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Radical Cyclization of Bromomethyldimethylsilyl Propargyl Ethers; Synthesis of a Carbocyclic Core of Steroid Skeleton by a Tandem Radical Cyclization.

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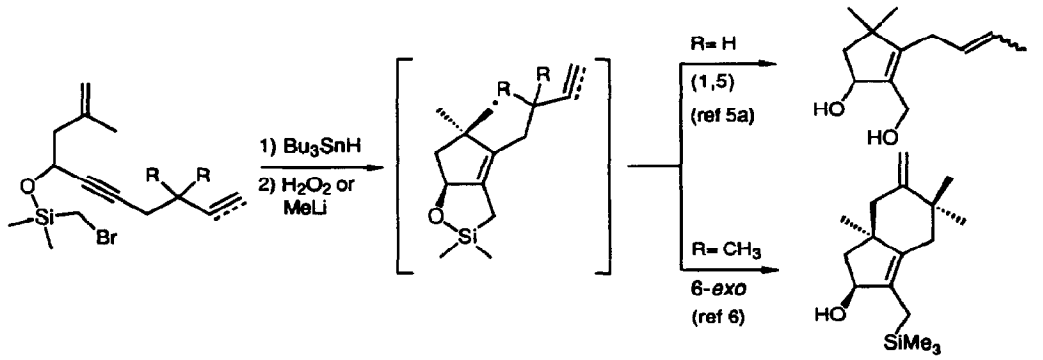
Abstract : *Homoallyl radical intermediates, generated from the cyclization of bromomethyl-dimethylsilyl propargyl ethers, have been trapped intramolecularly by a double bond in a 6-exo-trig radical process. In that instance, a carbocyclic core of steroid skeleton has been synthesized (58%) in a one-pot operation via a cascade of cylizations. Beside the 6-exo-trig radical process, an interesting 7-endo-trig one has been observed.*

Radical cyclizations have rapidly become an important method in the field of organic synthesis.[1] Although the radical reaction forms generally only one bond, it could indeed be multiplied in complex molecular frameworks to give several bonds *via* tandem processes.[2]

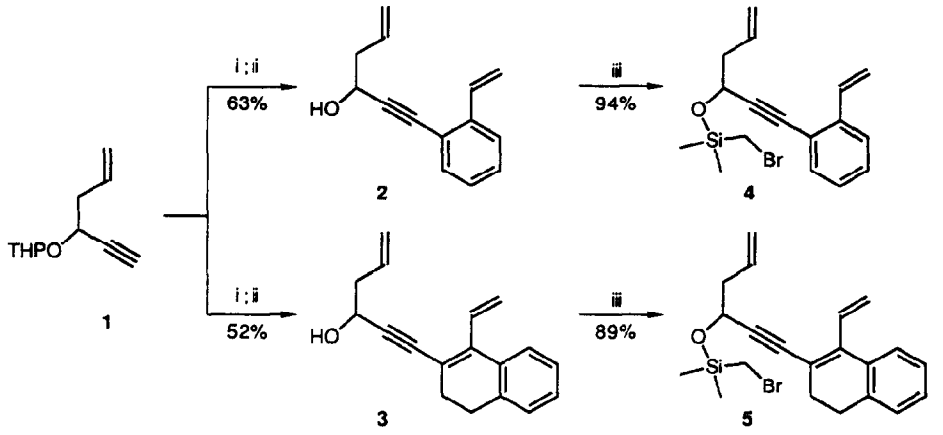
With the radical cyclization of bromomethyldimethylsilyl propargyl ethers, the construction of functionalized unsaturated five-membered carbocycles is well established in our laboratory.[3] In this case, two consecutive intramolecular cyclizations provide a homoallyl radical intermediate which can react in an intermolecular process leading to the stereocontrolled synthesis of a diquinane framework.[4] In the course of this work, we became interested in the 6-*exo-trig* mode cyclization but our previous studies shown that the allylic hydrogen was subject to undergo a kinetically rapid and thermodynamically favorable (1,5) hydrogen atom transfer (Scheme 1).[5] We surmounted this problem by the introduction of a quaternary center in the allyl



Scheme 1

position[6] and it has been reported that another solution consisted of using an alkene acceptor bearing an activating group.[7]

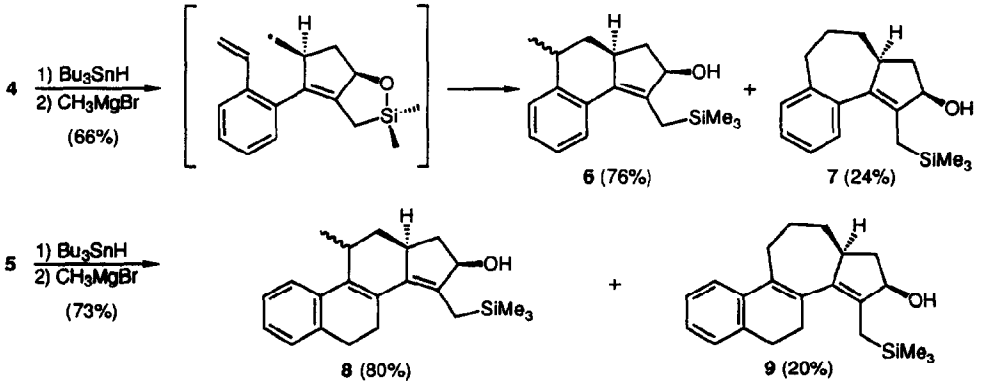
We report herein another way to solve this problem: replacing the allylic hydrogen by a group not reactive throughout the cyclization. The preparation of the needed precursors was achieved straighforward using the palladium-catalyzed coupling reaction[8] between an alkyne and an aryl or vinyl bromide[9] as the key step and is outlined in the Scheme 2.



i) $Pd(PPh_3)_2Cl_2$,Et_3N, RBr; ii) pTsOH cat., MeOH; iii) $(CH_3)_2CH_2BrSiCl$, Et_3N, DMAP.

Scheme 2

The cyclization[10] of **4** gave, *via* a cascade of radical cyclizations, the tricyclic compound **6** as an unseparable 10/3 mixture of stereomers in 50% isolated yield as the major product of the reaction. The byproduct **7** (16%) resulted from a final 7-*endo-trig* mode cyclization, rarely observed, but easily explained by the generated stabilized benzylic radical (Scheme 3). The total diastereoselective formation of **7** was the result of a chairlike

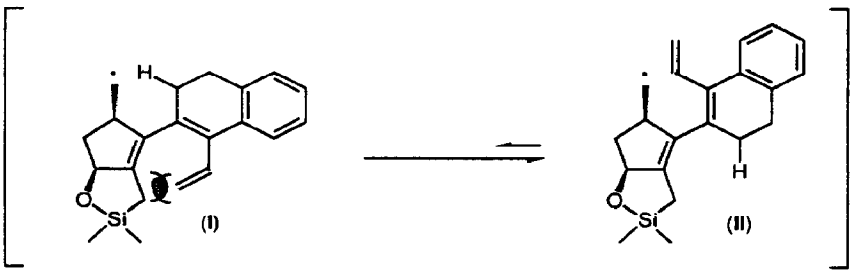


Scheme 3

transition state during the cyclization of the vinyl radical and indicated that the mixture of stereomers **6** was due to a lack of stereoselectivity during the 6-*exo-trig* radical process.[5a,6]

Ether **5** provided an even more impressive example of this sequence which was successfully accomplished to afford, in a one-pot operation, a steroid skeleton **8** which was isolated in 58% yield with the same level of stereoselectivity as **6**. Once again, the generated stabilized allylic radical in the 7-*endo* process may account for the fact that compound **9** was formed in 15% yield.

Finally, an interesting feature of the homoallyl radical intermediate, involved in the cyclization of **5**, was the total chemoselectivity in favor of the 6-*exo-trig* radical process. Indeed, the reaction proceeded through the most stable rotamer (II) *versus* (I) in which a repulsion between the vinyl moiety and the silane heterocycle was present. Consequently, it is not surprising that the (1,5) hydrogen atom transfer did not compete with the cyclization (Scheme 4).



Scheme 4

In summary, we have developed a new route for enhancing the performance of the 6-*exo-trig* radical cyclization processes. A very useful carbocyclic core of steroid skeleton **8** can be thus synthesized showing the potentiality of this tandem radical cyclization. Further investigations planned to test its generality is in course in our laboratory.

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(10) **Typical procedure for the cyclization of 4** and **5**: A benzene solution (10 mL) of Bu_3SnH (1.65 mmol) containing AIBN (0.15 mmol) was added by a syringe pump over a period of 8 h to a solution of **4** or **5** (1.5 mmol) in refluxing benzene (60 mL) under argon. After completion of the addition, the mixture was allowed to reflux for 5 additional hours and cooled at 0°C. CH_3MgBr (4.5 mmol) was then added and the mixture was stirred for 30 min under argon. The organic phase was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography (silica). All the products were fully characterized; as an example, a description of **6** and **7** is given. **6** (major + minor): ^{1}H-NMR (400 MHz, $CDCl_3$) d 7.52-7.58 (m, 1H), 7.12-7.21 (m, 3H), 4.72 (t, *J*= 7.7 Hz, 1H), 2.90-2.98 (m, 1H), 2.82-2.88 (m, 1H), 2.63 (dt, *J*= 12.4 and 6.7 Hz, 1H), 2.15 (AB, *J*= 55.0 Hz, 2H), 1.85 (ddd, *J*= 14.3, 6.6 and 2.9 Hz, 1H), 1.68 (td, *J*= 12.4 and 5.6 Hz, 1H), 1.36 and 1.29 (d, *J*= 7.1 Hz, 3H), 1.21-1.27 (m, 1H), 0.18 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) d 143.3 (s), 142.6, 138.0 (s), 137.0, 133.5, 133.1 (s), 133.0, 132.3 (s), 130.1, 129.1 (d), 128.5, 126.6 (d), 126.5, 126.3 (d), 126.2, 125.5 (d), 80.5, 79.8 (d), 42.2, 42.0, 41.2 (t), 38.5 (t), 36.7 (d), 34.1, 33.7 (d), 29.9, 24.0 (q), 21.9, 17.3 (t), 15.8, 0.04, 0.00 (q); IR (neat) 3420, 3060, 2940, 1600, 1550, 1500, 1440, 1240, 1030,740, 840 cm^{-1}; Anal. calcd. for $C_{18}H_{26}OSi$: C, 75.02; H, 9.09. Found: C, 75.13; H, 9.05. **7**: ^{1}H-NMR (400 MHz, $CDCl_3$) d 7.08-7.20 (m, 4H), 4.85 (t, *J*= 7.5 Hz, 1H), 2.43-2.73 (m, 3H), 2.03-2.15 (m, 1H), 1.83-1.93 (m, 1H), 1.77 (AB, *J*= 65.0 Hz, 2H), 1.18-1.45 (m, 4H), -0.11 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) d 143.0 (s), 142.2 (s), 139.9 (s), 138.8 (s), 130.2 (d), 129.9 (d), 127.4 (d), 126.6 (d), 80.1 (d), 46.9 (d), 43.7 (t), 41.3 (t), 38.2 (t), 28.7 (t), 16.5 (t), 0.0 (q); IR (neat) 3420, 3060, 2940, 1600, 1550, 1500, 1440, 1240, 1030, 740, 840 cm^{-1}; Anal. calcd. for $C_{18}H_{26}OSi$: C, 75.02; H, 9.09. Found: C, 74.95; H, 9.02.

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