5-*endo-trig* Radical Cyclizations: A New Means to the Stereoselective Synthesis of Cyclopentanes and Diquinanes

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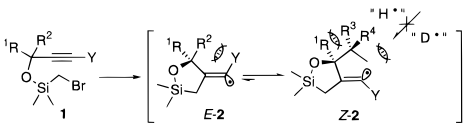
Received November 13, 1995

The disfavored nature of the 5-*endo-trig* ring closure in radical cyclizations is a matter of general agreement,[1,2] and pent-4-enyl radicals are well-known not to undergo such a process.[3] More recently, few heteroatomic exceptions to these guidelines have been reported,[4a−g] and to the best of our knowledge only one example is known for the construction of carbocycles derivatives which involves an acyl radical in the ring enlargement of cyclobutenones.[4h] Here, we describe a useful synthetic cascade involving a 5-*exo-dig* cyclization, a 1,5-(*π-endo*)-hydrogen transfer,[5] and finally an unusual 5-*endo-trig* ring closure which represents a new valuable stereoselective synthesis of highly functionalized cyclopentanes and diquinanes.

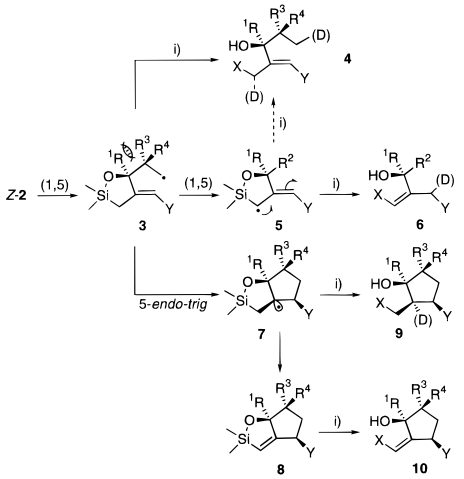
Radical-induced intramolecular 1,5-hydrogen transfers are known to be dependent upon the C−H bond dissociation energy[6] and are generally observed in cases where adjacent stabilizing groups are present.[7] Besides considering these thermodynamic factors, the proximity of the reacting centers and the transition state geometry may also be taken into account for these processes, as demonstrated by the *ab initio* studies of Houk[8] of the reaction of Barton and Heusler.[9] While developing new synthetic applications of the (bromomethyl)dimethylsilyl propargyl ethers in radical cyclizations, we discovered a remarkable chemoselective 1,5-hydrogen transfer between the initially generated vinyl radical and a nonactivated C−H bond. This was contrary to the expected hydrogen transfer with the acetal C−H activated bond.[10] Interestingly, the vinyl radical intermediate *E*-**2a** is stable enough to equilibrate to the less sterically hindered *Z*-**2a** conformation[11] (Scheme 1) without undergoing any intermolecular hydrogen abstraction.[12] The bulky allylic quaternary center hinders the incoming hydrogen donor and the acetal function. Experiments with Bu_3SnD[13] showed no deuterium incorporation, confirming that the reduction of the vinyl radical *Z*-**2a** was the result of a total 1,5-(*π-endo*)-hydrogen transfer taking place on the proximal isopropyl group. The resulting pent-4-enyl radical **3a** cyclized by a disfavored 5-*endo-trig* process to afford a cyclopentane derivative **9a** in 74% yield. A minor competing pathway was the reduction of **3a** to yield 15% of the olefinic compound **4a** (Scheme 2, Table 1). However, the diastereoselectivity of this sequence allowed *the formation of four contiguous stereogenic centers*. The product was obtained as a single diastereomer within the limits of ^1H and ^{13}C NMR analyses. The remarkable stereoselectivity observed is consistent with a totally diastereoselective 1,5-hydrogen shift between the vinyl radical *Z*-**2a** and the isopropyl group *via* the more reactive and less sterically hindered conformer. The structure and stereochemistry of **9b** were fully established by an X-ray analysis.[14]

In order to determine whether the chemoselective 1,5-hydrogen transfer was the result of steric hindrance between the hydrogen donor (Bu_3SnH/TMS_3SiH) and the diisopropyl group, the cyclization of **1c** bearing a *tert*-butyl group was studied next.[15] In this case, no vinyl product **4c** was detected. The expected compound **9c** was isolated, but the formation of

Scheme 1



Scheme 2[a]



[a] (i) (1) $Bu_3SnH(D)/TMS_3SiH$, (2) MeLi, X = $SiMe_3$; H_2O_2, X = OH.

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(5) 1,5-(*π-endo*) refers to internal position of olefin during 1,5-H transfer, in contrast to the generally observed 1,5-(*π-exo*)-H transfer.

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(13) The ratio of **9a**(D)/**4a**(D) (74%/8%) increases because deuteride is transfered less easily than hydride, and thus, the intramolecular process is favored over the intermolecular one.

(14) Atomic coordinates for **9b** can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 IEZ, UK.

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Table 1.

	R^1	R^2 (R^3, R^4)	Y	X	olefins **4**:**6**[a]	5-*endo-trig* **9**[a]
a	*i*-Pr	*i*-Pr (H, CH_3)	$(CH_2)_3CH(OCH_2)_2$	Me_3Si	15	74
b	*i*-Pr	*i*-Pr (H, CH_3)	CH_2OCPh_3	OH	13: −	63
c	*i*-Pr	*i*-Pr (H, CH_3)	*t*-Bu	Me_3Si		88[b]
d	*i*-Pr	*i*-Pr (H, CH_3)	Me_3Si	Me_3Si	17: -	69
e	*i*-Pr	*i*-Pr (H, CH_3)	H	Me_3Si	20[c]	55
f	Et	Et (H, H)	*t*-Bu	Me_3Si	19:39	21
g	H	*t*-Bu (CH_3, CH_3)	*t*-Bu	Me_3Si	22:51	14
h	H	*t*-Bu (CH_3, CH_3)	*t*-Bu	OH	23: −[d]	15
i	$PhCH_2$	*i*-Pr (H, CH_3)	*t*-Bu	Me_3Si	7: −	72[e]
j		$CH_2(CH_2)_2C(CH_3)_2$	CH_2OCPh_3	Me_3Si		45

[a] Percent isolated yield. [b] See Table 2. [c] The olefinic compound resulted from an initial 6-*endo-dig* cyclization. [d] No aldehyde was isolated. [e] Two diastereomers were isolated in a 95/5 ratio.

Table 2.

	H-donor (1.3 equiv)	AIBN (equiv)	**9c**:**10c**	yield (%)[a]
1	Bu_3SnH	0.3	81:19	88
2	TMS_3SiH	0.3	13:87	29
3	TMS_3SiH	0.5	12:88	44
4	TMS_3SiH	0.7	10:90	55
5	TMS_3SiH	0.9	10:90	65
6	TMS_3SiH	1.6	10:90	95

[a] Isolated yield.

the (silylmethylidene)cyclopentane **10c** was also observed. Alternatively, employing the bulky tris(trimethylsilyl)silane (TMS_3SiH) as the radical mediator *totally reversed* the **9c**/**10c** ratio and resulted in a breakdown in the chain transfer. The yields of **9c** and **10c** were found to be dependent on the quantity of AIBN used and could be increased by utilizing larger quantities of initiator (Table 2).[16] When the *tert*-butyl group was replaced by a TMS group, the above process was no longer observed. The longer C−Si bond allowed the reduction of the intermediate **7** to occur, hence allowing the cyclopentane **9d** to be isolated in 69% yield. In an effort to define the influence of the Y substituent, we studied the cyclization of the monosubstituted alkyne **1e**. Interestingly, the presence of the diisopropyl group was sufficient to prevent the reduction of the nonhindered vinyl radical, thereby promoting the 5-*endo-trig* radical cyclization to afford **9e** in 55% yield. This result appeared to be in good agreement with the important role of the transition state geometry.[8] In addition, the olefinic compound **11** was isolated in 20% yield presumably originating from an initial 6-*endo-dig* radical cyclization, an unprecedented process in all our previous studies.[17]

In order to precisely define the parameters favoring the 5-*endo-trig* radical sequence, the behavior of less sterically hindered precursors was next examined. The reaction of **1f** bearing a *gem*-diethyl group indicated this substitution was sufficient to allow the exclusive formation of intermediate **3f**; no reduction of the vinyl radical *Z*-**2f** was detected when the cyclization was performed with Bu_3SnD. However, in contrast to previous results, we observed a decrease of the 5-*endo-trig* radical process. After the 1,5-hydrogen shift, the resulting pent-4-enyl radical was able to undergo three competitive pathways: bimolecular reduction affording **4f** in 19% yield, 5-*endo-trig* cyclization leading to the cyclopentane derivative **9f** in 21% yield, and finally 1,5-hydrogen transfer yielding 39% of the vinyl silane **6f**. Experiments with Bu_3SnD confirmed that **6f** was the result of a 1,5-hydrogen transfer from the pent-4-enyl radical to the heterocycle moiety. The resulting β-silyl radical[18] could exist in two canonical forms, which upon rearrangement provided the more stable double bond. Compound **1g** (R^1 = H, R^2 = *tert*-butyl) displayed similar results, under identical conditions, olefinic compound **4g** being isolated in 22% yield. Furthermore, the rate of 5-*endo-trig* closure decreased in favor of the resulting in the double 1,5-hydrogen shift (**9g**/**6g**: 14%/51%). This double 1,5-hydrogen transfer represents a direct measure of the efficiency of the 5-*endo-trig* cyclization. The increasing steric bulk of the substituents enhances the ability of the pent-4-enyl radical to undergo 5-*endo-trig* cyclization, consistent with the Thorpe−Ingold effect.[19]

The 5-*endo-trig* pathway appears to be general since the unsymmetrical propargyl ether **1i** readily cyclizes to give the 5-*endo-trig* adduct **9i** with 90% diastereoselectivity (72% yield). The generality and observed stereoselectivity of the 5-*endo-trig* process should allow the synthesis of more elaborate carbocyclic systems, provided an appropriate radical terminator is located as the R^1 substituent to trap the β-silyl radical intermediate **7**. Finally, the goal of synthesizing polycyclic molecules has already been achieved by employing a cyclic precursor. Thus, the cyclization of ether **1j** formed the diquinane framework **9j** in 45% yield in a single step with the stereoselective formation of four stereogenic centers.

In conclusion, we have disclosed a new efficient one-pot cascade involving an unusual 5-*endo-trig* radical process. Our preliminary studies suggest that this sequence is a versatile synthetic tool enabling the efficient formation of functionalized carbocycles. Further investigations are under way in our laboratory using various pent-4-enyl radicals in order to define the scope of this sequence.

Acknowledgment. S. Bogen thanks Laboratoires Glaxo Wellcome for his financial support. The authors are greatly indebted to Dr. A. Bombrun, Laboratoires Glaxo Wellcome, for helpful discussions, to Dr. Jason P. Tierney from Imperial College, London, for improving our English manuscript, and to Dr J. Vaissermann, Université P. et M. Curie, for carrying out the X-ray structural determination of **9b.**

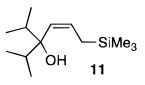
Supporting Information Available: Summary of characterization data for **9a, 9a(D), 4a(D), 9b, 8c, 9c, 10c, 9d, 9e, 11, 9f, 6f, 6f(D), 9h, 9i,** and **9j** (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA953806L

(15) Reduction of a vinyl radical bearing a *t*-Bu group has been observed: Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 1893−1896.

(16) Presumably, the steric effects developed by the bulky *tert*-butyl and isopropyl groups prevents the usual reduction from occurring. The formation of the heterodiquinene **8c** (which has been isolated and characterized) could be explained by an initial 5-*endo-trig* process followed by a rare β-hydrogen atom abstraction. One of the referees suggested an alternative explanation involving an oxidation of the radical **7** to the corresponding cation which then suffers proton loss.

(17) The 6-*endo-dig* cyclization is consistent with the Thorpe−Ingold effect of the bulky diisopropyl group. With a dimethyl group, this process is not observed. See: Magnol, E.; Malacria, M. *Tetrahedron Lett.* **1986**, *27*, 2255−2256.



11

(18) A minor quantity of the β-silyl radical incorporated deuterium proving that a 1,5-H transfer is effectively involved in the formation of **6d**.

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