5-*Endo-Trig* Radical Cyclizations of Bromomethyldimethylsilyl Diisopropylpropargylic Ethers. A Highly Diastereoselective Access to Functionalized Cyclopentanes

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An efficient radical sequence involving a 5-*exo-dig*, a diastereoselective 1,5-H transfer, and a rarely observed in an all-carbon system 5-*endo-trig* cyclization allows the construction of cyclopentyl derivatives **2** bearing four controlled stereogenic centers from diisopropyl precursors **1**. Olefins **3** were also isolated as minor side products. The effect of the acetylenic substituent Y has been investigated, and the scope and the limitations of the cascade have been delineated.

Because of its disfavored nature according to Baldwin's rules[1] and of several reported failures,[2] the 5-*endo-trig* radical cyclization has long been claimed to be a low-potential synthetic process. This too simplistic a view has been recently refuted by some very versatile 5-*endo-trig* radical processes involving heteroatomic reacting systems. The groups of Parsons[3] and of Ikeda and Ishibashi[4] have, for instance, devised an efficient 5-*endo-trig* radical cyclization of *N*-ethenyl-α-haloamides to form pyrrolidinones and substituted pyroglutamates. The 5-*endo* closure of the 2-formylbenzoyl radical has also been shown to be a particularly facile process.[5] Moreover, interesting examples have included the use of heteroatomic radicals such as silicon centered,[6] generated through a 1,5-H transfer,[7] or sulfur centered.[8]

In comparison, the all-carbon pentenyl system has not witnessed such a bloom: the 5-*endo-trig* radical cyclization has been rarely observed, and most often in low yield, as illustrated in Scheme 1.[9] Recently, we have evidenced a highly efficient 5-*endo-trig* cyclization,[10] based on a highly diastereoselective 1,5-H transfer from a vinyl radical.[11] Thus, when submitted to typical radical cyclizations,[12] bromomethyldimethylsilyl diisopropylpropargylic ether of type **1** gave cyclopentanol derivatives of type **2** in good yields and as single diastereomers, as well as olefins **3** (Scheme 2). Full mechanistic details, as well as the scope and limitations of this new process, have been determined by varying the acetylenic partner and are given in this paper.

Results and Discussion

1. Preparation of the Radical Cyclizations Precursors. The precursors **1** have been prepared from the corresponding alcohols **I** (Scheme 3) by silylation with bromomethyldimethylsilylchlorosilane using three different reaction conditions: triethylamine, DMAP in CH_2Cl_2 or imidazole in DMF, or BuLi in THF (see the Experimental Section). The alcohols **I** result from the addition of a lithium acetylide on diisopropyl ketone. Precursor **Ig** was obtained in 55% from the condensation of the magnesium dianion of the diisopropylpropargylic alcohol with (*S*)-menthylsulfinate (see the Supporting Information).

2. Mechanism of the 5-*Endo-Trig* Cyclization. This new reaction was initially discovered with precursor **1a** and gave a mixture of cyclopentane **2a** and olefin **3a** in 89% overall yield (Scheme 4). An initial 5-*exo-dig* cyclization of the α-silyl radical generates a vinyl radical that exists under two forms: (*E*)-**4** or (*Z*)-**4**. The (*E*)-vinyl radical intermediate displays a severe 1,3 allylic interaction. No intermolecular stannane reduction or a 1,5(π-*exo*)-H-transfer with the acetal C−H-activated bond[13] intervenes so that the equilibrium is shifted toward the (*Z*)-**4** vinyl radical. Only the staggered (*Z*)-**4st** vinyl radical undergoes a remarkably chemoselective 1,5-H transfer with a nonactivated C−H bond. Indeed, this diastereoselective 1,5(π-*endo*)-H takes place so that it minimizes the interaction between the methyl and the

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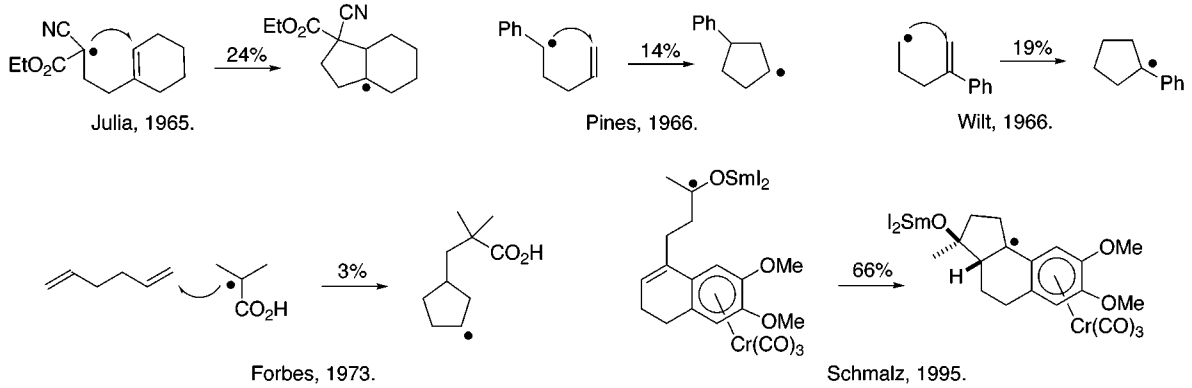
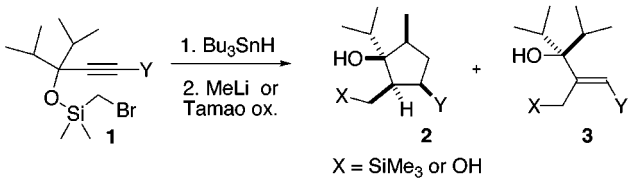
Scheme 1



Scheme 2



Scheme 3

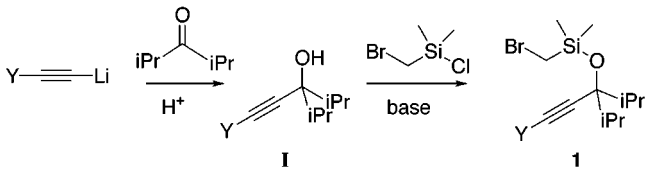


Table 1

entry	precursor **1**, Y	X	5-*endo-trig* **2**, %	olefin **3**, %
1	**1a**, $(CH_2)_3CH(OCH_2)_2$	$SiMe_3$	**2a**, 74	**3a**, 15
2	**1b**, CH_2OCPh_3	OH	**2bOH**, 63	**3bOH**, 13
3	**1b**, CH_2OCPh_3	$SiMe_3$	**2bSi**, 64	**3bSi**, 10
4	**1c**, $SiMe_3$	$SiMe_3$	**2c**, 69	**3c**, 17
5	**1d**, H	$SiMe_3$	**2d**, 55[a]	
6	**1e**, *t*-Bu	$SiMe_3$	**2e**, 71[b]	
7	**1f**, Ph		**2f**, 18[c]	

[a] 6-*Endo-dig* adduct **7** (20%) was also isolated (Scheme 5). [b] See Table 2. [c] Rearranged 4-*exo* products **12** were also isolated in 63% yield (Scheme 8).

isopropyl group: eclipsed (*Z*)-**4ec** versus staggered (*Z*)-**4st**. Moreover, no deuterium was incorporated on the vinyl moiety of (*Z*)-**3**, suggesting that the hydrogen transfer is complete. In this single step the stereochemistry of the double bond (*Z*) as well as two new stereogenic centers are set. The resulting methylene radical **5** can be reduced to furnish **3a** or then it cyclizes according to the disfavored 5-*endo-trig* mode of cyclization, placing the dioxolanyl chain syn to the methyl group and to the C−O bond. A diastereoselective stannane reduction of the β-silyl radical **6** installs a cis ring juncture and terminates the sequence. The proposed relative stereochemistry of the four new stereogenic centers was confirmed by an X-ray crystallography of diol **2bOH**, obtained from **1b** in 63% yield (Table 1, entry 2).

This intriguing 5-*endo* closure may be rationalized by a particularly congested transition state, in which the 5-*endo-trig* cyclization appears as the main way out for the methylene radical **5**. We also feel that a repulsion effect between the two isopropyl groups modifies the angle of attack of the 4-pentenyl radical and ensures the efficiency of the 5-*endo-trig* cyclization. This was proved with precursors bearing less sterically demanding propargylic substituents.[14]

3. Varying the Acetylenic Partner. The reaction was shown to be fairly general (Table 1, entries 1−6) since good yields of 5-*endo* products **2** were observed, generally accompanied by the minor vinylic compound **3**, resulting from the 1,5-H transfer followed by an intermolecular reduction of the methylene radical analogue to **5**. Interestingly, even in the case of the monosubstituted alkyne **1d**, the diisopropyl moiety was sufficient to prevent the reduction of the nonhindered vinyl radical, thereby promoting the 5-*endo-trig* on an unsubstituted position in 55% yield (**2d**). In addition, the olefinic compound **7** was isolated in 20% yield, presumably originating from an initial 6-*endo-dig* radical cyclization.[15] This is an unprecedented process in all our previous studies[16] but easily explained here by an unsubstituted pole for the 6-*endo* attack compared to a particularly sterically congested 5-*exo* position (Scheme 5).

The *tert*-Butyl Case. When a *tert*-butyl group was introduced on the acetylenic partner (precursor **1e**), no vinyl product **3** was detected, suggesting that, because of the steric bulk, no bimolecular reduction of the intermediate methylene radical is possible (Scheme 6). The expected compound **2e** was isolated, but the formation of the (silylmethylidene)cyclopentane **8** was also observed. Alternatively, employing the bulky tris(trimethylsilyl)silane (TTMS) as the radical mediator totally reversed the **2e**:**8** ratio and resulted in a breakdown in the chain transfer, yielding only 29% of cyclization products (Table 2, entry 2). The yields of **2e** and **8** were found to be dependent on the quantity of AIBN used and could be increased by utilizing larger quantities of initiator. Presumably, the steric effects developed by the *tert*-butyl and isopropyl groups also prevent the final reduction from occurring.[17] The formation of the heterodiquinene **11** (which has been isolated and character-

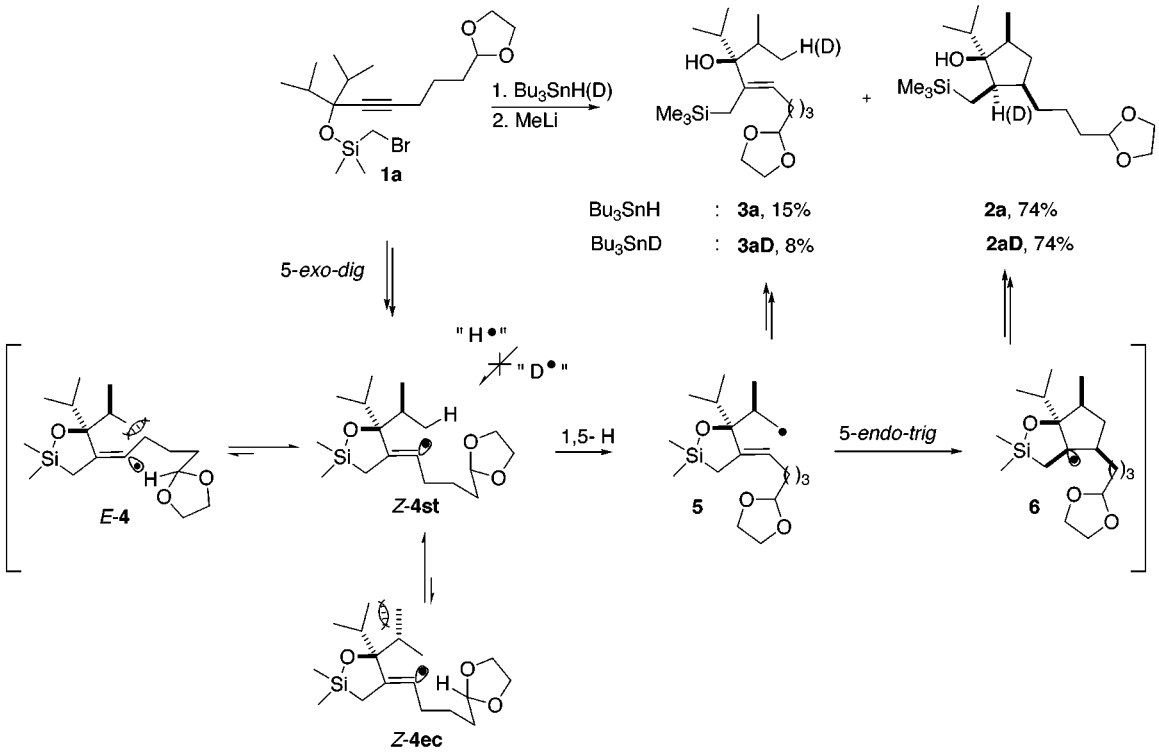
(14) For initial findings, see ref 10. For other confirming examples, see: Bogen, S.; Gulea, M.; Fensterbank, L.; Malacria, M. To be published.

(15) For other examples of 6-*endo-dig* cyclizations, see: (a) Snider, B. B.; Merritt, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* **1991**, *56*, 5544−5553. (b) Khim, S.-K.; Cederstrom, E.; Ferri, D. C.; Mariano, P. S. *Tetrahedron* **1996**, *52*, 3195−3222. (c) Marco-Contelles, J.; Bernabé, M.; Ayala, D.; Sanchez, B. *J. Org. Chem.* **1994**, *59*, 1234−1235. (d) Breithor, M.; Herden, U.; Hoffmann, H. M. R. *Tetrahedron* **1997**, *53*, 8401−8420.

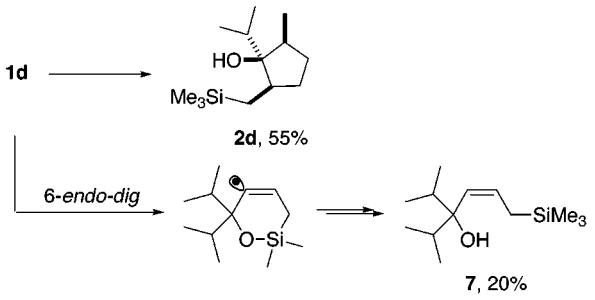
(16) With a dimethyl group, this process is not observed, see: Magnol, E.; Malacria, M. *Tetrahedron Lett.* **1986**, *27*, 2255−2256.

(17) Bogen, S.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 5037−5038.

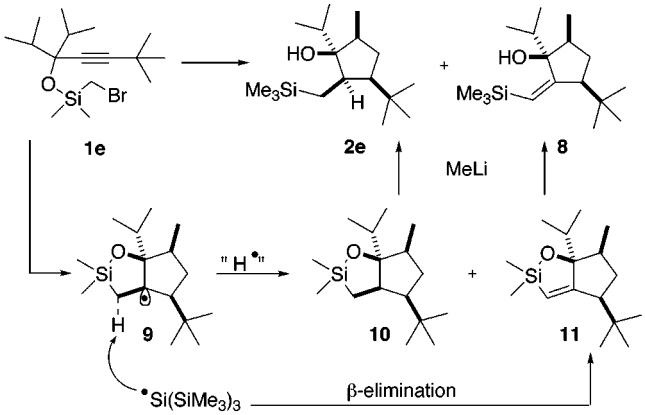
Scheme 4



Scheme 5



Scheme 6



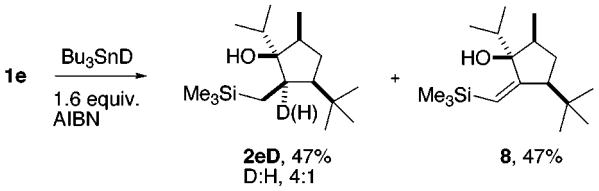
ized) could be explained by an initial 5-*endo-trig* process followed by a rare β-hydrogen atom abstraction.[18] It is worthy of note that this phenomenon is not observed when the *tert*-butyl group is replaced by a TMS group. The longer C−Si bond allows the complete reduction of the intermediate β-silyl radical to occur, providing cyclopentane **2c** in 69% yield.

Table 2

entry	H-donor (1.3 equiv)	AIBN (equiv)	**2e**:**8**	yield (%)
1	Bu_3SnH	0.3	81:19	88
2[a]	$(TMS)_3SiH$	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] With no methyllithium treatment, heterocycles **10** (3%) and **11** (27%) could also be directly isolated.

Scheme 7

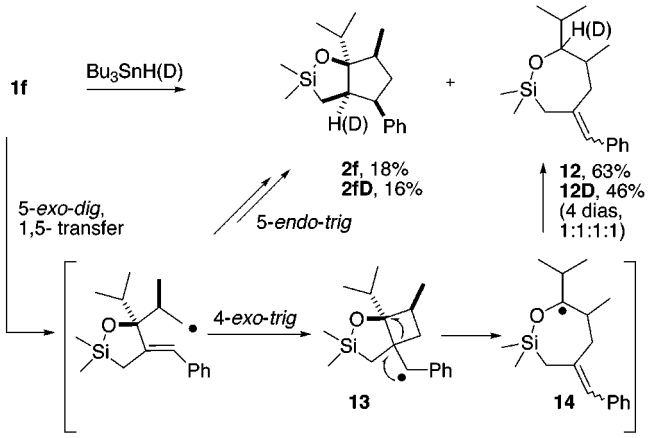


The β-hydrogen abstraction was further evidenced by running the reaction with Bu_3SnD and in the presence of 1.6 equiv of AIBN (Scheme 7). A mixture of reduced 5-*endo-trig* adduct **2eD** and vinylsilane **8D** was obtained in a 1:1 ratio, reflecting again that a slower reducing agent[19] favors the β-elimination process. More interestingly, the deuterium incorporation on **2eD** was only 82%, whereas the tin deuteride used was at least 97% enriched. Clearly, this suggests that a hydride source, most likely the tin hydride resulting from the β-elimination, has been produced in the reaction medium and has served to reduce **9** into **10**.

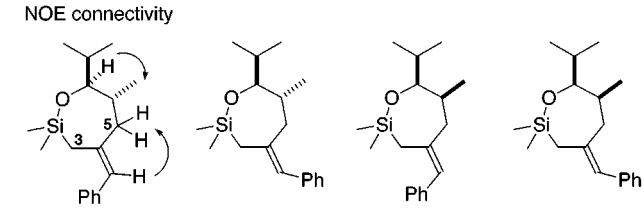
(18) (a) Chen, S. H.; Huang, S.; Gao, Q.; Golik, J.; Farina, V. *J. Org. Chem.* **1994**, *59*, 1475−1484. (b) Ripa, L.; Hallsberg, A. *J. Org. Chem.* **1998**, *63*, 84−91. (c) Gross, A.; Fensterbank, L.; Bogen, S.; Thouvenot, R.; Malacria, M. *Tetrahedron* **1997**, *53*, 13797−13810.

(19) The kinetic isotope (Bu_3SnH/Bu_3SnD) for the reduction of the *tert*-butyl radical is 2.74; see: Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1968**, *90*, 7047−7055.

Scheme 8



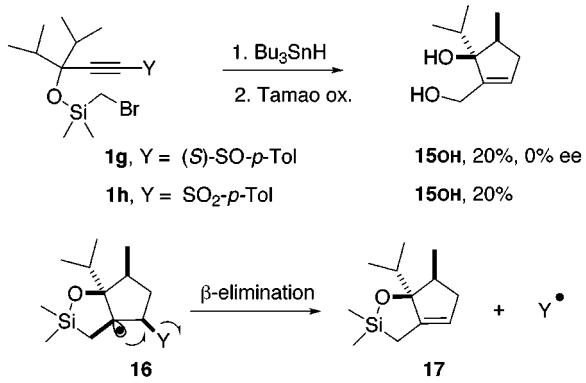
Scheme 9



The Phenyl Case. The reaction with the phenylacetylene precursor **1f** marked a sharp difference with previous results. Several products were formed, and we found it more convenient to directly isolate the heterocycles by adding just 1.5 equiv of methyllithium, which transforms the tin residues into purely apolar material (Scheme 8). The 5-*endo* adduct **2f** is now the minor product (18%). It is accompanied by a mixture of diastereomeric heterocycles **12** (63%). The formation of these seven-membered rings originates from the following cascade: 5-*exo-dig*, 1,5-H transfer, 4-*exo-trig*, fragmentation of **13,** and reduction of the secondary radical **14**. A deuterium labeling was consistent with this mechanism. No diastereoselectivity intervenes during the fragmentation and the final reduction so that the four diastereomers of **12** are produced in an equimolar ratio. The relative *Z*-anti stereochemistry was deduced for *anti*-(*Z*)-**12** from NOE measurements. This compound was eluted by flash chromatography in second position, following probably the *anti*-(*E*)-**12** isomer. This tentative assignment was based on ^{13}C NMR using γ-gauche effects[20] observed for carbons C3 and C5 (Scheme 9), the phenyl ring shielding alternatively the C3 and the C5 carbons. Similarly, the following fraction consisted in a mixture of *syn*-(*Z*)- and *syn*-(*E*)-**12**.

Examination of the Dreiding models reveals that the approach for the 4-*exo-trig* cyclization[21] is not really less favorable than the one for the 5-*endo-trig* cyclization. And only a cyclization under stereoelectronic control, involving a styryl moiety that activates the 4-*exo* attack, can explain this complete selectivity. This was the only case where a 4-*exo-trig*/5-*endo-trig* competition occurred.

Scheme 10



Toward an Asymmetric 5-*Endo-Trig* Process. We next focused on a potential asymmetric version of the 5-*endo-trig* cyclization. A sulfur-based chirality source like a homochiral sulfoxide was first chosen because it could be readily appended. Moreover, the attachment of this chiral auxiliary would be only temporary, since after the 5-*endo-trig* cyclization the resulting radical **16** should undergo a β-elimination of the sulfinyl radical (Scheme 10).[22]

The radical cyclization of the sulfoxide **1g** furnished a complex mixture of products, including the expected diol **15OH** bearing no sulfoxide moiety. This diol proved relatively unstable, and this could partly explain the low yield observed in this reaction. No ee was detected by chiral GC on the diol **15OH**, as a racemic sample could be obtained from the radical cyclization of sulfone **1h** (in this case, the presence of 2 equiv of Bu_3SnH is necessary).[23] This failure in inducing any facial selectivity in the 1,5-H transfer may be attributed to the distance of the chiral auxiliary from the isopropyl groups.

We next selected a phosphorus moiety (**1i**),[24] anticipating that the stereoselectivity, in that case a de, could be easily estimated by ^{31}P NMR. Three phosphorylated products were formed in this reaction: two diastereomeric 5-*endo-trig* adducts **2iM** (major) and **2im** (minor) in a 1.3:1 ratio, the second diastereomer **2im** being difficult to separate from the olefinic compound **18** (Scheme 11). The structure for **18** was proposed on the following grounds: two diastereotopic isopropyl protons, an allylic ABX system involving coupling with phosphorus: δ 2.95 (dd, $J_{H-H} = 13.7$, $J_{P-H} = 10.1$ Hz, 1H) and δ 3.23 (dd, $J_{H-H} = 13.7$, $J_{P-H} = 20.1$ Hz, 1H) and a vinylic proton coupled to the phosphorus nucleus ($^4J_{P-H} = 5.1$ Hz).[25] The ionic formation of the vinylsilane **18** from the heterocycle **19** was deduced from the following data. When the reaction mixture after treatment with MeLi was quenched with D_2O, the deuterium atom was incorporated at the

(20) Knorr, R.; Hintermeyer-Hilpert, M.; Böhrer, P. *Chem. Ber.* **1990**, *123*, 1137−1141.

(21) For studies concerning the competition between 4-*exo-trig* and 5-*endo-trig* cyclization on styryl systems, see: Ikeda, M.; Ohtani, S.; Yamamoto, T.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1763−1768. See also: D'Annibale, A.; Pesce, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.* **1997**, *38*, 1829−1832.

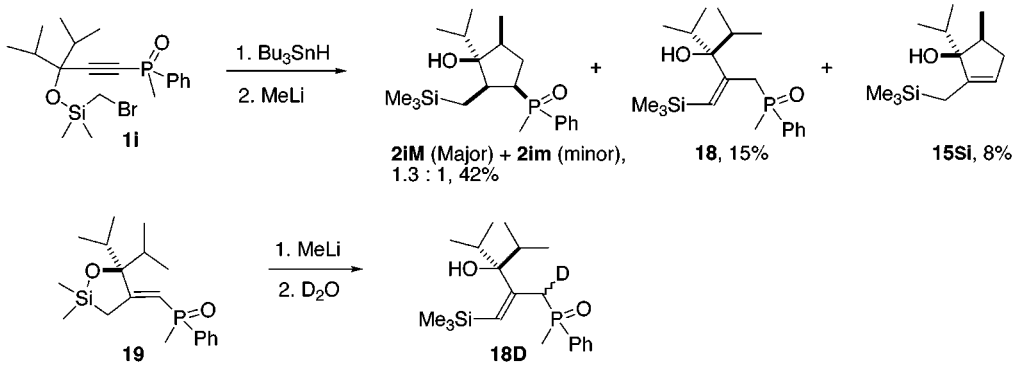
(22) Lacôte, E.; Delouvrié, B.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2116−2118 and references therein.

(23) Van Dort, P. C.; Fuchs, P. L. *J. Org. Chem.* **1997**, *62*, 7142−7147.

(24) For a previous study involving the use of this chiral phosphorus moiety in cobalt-mediated cycloadditions, see: Slowinski, F.; Aubert, C.; Malacria, M. *Tetrahedron Lett.*, submitted.

(25) For similar $^4J_{H-P}$ coupling constants on allylic phosphonates obtained via a base-catalyzed isomerization of the corresponding vinylphosphonates, see: (a) Kiddle, J. J.; Babler, J. H. *J. Org. Chem.* **1993**, *58*, 3572−3574. (b) Al Badri, H. Ph.D. Dissertation, Université de Rouen, 1996.

Scheme 11



allylic position of **18D**,[26] altering the previous ABX system to two doublets: δ 2.95 (d, $J_{P-H} = 10.1$ Hz, 0.4H) and δ 3.23 (d, $J_{P-H} = 20.1$, 0.6H). Consistent with literature reports, an anionic isomerization of the vinylphosphine oxide to an allylphosphine oxide takes place.

In addition, the β-elimination adduct **15Si** was also detected (8%). Phosphorus-centered radicals are known to be particularly stable.[27] As far as we are aware, however, the radical β-elimination of a phosphorus moiety is an unknown process. Interestingly, when this cyclization was run with TTMS, the TLC of the crude product after treatment with MeLi showed only the presence of **15Si**, clearly suggesting that a slower hydrogen donor favors this β-elimination process. After chromatography, an inseparable mixture of the alcohol **15Si** and residues from the silane were isolated. This compound also appears volatile and unstable, and the amount of β-elimination could not be really assessed.

The slight diastereomeric excess (12% de) observed on the 5-*endo-trig* products **2iM** and **2im** may suggest some facial diastereoselectivity in the 1,5-H transfer, but this should be handled with caution, since the β-elimination process probably modifies the initial ratio.

Facing these issues, a probably too remote chiral auxiliary and a competitive β-elimination process, we did not continue in this direction, and we are envisaging preparing new precursors bearing the chirality at the propargylic position. Nevertheless, this study showed that heteroatomic groups were compatible with these synthetic sequences and could provide intriguing phosphorylated cyclopentyl derivatives.

Conclusion

The 5-*endo-trig* cyclization of bromomethyldimethylsilyldiisopropyl propargylic ethers represents one of the most efficient radical 5-*endo-trig* involving an all-carbon 4-pentenyl system. This highly unusual process may be attributed here to a particularly congested transition state, in which the repulsion between the two isopropyl groups ensures a favorable angle of attack. It allows the completely diastereoselective construction of cyclopentanes, bearing four stereogenic centers. The second key step of the sequence is a diastereoselective 1,5-H transfer involving a nonactivated but well-disposed methyl on an isopropyl group. Attempts to control the face selectivity of this hydrogen transfer using heteroatomic chiral auxiliary have been plagued by a too remote position of the chirality source, lower yields, and a partial radical β-elimination of the phosphine oxide moiety but could evolve into valuable phosphorylated carbocycles. We are now focusing on an approach involving chirality at the propargylic position. Applications of the 5-*endo* process toward the synthesis of polyclic derivatives are also under investigation.

Experimental Section

Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F 254. Silica gel Merck Geduran SI (40−63 μm) was used for column chromatography using Still's method.[28]

Solvents. Ethyl ether and THF were distilled from sodium−benzophenone ketyl. Benzene, toluene, dichloromethane, and triethylamine were distilled from calcium hydride. Chromatography solvents: EE refers to ethyl ether, PE refers to petroleum ether.

Alcohol **Id** was purchased from Lancaster.

Typical Silylation Procedure. Procedure A. To a 0.5 M CH_2Cl_2 solution of the propargyl alcohol, in the presence of 0.1 equiv of DMAP and 1.1 equiv of triethylamine, was added dropwise at 0 °C bromomethyldimethylsilyl chloride (1 equiv). After completion of the silylation, the reaction mixture was diluted with CH_2Cl_2 and washed twice with a saturated NH_4Cl solution and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified through a rapid filtration over a short pad of silica gel.

Procedure B. To a 2 M DMF solution of the propargyl alcohol, in the presence of 2 equiv of imidazole, was added dropwise at room temperature bromomethyldimethylsilyl chloride (1.00 equiv). After completion of the silylation (around 1 h), the reaction mixture was diluted with ether and washed twice with a saturated NH_4Cl solution and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified through a rapid filtration over a short pad of silica gel.

Procedure C. To a 0.1 M THF solution of the propargyl alcohol was added dropwise at −78 °C a 2.3 M solution of *n*-BuLi in hexane (1 equiv). After 15 min, bromomethyldimethylsilyl chloride (1.00 equiv) was added at −78 °C. Then, the mixture was warmed to room temperature (around 30 min), diluted with ether, and washed with brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified through a rapid filtration over a short pad of silica gel.

Typical Procedure for the Radical Cyclization of Bromomethyldimethylsilyl Propargyl Ethers. A benzene solution (13.5 mL) of Bu_3SnH (360 μL, 1.34 mmol) containing

(26) Some deuterium was incorporated on the methyl of the phosphine oxide moiety of **2im**.

(27) For an illustration of this, see: Chatgilialoglu, C.; Timokhin, V. I.; Ballestri, M. *J. Org. Chem.* **1998**, *63*, 1327−1329.

(28) Still, W.; Kahn, M.; Mitra, A.*J. Org. Chem.* **1978**, *43*, 2923−2925.

AIBN (30 mg, 0.18 mmol) was added by a syringe pump over a period of 6.5 h (2×10^{-4} mol h^{-1}) to a solution of **1** (1.0 mmol) and AIBN (10 mg, 0.06 mmol) in refluxing benzene (40 mL) under argon. After completion of the addition, the mixture was allowed to reflux for an additional 2 h.

Treatment with Methyllithium. Low chloride methyllithium in ether (5.0 mmol) was added at 0 °C to the reaction mixture, and stirring was maintained 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 on silica gel.

Tamao Oxidation. The cyclization reaction mixture was evaporated and dissolved in 15 mL of a 1:1 mixture of MeOH/THF. To this solution were added $KHCO_3$ (2 mmol), KF (2 mmol), and 30% H_2O_2 (10−30 mmol). The reaction mixture was taken to reflux. After completion of the oxidation (monitored by TLC), the reaction mixture was dissolved in ether, filtered over Celite, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel.

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Supporting Information Available: The synthesis and the spectral data of alcohols (**Ia**−**c** and **Ie**−**i**) and the spectral data of the bromomethyldimethylsilyl ethers **1** and of the cyclization products are reported. ^{1}H NMR spectra for **1d**, **1h**, **1i**, **3a**, the **2bOH** and **3bOH** mixture, **3bSi**, **3c**, **10**, **11**, the isomers **12**, **15OH**, **2iM**, the **2im** and **18** mixture, **2im**, the **2imD** and **18D** mixture, and **15Si**, ^{13}C NMR spectra for **2aD**, **3aD**, **2fD**, and the isomers **12D,** and a chiral GC spectrum for **15OH** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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