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Communication

Unexpected Ethyltellurenylation of Epoxides with Elemental Tellurium under Lithium Triethylborohydride Conditions

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Abstract: The one-pot multistep ethyltellurenylation reaction of epoxides with elemental tellurium and lithium triethylborohydride is described. The reaction mechanism was experimentally investigated. Dilithium ditelluride and triethyl borane, formed from elemental tellurium and lithium triethylborohydride, were shown to be the key species involved in the reaction mechanism. Epoxides undergo ring-opening reaction with dilithium ditelluride to afford β-hydroxy ditellurides, which are sequentially converted into the corresponding β-hydroxy-alkyl ethyl tellurides by transmetalation with triethyl borane, reasonably proceeding through the S_H2 mechanism.

Keywords: tellurium; tellurides; ditellurides; superhydride; boranes; ring-opening-reactions; epoxides; transmetalation; radicals

1. Introduction

Organoselenium [1,2] and organotellurium [3] compounds continue to find wide application in chemical sciences and biology [4–8]. Tellurium-containing derivatives play an important role in organic synthesis [3,9], materials science [10,11], and medicinal chemistry [8,12–15]. The incorporation of tellurium atoms into organic structures is often a rewarding strategy in developing new enzyme modulators [14–17], catalysts [18], smart materials [10,11], and glutathione-peroxidase-like antioxidants [19–25]. Additionally, often undergoing regio- and stereo-selective transformations, organotellurium compounds can be employed in synthetically useful functional group conversion reactions [26,27] and carbon-carbon bond-forming processes [28–31]. Owing to these features, tellurenylation reactions provide an attractive functional handle for further elaboration. Selected examples of biological and synthetic applications of organotellurium compounds are presented in the Figure 1.

The development of new, reliable, and general methodologies towards these chalcogen-containing organic molecules is thus highly sought after in organic synthesis. Particularly, the possibility to access densely functionalised and sp^3-rich compounds, characterised by high molecular complexity, enables the possibility to define and explore new chemical space and plays a key role in terms of successfully developing new catalysts and drug candidates [32,33]. Furthermore, sp^3-rich organochalcogens bearing O- and N-containing functionalities have been demonstrated to possess improved catalytic and pharmacological properties [15–17,20,23,34]. However, although a number of methods for the synthesis of selenides and tellurides have been reported, a number of limitations remain, including functional-group compatibility and the harsh reaction conditions. Therefore, the development of mild procedures for the synthesis of densely functionalised molecules still remains challenging.

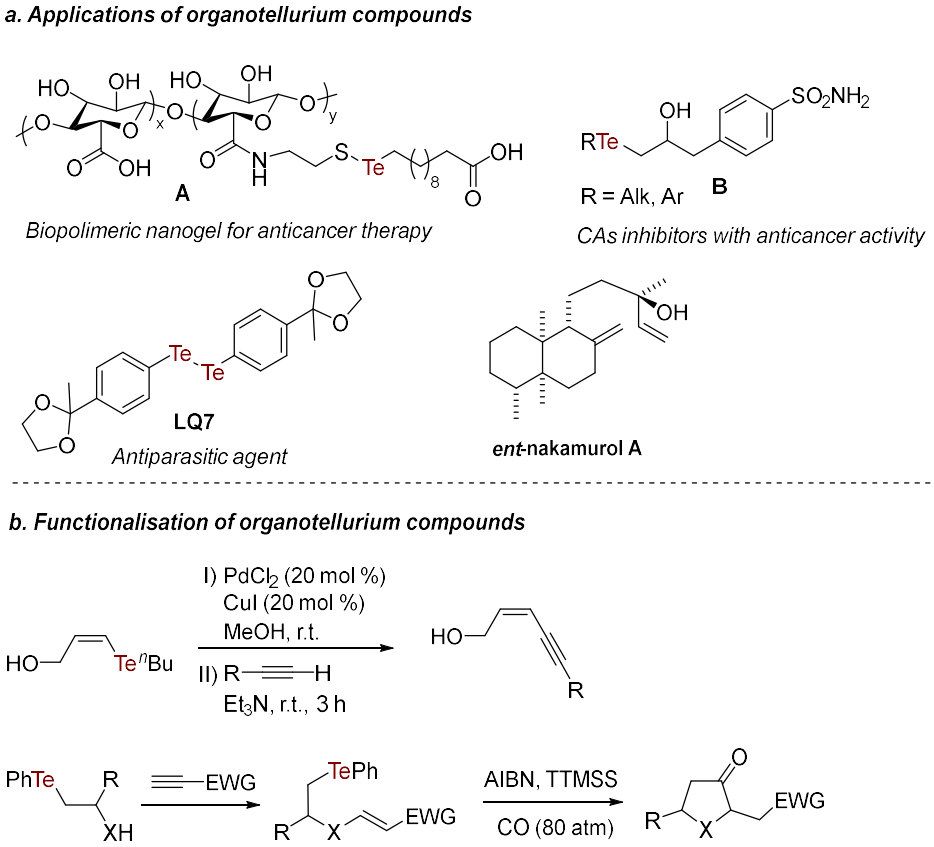


Figure 1. Biological and synthetic applications of organotellurium compounds (selected examples). ***Part a***. **A**: a tellurium-containing biopolimeric nanogel for anticancer therapy [11]; **B**: tellurium-containing carbonic anhydrases inhibitors with anticancer activity [15]; **LQ7**: a ditelluride active as antiparasitic agent [29]; ***ent*-nakamurol A**: an organotelluride is involved in the key step of its total synthesis [35]. ***Part b***. Functionalization of organotellurium compounds [29,31].

Three-membered heterocycles such as epoxides and aziridines, often undergoing regioselective nucleophilic ring-opening reactions (NRORs), represent convenient starting materials for the synthesis of functionalised chalcogen-containing systems [36]. A number of ring-opening-based procedures for the synthesis of hydroxy- and amino-substituted selenides and tellurides have been developed over the last decade [37–42]. Such functionalised chalcogenides have also been employed as intermediates for the synthesis of valuable compounds [35,43,44] and as organocatalysts for the asymmetric addition of diethylzinc to aldehydes [45].

In this communication, as a part of our growing interest in the study of the chemistry of organotellurium compounds, we report a study on the mechanism of an unexpected reaction of epoxides with elemental tellurium and lithium triethylborohydride, leading to the formation of β-hydroxy-alkyl ethyl tellurides.

2. Materials and Methods

2.1. Experimental Section

All reactions were carried out in an oven-dried glassware. Solvents were dried using a solvent purification system (Pure-Solv™, Darmstadt, Germany). 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). In the control experiment with degassed solvent, tetrahydrofuran (THF) was degassed by freeze–pump–thaw cycles (×3) on the high vacuum line.

The ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ with Mercury 400, Bruker 400 Ultrashield (Bruker, Milan, Italy), and Varian Gemini 200 spectrometers operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. NMR signals were referenced to nondeuterated residual solvent signals: 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C. The ^{125}Te-NMR spectra were recorded in $CDCl_3$ at 126 MHz with a Bruker Ultrashield 400 Plus instrument (Bruker, Milan, Italy). $(PhTe)_2$ was used as an external reference (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. The ^{1}H-NMR data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet, ap = apparent), coupling constant (J), and assignment. Mass spectra (MS) were determined by ESI (Thermo Fisher Scientific, Milan, Italy).

Ditelluride **3a** [46] and diselenide **6a** [47] were prepared from 2-((benzyloxy)methyl)oxirane according to procedures reported in the literature.

2.2. General Procedure for the Synthesis of β-Hydroxy-alkyl Ethyl Tellurides 2

Li_2Te_2 was generated according to the literature [48,49] from 1.0 mL of a 1 M THF solution of $LiEt_3BH$ (1.0 mmol, 1.0 eq.) and elemental tellurium powder (128 mg, 1.0 mmol, 1.0 eq.), stirred at ambient temperature under inert atmosphere (N_2) for 6 h. The dark red suspension of Li_2Te_2 in THF was treated with the epoxide (1.0 mmol, 1.0 eq.) and the reaction was stirred for 6 h at ambient temperature. Afterwards, the mixture was diluted with Et_2O (10 mL), filtered through a short pad of celite, and washed with saturated *aq*. NH_4Cl and then with H_2O (2 × 5 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was then purified by flash chromatography (Et_2O/petroleum ether) to yield β-hydroxy-alkyl ethyl tellurides **2**.

2.2.1. Synthesis of 1-(Benzyloxy)-3-(ethyltellanyl)propan-2-ol **2a**

Following the general procedure, 2-((benzyloxy)methyl)oxirane (152 µL, 1.0 mmol) and elemental tellurium (128 mg, 1.0 mmol) gave, after purification by flash chromatography (Et_2O/petroleum ether 1:1), **2a** as a colourless oil (61 mg, 38%) [49]. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 1.60 (3H, t, J = 7.6 Hz, CH_3), 2.63 (2H, ap q, J = 7.6 Hz, CH_3CH_2Te), 2.63 (1H, bs, OH), 2.76–2.89 (2H, m, CH_2Te), 3.41–3.48 (1H, m, CH_aH_bO), 3.59 (1H, dd, J = 4.2, 9.6 Hz, CH_aH_bO), 3.45–3.97 (1H, m, CHOH), 4.55 (2H, ap s, CH_2Ph), 7.26–7.40 (5H, m). ^{13}C-NMR (100 MHz, CDCl3): δ (ppm) −4.5(CH_3CH_2Te), 7.7 (CH_2Te), 17.8, 70.6, 73.4, 74.3, 127.8, 127.8, 128.4, 137.9. ^{125}Te-NMR (126 MHz, CDCl3): δ (ppm) 213.6.

2.2.2. Synthesis of 1-(Ethyltellanyl)-3-isopropoxypropan-2-olol **2b**

Following the general procedure, 2-(isopropoxymethyl)oxirane (32 µL, 0.25 mmol), $LiEt_3BH$ (0.25 mL, 0.25 mmol) and elemental tellurium (32 mg, 0.25 mmol) gave, after purification by flash chromatography (Et_2O/petroleum ether 1:1), **2b** as a colourless oil (30 mg, 44%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 1.18 (6H, ap d, J = 6.5 Hz), 1.62 (3H, t, J = 7.6 Hz), 2.64 (2H, ap q, J = 7.6 Hz), 2.75 (1H, ap s, OH), 2.74–2.92 (CH_2Te), 3.38 (1H, dd, J = 6.7, 9.3 Hz, CH_aH_bO), 3.54 (1H, dd, J = 3.6, 9.3 Hz, CH_aH_bO), 3.59–3.67 (1H, m, $CH(CH_3)_2$), 3.83–3.92 (1H, m, CHOH). ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) −4.6 (CH_3CH_2Te), 7.6 (CH_2Te), 17.5 (CH_3), 21.8, 71.3, 71.6, 72.2. MS (ESI, positive) $[M + H]^+$ 276.8.

2.2.3. Synthesis of 1-(Ethyltellanyl)hexan-2-ol **2c**

Following the general procedure, 2-butyloxirane (25 mg, 0.25 mmol), $LiEt_3BH$ (0.25 mL, 0.25 mmol) and elemental tellurium (32 mg, 0.25 mmol) gave, after flash chromatography (Et_2O/petroleum ether 2:1), **2d** as a colourless oil (31 mg, 48%) [49]. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm): 0.86–0.97 (3H, m, CH_3), 1.24–1.62 (6H, m, CH_2), 1.61 (3H, t, J = 7.6 Hz), 2.16 (1H, ap s, OH), 2.64 (2H, ap q, J = 7.6 Hz),

2.71–2.94 (2H, m, CH_2Te), 3.73–3.78 (1H, m, CHOH). ^{13}C-NMR (100 MHz, $CDCl_3$); δ (ppm): −4.7, 17.6, 14.6, 15.3, 23.3, 28.6, 38.0, 73.3. HRMS (ESI) calculated for $C_8H_{18}NaOTe$: 283.0318; found: 283.0331.

2.2.4. Synthesis of 1-(Ethyltellanyl)propan-2-ol **2d**

Following the general procedure, 2-methyloxirane (70 µL, 1.0 mmol), $LiEt_3BH$ (1.0 mL, 1.0 mmol) and elemental tellurium (126 mg, 1.0 mmol) gave, after flash chromatography (Et_2O/petroleum ether 1:1), **2d** as a colourless oil (45 mg, 41%) [49]. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 1.30 (3H, d, J = 6.1 Hz, CH_3), 1.61 (3H, t, J = 7.6 Hz, CH_3CH_2), 2.24 (1H, bs, OH), 2.63–2.72 (2H, m, CH_3CH_2), 2.73 (1H, dd, J = 12.2, 7.4 Hz, CH_aH_bTe), 2.87 (1H, dd, J = 4.6, 12.2 Hz, CH_aH_bTe), 3.78–4.02 (1H, m, CHOH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) −4.7 ($CH_3\mathbf{C}H_2Te$), 16.0, 17.7, 23.7, 67.3.

Copy of ^{1}H-NMR, ^{13}C-NMR, and ^{125}Te-NMR spectra can be found in Supplementary Materials.

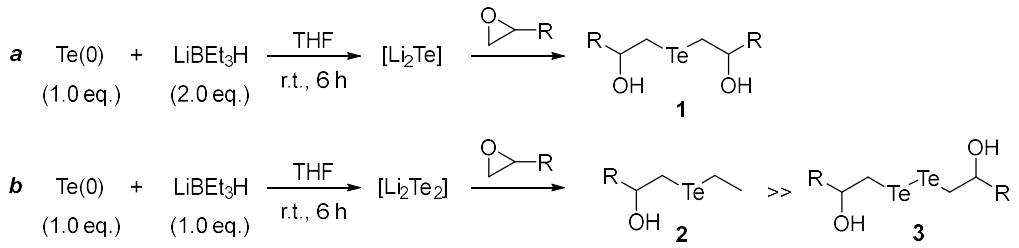
2.2.5. Control Experiment with the Radical Inhibitor

A solution of 3,3′-ditellanediylbis(1-(benzyloxy)propan-2-ol) **3a** (29 mg, 0.05 mmol) and BHT (3,5-di-tert-butyl-4-hydroxytoluene, 22 mg, 0.1 mmol) in dry THF (2 mL) was treated with triethylborane (0.1 mmol, 100 µL of a 1 M solution in THF). The reaction mixture was stirred at ambient temperature for 6 h, and afterwards, the solvent was removed under vacuum.

3. Results

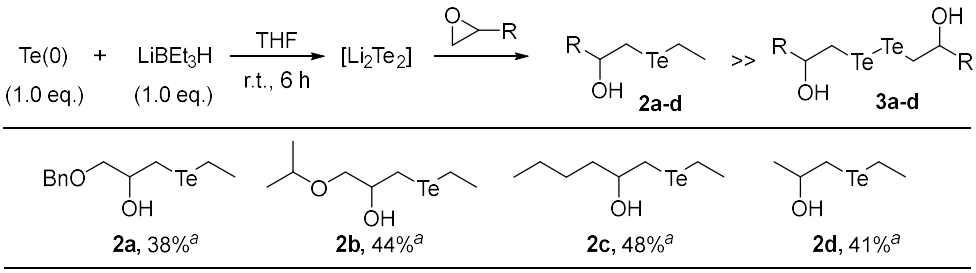
During the course of our studies on the reactivity of strained heterocycles with selenium-centered nucleophiles we developed convenient routes towards generating a variety of hydroxy-, amino-, and mercapto-substituted Se-containing systems [50–53]. For example, through the tuning of the stoichiometry and the conditions of the reaction of $(Me_3Si)_2Se$ [(bis(trimethylsilyl)selenide, a synthetic equivalent of hydrogen selenide] with epoxides, thiiranes, and aziridines, we were able to successfully achieve a range of functionalised selenols [50], selenides, and diselenides [47].

Attracted by the synthetic utility and versatility of organotellurium compounds, we recently moved to evaluate the chemistry of tellurium-centered nucleophiles with strained heterocycles [46,49]. The poor stability of $(Me_3Si)_2Te$ [48,49] prompted us to employ dilithium telluride and dilithium ditelluride, generated from elemental tellurium and lithium triethylborohydride (superhydride), as tellurenylation reagents for the NRORs of epoxides and aziridines [49]. However, while the ring-opening of epoxides with Li_2Te provided access to symmetrical β-hydroxy-tellurides **1** (Scheme 1, part a), the reaction with Li_2Te_2 gave almost exclusively β-hydroxy-alkyl ethyl tellurides **2** instead of the expected β-hydroxy-ditellurides **3**, which were isolated only in trace amounts (Scheme 1, part b). Intrigued by this result, we wished to deeper investigate such a transformation in order to establish the mechanism involved in the formation of asymmetrical β-hydroxy-alkyl ethyl tellurides **2**.



Scheme 1. Reactivity of epoxides with Li_2Te and Li_2Te_2, generated from elemental tellurium under lithium triethylborohydride conditions. (**a**) Synthesis of tellurides **1**. (**b**) Formation of β-hydroxy-alkyl ethyl tellurides **2**.

Notably, this ethyltellurenylation reaction proved to be general and differently substituted epoxides could be smoothly converted into the corresponding β-hydroxy-alkyl ethyl tellurides through this one-pot multistep procedure (Scheme 2).



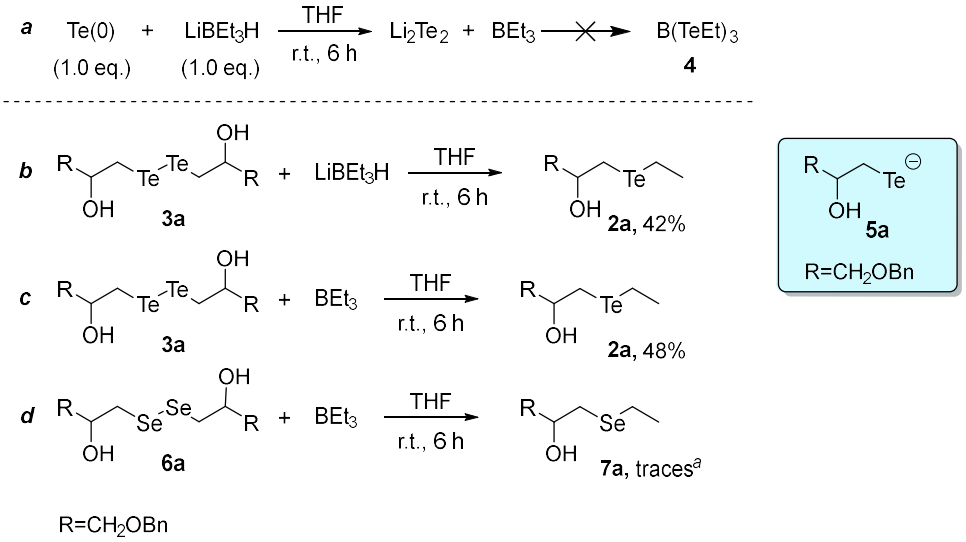
Scheme 2. One-pot ethyltellurenylation of epoxides. Traces of ditellurides **3a**–**d** (3%–7%) were detected in the crude material. Isolated yields are reported.

A plausible explanation for the formation of unsymmetrical tellurides **2** involves the transmetalation of triethylborane with β-hydroxy-ditellurides **3**. However, an alternative path could proceed through the ring-opening of epoxides with tris(ethyltelluro)borane **4** (Scheme 3) which, in principle, could be generated from dilithium ditelluride and triethyl borane. A series of control experiments were therefore undertaken in order to test these hypotheses.

We initially evaluated whether tris(ethyltelluro)borane **4** could be generated upon the treatment of elemental tellurium with lithium triethylborohydride. However, the formation of **4** was not observed under the standard reaction conditions (Scheme 3, reaction *a*). Traces of **4** were not detected performing the reaction in a coaxial NMR tube and monitoring its progress over the time.

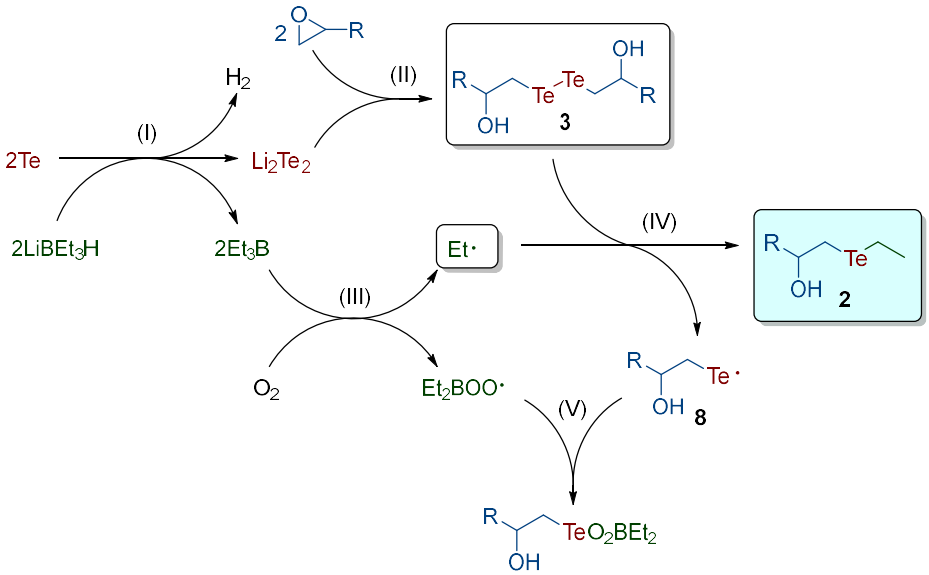
On the basis of these results, we next turned our attention to evaluating whether under the studied conditions ditellurides **3** could behave as precursors of β-hydroxy-alkyl ethyl tellurides **2**. We recently developed an on-water methodology to access functionalised dialkyl ditellurides from elemental tellurium, sodium hydroxymethanesulfinate, and strained heterocycles [46]. Therefore, we employed this route to prepare β-hydroxy-ditelluride **3a** and then we studied its reactivity with organoboranes. As a result, **3a** was thus treated with lithium triethylborohydride and, pleasingly, β-hydroxy-alkyl ethyl telluride **2a** was formed in 42% yield (Scheme 3, reaction *b*). However, under these conditions the alkyltellurolate **5a**, arising from the $LiBEt_3H$-induced reduction of the ditelluride **3a**, could be the species actually involved in the formation of **2a**. Unequivocal proof for the direct involvement of ditelluride **3a** and triethylborane was obtained by the reaction of these two compounds which, in the absence of hydrides, afforded **2a** in 48% yield (Scheme 3, reaction *c*). Notably, related diselenide **6a** reacted slowly with triethylborane under the same conditions and only traces (<5%) of unsymmetrical ethyl-selenide **7a** were detected after 6 h (Scheme 3, reaction *d*).

Trialkyl boranes readily undergo radical reactions generating alkyl radicals. Such processes can be initiated by oxygen, light or radical initiators, such as AIBN (Azobisisobutyronitrile) [54,55]. Additionally, ditellurides have been demonstrated to easily react with alkyl radicals, exhibiting remarkable radical-trapping activity [56]. On the basis of these considerations and supported by a literature precedent describing the reactivity of diphenyl ditelluride with organoboranes [57], we hypothesised a radical process involving ditellurides **3** and ethyl radicals. Control experiments performed using 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) as a radical inhibitor further demonstrated a radical pathway. Additionally, performing reactions b and c (Scheme 3) in the dark had no significant effect on the reaction outcome, showing that light was not required for the process leading to **2a**. On the other hand, when degassed tetrahydrofuran (THF) was used as the solvent, the ethyltellurenylation reaction was strongly inhibited and only traces of **2a** (<10%) were isolated.



Scheme 3. Control experiments. [a] Only traces (<5%) of **7a** were detected by ^{1}H-NMR of the crude material.

On the basis of the control experiments and previous reports, a proposed reaction mechanism is reported in Scheme 4. The first step (I) involves the reduction of elemental tellurium with lithium triethylborohydride, leading to the formation of dilithium ditelluride and triethylborane [58]. Subsequently (II), Li_2Te_2 reacts with two equivalents of epoxide to afford the corresponding ditelluride **3** through a regioselective nucleophilic ring-opening reaction. The following transmetalation of Et_3B with **3** reasonably proceeds through the oxygen-mediated formation of ethyl radicals (III) [54,55] which, in turn, react with ditelluride **3** providing unsymmetrical β-hydroxy-alkyl ethyl telluride **2** through an S_H2 process (IV) [59,60]. The tellurium-centered radical **8**, formed in the S_H2 reaction, undergoes typical propagation and termination processes, including the recombination with a second equivalent of **8** providing ditelluride **3** [61]. Furthermore, the reaction of **8** with oxygen or borylperoxyl radicals (V) would afford reactive tellurenyl peroxides which plausibly decompose, thus explaining the rather low yield of the transmetalation reaction and the absence of ditelluride **3**, or unreacted epoxide in the crude mixture.



Scheme 4. Proposed mechanism for the formation of unsymmetrical β-hydroxy-alkyl ethyl tellurides **2**.

4. Conclusions

In conclusion, we have described a one-pot multistep reaction in which epoxides are converted into the corresponding unsymmetrical β-hydroxy-alkyl ethyl tellurides upon treatment with elemental tellurium under lithium triethylborohydride-reducing conditions. The reaction mechanism was experimentally investigated; β-hydroxy ditellurides and triethyl borane were demonstrated to be the key species involved in this one-pot ethyltellurenylation reaction. The transmetalation of triethyl borane with hydroxy-dialkyl ditellurides, reasonably occurring through an oxygen-induced S_H2 mechanism, represents the key step of the process. The findings here described can be exploited for the development of novel general methodologies towards the synthesis of synthetically and biologically valuable complex sp^3-rich unsymmetrical tellurides. Further studies on the application of this reaction to functionalised boranes (and boronic esters) for the preparation and the elaboration of poly-functionalised unsymmetrical tellurides are currently ongoing in our laboratories.

Supplementary Materials: The following are available online at http://www.mdpi.com/2624-8549/2/3/41/s1, Figure S1. ^{1}H NMR spectrum of compound **2a** (CDCl3, 400 MHz); Figure S2. ^{13}C NMR spectrum of compound **2a** (CDCl3, 100 MHz); Figure S3. ^{125}Te NMR spectrum of compound **2a** (CDCl3, 126 MHz); Figure S4. ^{1}H NMR spectrum of compound **2b** (CDCl3, 400 MHz); Figure S5. ^{13}C NMR spectrum of compound **2b** (CDCl3, 100 MHz); Figure S6. ^{1}H NMR spectrum of compound **2d** (CDCl3, 400 MHz); Figure S7. ^{13}C NMR spectrum of compound **2d** (CDCl3, 100 MHz); Figure S8. ^{125}Te NMR spectrum of compound **2d** (CDCl3, 126 MHz); Figure S9. ^{1}H NMR spectrum of compound **3a** (CDCl3, 400 MHz); Figure S10. ^{13}C NMR spectrum of compound **3a** (CDCl3, 100 MHz); Figure S11. ^{125}Te NMR spectrum of compound **3a** (CDCl3, 126 MHz).

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Conflicts of Interest: The authors declare no conflict of interest.

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61. If regenerated, ditellurides **3** reasonably undergoes transmetalation with ethyl radicals affording β-hydroxy-alkyl-ethyl-tellurides **2** and radicals **8**, following the proposed mechanism reported in the Scheme 3.