Unprecedented Radical Cyclizations Cascade Leading to Bicyclo[3.1.1]Heptanes. Toward a New Generation of Radical Cascades

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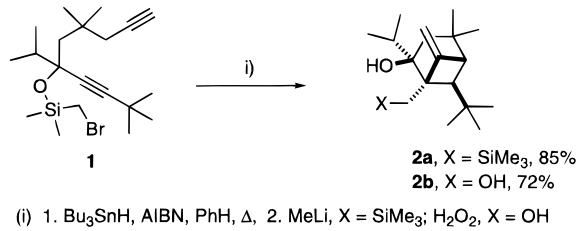
One-pot reactions leading to complex molecular frameworks with high stereocontrol and using readily available precursors have become a very fruitful area of research in organic synthesis.[1] On the basis of cascades of radical cyclizations or transition metal multicomponent cycloadditions, some recent one-pot sequences have confirmed this interest and have efficiently served in the synthesis of natural products[2] and the elaboration of novel polycyclic ring systems.[3] We have illustrated, over the last decade, how this quest for molecular complexity from structurally simple precursors also allows the discovery of uncommon molecular processes in radical organic chemistry, such as 1,4-H transfers,[4] cyclopropanations,[5,6] 5-*endo-trig* cyclizations,[7] and herein a mixed hydrogen transfer−radical cyclization cascade leading to the bicyclo[3.1.1]heptane framework.

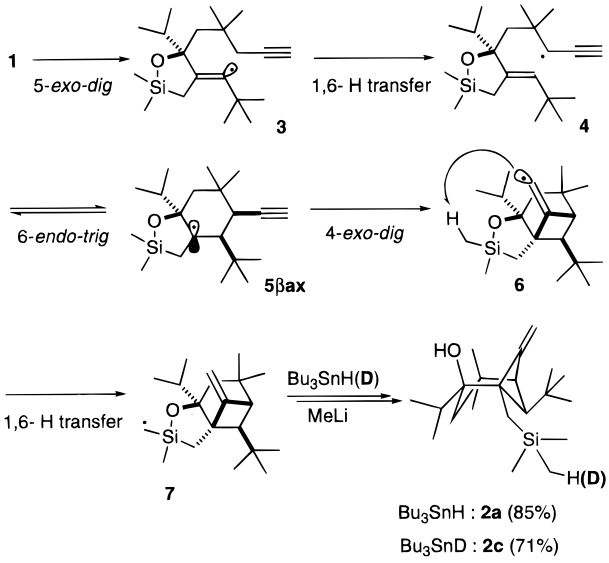
While exploring the potentialities of the recently reported radical 5-*endo-trig* cyclization of (bromomethyl)dimethylsilyl ethers[7] in the construction of polycyclic frameworks, we observed that when silyl ether **1** was submitted to radical cyclization conditions, bicyclo[3.1.1]heptane **2a** was obtained after treatment with methyllithium in 85% yield as a single diastereomer (Scheme 1). The structure and stereochemistry of the bicyclo[3.1.1]heptane derivative were fully established by an X-ray analysis of **2b**,[8] obtained after Tamao oxidation.

Clearly, this reaction that consumes the two acetylenic moieties to create three carbon−carbon bonds and three new stereogenic centers in a bridged bicyclic structure involves a novel type of cascade. After an initial 5-*exo-dig* cyclization, the resulting vinyl radical **3** undergoes a 1,6-H transfer at the expense of an entropically[9] and statistically more favorable 1,5-H transfer[7] on the *iso*-propyl group (Scheme 2). Stabilized[10] propargyl radical[11] **4** then follows a completely diastereoselective 6-*endo-trig* cyclization[12] from the β-face, minimizing the 1,3 interactions between the *gem*-dimethyl and *iso*-propyl groups in a pseudoboat transition state (intermediate **4**α *vs* **4**β, R = *i*-Pr, Scheme 3). This leads presumably to cyclohexyl radical **5**βeq (R = *i*-Pr) bearing the acetylenic chain in a pseudoequatorial position on the less-occupied α-face. However, no stannane reduction (*syn* to a *tert*-butyl or an *iso*-propyl group) or a 4-*exo-dig* cyclization orienting the *tert*-butyl group in an axial position seems possible. Rather, equilibration to **5**βax (R = *i*-Pr) *via* **4**βax now places the acetylenic partner in a particularly favorable pseudoaxial position for a further 4-*exo-dig* cyclization[13] that achieves the construction of the bridged bicyclic framework. The reversibility of the formation of α-cyclobutyl radicals is well established[14] and has been usually overcome using electronic effects,[15] often mixed with Thorpe−Ingold effects,[16] or by introducing a fast irreversible step such as a fragmentation or an intermolecular trapping.[17] In our case, no such effect is present. Deuterium labeling, however, shows that an additional 1,6-H transfer from the vinyl radical **6** occurs

Scheme 1



Scheme 2



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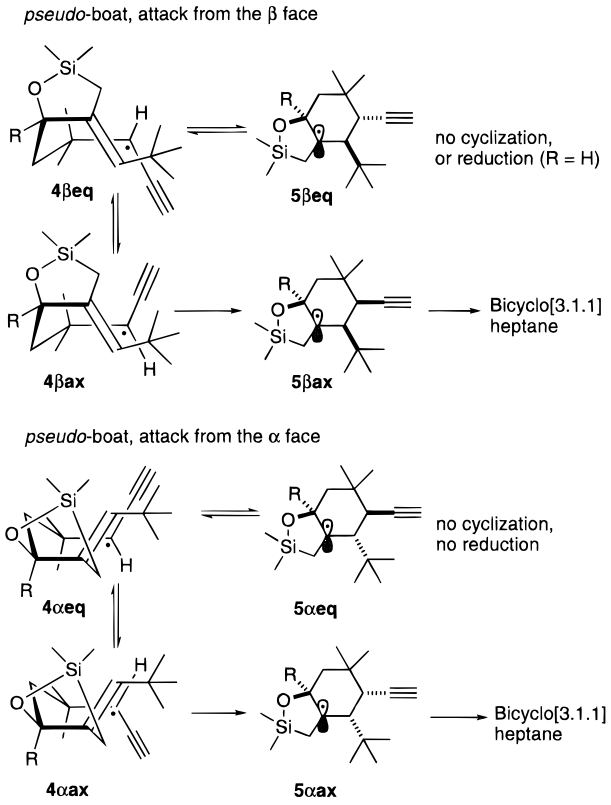
Scheme 3

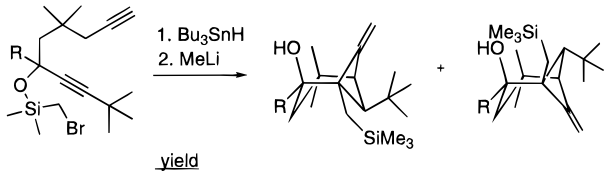


to give stabilized[18] α-silyl radical **7**, as proven by the exclusive formation of **2c** when using tributyltindeuteride. No deuterium is observed on the *exo*-methylene moiety. This would constitute to our knowledge *the first example of an unfavorable cyclization process, a 4-exo-dig ring closure, driven by a hydrogen transfer*.

Determining factors of this sequence have been investigated, notably focusing on the diastereoselectivity of the 6-*endo* cyclization, and precursors **8**, **11**, and **14** possessing less sterically demanding groups than an *iso*-propyl group were examined (Scheme 4). As expected, replacing the *iso*-propyl group by an ethyl group reduced the diastereoselectivity of the 6-*endo*-cyclization, as two diastereomers **9** and **10** were obtained in a 63:37 ratio from **8**. Major diastereomer **9** presumably results from the identical pathway that leads to **1a**, and a minor diastereomer would originate from the 6-*endo-trig* cyclization on the α-face. Examination of molecular models indeed reveals that a weaker interaction between the ethyl group and the *gem*-dimethyl group on intermediates **4**α now renders this ring closure possible. Consistent results were obtained with the even less-demanding methyl-substituted derivative **11**, for which the 6-*endo* cyclization is now nonstereoselective, and the two bicyclic products **12** and **13** are obtained in an equimolar ratio.

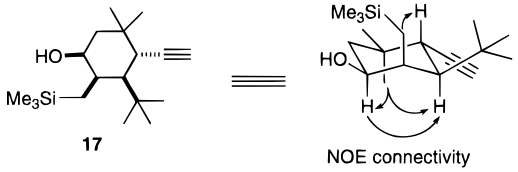
It also appears that the substitution at the propargylic position prevents any intermolecular reduction of the *β*-silyl radical, resulting from the 6-*endo-trig* cyclization. Thus, for the monosubstituted silyl ether **14**, the 4-*exo-dig* cyclization is much

Scheme 4



	yield			
8, R = Et	67%, X = $SiMe_3$	**9**	63 : 37	**10**
11, R = Me	75%, X = OH	**12**	50 : 50	**13**
14, R = H	46%[a], X = $SiMe_3$	**15**	50 : 50	**16**

[a] In addition, cyclohexane **17** (42%) was isolated.



less efficient (**15** + **16** 46%), and cyclohexane **17** is obtained in 42% yield as a single diastereomer, whose stereochemistry was unambiguously determined by NOE analysis. Formation of **17** is ascribed to the stannane reduction of intermediate **5***β*eq, *anti* to the *tert*-butyl group. This also confirms, our initial assumption that the 6-*endo-trig* pathway proceeds more easily from **4***β*eq to **5***β*eq, placing the acetylenic moiety in the pseudoequatorial position on the less-occupied α-face. The large amount of **17** should not be included in a measurement of the diastereoselectivity of the 6-*endo-trig* cyclization. Rather, it originates from a reversible 6-*endo-trig* cyclization, for which an intermolecular stannane reduction is possible.

In summary, an unprecedented radical cascade mixing hydrogen transfers and cyclizations in the order 5-*exo-dig*, 1,6-H transfer, 6-*endo-trig*, 4-*exo-dig*, and a final 1,6-H transfer allows the efficient and diastereoselective assembly of strained bicyclo-[3.1.1]heptanes. The driving force for the previously unknown 4-*exo-dig* cyclization is a hydrogen transfer. Clearly, this initiates a new generation of radical cascades in which designed translocations of radicals through hydrogen transfers[19] could ensure particularly unfavorable cyclization processes. Further studies will focus on the use of other unsaturated partners in order to prepare bicyclo[3.1.1]heptanes of biological and theoretical relevance.

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Supporting Information Available: Typical experimental procedures, summary of characterization data for **1**, **2a**−**c**, **8**−**17**, X-ray structure of **2b**, and NOE spectra of **17** (18 pages). See any current masthead page for ordering and Internet access instructions.

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