH (30 μL, 5% v/v), 1 mmol L⁻¹ NADP⁺ (60 μL of a 10 mmol L⁻¹ stock solution) and 10 mmol L⁻¹ MgCl₂ (60 μL of a 100 mmol L⁻¹ stock solution) were added into an Eppendorf tube containing telluroketones **3a-g** (25 mmol L⁻¹) in a 50 mmol L⁻¹ Tris.HCl buffer pH 7.5 (480 μL). The reaction was shaken at 30 °C and 250 rpm for 24 h, and after this time, the mixture was extracted with ethyl acetate (3 x 500 μL). The organic layers were separated by centrifugation (2 min, 5700

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rpm), combined and finally dried over Na₂SO₄. An aliquot was taken to inject in the GC for the measurement of conversion and enantiomeric excess values.

Bioreduction mediated by E. coli/Sy-ADH, E. coli/TeS-ADH and E. coli/ADH-T

Lyophilized cells of *E. coli*/ADH (12 mg), ¹H₂O (30 μL, 5% v/v) and 1 mmol L⁻¹ NADP⁺ (60 μL of a 10 mmol L⁻¹ stock solution) were added into an Eppendorf tube containing telluroketones **3a-g** (25 mmol L⁻¹) in a 50 mmol L⁻¹ Tris-HCl buffer pH 7.5 (510 μL). The reaction was shaken at 30 °C and 250 rpm for 24 h, and after this time, the mixture was extracted with ethyl acetate (3 x 500 μL). The organic layers were separated by centrifugation (2 min, 5700 rpm), combined and finally dried over Na₂SO₄. An aliquot was taken to inject in the GC for the measurement of conversion and enantiomeric excess values.

Bioreduction mediated by E. coli/ADH-A

Lyophilized cells of *E. coli*/ADH-A (12 mg), ¹H₂O (30 μL, 5% v/v) and 1 mmol L⁻¹ NAD⁺ (60 μL of a 10 mmol L⁻¹ stock solution) were added into an Eppendorf tube containing telluroketones **3a-g** (25 mmol L⁻¹) in a 50 mM Tris-HCl buffer pH 7.5 (510 μL). The reaction was shaken at 30 °C and 250 rpm for 24 h, and after this time, the mixture was extracted with ethyl acetate (3 x 500 μL). The organic layers were separated by centrifugation (2 min, 5700 rpm), combined and finally dried over Na₂SO₄. An aliquot was taken to inject in the GC for the measurement of conversion and enantiomeric excess values.

Bioreduction mediated by evo-1.1.200

Commercially available evo-1.1.200 (10 mg), ¹H₂O (25 μL, 5% v/v), 1 mmol L⁻¹ NAD⁺ (50 μL of a 10 mmol L⁻¹ stock solution) and 10 mmol L⁻¹ MgCl₂ (50 μL of a 100 mmol L⁻¹ stock solution) were added into an Eppendorf tube containing telluroketones **3a-g** (25 mmol L⁻¹) in a 50 mM Tris-HCl buffer pH 7.5 (325 μL). The reaction was shaken at 30 °C and 250 rpm for 24 h, and after this time, the mixture was extracted with ethyl acetate (3 x 500 μL). The organic layers were separated by centrifugation (2 min, 5700 rpm), combined and finally dried over Na₂SO₄. An aliquot was taken to inject in the GC for the measurement of conversion and enantiomeric excess values.

Derivatization of optically active hydroxy tellurides (4a-g) into 1-phenylethanol for enantiomeric excess measurements

Enantiomeric excesses (ee) values were determined using an Agilent 6890A GC-system equipped with a chiral stationary phase Chirasil β-Dex column (25 m x 0.25 mm, 0.25 μm), after treatment of the hydroxy telluride samples with ^tBuLi for the removal of the tellurium moiety ("TeR") at the aromatic ring. For this purpose, a solution of ^tBuLi in pentane 1.9 mmol L⁻¹ (0.195 mmol, 100 μL) was added dropwise to a solution of optically active hydroxy telluride **4a-g** (approximately 0.015 mmol) in dry THF (200 μL) under nitrogen atmosphere at -78 °C. The mixture was left to warm until 0 °C and stirred for 2 h and after this period unreacted ^tBuLi was destroyed adding brine (300 μL). The mixture was extracted with EtOAc (2 x 250 μL), the organic layers separated by centrifugation (1 min, 5700 rpm), combined and finally dried over Na₂SO₄. Then, an aliquot was promptly analyzed in the GC (see the Supporting Information for further details).

Semi-preparative bioreduction of 3b into (S)-4b mediated by Ras-ADH

Lyophilized cells of *E. coli*/Ras-ADH (290 mg), DMSO (362 μL, 2.5% v/v), 1 mmol L⁻¹ NADP⁺ (1.45 mL of a 10 mmol L⁻¹ stock solution), 50 mmol L⁻¹ glucose (1.45 mL of a 500 mmol L⁻¹ stock solution) and glucose dehydrogenase (10 U) were added into an Erlenmeyer flask containing telluro-acetophenone **3b** (100 mg, 0.36 mmol, 25 mmol L⁻¹) in a 50 mmol L⁻¹ Tris-HCl buffer pH 7.5 (10 mL). The reaction was shaken at 30 °C and 250 rpm for 24 h, and after this time, the mixture was extracted with ethyl acetate (3 x 500 μL). The organic layers were combined, dried over Na₂SO₄ and filtered. The resulting reaction crude was purified by column chromatography on silica gel (20% EtOAc/hexane), affording (S)-(-)-**4b** [42% isolated yield and >99% ee, [α]_D²⁰ = -10.2 (c = 2.0, CHCl₃)].

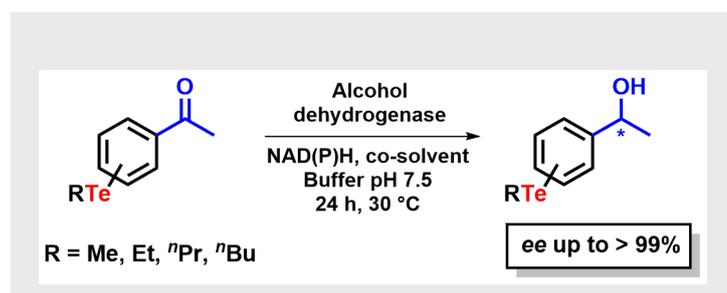
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**Tellurium chemistry**

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Stereoselective Bioreduction of Telluro-acetophenones to Optically Active Hydroxy Tellurides

A series of telluro-acetophenones has been chemically synthesized and later reduced using alcohol dehydrogenases of complementary selectivity. Therefore, (*R*) and (*S*)-hydroxy tellurides have been obtained in good to excellent optical purities under mild reaction conditions in aqueous medium.