

The stereochemistry of a retro-carbolithiation reaction

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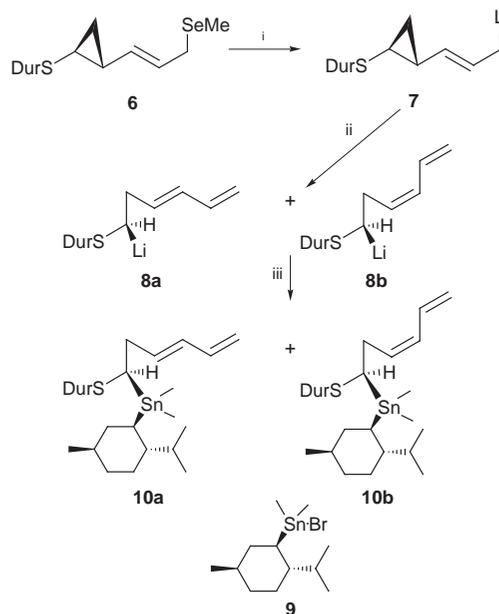
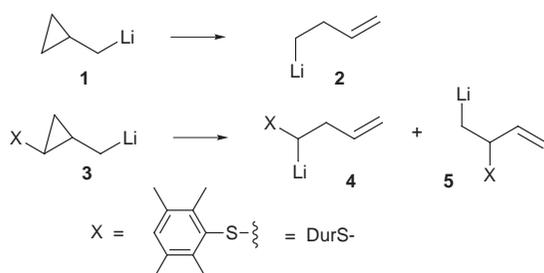
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Ring-opening of the cyclopropylmethyl lithium compound **7 to give the α -duryl thio-substituted alkyllithium compound **8** proceeds in a stereochemically defined manner at the lithium-bearing stereocentre.**

The stereochemical course of reactions in which organolithium compounds are generated may reveal fundamental details of organolithium chemistry. For instance, tin–lithium exchange to generate alkyllithium compounds has been found to proceed with retention of configuration.^{1–3} The carbolithiation of vinyl sulfides has been shown to proceed in a non-stereospecific manner.⁴ Here we would like to address the stereochemistry of a retro-carbolithiation reaction, the ring-opening of cyclopropylmethyl lithium compounds. The prototype of this rearrangement (**1**→**2**) was shown by Lansbury⁵ to proceed at -70°C with a half life of 53 min in Et_2O (Scheme 1).

The related ring-opening of **3** should create a chiral organolithium compound **4**. This would allow the determination of the stereochemistry in the generation of the new carbon–lithium bond, provided that the resulting organolithium compound **4** is configurationally stable and the regioselectivity of the ring opening is such as to generate compound **4** and not the isomer **5**. We surmised that both conditions would be met when X is a durylthio group. α -Durylthio alkyllithium compounds are configurationally stable at -110°C ⁴ and stabilization of the negative charge by a sulfur substituent should direct the ring opening of **3** to give **4**. There remains, however, the necessity to effect the ring opening at -110°C . We surmised that breaking of the carbon–lithium bond in **3** would be rate determining. Therefore, a delocalized allylic system at the migration origin should facilitate this process. This led us to investigate the ring-opening of the lithium compound **7**, generated by a low temperature selenium–lithium exchange reaction.⁶

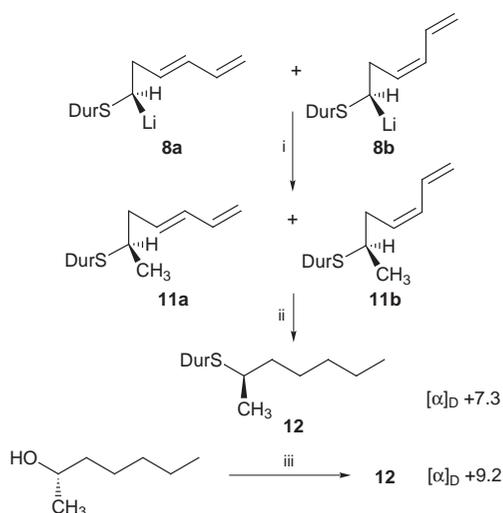
The seleno ether **6** of 90% ee (determined by Mosher ester analysis of the precursor **14**) was treated with $\text{Bu}^\text{t}\text{Li}$ at -107°C in THF in a two-compartment low temperature reaction vessel (Scheme 2).⁷ The organolithium compound **7** formed in this manner immediately underwent ring opening, since quenching with (–)-menthyl(dimethyl)tin bromide **9**^{2,8} after 30 min led to the tin compounds **10a** and **10b** in a 9:1 *E/Z* ratio (67% yield). ¹¹⁹Sn NMR analysis revealed that the major *E*-isomer was formed with 76% diastereomeric excess. Quenching after 10 or 60 min, or quenching with the enantiomeric reagent *ent*-**9**, generated the tin compounds with a constant de in the range of 76–82%. This shows that the organolithium compound **8** is configurationally stable under the conditions applied, and that



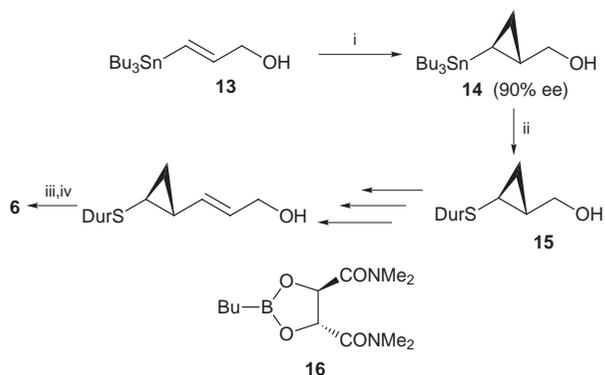
Scheme 2 Reagents and conditions: i, $\text{Bu}^\text{t}\text{Li}$, THF, -107°C ; ii, -107°C , 30 min; iii, **9**.

quenching of **8** with **9** is not complicated by kinetic resolution.

In order to determine the stereochemistry of the ring opening process, pre-cooled MeI was added to the organolithium compound **8** after 30 min at -107°C (Scheme 3). This resulted in 88% of a 88:12 *E/Z* mixture of the hexadienyl thioether **11**. Hydrogenation of the mixture provided uniform dextrorotatory 2-durylthiopentane **12**. The optical purity and the absolute configuration of **12** was determined with the aid of a sample prepared from (*S*)-heptan-2-ol.



Scheme 3 Reagents and conditions: i, MeI ; ii, H_2 , $(\text{Ph}_3\text{P})_3\text{RhCl}$; iii, MsCl , pyridine; iv, DurSLi .



Scheme 4 Reagents and conditions: i, **16**, $\text{Zn}(\text{CH}_2\text{I})_2 \cdot \text{DME}$; ii, Bu^nLi , $(\text{DurS})_2$; iii, Bu^nLi , TsCl ; iv, MeSeLi .

The optical purity of **12** (ca. 80% o.p.) corresponds to the values of the tin compounds **10** and shows that the ring opening of **7** to give **8** proceeds with at most 10% loss of enantiomeric composition. The minor loss in enantiomeric purity of **8** during its generation at -107°C from **7** should be associated with the ring opening process of **7**.⁹

Knowledge of the absolute configuration of the starting material **6** and that of the product **11** shows that the overall transformation proceeds with retention of configuration at the sulfur-bearing carbon atom. There is, however, some element of uncertainty regarding the stereochemistry of the individual steps. It is generally accepted¹⁰ that the methylation of 'low reactive' sp^3 -hybridized organolithium compounds by MeI proceeds with retention of configuration. If this applies also to the transformation of **8** into **11** it follows that the ring opening of **7** to give **8** proceeds with predominant retention of configuration at the lithium-bearing carbon atom.

The synthesis of the starting material **6** relied on the asymmetric cyclopropanation developed by Charette.¹¹ Cyclopropanation of **13** should furnish the cyclopropane **14** of the absolute configuration shown (Scheme 4). The latter was then

converted to **15** and on to the selenoether **6** in a series of standard transformations (Swern oxidation, Horner olefination, DIBAL-H reduction).

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