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Cleavage of the C-Se bond of Cyclic Selenoacetals derived from 4-t-Butyl Cyclohexanone with Butyllithiums and Tin and Silyl Hydrides

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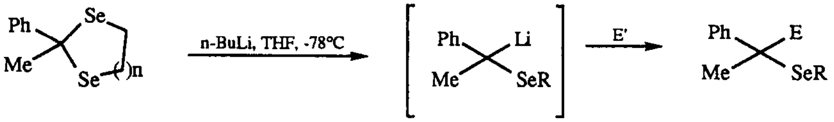
Abstract: Selenoacetals derived from 1,3-propanediselenol and 1,2-ethanediselenol are much less prone to be cleaved by butyllithiums than their open chain analogues. The stereochemistry of the products resulting from these reactions as well as from the cleavage of the C-Se bond under radical conditions is disclosed.

In the course of our studies on the C-Se bond cleavage,[1] we focused on the behaviour of cyclic selenoacetals **2, 6** derived from 1,3-propanediselenol or 1,2-ethanediselenol and acetophenone **1** or 4-t-butyl cyclohexanone **5** towards butyllithiums and tributyltin- or tris(trimethylsilyl)silyl hydrides.

Selenoacetals derived from 1,3-propanediselenol were readily synthesised under standard conditions ($ZnCl_2$, CH_2Cl_2, 20°C, **2a** or **6a**, 67% each) [2] whereas those derived from 1,2-ethanediselenol were obtained in low yields due to the high propensity of this selenol to be oxidised ($ZnCl_2$, CH_2Cl_2, 20°C, **2b** or **6b**: 22% each). The required diselenols have been prepared from the corresponding dibromides on sequential reaction with potassium selenocyanate (2.3 equiv. KSeCN, DMF, 80°C, 95%) and with hypophosphorous acid (50% aq. H_3PO_2, 60°C) and the crude extract containing diselenols was immediately reacted without further purification.

The reaction of **2a** and **2b** with n-butyllithium takes place very rapidly already at -78°C. The yields of **4a** resulting from the trapping of α-selenocarbanion **3a** are reasonably high (Scheme 1, entry 1 and 2). However under the same conditions the yields in **4b** were quite poor probably due to the unstability of the corresponding α-selenocarbanion **3b** (Scheme 1, compare entries 3 and 4 to 1).

Scheme 1



n	N°	N°	N°
2	**2a**	**3a**	**4a**
1	**2b**	**3b**	**4b**

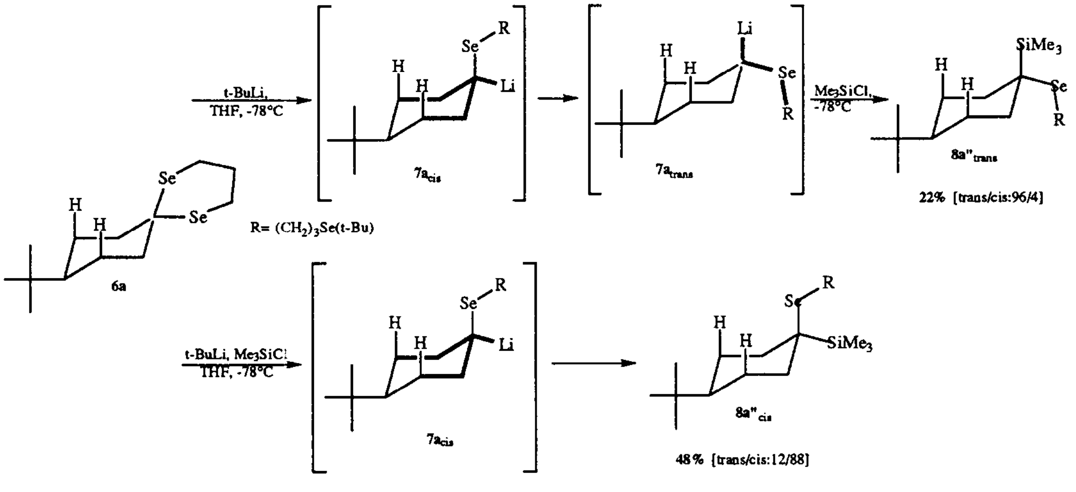
Entry	n	E'	t (h)	R	E	Yield in **4a** or **4b** %
1	2	MeOH	0.5	$(CH_2)_3SeBu$	H	77
2	2	PhCH=O	0.5	$(CH_2)_3SeBu$	PhCHOH	85
3	1	MeOH	0.5	$(CH_2)_2SeBu$	H	30
4	1	MeOH	0.1	$(CH_2)_2SeBu$	H	52
5	1	PhCH=O	0.1	$(CH_2)_2SeBu$	PhCHOH	41

The reaction is even more difficult with selenoacetals **6** derived from 4-t-butyl cyclohexanone **5** since the starting material is almost completely recovered if n-BuLi is used (THF, -78°C, 0.5h, **6a**: 100%, **6b**: 85% SM recovery). If t-butyllithium is instead used we observed, in both cases, the disappearance of the starting material. Addition of an electrophile to the medium led to an intractable mixture of compounds from **6b** which we have been unable to isolate or characterise. Its higher homologue **6a** however produced, in modest yields, the expected adducts after protonation or silylation (1 eq. t-BuLi, THF, -78°C, 0.15h then MeOH, **8a'**, 40% yield, trans/cis 92/8 or Me_3SiCl, -78°C, **8a"**, 22% yield, trans/cis[3] 96/4). Trapping with benzaldehyde led to several products which have not been identified but in which the expected alcohol was missing.

The above reactions have been then performed in the presence of trimethylsilyl chloride. Trapping of the carbanion was successful from **6a** but not from its lower homologue **6b**. Interestingly, in the former case, the resulting α-silyl cyclohexylselenide bears the silyl moiety in equatorial position (3 equiv. t-BuLi on equimolecular amount of **6a** and Me_3SiCl, THF, -78°C, 1h, 48% yield in **8a"**, trans/cis[3] 12/88).

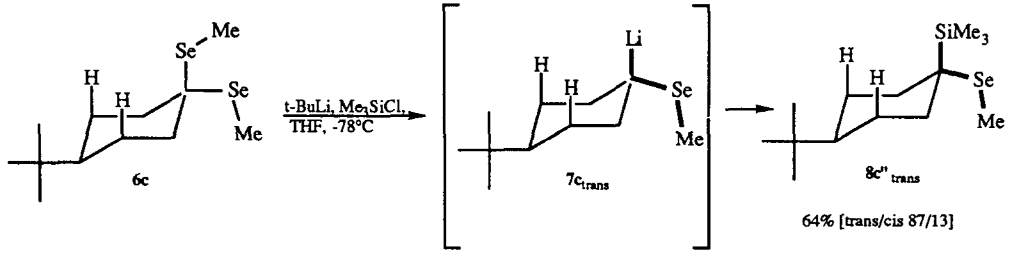
These results indicate that in the cyclic selenoacetal **6a**, the equatorial C-Se bond is preferentially cleaved. They also show that the resulting carbanion $\mathbf{7a}_{cis}$ readily epimerises, if not quenched immediately, to its diastereoisomer $\mathbf{7a}_{trans}$ bearing the lithium in axial position (Scheme 2).

Scheme 2



Such preferential cleavage of equatorial C-Se bond was not observed [1,4a] for related 1,1-bis(methylseleno) and 1,1-bis(phenylseleno)-4-t-butylcyclohexanes[1] and we have been unable in this work to observe the preponderant formation of compounds possessing the axial C-Se bond even if the reaction is carried out on **6c** in the presence of pre-added Me_3SiCl (Scheme 3). These results contrast with those we previously disclosed on 1-(methylseleno)-1-(phenylseleno)-4-t-butylcyclohexane in which the cleavage of the equatorial C-SeMe bond occurs predominantly. In this case, we assumed that the production of the more stabilised carbanion is responsible for such reversed selectivity. We however found that a very fast epimerisation occurs leading finally to the organometallic bearing the phenylseleno group in the equatorial position.

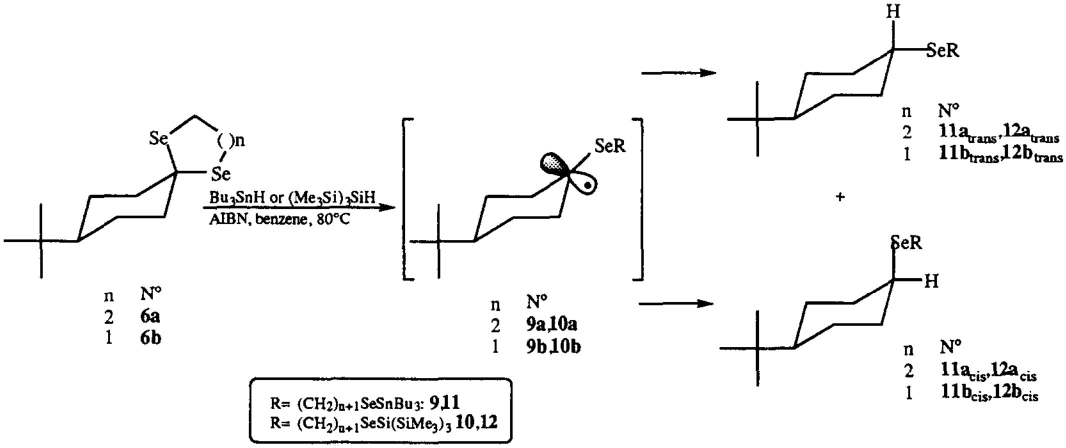
Scheme 3



A tentative explanation may be proposed by assuming that the conformation of the first incipient carbanion and even more of the presumed ate-complex intermediate is similar to that of the starting material. According to that proposal, the axial carbanion 7c$_{\text{trans}}$, from the acyclic compound, is better stabilised than its equatorial epimer, due to more favourable dispersion of the negative charge of the carbanion lone pair in the sigma Se-CH$_3$ bond. The presence of the polarisable selenium atom and of an antiperiplanar arrangement, which we already observed [1] in the X-ray analysis of a related selenoacetal, are without doubt crucial in that respect. Such stabilisation cannot be achieved on the carbanion 7a$_{\text{trans}}$ derived from the cyclic selenoacetal **6a**.[4]

Both cyclic selenoacetals **6a** and **6b** have been also reacted with tributyltin hydride or tris (trimethylsilyl)silyl hydride in the presence of AIBN producing a stereoisomeric mixture of selenides [1 equiv. hydride, AIBN, benzene, 80°C, 3h; Scheme 4]. Apparently, the ring size does not affect the stereochemical outcome of the reaction which is related to the nature of the reagent (Scheme 4, compare entries 1 and 3 to 2 and 4). We have not yet determined whose of the seleno substituents is attacked by the reagent but we found that tris(trimethylsilyl)silyl hydride possesses the higher propensity to deliver an hydride via an equatorial attack. Although the reasons of such selectivity have not been clearly established, we might assume that this is related to the steric bulk of this reagent.

Scheme 4



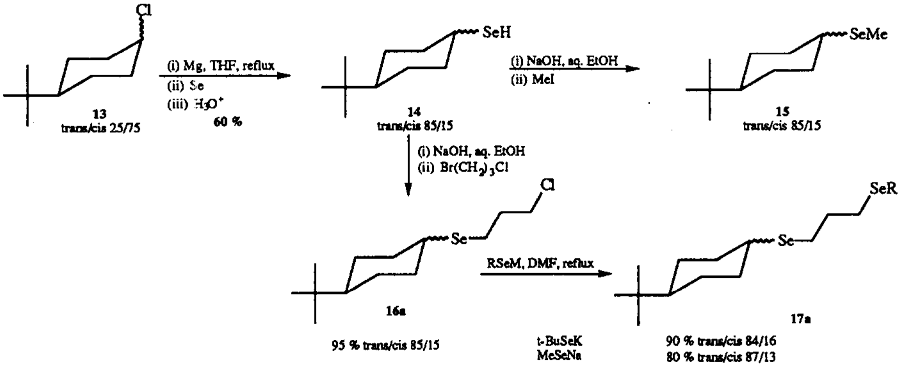
Entry	n	Reagent	R	N°	[trans/cis]
1	1	Bu$_3$SnH	(CH$_2$)$_2$SeSnBu$_3$	**11b**	61/39
2	1	(Me$_3$Si)$_3$SiH	(CH$_2$)$_2$SeSi(SiMe$_3$)$_3$	**12b**	30/70
3	2	Bu$_3$SnH	(CH$_2$)$_3$SeSnBu$_3$	**11a**	68/32
4	2	(Me$_3$Si)$_3$SiH	(CH$_2$)$_3$SeSi(SiMe$_3$)$_3$	**12a**	25/75

Stannyl **11a** and silyl **12a** selenides have been transformed to the corresponding methylselenide **17a** whose stereochemistry has been assigned by comparison with authentic samples prepared from 4-t-butylcyclohexylselenol **14** . Similar correlation have been carried out on the related t-butylselenide **8'a**.

4-t-Butylcyclohexylselenol **14** [trans/cis 25/75] has been in turn prepared from 1-chloro-4-t-butylcyclohexane (cis/trans 75/25) on sequential treatment with magnesium, selenium and an acid [(i) Mg, THF, reflux (ii) Se, 20°C (iii) H_3O^+, 60%, trans/cis 85/15]. Its stereochemistry has been assigned by derivatisation to 1-methylseleno-4-t-butylcyclohexane **15** whose stereochemistry has been previously firmly established [(i) aq. NaOH, EtOH (ii) 1eq. , MeI, 20°C, 2h, 20°C, 95%, trans/cis 85/15, ^{77}Se NMR ($CDCl_3$, Me_2Se as external standard in these and following data): 182/127 ppm respectively, Scheme 5].[1a]

Otherwise, this stereoisomeric mixture of 4-t-butylcyclohexylselenol **14** has been then transformed to a mixture of the selenides **8a'** [R= $(CH_2)_3Se(t\text{-}Bu)$] and **17a** [R= $(CH_2)_3SeMe$] on sequantial treatment with 1-bromo-3-chloropropane [(i) aq. NaOH, EtOH (ii) $Br(CH_2)_3Cl$, 20°C, 1h, 95% yield in **16a**, trans/cis 87/13, ^{77}Se NMR: 262 /199ppm] then with potassium t-butylselenolate [2 eq., DMF, 80°C, 2h, 90%, trans/cis 84/16, ^{77}Se NMR: 266/203ppm respectively] or sodium methylselenolate [2 eq. MeSeNa, DMF, reflux, 80°C, 2h, 80%, trans/cis 87/15, ^{77}Se NMR: 276/212 ppm] respectively. **8a'** and **17a** have been compared to the sample obtained by cleavage of the cyclic acetal **6a** with tBuLi (see above) and to the compound derived from silyl and stannyl selenides respectively.[5] Finally the stereochemistry of **11b** and **12b** has been assigned by comparison of their ^{77}Se NMR to those of **11a** and **12a**.

Scheme 5



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1. (a) Krief, A.; Evrard, G; Badaoui, E; De Beys, V.; Dieden, R. *Tetrahedron Lett.* **1989**, *30*, 5635 (b) Krief, A.; Badaoui, E; Dumont, W.; Hevesi L.; Herman, B.; Dieden, R. *Tetrahedron Lett.* **1991**, *32*, 3234.
2. Clarembeau, M.; Cravador, A.; Dumont, W.; Hevesi L.; Krief, A.; Lucchetti, J.; Van Ende, D. *Tetrahedron* 1985, 41, 4793.
3. Refers to the relative stereochemistry between the t-butyl group and the side chain containing the Se atom.
4. (a) Reich, H.J.; Bowe, M.D. J. Amer. Chem. Soc. **1990**, *112*, 8994 (b) Closely related results have been disclosed by Reich [4a] on selenoacetals derived from 3,5-diphenyl cyclohexanone (c) Products resulting from protonation of the carbanion have been also observed [trans/cis 80/20, ^{77}Se NMR ($CDCl_3$, Me_2Se as internal standard) 266/203 ppm respectively. This ratio proved to be independent from the time ellapsed before trapping of the carbanion. These results contradict those described by Reich on a related derivative.[4a]
5. See accompanying paper.

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