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[d005]

Laboratório de Compostos de Selênio e Telúrio

Tellurium / Lithium Exchange Reaction in the Synthesis of Spiroketals and 1,6-dioxigenated Systems

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Abstract- 1,4-C,O-dianions, produced through concomitant acid / base and tellurium / lithium exchange reactions were generated. The di-lithium salts were transmetallated with $CeCl_3$ to the corresponding di-cerium salts and reacted with carbonyl compounds yielding spiroketals. The di-lithium entities were also converted into the corresponding cyanocuprates which add in a 1,4-maner to 2-cyclohexen-1-one giving 1,6-dioxigenated compounds.

1.0 Introduction

The spiroketal ring system (**1**, Scheme 1) is a subunit found in structurally very simple, as well as in highly complex naturally occurring molecules from different sources, such as insects, bacteria, fungi and plants.[1] Most of the work in the spiroketal area is focused in the 1,7-Dioxaspiro[5.5]undecane, 1,6-Dioxaspiro[4.5]decane and 1,6-Dioxaspiro[4.4]nonane ring systems, because most of the natural products bearing the spiroketal subunity **1** fall into these

[1] Perron, F.; Albizati, K. F.; *Chem. Rev.* **1989**, *89*, 1617-1661.

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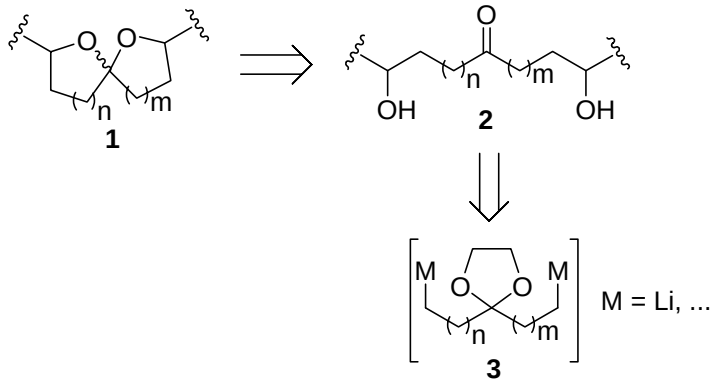
structural categories.[1,2] The systems mentioned above are present in most of the pheromones with a spiroketal ring in their structures.[1]

The biological activities of the compounds with a spiroketal moiety, and the synthetic challenge to construct it, led to the development of several strategies to its synthesis.[1,2] The acid-catalyzed cyclization of di-hydroxy ketones **2**, or an equivalente thereof, is the predominant route to **1** (Scheme 1).[1]



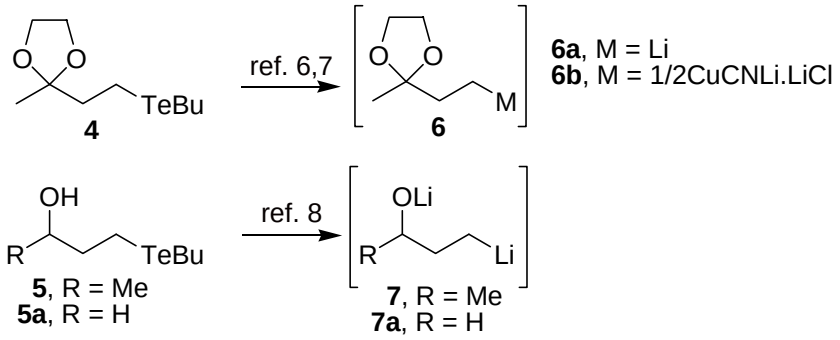
Scheme 1. Common synthetic route to **1**.

An useful approach to **2** makes use of organometallic species of the type **3** (Scheme 1). Among the most employed organometallics for this purpose are organolithium compounds, which can be prepared by a number of methods, one of them being the lithium / halogen or lithium / tin exchange.[3] In addition, organolithium compounds can be transformed into others organometallics by transmetallation with salts of metals more electroctronegative than lithium. The tellurium / lithium exchange is an advantageous alternative to these approaches for being fast and clean.[4] This methodology, however, has been very little employed, probably as a consequence of negative comments found in the literature about the bad smell and instability of organic tellurium

[2] Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406-4440.
[3] a) Chinchilla, R.; Nájera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139-3176; b) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron*, **2003**, *59*, 9255-9303.
[4] a) Comasseto, J. V.; Barrientos-Astigarraga, R. E. *Aldrichimica Acta* **2000**, *33*, 66-78; b) Petragnani, N. *Tellurium in Organic Synthesis; Best Synthetic Methods*; Academic Press: London, U. K., 1994 c) Petragnani, N.; Stefani, H. A. *Tetrahedron* **2005**, *61*, 1613-1679; d) Zeni, G.; Lüdtke, D. S.; Panatieri, S. B.; Braga, A. L. *Chem. Rev.* **2006**, *106*, 1032-1076;

compounds. As we pointed out recently, these comments do not always apply.[5]

Recently we demonstrated that the functionalized alkyltellurides **4** and **5** are efficient precursors of homoenolates **6**[6,7] and diânion **7**[8] (Scheme 2).



Scheme 2. Homoenolate and 1,4-dianions derived from alkyl tellurides.

In this work we employed the lithium salts **7** and **7a** derived from tellurides **5** and **5a**, as precursors of 1,6-[4.4]-spiroketals and 1,6-hydroxy-ketones. For this end, the initially obtained lithium compounds were transformed into cerium and copper species.

2.0 Results and discussion

n-Butyltellurol, generated in situ from elemental tellurium and *n*-butyllithium followed by a proton source such as water or ethanol, with methylvinyl ketone, producing the corresponding β-butyltelluro ketone **8**.[9] Telluride **8** can be transformed into the telluro-ketal **1** by reaction with ethyleneglycol in the presence of Amberlist®, and into the hydroxy telluride 5, when treated with aqueous or ethanolic solution of sodium borohyadride (Scheme 3). Alternativelly, hydroxy telluride **5** was produced in 70% isolated yield in a single operation by sequential hydrotelluration of methylvinyl ketone and *in situ* reduction of **8** by addition of sodium borohydride to the reaction mixture.

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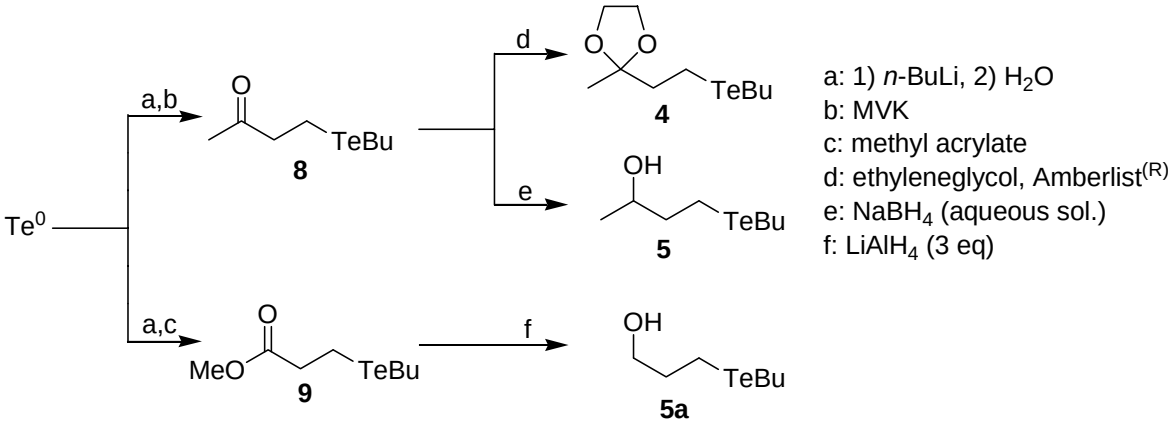
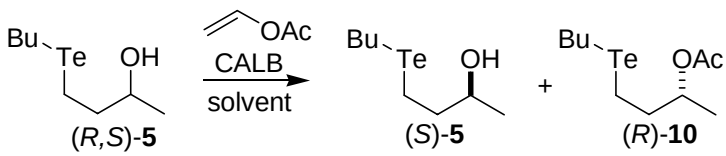
[5] Dos Santos, A. A.; Castelani, P.; Bassora, B. K.; Fogo, J. C.; Costa, C. E.; Comasseto, J. V. *Tetrahedron* **2005**, *61*, 9173-9179.
[6] Dos Santos, A. A.; Comasseto, J. V. *J. Braz. Chem. Soc.* **2005**, *16*, 511-513.
[7] Dos Santos, A.A.; Ferrarini, R. S.; Princival, J. L.; Comasseto, J. V. *Tetrahedron Lett.* **2006**, *in press*.
[8] Princival, J. L.; Barros, S. M. G.; Comasseto, J. V.; Dos Santos, A. A. *Tetrahedron Lett.* **2005**, *46*, 4423-4425.
[9] Zinn, F. K.; Righi, v. E.; Luque, S. C.; Formiga, H. B.; Comasseto, J. V. *Tetrahedron Lett.* **2002**, *43*, 1625-1628;

Telluride **5a** was prepared in 78% yield by hydrotelluration of methyl acrylate (9), followed by reduction of the ester group with $LiAlH_4$. These protocols complement our earlier studies on the reduction of butyltelluro carbonyl compounds to the corresponding alcohols.[5]



Scheme 3. Preparation of tellurides **4**, **5** and **5a**.

Telluride **5** was submitted to enzymatic kinetic resolution.[10] In a typical procedure CALB (*Candida antarctica* lipase-B) and vinyl acetate were sequentially added to the racemic mixture of hydroxy telluride **5** dissolved in an appropriate solvent (hexane or THF). In hexane the chiral acetate (R)-**10** was obtained with 96% *e.e*. However, the isolated yield was very low (< 5%). The low yield and the observation of a white powder in the reaction media suggested that **5** was presumably transformed into a telluroxide. This problem was circumvented by performing the resolution in THF. In this solvent, the enzymatic resolution of **5** was achieved with an improved isolated yield. The acetate (R)-**10** was obtained with 36% yield and with high enantioselectivity (>200). The unreacted alcohol was recovered with 30% yield and high enantiomeric excess (99% *e.e.*) (Scheme 4 – Table 1).



[10] Dos Santos, A. A.; Da Costa, C. E.; Princival, J. L.; Comasseto, J. C. *Tetrahedron: Asymm.* **2006**, *17*, 2252-2259.

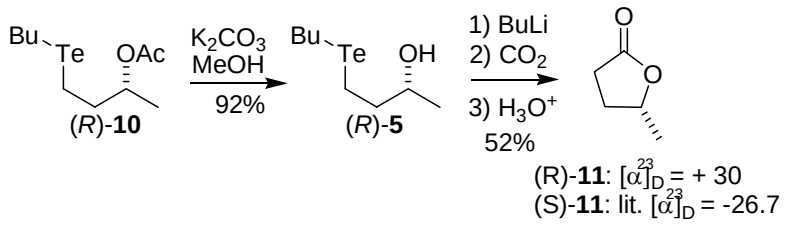
Scheme 4. Enzymatic kinetic resolution of hydroxy telluride (*R,S*)-**5**.

Table 1. Enzymatic resolution of hydroxy telluride (*R,S*)-**5**

Entry	Solvent	Time (h)	Conv.(%)	*e.e.* (*S*)-5 (%)	*e.e.* (*R*)-10 (%)	Y.(%)	*E*
1	hexane	1	45	80	96	-	
2	hexane	4	49	90	95	<5	120
3	THF	8	48	93	99		
4	THF	12	50	99	98	36	>200

Substrate (0.5 mmol), CALB: 30 mg in hexane (10 mL) or 50 mg in THF (10 mL); Temperature: 30 ^{0}C.

The absolute configurations of the acetate **10** and the unreacted alcohol **5** were indirectly assigned by conversion of the chiral acetate obtained from the enzymatic process, in the natural product γ-valerolactone (**11**), followed by comparison of the values of optical rotation of synthetic **11** with the literature data.[11] The reaction of 1,4-C,O-dianion generated by reaction of hydroxy telluride (R)-**5** with two equivalents of *n*-butyllithium in THF, followed by reaction with carbon dioxide and acid work-up, yielded γ-valerolactone (**11**) in 52% isolated yield (Scheme 5).

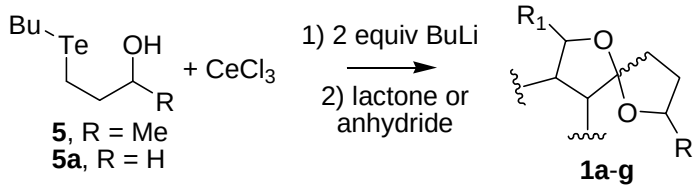


Scheme 5. Preparation of γ-Valerolactone from chiral alcohol (*R*)-**10**.

The lithium salts **7** and **7a** (Scheme 2) were transformed into the cerium analogues by transmetallation with cerium trichloride. These intermediates were reacted with lactones and anhydrides affording the corresponding spiroketals (**1a**-**g**) after acid workup. Initially, these reactions were performed following the classical procedures for the preparation of organocerium compounds, i.e. generation of the organolithium compound followed addition of a suspension of cerium trichloride in THF.[12] Commonly the generation of organoceriums, demands long reaction times (> 1 h) at approximately -40 ^{0}C.

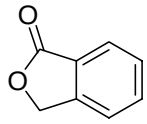
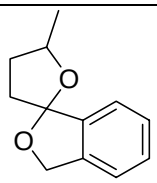
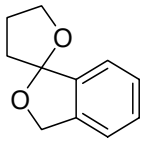
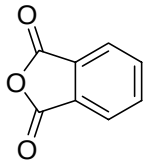
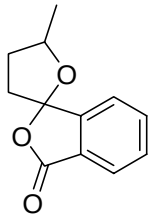
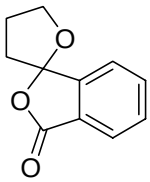
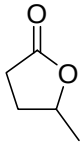
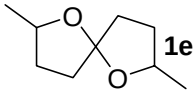
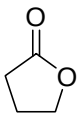
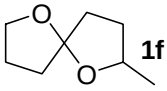
[11] Clososki, G. C.; Costa, C. E.; Missio, L. J.; Cass, Q. B.; Comasseto, J. V. *Synthetic Comm.* **2004**, *34*, 817-828.
[12] a) Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803-3830; b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29-68; c) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573-6614.

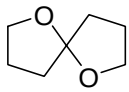
In this work, mixtures of cerium trichloride and **5** or **5a** in THF at -70 ^{0}C were prepared and then reacted with n-butyllithium (Scheme 6). Five minutes after the addition of n-butyllithium total consumption of the hydroxy telluride was observed by TLC. This procedure is operationally simpler than the mentioned before. The di-cerium salt was then added to the appropriate lactone or anhydride in ethyl ether at -70 ^{0}C (Scheme 6 – Table 2).



Scheme 6. Reaction of di-cerium salt with lactones and anhydrides yielding [4.4]-spiroketals **1a-g**.

Table 2. Reaction of di-cerium salts with lactones and anhydrides

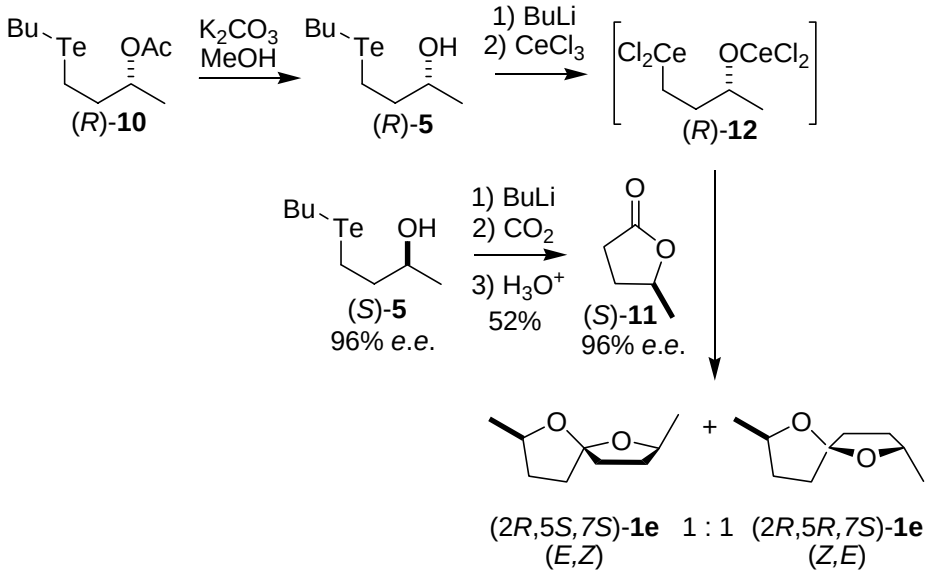
Entry	Substrate	Telluride	Product	Yield (%)
1		**5**[a]	 **1a**	65[b]
2		**5a**[a]	 **1b**	65[b]
3		**5**[a]	 **1c**	52[b]
4		**5a**[a]	 **1d**	56[b]
5		**5**[a]	 **1e**	74[c]
6		**5**[a]	 **1f**	66[c]

7	**5a**[a]		**1g**	68[d]

[a] *n*-Butyllithium was added to the mixture of the hydroxy telluride and cerium trichloride; [b] Isolated yields; [c] Yields determined by GC analyses (spiroketal **1g** was employed as internal standard); [d] Yield determined by GC analyses (spiroketal **1f** was employed as internal standard).

The preparation of spiroketals by the present methodology proceeds with reasonable yields. The mono-spiroketals **1c** and **1d** (Table 2, entries 3 and 4) were formed as the only products even when two equivalents of the di-cerium salt was employed. In the case of spiroketals **1a**, **1c**, **1e** and **1f** mixtures of *E* and *Z* stereomers were produced and the yields refer to the sum of all them.

γ-Valerolactone (*S*)-**11** produced by the route described in Scheme 4 was reacted with the chiral di-cerium salt (*R*)-**12** of the inverse configuration (derived from (*R*)-**5**). The chiral spiroketal **1e** was produced as a 1:1 mixture of *E* and *Z* stereomers (Figure 1 B). Less than 3% of the other stereomers were detected by chiral GC (Scheme 7, Figure 1A and 1B).



Scheme 7. Reaction of chiral di-cerium salt (*R*)-**12** with chiral lactone (*S*)-**11** yielding a 1:1 mixture of E,Z- and *Z,E*- stereomers of spiroketal **1e**.

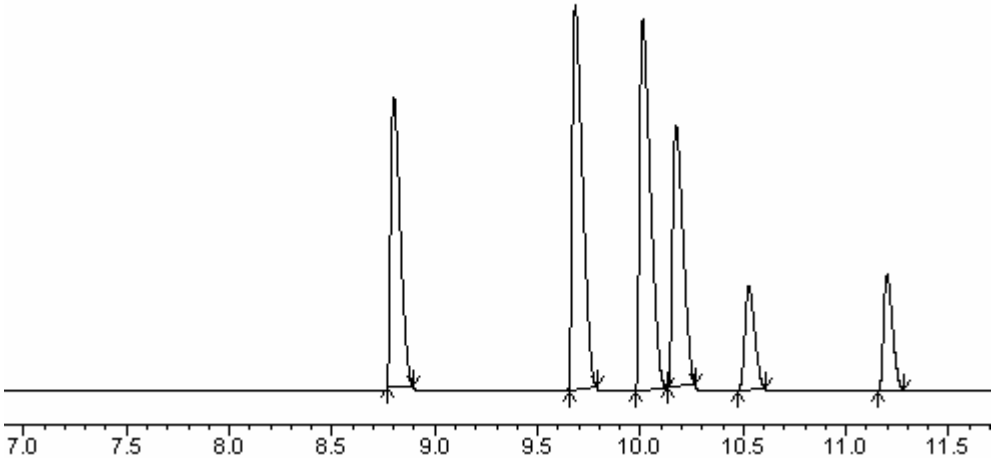


Figura 1A: Chiral GC analyses of the racemic mixture of **1e**

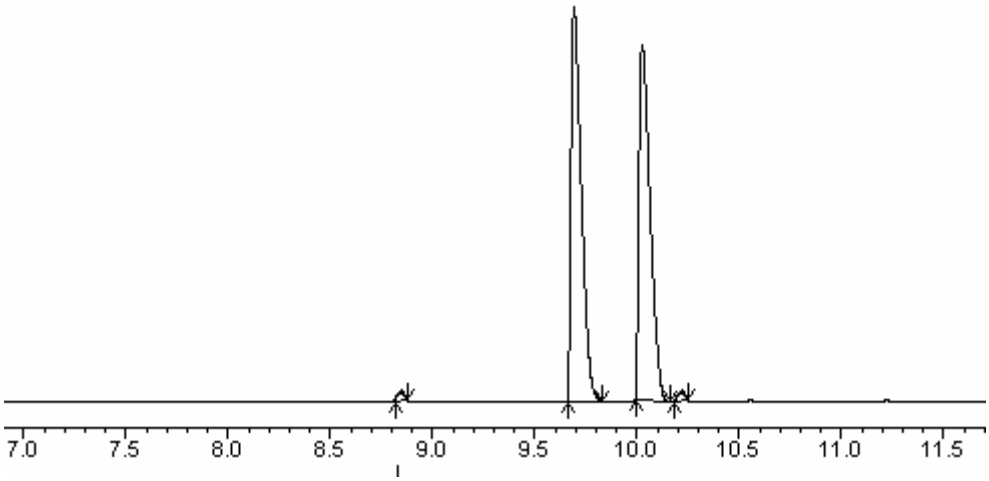


Figura 1B: Chiral GC analyses of the chiral *E,Z* mixture of ((2R,5S,7S)-**1e**) and **(**(2R,5R,7S)-**1e**)

The volatile spiroketals **1e**, **1f** and **1g** were isolated in pure form in low yields (< 30%), even by accurate distillation of the solvent. This result is in agreement with previous works about this class of volatile compounds.[13]

As a part of our studies concerning the preparation of functionalized organometallics, the dianions **7** and **7a** were also converted into the corresponding cyanocuprates by reacting with CuCN.2LiCl (1/2 equivalent). The pre-formed cyanocuprate[14] was added to a solution of 2-cyclohexen-1-one and the corresponding hydroxy ketones **13** and **13a** were obtained in 62% and 67% isolated yield respectively (Scheme 8).

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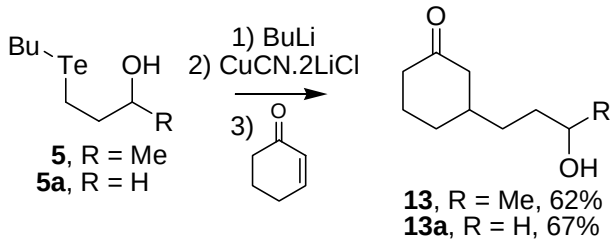
[13] Solladié, G.; Huser, N.; Fischer, J.; Decian, A. *J. Org. Chem.* **1995**, *60*, 4988-4990;

[14] The stoichiometry of this reagent was not directly determined; We assumed that the reagent is the type $R_2CuLi.LiCN$ (R = C,O-dianion);



Scheme 8: Michael addition of the cyanocuprates derived from **5** and **5a** to 2-cyclohexen-1-one

Finally it must be pointed out that as many other tellurides prepared in our laboratory, those presented here are light yellow oils and are either odourless or present a smell not more unpleasant than other chemicals usually employed in organic synthesis. They are stable to ambient light and air, and can be manipulated under ordinary conditions with no appreciable decomposition. Prolonged contact with air, especially when dissolved in hexane should be avoided to prevent their transformation into telluroxides. However, this problem can be considerably minimized by using deoxygenated solvents. The tellurides are totally compatibles with many common functional group transformations, such as carbonyl reduction or protection, enzymatic and chemical acylation and de-acylation.

In summary we demonstrated the applicability of hydroxy tellurides as versatile source of functionalized organometallics.

3.0 Experimental

3.1 General

All reagents and solvents used were previously purified and dried.[15] THF was distilled from sodium / benzophenone under nitrogen immediately before use. *n*-Butyllithium was titrated using 1,10-phenanthroline as indicator prior to use. Nitrogen gas was deoxygenated and dried. All operations were carried out in flame-dried glassware. Cerium trichloride heptahydrate was dried according to reported procedure.[16] Column Chromatography separations were performed

[15] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1980.
[16] Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787-6790.

with Vetec silicagel 60 (0.063-0.200 mm, 70-230 mesh) or Acros Organics silicagel (0.035-0.075 mm, pore diameter ca 6 nm). Tellurium metal (-200 mesh), lithium aluminum hydride, sodium borohydride and cerium trichloride heptahydrate were purchased from Aldrich Chemical Co.

CALB (Novozym 435®; immobilized lipase-B from *Candida antarctica*; 10,000 PLU/g) was kindly donated by Novozymes Inc. NMR spectra were recorded on Bruker models AC-200 and Varian model FT-300, spectrometers with samples dissolved in $CDCl_3$. The internal references were TMS (^{1}H NMR), the central peak of the $CDCl_3$ signal (^{13}C NMR), and a capillary of diphenyl ditelluride 1M (^{125}Te NMR). IR spectra were recorded on a Bomem MB-100 spectrophotometer, and optical rotations were determined on a Jasco DIP 370 digital polarimeter. Chiral GC analyses were performed on a Shimadzu GC-17A instrument coupled to a flame ionization detector (FID) and equipped with a Varian Chromopack™ Chirasil-Dex CB (β-cyclodextrin packing) capillary column (25 m x 0.25 mm i.d.; 0.25 μm). In both cases, the carrier gas was H_2. Mass spectra were recorded by coupling the GC to a Shimadzu model QP 5050A mass spectrometer.

3.2.1 One pot procedure to prepare 4-(butyltellanyl)butan-2-ol (5)[8]

To a suspension of elemental tellurium (5.10 g, 40 mmol) in dry THF (80 mL), at room temperature was slowly added *n*-butyllithium (1.69 mol.L^{-1} in hexane: 23.7 mL, 40 mmol). To the light yellow solution of lithium butyl tellurolate was added deoxygenated water (1.8 mL, 100 mmol) and the resulting red browned mixture was stirred at the same temperature for 10 min, than cooled to 0 ^{0}C. Methyl vinyl ketone (3.32 mL, 40 mmol) was added in a portion and the resulting mixture was stirred while warmed to room temperature. The progress of the reaction was monitored by TLC. After 1 h under stirring at room temperature, it was added sodium borohydride (1.52 g, 40 mmol) then the mixture was gently warmed at 50 ^{0}C. TLC analyses of the reaction mixture revealed that all the telluro ketone was converted into the hydroxy telluride after 10 min of reaction. The resulting brown solution was cooled to room

temperature and then deoxygenated water (20 mL) was slowly added over a period of 20 min. After 30 min under vigorous stirring, more deoxygenated water (40 mL) was introduced and the phases were separated. The organic phase was washed with saturated ammonium chloride solution (100 mL). The aqueous phases were combined and extracted with ethyl acetate (2 x 200 mL). The organic phases were combined and the solution was dried with $MgSO_4$, filtered and the solvents were removed under reduced pressure. The crude oil was purified by column chromatography over silica gel eluting with cyclohexane:ethyl acetate (4:1). **4-(butyltellanyl)butan-2-ol (5)**. Oil; yield: 7.7 g (74%). CAS NR. 861399-10-2; ^{1}H RMN: (300 MHz**,** $CDCl_3$, ppm) δ 0.89 (*t*, J^3 = 7.5 Hz, 3H); 1.18 (*d*, J^3 = 6.0 Hz, 3H); 1.35 (*sext*, J^3 = 7.5 Hz, 2H); 1.64-1.75 (*m*, 2H); 1.81-1.89 (*m*, 2H); 2.55-2.69 (*m*, 4H); 3.80 (*sext,* J^3 = 6 Hz, 1H). ^{13}C RMN: (75 MHz, $CDCl_3$, ppm) δ -2.3, 2.7, 13.3, 23.2, 25.0, 34.2, 41.2, 69.1. ^{125}Te NMR (157.79 MHz, $CDCl_3$, 25 ^{0}C Ph_2Te_2, ppm) δ 251.43. MS *m/z* (rel. int.) 260 [M^{+2}] (13%), 258 [M^+] (13%), 256 (7%), 255 (3%), 254 (2%), 215 (3%), 215 (3%), 186 (8%), 72 (5%), 57 (73%), 55 (100%), 45 (44%).

3.2.2 One pot procedure to prepare 3-(butyltellanyl)propan-1-ol (5a)

To a suspension of elemental tellurium (3.83 g, 30 mmol) in dry THF (60 mL), at room temperature was slowly added *n*-butyllithium (1.69 mol.L^{-1} in hexane: 17.7 mL, 30 mmol). To the light yellow solution of lithium butyl tellurolate was added deoxygenated water (1.35 mL, 75 mmol) and the resulting red browned mixture was stirred at the same temperature for 10 min, and then cooled to 0 ^{0}C. Methyl acrylate (2.7 mL, 30 mmol) was added in a portion and the resulting mixture was stirred while warmed to room temperature. The progress of the reaction was monitored by TLC. After 1 h under stirring at room temperature, the reaction mixture was cooled to 0 ^{0}C and lithium aluminum hydride (3.4 g, 90 mmol) was slowly added in three portions (0.5, 1.0 and 1.9 g respectively). The mixture was warmed to room temperature and then gently heated at 50 ^{0}C. TLC analyses of the reaction mixture revealed that all the telluro ester was converted into the hydroxy telluride after 20 min of reaction. The resulting

mixture was cooled to 0 ^{0}C, and then deoxygenated water (~ 30 mL) was slowly added over a period of 30 min. The resulting slurry was filtered and the resulting residue was washed with ethyl ether (2 x 30 mL). The organic phases were combined, washed with saturated ammonium chloride solution (2 x 30 mL), dried with $MgSO_4$, filtered and the solvents were removed under reduced pressure. The crude oil was purified by column chromatography over silica gel eluting with cyclohexane:ethyl acetate (3:1). **3-(butyltellanyl)propan-1-ol (5a)**. Oil; yield: 5.7 g (78%). Found: C, 34.79; H, 6.56. Calcd. For $C_7H_{16}OTe$: C, 34.49; H 6.61. ^{1}H RMN: (300 MHz**,** $CDCl_3$, ppm) δ 0.89 (*t*, J^3 = 7.2 Hz, 3H), 1.36 (*sext*, J^3 = 7.2 Hz, 2H), 1.70 (*quint*, J^3 = 7.5 Hz, 2H), 1.91-2.00 (*m*, 3H), 2.63 (*t*, J^3 = 7.5 Hz), 2.66 (*t*, J^3 = 7.5 Hz), 3.66 (*t*, J^3 = 6.3 Hz). ^{13}C RMN (75 MHz, $CDCl_3$, ppm) δ - 2.1, 2.8, 13.3, 25.0, 34.2, 34.6, 63.9. ^{125}Te NMR (157.79 MHz, $CDCl_3$, 25 ^{0}C Ph_2Te_2, ppm) δ 244.45. MS: *m/z* (rel. int.) 246 [M^{+2}] (26%), 244 [M^+] (24%), 242 (15%), 240 (3%), 188 (6%), 186 (7%), 172 (23%), 170 (23%), 168 (13%), 144 (4%), 142 (2%), 130 (6%), 126 (4%), 57 (100%), 41 (86%).

3.2.3 Enzymatic kinetic resolution of 4-(butyltellanyl)butan-1-ol (5)

CALB (0.03 g for hexane or 0.05 g for THF) and vinyl acetate (5 equivalents) were added to a solution of the hydroxy telluride **5** (0.13 g, 0.5 mmol) in hexane or THF (10 mL, both deoxygenated). The reaction mixture was stirred and the course of the reaction was monitored by chiral GC. After *ca*. 50% conversion had been achieved, the enzyme was removed by filtration and the resulting solution was concentrated under reduced pressure. The organic residue was subjected to silica gel column chromatography eluting with hexane:ethyl acetate (4:1) yielding the corresponding acetate (*R*)-**10** and alcohol (*S*)-**5**. **(*R*)-4-(butyltellanyl)butan-2-yl acetate** (*R*)-**10**: Oil; 0.027 g (36%); Found: C, 40.02; H, 6.53. Calcd. for $C_{10}H_{20}O_2Te$: C, 40.05; H, 6.72. ^{1}H NMR (300 MHz; $CDCl_3$) δ 0.92 (t, *J* = 7.5 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.38 (sext, *J* = 7.5 Hz, 2H), 1.72 (quint, *J* = 7.5 Hz, 2H), 2.04 (s, 3H), 1.87-2.11 (m, 2H), 2.49-2.67 (m, 4H). ^{13}C NMR (125 MHz; $CDCl_3$) δ -3.6, 2.8, 13.4,

19.5, 21.3, 25.0, 34.2, 38.8, 72.2, 170.6. ^{125}Te NMR (157 MHz, 300K, $CDCl_3$) δ 270.15. $[\alpha]_D^{22}$ = +18 (c 1.0, CH_2Cl_2); *e.e.* = 98%. **(*S*)-4-(butyltellanyl)butan-2-ol** (*S*)-**5**: Oil; 0.019 g (30%); $[\alpha]_D^{22}$ = +7 (c 1.0, CH_2Cl_2); *e.e.* = 99%.

3.2.4 Hydrolysis of (R)-4-(butyltellanyl)butan-2-yl acetate ((R)-10)

Telluride **(*R*)-10** (0.30 g, 1 mmol) was dissolved in methanol (5 mL) and water (1 mL), then K_2CO_3 (0.03 g, 0.2 mmol) was added. The mixture was stirred 1 h at room temperature then the mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 5 mL). The organic phase was washed with brine (2 mL), dried over magnesium sulfate and the solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography eluting with hexane:ethyl acetate (4:1) yielding **(*R*)-5** as a light yellow oil; 0.24 g (92%).

3.2.5 Synthesis of (*R*)-(+)-γ-Valerolactone (11)

To a solution of the hydroxy telluride **(*R*)-5** (96% *e.e.*, 1.28 g, 5 mmol) dissolved in dry THF (25 mL) cooled at – 70 ^{0}C was added *n*-butyllithium (1.4 mol.L^{-1} in hexane, 7.15 mL, 10 mmol). The light yellow solution was stirred at the same temperature for 5 min and then dry carbon dioxide was introduced by means of a needle immersed into the solution. A white gel was formed after approximately 15 min. The mixture was warmed to room temperature and hydrochloric acid (50%, V/V, 6 mL) was added. The mixture was stirred for 30 min at room temperature and then the phases were separated. The aqueous phase was washed with ethyl acetate (2 x 5 mL). The combined organic phases were dried with magnesium sulfate, filtered and the solvents were removed by distillation. The resulting residue was purified by silica gel column chromatography eluting with hexane:ethyl acetate (1:1). **(*R*)-(+)-γ-Valerolactone (11)**. Colorless oil; 0.26 g (52%); *e.e.* 96%. CAS NR. 58917-25-2; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.43 (3H, d, *J* = 6.3 Hz), 1.78-1.91 (1H, m), 2.54-2.59 (2H, m), 4.6-4.71 (1H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ 21.0, 29.1, 29.8, 77.4, 177.6. IR (ν/cm^{-1}) 2998, 1777, 1432, 1130. MS *m/z* (rel. int.): 41 (47), 43 (34), 56 (100), 85 (45), 100 (8).

3.2.6 General procedure to prepare spiroketals – Method B

To a mixture of anhydrous cerium chloride (0.98 g, 4 mmol) and hydroxy telluride (**5**, 0.51 g or **5a**, 0.48 g, 2 mmol) in dry THF (40 mL), cooled to – 70 ^{0}C was slowly added a solution of *n*-butyllithium (1.4 mol.L^{-1}, in hexane, 2.87 mL, 4 mmol). The resulting mixture was stirred at the same temperature for 2 h and then warmed to – 40 ^{0}C and stirred for 1 h at this temperature. After this time, the mixture was re-cooled to – 70 ^{0}C and then transferred via canula to another flask containing a solution of the appropriate carbonyl compound (lactone or anhydride, 2 mmol) in diethyl ether (5 mL). The resulting mixture was stirred for 1.5 h at the same temperature and then warmed to room temperature. To the mixture was added hydrochloric acid (10% V/V, 20 mL) under stirring for 20 min. The phases were separated and the aqueous phase was extracted with ethyl ether (2 x 5 mL). The combined organic phases were washed, dried and the solvents were removed by distillation in the case of the volatile spiroketals **1e-g** or at reduced pressure in the case of compounds **1a-d**. The residue was purified by silica gel column chromatography.

1a: Found: C, 75.66; H, 7.53. Calcd. For $C_{12}H_{14}O_2$: C, 75.76; H 7.42; (hexane:ethyl ether, 7:1); Oil; 0.74 g (65%); ^{1}H RMN: (300 MHz**,** $CDCl_3$, ppm) δ 1.32 (*d*, J^3 = 6.3 Hz, 1H), 1.41 (*d*, J^3 = 6.0 Hz, 1H), 1.71-1.87 (*m*, 1H), 2.30-2.47 (*m*, 3H), 4.37 (*sext*, J^3 = 6.0 Hz, 1H), 4.45 (*sext*, J^3 = 6.3 Hz, 1H), 4.95 (*d*, J^1 = 12.6 Hz, 1H), 4.98 (*d*, J^1 = 12.6 Hz, 1H), 5.17 (*d*, J^1 = 12.6 Hz, 1H), 5.22 (*d*, J^1 = 12.6 Hz, 1H), 7.23-7.27 (*m*, 1H), 7.33-7.37 (*m*, 3H). ^{13}C RMN (75 MHz, $CDCl_3$, ppm) δ 21.2, 22.4, 32.6, 32.8, 37.1, 38.5, 70.6, 70.7, 75.4, 77.2, 116.9, 117.0, 121.0, 121.9, 127.6, 127.7, 128.7, 139.4, 139.5, 139.9, 140,0. MS: *m/z* (rel. int.) 190 [M$^+$] (22%), 175 (29%), 146 (35%), 135 (100%), 117 (16%), 105 (25%), 89 (21%), 77 (26%), 63 (10%), 51 (12%), 41 (11%).

1b: CAS NR: 139697-84-0; (hexane:ethyl ether, 7:1); Oil; 0.72 g (65%); ^{1}H RMN: (300 MHz**,** $CDCl_3$, ppm) δ 2.09-2.36 (*m*, 4H), 4.02-4.10 (*m*, 1H), 4.13-4.20 (*m*, 1H), 4,97 (*d*, J^1 = 12.6 Hz, 1H), 5.18 (*d*, J^1 = 12.6 Hz, 1H), 7.23-7.38 (*m*, 4H). ^{13}C RMN (75 MHz, $CDCl_3$, ppm) δ 25.0, 36.9, 68.3, 70.6, 116.8, 120.8, 121.8, 127.5, 128.7, 138.9, 140.0; MS: *m/z* (rel. int.) 176 [M$^+$] (3%), 175 (15%), 146 (31%), 135 (100%), 117 (12%), 105 (25%), 89 (14%), 77 (18%), 63 (9%), 51 (10%).

1c: CAS NR: 180198-87-2; (hexane:ethyl acetate, 1:2); Oil; 0.21 g (52%); ^{1}H RMN: (300 MHz**,** $CDCl_3$, ppm) δ 1.36 (*d*, J^3 = 6.3 Hz, 3H), 1.43 (*d*, J^3 = 6.0 Hz, 3H), 1.96-2.55 (*m*, 4H), 4.54-4.70 (*m*, 1H), 7.49 (*ddd*, J^3 = 7.5, J^4 = 1.5 , J^5 = 0.9 Hz, 1H), 7.54 (*td*, J^3 = 7.5, J^4 = 0.9 Hz, 1H), 7.55 (*td*, J^3 = 7.5, J^4 = 0.9 Hz, 1H), 7.67 (*td*, J^3 = 7.5, J^4 = 1,.2 Hz, 1H), 7.68 (*td*, J^3 = 7.5, J^4 = 1.2 Hz, 1H), 7.80-7.84 (*m*, 1H); ^{13}C RMN (75 MHz, $CDCl_3$, ppm) δ 21.1, 22.1, 31.3, 32.1, 36.7, 38.8, 78.3, 80.1, 114.0. 114.2. 122.2, 125.1, 127.3, 127.5, 130.4, 134.3, 146.6, 146.7, 168.0, 168.1; MS: *m/z* (rel. int.) 205 [M^{+1}] (1%), 160 (86%), 149 (55%), 131 (13%), 115 (24%), 104 (100%), 76 (74%), 56 (31%).

1d: CAS NR: 177780-65-3; (hexane:ethyl acetate, 1:2); Oil; 0.21 g (56%); ^{1}H RMN: (300 MHz**,** $CDCl_3$, ppm) δ 2.23-2.46 (*m*, 4H), 4.20-4.36 (*m*, 2H), 7.50 (*ddd*, J^3 = 7.5, J^4 = 1.2, J^5 = 0.9 Hz, 1H), 7.56 (*td*, J^3 = 7.5, J^4 = 1.2 Hz, 1H), 7.68 (*td*, J^3 = 7.5, J^4 = 1.2 Hz, 1H), 7.83 (*ddd*, J^3 = 7.5, J^4 = 1.2, J^5 = 0.9 Hz, 1H). ^{13}C RMN (75 MHz, $CDCl_3$, ppm) δ 24.2, 37.2, 70.7, 114.0, 122.3, 125.1, 127.4, 130.5, 134.3, 146.3, 168. MS: *m/z* (rel. int.) 190 [M^+] (1,4%), 160 (7%), 149 (46%), 146 (57%), 132 (5%), 115 (16%), 105 (100%), 76 (44%), 66 (9%), 50 (26%).

1e: CAS NR: 106356-13-2; (pentane:ethyl ether, 5:1); GC yield (74%, compound **1g** was used as internal standard); ^{1}H RMN: (300 MHz**,** $CDCl_3$, ppm) δ 1.16 (*d*, J^3 = 6.0 Hz, 3H), 1.17 (*d*, J^3 = 6.3 Hz, 3H), 1.25 (*d*, J^3 = 6.0 Hz, 3H), 1.26 (*d*, J^3 = 6.3 Hz, 3H), 1.65-2.15 (*m*, 8H), 4.01-4.27 (*m*, 2H). ^{13}C RMN (75 MHz, $CDCl_3$, ppm) δ 21.1, 21.3, 22.7, 31.8, 32.2, 32.7, 35.4, 35.8, 36.9, 73.9, 74.0, 75.8, 114.4, 114.7, 114.9. MS: *m/z* (rel. int.) 156 [M^+] (3%), 141 (15%), 112 (28%), 101 (100%), 83 (45%), 56 (60%), 43 (34%).

1f: CAS NR: 5451-15-0; (pentane:ethyl ether, 5:1); Yield 66%, determined by GC analyses using compound **1g** as internal standard); ^{1}H RMN: (300 MHz**,** $CDCl_3$, ppm) δ 1.21 (*d*, J^3 = 6.3Hz, 3H), 1.29 (*d*, J^3 = 6.3 Hz, 3H), 1.83-2.20 (*m*, 8H), 3.77-4.02 (m, 2H), (*m*, 4.06-4.15), 4.21 (*sext*, J^3 = 6.3 Hz, 1H); ^{13}C RMN (75 MHz, $CDCl_3$, ppm) δ 21.4, 22.9, 32.3, 32.9, 34.9, 35.2, 35.5, 35.6, 36.5, 67.2, 74.4, 76.3, 114.9, 115. MS: *m/z* (rel. int.) 142 [M^+] (12%), 127 (27%), 112 (11%), 101 (49%), 98 (53%), 87 (100%), 56 (97%), 45 (18%).

1g: CAS NR: 76041-89-9; (pentane:ethyl ether, 5:1); Yield 68%, determined by GC analyses using compound **1f** as internal standard); ^{1}H RMN: (200 MHz**,**

$CDCl_3$, ppm) δ 1.88-2.11 (*m*, 8H), 3.82-3.97 (*m*, 4H). ^{13}C RMN (50 MHz, $CDCl_3$, ppm) δ 24.5, 34.6, 67.0, 114.6. MS: *m/z* (rel. int.) 128 [M^+] (7%), 98 (36%), 87 (100%), 56 (68%), 45 (19%).

3.2.7 General procedure to cyanocuprates from hydroxy tellurides 5 and 5a and their reaction with 2-cyclohexen-1-one

To a solution of CuCN.2LiCl (1 $mol.L^{-1}$ solution in THF, 2 mL, 2 mmol) in THF (10 mL) cooled to – 70 ^0C was transferred a solution of the appropriate dianion (**7** or **7a**, 4 mmol, prepared as described in section 3.2.5). The resulting clear light yellow solution was stirred at the same temperature for 1 h and then transferred via canula to another flask containing 2-cyclohexen-1-one (0.2 g, 2 mmol) in THF (4 mL). The resulting solution was stirred at the same temperature for 30 min and then warmed to room temperature and diluted with cooper sulfate solution (10% m/V solution, 5 mL) and ethyl ether (5 mL). The mixture was maintained under vigorous stirring for 30 min and then the phases were separated and the organic phase was washed with saturated ammonium chloride solution (2 x 3 mL). The aqueous phase was extracted with ethyl acetate (5 mL). The combined organic phases were dried with magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate:hexane (3:1).

13: Found: C, 70.35; H, 10.53. Calcd. For $C_{10}H_{18}O_2$: C, 70.55; H 10.66; **(**ethyl acetate:hexane, 3:1); Oil; 0.21 g (62%); ^1H RMN: (200 MHz**,** $CDCl_3$, ppm) δ 1.19 (*d*, J^3 = 6.1 Hz, 3H), 1.33-2.48 (*m*, 13H), 3.77 (*sext*, J^3 = 6.1 Hz, 1H); ^{13}C RMN (50 MHz, $CDCl_3$, ppm) δ 23.4, 25.0, 25.1, 31.0, 31.2, 32.5, 36.1, 36.2, 38.9, 39.0, 41.3, 47.9, 48.0, 67.8, 67.9, 212.0; MS: *m/z* (rel. int.) 170 [M^+] (2%), 152 (6%), 110 (69%), 97 (100%), 82 (48%), 67 (62%), 55 (82%), 45 (84%), 41 (88%).

13a: CAS NR: 69441-81-2; (ethyl acetate:hexane, 3:1); Oil; 0.21 g (67%); ^1H RMN: (300 MHz**,** $CDCl_3$, ppm) δ 1.32-2.09 (*m*, 10H), 2.25-2.46 (*m*, 3H), 3.63 (*t*,

J^3 = 4,3 Hz, 2H); ^{13}C RMN (75 MHz, $CDCl_3$, ppm) δ 25.1, 29.7, 31.2, 32.6, 38.8, 41.3, 48.0, 62.7, 212.0; MS: *m/z* (rel. int.) 170 [M^+] (4%), 138 (8%), 112 (14%), 97 (100%), 79 (11%), 67 (48%), 55 (64%).

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