Advanced Synthesis & Catalysis

Accepted Article

Title: Rongalite-promoted on water synthesis of functionalised tellurides and ditellurides

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201901536

Link to VoR: http://dx.doi.org/10.1002/adsc.201901536

10.1002/adsc.201901536

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Rongalite-promoted *on water* synthesis of functionalised tellurides and ditellurides

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. The *on water* reaction of sodium telluride with electrophiles has been explored. Na_2Te, generated *in situ* through the rongalite (sodium hydroxymethanesulfinate)-promoted reduction of elemental tellurium, reacts with a wide variety of electrophiles, including strained heterocycles, haloalkanes, Michael acceptors, and aryl diazonium salts, providing simple and rapid access to a broad range of novel functionalised symmetrical tellurides. The methodology well tolerated the presence of versatile functional groups such as alchohols, amines, esters, nitriles, and sulfones and allowed the incorporation of tellurium atoms into biologically relevant natural-derived products. Furthermore, in the case of the nucleophilic ring opening of epoxides, a judicious tuning of the reaction conditions enabled the synthesis of unreported β-hydroxy- and β-amino-ditellurides, which were further employed as precursors of new functionalised unsymmetrical dialkyl tellurides. The thiol-peroxidase catalytic activity of hydroxy-ditellurides has also been investigated in order to compare their antioxidant properties with those of homologous tellurides.

Keywords: Tellurides; Ditellurides; On water, Rongalite; Antioxidants, Glutathione peroxidase

Introduction

Chalcogen-containing organic molecules are of significant importance in organic chemistry, material science, medicinal chemistry, and biology.[1] In particular, organotellurium compounds play a central role in organic synthesis, readily undergoing nucleophilic, electrophilic, and radicophilic reactions.[2] These transformations, which often occur with good regio- and stereo-selectivity, have been widely employed in an array of functional group conversions,[3] as well as in the formation of new carbon-carbon bonds[4] and in the synthesis of natural products.[5] The chemistry of organotellurides has also been applied in the development of new catalysts[6] and functional materials.[7] Furthermore, a number of organotellurium derivatives have been studied for their biological activities as thioredoxine reductase modulators,[8] glutathione peroxidase mimics,[9] cancer cells growth inhibitors,[8,10] and antibacterials.[11]

In this *scenario*, functionalised dialkyl tellurides and ditellurides are arguably one of the most interesting and versatile classes of organotellurium derivatives, representing valuable compounds both in organic synthesis and in biology. In addition, the promising catalytic and pharmacological properties of O- and N-containing organochalcogenides have prompted researchers to design and synthesise novel functionalised organochalcogenides.[9,12] Suitably substituted β-hydroxy- and β-amino- tellurides were demonstrated to be excellent mimics of GPx[9b,c,f] and also exhibited remarkable activity as carbonic anhydrase activators[13] and inhibitors.[14]

However, while diaryl-ditellurides[15] and diaryl or aryl-alkyl-tellurides[16] have been widely studied, dialkyl substituted analogues have been far less explored and the development of a general and convenient route towards functionalised organotellurides would be highly desirable.

Symmetrical dialkyl tellurides and ditellurides are commonly prepared through the reaction of alkali tellurides and ditellurides with haloalkanes[2a,17] or alkyl tosylates.[2a,18] Other methods involve the insertion of tellurium into the carbon-metal bond of organolithium compounds or Grignard reagents.[2,19] Further functionalisable β-halo dialkyl tellurides and ditellurides can be accessed from terminal alkenes and tellurium tetrahalides.[20] In this context, despite their interest, tellurides and ditellurides bearing O- and N-containing functionalities have been scarcely explored.

Only a few examples of β-amino substituted systems, including tellurocystine and tellurolanthionine derivatives, obtained from suitable β-haloamines[17a,b] or β-lactones[21] have been reported. In this context, the nucleophilic ring-opening-reaction (NROR) of strained heterocycles[22] such as epoxides, aziridines and thiiranes, as well as the telluro-Michael addition, could represent

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powerful as yet unexploited tools to access O-, N-, and S-containing symmetrical dialkyl tellurides and ditellurides.

During the course of our studies on the reactivity of chalcogen-containing nucleophiles, we developed a ring-opening-based procedure for the synthesis of β-hydroxy-and β-amino-tellurides from Li_2Te and epoxides or aziridines. Lithium triethylborohydride ($LiHBEt_3$) was used as reducing agent to *in situ* generate Li_2Te from elemental tellurium.[23] This methodology is the sole example of synthesis of hydroxy- and amino- functionalised symmetrical tellurides through NROR of three-membered heterocycles and, to the best of our knowledge, represents the most general and reliable procedure to access this class of organochalcogenides. However, its Achilles' heel is the rather low yield and the always required purification step (due to the presence of triethylborane and tellurium-containing side-products) with the consequent use of toxic volatile organic compounds (VOCs) and production of large amount of solvent waste. The formation of unsymmetrical β-hydroxy ethyltellurides, presumably occurring through the triethyl borotritelluroate-induced ring-opening of epoxides,[23,24] represents an additional drawback of this route, limiting its scalability and hampering its application to the synthesis of ditellurides.

To address these limitations, we considered the use of *on water* conditions and evaluated whether sodium hydroxymethanesulfinate ($HOCH_2SO_3Na$, rongalite, **1**),[25] a cheap and versatile reducing agent, could be employed to generate tellurolate anions able to react with functionalised electrophiles under mild and environmentally friendly conditions.

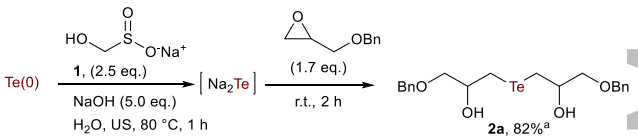
Herein, we describe the successful development of a novel procedure for the synthesis of functionalised symmetrical dialkyl tellurides through the *on water*[26] reaction of Na_2Te with a wide array of electrophiles, including three-membered heterocycles, alkyl halides, electron-deficient alkenes and alkynes. Diaryl tellurides could also be synthesised exploiting the reactivity of diazonium salts with Na_2Te. Furthermore, in the case of NROR of strained heterocycles, a judicious tuning of the reaction stoichiometry enabled the synthesis of novel further functionalisable ditellurides, bearing hydroxy or amino moieties.

Results and Discussion

We commenced our studies by generating sodium telluride from elemental tellurium and sodium hydroxymethanesulfinate **1** using Tschugaeff's method.[27] Thus, elemental tellurium (1.0 eq.) was treated with rongalite (2.5 eq.) and NaOH (5.0 eq.) at 90 °C, using H_2O as the solvent. The reduction of Te(0) to Na_2Te, highlighted by the grey to purple colour change of the reaction mixture, along with almost complete dissolution of elemental grey tellurium, was achieved with a reaction time of 2 h. The reaction mixture was then treated with an excess (1.7 eq.) of benzyl glycidyl ether, in order to test whether the so generated Na_2Te could be employed in '*on water*' NRORs of epoxides. Pleasingly, after stirring the reaction mixture at ambient temperature for 2 h, the oxirane was smoothly converted into the corresponding β-hydroxy telluride **2a**, which was isolated in 70% yield after simple extraction in ethyl acetate, without purification (Scheme 1).

In order to further optimise the reaction, envisioning the generation of Na_2Te as the critical step, we evaluated whether the use of ultrasound irradiation would have improved the efficiency of the tellurium reduction. Gratifyingly, complete dissolution of Te(0) and formation of the purple Na_2Te solution were achieved irradiating the aqueous mixture at 80 °C for 1h. Subsequent treatment with benzyl glycidyl ether led to the formation of β-hydroxy telluride **2a** in 82% yield.

Having established the optimal conditions, we next explored the scope of the reaction, which was found to be wide, encompassing a large variety of electrophiles (Table 1). Epoxides worked well in this transformation, enabling the regioselective synthesis of variously substituted tellurides, including protected glycidol derivatives **2a**,**b** as well as β-hydroxy tellurides **2c**,**d**, obtained from propylene oxide and 1,2-epoxy-5-hexene, respectively.



Scheme 1. Rongalite-promoted *on water* synthesis of β-hydroxy telluride **2a**. US irradiation was provided by using an ultrasonic bath. [a]70% of isolated yield was achieved performing the reduction step in oil bath, at 90 °C for 2h.

Intriguingly, the reaction of epichlorohydrin with Na_2Te under the standard conditions gave the telluride **2c**, bearing a methyl group instead of the expected chloromethyl moiety at the C-2. The dehalogenated product **2c** is reasonably formed through a chalcogen-mediated reduction, following an S_N2X mechanism.[28]

The ring opening reaction was also extended to natural-product-derived epoxides such as eugenol oxide and limonene oxide, providing the corresponding functionalised tellurides **2e** and **2f**. Therefore, the reaction well tolerated protected alcohols (Table 1, entries 1,2), olefins (Table 1, entries 2,4,7), and phenols (Table 1, entry 6). Furthermore, both mono- and poly-substituted epoxides were successfully employed, affording the ring opening products with excellent regioselectivity on the less hindered position of the three-membered ring. Butadiene diepoxide was also treated with Na_2Te under the standard conditions, providing high

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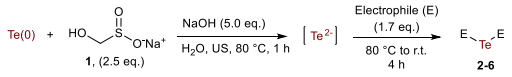
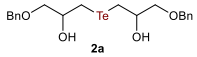
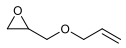
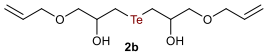
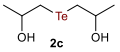
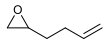
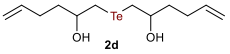
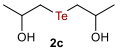
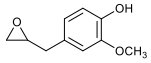
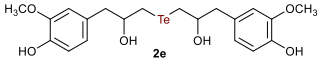
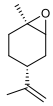
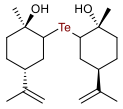
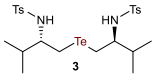
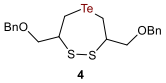
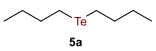
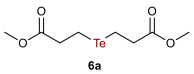
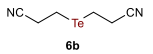
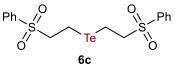
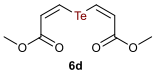
yield of the dihydroxy-substituted tetrahydrotellurophene **2g**, arising from the ring opening of one of the two oxirane ring followed by an intramolecular ring closure occurring onto the second epoxide function.[29] The reaction scope was also extended to include aziridines[30] and thiiranes, enabling the synthesis of the β-amino telluride **3** and the dithiatellurepane **4**.

Table 1. Reaction scope of *on water* synthesis of functionalised dialkyl tellurides.



Entry	Electrophile (E)	Telluride	Yield (%)[a]
1		 **2a**	82[b]
2		 **2b**	76[b]
3		 **2c**	68[b]
4		 **2d**	84[b]
5		 **2c**	56[b]
6		 **2e**	64[b]
7		 **2f**	53[b,c]
8		 **2g**	88
9		 **3**	62[c]
10		 **4**	48[b,c]
11		 **5a**	94
12		 **5b**	91
13		 **6a**	67
14		 **6b**	55
15		 **6c**	74
16		 **6d**	72[d]

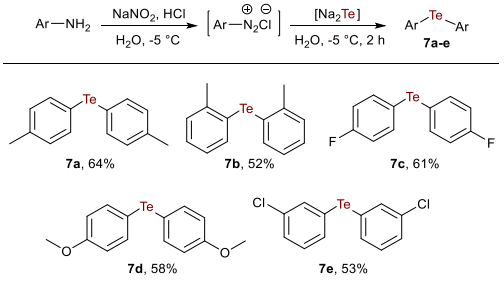
[a]Isolated yield, after EtOAc extraction, is reported. Chromatographic purification was not required. [b]Mixture of diastereoisomers. [c]Chromatographic purification was required. [d]*Z*/*E* ratio > 98:2 (d.r. determined by ^{1}H NMR). US irradiation was provided by using an ultrasonic bath. Slightly lower yields (5-10%) were observed upon performing the reduction step under conventional heating (oil bath at 90 °C for 2 h).

Prompted by these results, we further explored the scope of the reaction by varying the nature of the electrophile. Pleasingly, both primary and secondary alkyl bromides could be converted into the corresponding dialkyl tellurides **5a** and **5b** in excellent yield (Table 1, entries 11,12).

As expected, the tellurenylation reaction did not occur when tertiary alkyl halides, such as ^{t}BuBr, were reacted with Na_2Te under the standard conditions. For these substrates, the E2 process is indeed favoured over the S_N1 reaction in the presence of strong bases and nucleophiles. In addition, this methodology could not be applied to the synthesis of dibenzyl tellurides. Indeed, reduction of the C-Br bond – with the consequent formation of toluene – takes place upon treatment of benzyl bromide with Na_2Te under the above-described conditions. A tellurium-mediated S_N2X-type mechanism presumably accounts for this process.[28]

This *on water* methodology was also amenable to Michael acceptors, thus providing a simple and direct access to novel functionalised tellurides (Table 1, entries 13-16). Indeed, tellurium-containing bis-ester **6a**, bis-nitrile **6b**, and bis-sulfone **6c** were smoothly achieved through a clean unprecedented telluro-Michael addition of Na_2Te to electron-deficient alkenes, such as methyl acrylate, acrylonitrile, and phenyl vinyl sulfone. In addition, divinyl telluride **6d**, bearing two ester functionalities, was obtained in good yield and excellent stereoselectivity (*Z*/*E* ratio > 98:2) upon treatment of methyl propiolate with Na_2Te under the standard conditions (Table 1, entry 16).[31]

An attractive feature of this protocol is that, in almost all cases, simple extraction using ethyl acetate, which is a recommended solvent the CHEM21 guide,[32] provided pure tellurides **2-6**, thus avoiding chromatographic purification and limiting the use of toxic VOCs and the production of large amount of solid waste.



Scheme 2. Synthesis of diaryl tellurides **7a-e** from diazoniun salts and Na_2Te. Isolated yields are reported.

Notably, also aryl diazonium salts proved to be effective substrates for this rongalite-promoted tellurenylation methodology. A range of differently substituted aryl amines were convereted into the corresponding valuable[33] diaryl tellurides **7a-e** upon treatment with Na_2Te through a copper-free Sandmeyer-type reaction[34] (Scheme 2).

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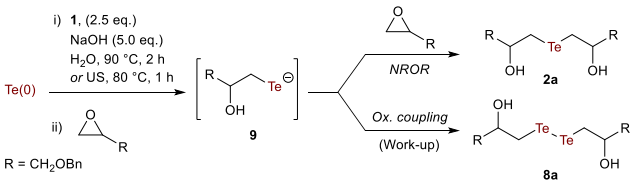
Unfortunately, the use of anilines bearing nitro-, cyano-, and hydroxy- groups did not lead to the formation of the expected diaryl tellurides.

Having developed a novel *on water* methodology for the synthesis of β-functionalised tellurides, we sought to evaluate whether a related rongalite-mediated procedure could be exploited for the synthesis of symmetrical functionalised ditellurides. We envisaged that the exquisite nucleophilicity of tellurium anions in H_2O could also be harnessed to develop an environmentally friendly route towards β-functionalised ditellurides, simply tuning the stoichiometry of the reaction.

We began our studies by establishing the optimal reaction conditions to synthesise β-hydroxy ditelluride **8a**. Initially we sought to access **8a** by exploiting the reactivity of benzyl glycidyl ether and ditelluride dianions (Te_2^{2-}), generated *in situ* from elemental tellurium and rongalite. Thus, Te(0) was treated with 1.0 eq. of sodium hydroxymethanesulfinate in H_2O at 90 °C in order to generate Na_2Te_2. However, after stirring for 2 h, both the purple colour of the reaction mixture and the presence of unreacted black tellurium were suggestive of the formation of Na_2Te, instead of the expected dark red Na_2Te_2. Furthermore, when the mixture was treated with benzyl glycidyl ether, the β-hydroxy telluride **2a** was the sole tellurium-containing product detected in the crude material, hence confirming that Na_2Te_2 was not formed under the above described reaction conditions. Neither variating the reaction temperature nor increasing the reaction time allowed to form Na_2Te_2. We also attempted to obtain Na_2Te_2 through dismutation of Na_2Te (*vide infra*) and elemental tellurium.[18a] However, albeit different conditions were evaluated, no reaction occurred and black unreacted tellurium was always observed. In all cases, treatment of the mixture with benzyl glycidyl ether yielded exclusively the telluride **2a**. Thus, we sought to approach the problem from a different perspective and evaluated the possibility to access ditellurides by oxidative dimerization of sodium alkyltellurolates, generated *in situ* through NROR of epoxides with Na_2Te (Scheme 3). The key intermediate **9** is both a strong nucleophile and an easily oxidisable species. Therefore, it can afford the telluride **2** upon reacting with a second molecule of epoxide or undergo oxidation to provide the ditelluride **8** (Scheme 3). The stoichiometry of the reaction is arguably the crucial parameter that needs to be considered in order to modulate the outcome of the reaction towards the formation of **2** or **8**.

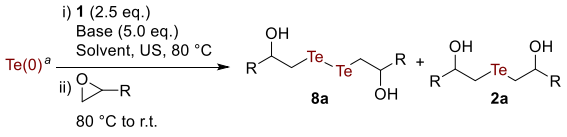
An equimolar mixture of telluride **2a** and ditelluride **8a** was indeed formed upon reacting Na_2Te with 1.0 eq. of benzyl glycidyl ether. Notably, we found that the **8a**:**2a** ratio could be appreciably improved by decreasing the amount of epoxide (Table 2, entries 1-4). Particularly, less than 15% of β-hydroxy telluride **2a** was detected when using 0.4 eq. of benzyl glycidyl ether (Table 2, entry 4). Evaluation of different solvents (Table 2, entries 5-9) gave no improvements in terms of **8a**:**2a** ratio. On the other hand, the use of ethylene glycol or acetonitrile (Table 2, entries 8, 9) led to the essentially selective formation of the telluride **2a**.



Scheme 3. Formation of tellurides and ditellurides from intermediate **9**.

The use of different bases such as Cs_2CO_3 or KOH proved to be detrimental to the **8a**:**2a** ratio. Finally, we considered the effect of the concentration. Surprisingly, when the reaction was performed in 0.5 mL of H_2O (Table 2, entry 12) the **8a**:**2a** ratio decreased from 5:1 to 2:1, thus demonstrating that the formation of ditellurides is disfavoured by higher concentrations. On the contrary, we were pleased to notice that the **8a**:**2a** ratio resulted improved under diluted conditions. Only ca. 10% of telluride **2a** was indeed detected upon performing the reaction in 6 mL of H_2O ($[Na_2Te]_0$ = 0.08 M) and with 0.6 eq. of epoxide (Table 2, entry 13). Under these conditions, the desired β-hydroxy ditelluride **8a** could be obtained in 68% yield. Higher dilution (Table 2, entry 14) gave neither selectivity nor yield improvements. Such a striking "dilution effect" was not observed when other solvents, including MeOH and DMF, were used.

Table 2. Optimisation of the reaction conditions.



R = CH_2OBn

Entry	Solvent (mL)	Epoxide (eq.)	Base	**8a**:**2a**[f]	Yield (%)
1	H_2O (2)[b]	1.0	NaOH	1:1	54
2	H_2O (2)	0.8	NaOH	2:1	61
3	H_2O (2)	0.6	NaOH	5:1	49
4	H_2O (2)	0.4	NaOH	6:1	62
5	EtOH (2)	0.6	NaOH	3:1	58
6	MeOH (2)	0.6	NaOH	5:1	73
7	DMF (2)	0.6	NaOH	4:1	66
8	Ethylene glycol (2)	0.6	NaOH	<1:9	36
9	CH_3CN (2)	0.6	NaOH	<1:9	71
10	H_2O (2)	0.6	Cs_2CO_3	1:1	57
11	H_2O (2)	0.6	KOH	2:1	60
12	H_2O (0.5)[c]	0.6	NaOH	2:1	63
13	H_2O (6)[d]	0.6	NaOH	7:1	68
14	H_2O (10)[e]	0.6	NaOH	7:1	65

[a]Reactions were performed using 0.5 mmol of Te(0); [b]$[Na_2Te]_0$ = 0.25 M; [c]$[Na_2Te]_0$ = 1.0 M; [d]$[Na_2Te]_0$ = 0.08 M; [e]$[Na_2Te]_0$ = 0.05 M; [f]**8a**:**2a** ratio was determined by ^1H NMR. The epoxide was added when Te(0) was completely consumed.

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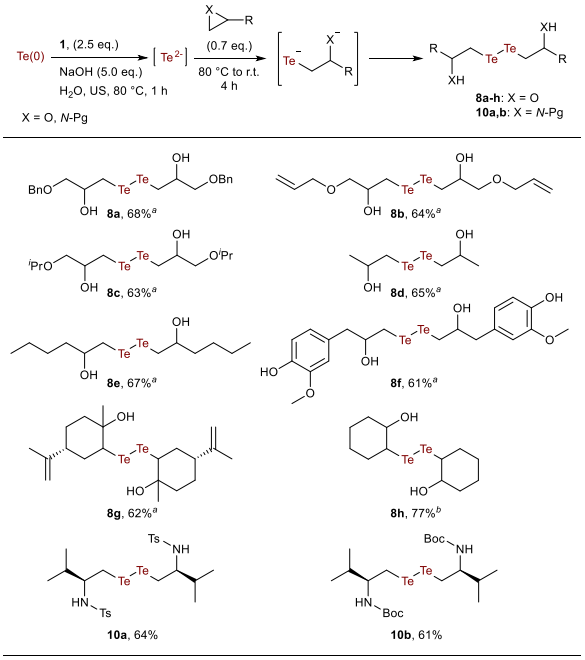
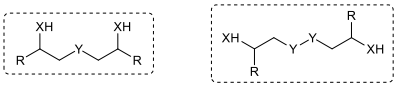
With the optimised conditions in hand, we next explored the scope of the tellurenylation ring opening reaction by varying the nature and the structure of the strained heterocycle. The robustness of the procedure was demonstrated by the preparation of a range of new variously substituted and functionalised ditellurides (Scheme 4). Glycidol derivatives protected as benzyl-, allyl-, and isopropyl-ethers were efficiently converted into the corresponding β-hydroxy ditellurides **8a-c** in rather good yield through an highly regioselective ring opening route. Monosubstituted epoxides bearing methyl or *n*-butyl substituents, also underwent telluride-promoted ring-opening to give the desired ditellurides **8d-e**.

To further demonstrate the utility of this tellurenylation reaction, we applied the methodology to natural-product-derived strained heterocycles. For example, functionalised ditellurides **8f** and **8g** were successfully achieved from eugenol and limonene oxides, respectively. Remarkably, both tri- and di-substituted epoxides were shown to be viable substrates, enabling the synthesis of functionalised ditellurides **8g** and **8h** in rather good yield. Having demonstrated that the scope of this procedure encompasses a wide variety of epoxides, we wondered whether it could be enlarged to enclose aziridines, in order to provide access to β-amino ditellurides. Thus, enantioenriched *N*-Tosyl and *N*-Boc aziridines, synthesised from L-valine, were treated with Na_2Te under the optimised reaction conditions. Pleasingly, the expected β-amino ditellurides **10a** and **10b** were formed in 64% and 61% yield, with complete stereospecificity and excellent regioselectivity.



Scheme 4. Synthesis of β-hydroxy- and β-amino-dialkyl ditellurides. Isolated yields are reported. [a]Mixture of diastereoisomers. [b]Racemic.

Table 3. Spectroscopic properties of functionalised dialkyl-chalcogenides and -dichalcogenides.



	Y = Te[a]	Y = Se[b]	Y = Te[a]	Y = Se[b]
R = CH_2OBn; X = O	n.d.	124.8; 126.7	80.7; 82.8	310.8; 311.6
R = CH_2OAll; X = O	94.1; 91.0	279.4	80.4; 82.4	68.3; 71.0
R = Me; X = O	29.7; 36.5	n.d.	49.3; 52.0	268.0
R = CH_2Ar;[c] X = O	67.1; 71.9	n.d.	65.6; 68.3	n.d.
R = CH_2O^iPr; X = O	n.d.	67.9; 70.3	79.8; 81.5	279.8; 280.4
R = ^{i}Pr; X = *N*-Ts	n.d.	n.d.	87.0	288.6

[a] ^{125}Te NMR (δ, ppm, $CDCl_3$); PhTeTePh was used as external standard (δ = 420 ppm). [b] ^{77}Se NMR (δ, ppm, $CDCl_3$); PhSeSePh was used as external standard (δ = 461 ppm). [c] Ar = 3-MeO-,4-OH-C_6H_3.

The ^{125}Te NMR chemical shift of these unreported dialkyl ditellurides was recorded in order to compare their resonance frequencies with those of the related dialkyl tellurides (Table 3 and ESI). The ^{125}Te NMR chemical shift of ditellurides resulted just slightly shielded (5-10 ppm) with respect to that of the corresponding tellurides. Notably, this trend contrasts with the huge differences observed for the ^{77}Se NMR chemical shift of the selenium containing analogues; indeed, the ^{77}Se NMR resonance frequencies of β-functionalised diselenides resulted shifted downfield (up to 230 ppm) when compared with those of the corresponding selenides.[35] Therefore, unlike ^{77}Se NMR spectroscopy in the case of selenides and diselenides, ^{125}Te NMR is not a completely reliable tool to establish whether tellurides, ditellurides, or a mixture of the two is formed.[36] Typical direct and geminal ^{125}Te-^{13}C and geminal ^{125}Te-^{1}H spin-spin coupling constants have also been measured (see Table S1 and S2, ESI).

To demonstrate the versatility and the synthetic utility of the obtained functionalised dialkyl ditellurides, we sought to employ this unreported organotellurium derivatives as precursors of potentially valuable polyfunctionalised unsymmetrical dialkyl tellurides (Table 4).

Thus, β-hydroxy ditellurides **8a-c**,**g** were subjected to $NaBH_4$-promoted reduction to afford the corresponding alkyl tellurolates, which were *in situ* treated with suitable electrophiles to yield variously substituted unsymmetrical tellurides. Both alkyl halides and strained heterocycles could be efficiently employed, enabling the synthesis of the corresponding unsymmetrical tellurides **11-15**. Particularly, this route provided access to polyfunctionalised natural-product-derived systems such as the triol **12**, obtained by ring-opening of (*S*)─glycidol, and the diol **14**, arising from the limonene-derived ditelluride **8g**. Furthermore, the telluride **15**, bearing both the hydroxyl and the amino group, was easily synthesised through the regioselective and stereospecific ring opening of (*S*)-2-benzyl *N*-Tosyl aziridine. Unfortunately, Michael acceptors such as methyl vinyl ketone or methyl

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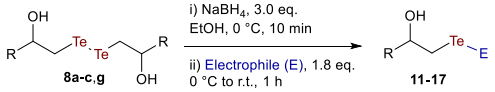
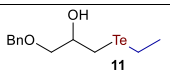
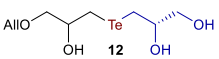
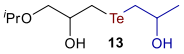
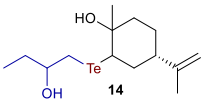
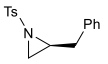
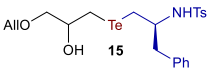
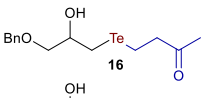
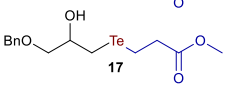
acrylate were found to be scarcely reactive under these conditions, only traces of the desired conjugated adducts being observed (Table 4, entries 6, 7). These results are in line with our recent findings on the reactivity of structurally related functionalised diselenides with electron-deficient olefins under reducing conditions.[37]

Table 4. Synthesis of functionalised unsymmetrical tellurides.



Entry	Ditelluride	Electrophile	Unsymmetric telluride	Yield (%)
1	**8a**		 **11**	57[a]
2	**8b**		 **12**	63[a,b]
3	**8c**		 **13**	56[a,b]
4	**8g**		 **14**	74[a,b]
5	**8a**		 **15**	60[a,b]
6	**8a**		 **16**	<10
7	**8a**		 **17**	<10

[a]Isolated yield is reported. [b]Mixture of diastereoisomers.

As stated above, a number of organotellurium compounds have been employed as glutathione-peroxidase (GPx) mimics, being often capable to efficiently reduce harmful hydrogen peroxide to water by using thiols as co-substrate. In this context, the GPx-like activity of O-, N-, and S-containing dialkyl- and aryl-alkyl tellurides has been recently reported.[9b,13,38] However, the catalytic antioxidant activity of homologous functionalised ditellurides remained unexplored, mainly because of the lack of methodologies for their synthesis. Therefore, having developed a route to access unreported substituted ditellurides, their thiol-peroxidase-like activity was next pursued in order to compare their catalytic properties with those of structurally related functionalised tellurides.[9b,38] The dithiothreitol (DTT) oxidation assay was chosen as model method.

Results of this investigation are summarised in the Figure 1 and in the Table 5. β-Hydroxy ditellurides **8a**,**b** behaved as effective catalyst, promoting complete DTT oxidation within 6 minutes from the addition of H_2O_2. The eugenol-derived ditelluride **8f**, which bears on the same skeleton two tellurium atoms and two phenolic moieties, displayed slightly lower catalytic properties (Figure 1). Intriguingly, hydroxy-ditellurides **8** proved to be poorer catalysts with respect to homologous tellurides **2**; for example, the thiol-peroxidase-like activity of telluride **2g** was found to be ten-fold higher than the related ditelluride **8f**. The kinetic of the reactions involved in the two distinct pathways operating for tellurides and ditellurides reasonably accounts for the observed different catalytic properties of compounds **2** and **8**.[9f,39]

Notably, the dihydroxy-substituted tetrahydrotellurophene **2g** exhibited excellent GPx-like properties (Figure 1). Noticeably, **2g** represents the tellurium-containing analogue of DHS^{red} (*trans*-3,4-dihydroxyselenolane), a water-soluble selenide synthesised and widely studied by Iwaoka et al.[40]

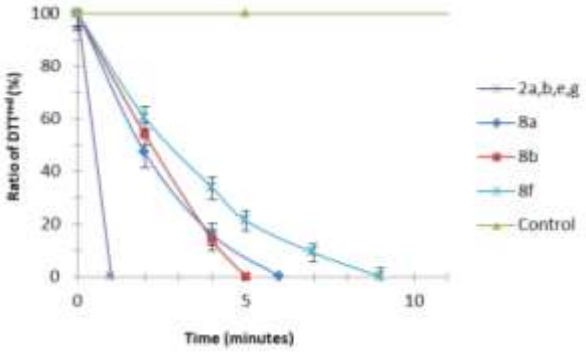
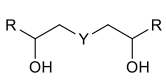
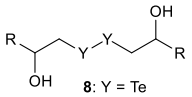


Figure 1. Oxidation of DTT^{red} with H_2O_2 in the presence of Te-containing catalysts (1 mol%). Reaction conditions: $[DTT^{red}]_0$ = 0.14 M, $[H_2O_2]_0$ = 0.14 M, [catalyst] = 0.014 M, CD_3OD (0.6 mL). In the control experiment the reaction was run with no catalyst. The mean ± SD values of three separate experiments are reported.

Table 5. Comparison of the thiol-peroxidase like activity of β-hydroxy- chalcogenides and dichalcogenides according to the DTT method.


2: Y = Te
18: Y = Se


8: Y = Te
19: Y = Se

Entry	Catalyst[a]	Y	R	T_{50}[b]
1	**2a**	Te	CH_2OBn	<60
2	**2b**	Te	CH_2OAll	<60
3	**2g**	Te	CH_2Ar^c	<60
4	**8a**	Te	CH_2OBn	115 (19)
5	**8b**	Te	CH_2OAll	124 (31)
6	**8f**	Te	CH_2Ar^c	178 (42)
7	**18**	Se	CH_2OBn	3246 (256)
8	**19**	Se	CH_2OBn	3496 (282)

[a]1 mol% of tellurium-containing catalysts **2** or **8** and 10 mol% of selenium-containing catalysts **18** or **19** were used for the test. [b]T_{50} is the time required, in seconds, to halve the initial thiol concentration after the addition of H_2O_2; data in parenthesis are the experimental error. Dithiothreitol (DTT) oxidation was monitored by the mean of ^1H NMR spectroscopy. [c]Ar = 3-MeO-4-OH-C_6H_3.

As expected,[1j,9b,9f,38] replacing tellurium with selenium brought about a dramatic decrease of the thiol-peroxidase properties (Table 5). However, in contrast to the behaviour of telluride **2** and ditellurides **8**, β-hydroxy-diselenide **19** was only slightly less active than selenide **18**.

Conclusion

In conclusion, we have developed a novel *on water* procedure to access variously functionalised dialkyl tellurides through the reaction of Na_2Te with electrophiles under mild conditions. The use of sodium hydroxymethanesulfinate, a cheap and water soluble reducing agent, was critical to the success of the reaction. The scope of the procedure proved to be broad and was demonstrated over a wide array of electrophiles, including strained heterocycles, haloalkanes, electron-deficient alkenes and alkynes, which were efficiently converted into the corresponding tellurides. Notably, in almost all cases simple ethyl acetate extraction provided pure tellurides, thus avoiding chromatographic purification and limiting the use of toxic VOCs and the production of large amount of solid waste. Furthermore, a fine tuning of the stoichiometry of the reaction enabled the synthesis of β-hydroxy- and β-amino-ditellurides by NROR of epoxides and aziridines with Na_2Te. Such unprecedented ditellurides were further employed as precursors of new functionalised unsymmetrical dialkyl tellurides. Finally, the synthesised organotellurium derivatives showed remarkable GPx-like properties.

Experimental Section

General information. All commercial materials were purchased from various commercial sources and used as received, without further purification. Flash column chromatography purifications were performed with Silica gel 60 (230-400 mesh). Thin layer chromatography was performed with TLC plates Silica gel 60 F_{254}, which was visualised under UV light, or by staining with an ethanolic acid solution of *p*-anisaldehyde followed by heating. High resolution mass spectra (HRMS) were recorded by Electrospray Ionization (ESI). Reactions were performed in demineralised water.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Varian Mercury 400, Bruker 400 Ultrashield, and Varian Gemini 200 spectrometers operating at 400 MHz and 200 MHz (for ^1H), 100 MHz and 50 MHz (for ^{13}C). ^{125}Te NMR spectra were recorded using a Bruker 400 Ultrashield spectrometer, operating at 126 MHz. NMR signals were referenced to nondeuterated residual solvent signals (7.26 ppm for ^1H, 77.0 ppm for ^{13}C). Diphenyl ditelluride $(PhTe)_2$ was used as an external reference for ^{125}Te NMR (δ = 420 ppm). Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz), rounded to the nearest 0.1 Hz. ^1H NMR data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, ap d = apparent doublet, m = multiplet, dd = doublet of doublet, bs = broad singlet, bd = broad doublet, ecc.), coupling constant (*J*) or line separation (ls), and assignment. Where reported, NMR assignments are made according to spin systems, using, where appropriate, 2D NMR experiments (COSY, HSQC, HMBC) to assist the assignment.

General Procedure for the synthesis of functionalised tellurides 2-6. A 10 mL vial was charged with elemental tellurium (128 mg, 1.0 mmol, 1.0 eq.), sodium hydroxymethanesulfinate dihydrate (385 mg, 2.5 mmol, 2.5 eq.), NaOH (200 mg, 5.0 mmol, 5.0 eq.) and H_2O (3 mL). The vial was sealed and the reaction mixture was heated at 80 °C for 1 h under ultrasound irradiation. The colour of the suspension turned from grey to purple, thus indicating the reduction of Te(0) to Te^{2-}. Complete dissolution of black elemental tellurium and formation of a purple solution was achieved. Then, ultrasound irradiation was stopped and the electrophile (epoxide, aziridine, alkyl halide, or Michael acceptor; 1.7 mmol, 1.7 eq.) was introduced into the vial. The reaction mixture was allowed to cool to r.t. and stirred for additional 4 h. Afterwards, the mixture was treated with saturated *aq.* NH_4Cl (2 mL) and then EtOAc (5 mL) was added. The organic phase was collected and the aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield the desired β-hydroxy telluride **2-6**. If not differently specified (see ESI for details), simple ethyl acetate extraction provided dialkyl tellurides pure enough to be used without further purification.

General Procedure for the synthesis of β-hydroxy- and β-amino-ditellurides 8 and 10. A 25 mL vial was charged with elemental tellurium (128 mg, 1.0 mmol, 1.0 eq.), sodium hydroxymethanesulfinate dihydrate (385 mg, 2.5 mmol, 2.5 eq.), NaOH (200 mg, 5.0 mmol, 5.0 eq.) and H_2O (12 mL). The vial was sealed and the reaction mixture was heated at 80 °C for 1 h under ultrasound irradiation. The colour of the suspension turned from grey to purple, thus indicating the reduction of Te(0) to Te^{2-}. The ultrasound irradiation was stopped and the epoxide or the aziridine (0.6 mmol, 0.6 eq.) was then added dropwise. The reaction mixture was cooled at r.t. and stirred for additional 4 h. Afterwards, the mixture was treated with saturated *aq.* NH_4Cl (2 mL) and then EtOAc (5 mL) was added. The organic phase was collected and the aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography to yield the desired β-hydroxy- or β-amino-ditelluride.

General procedure for the synthesis of unsymmetrical functionalised tellurides. $NaBH_4$ (0.75 mmol, 3.0 eq.) was portionwise added to a solution of functionalised dialkyl ditelluride **8** (0.25 mmol, 1.0 eq.) in EtOH (2 mL) at 0°C under inert atmosphere (N_2). After 10 min, the electrophile (0.45 mmol, 1.8 eq.) was slowly added and the reaction mixture was allowed to warm to room temperature and stirred for additional 1 h. The reaction was quenched

by addition of saturated aq. NH_4Cl (2 mL) and diluted with EtOAc (5 mL), The layers were separated and the aqueous layer was extracted with EtOAc (3 x 3 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by flash chromatography to yield unsymmetrical β-functionalised tellurides.

Full experimental details, products characterisation, and copy of NMR spectra are described in the Electronic Supplementary Information.

Acknowledgements

We thank MIUR-Italy (''Progetto Dipartimenti di Eccellenza 2018–2022'' allocated to Department of Chemistry ''Ugo Schiff'').

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