Study of a Radical Cyclizations Cascade Leading to Bicyclo[3.1.1]heptanes

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An efficient radical cascade involving a 5-*exo-dig*, a 1,6-H transfer, a 6-*endo-trig*, a 4-*exo-dig*, and a final 1,6-H transfer allows the diastereoselective construction of bicyclo[3.1.1]heptanes. The size of the R substituent at the propargylic position governs the diastereoselectivity of the 6-*endo-trig* step. Other parameters (acetylenic substituents, unsaturated partners, ...) have been investigated, and the scope and the limitations of the cascade have been delineated.

Over the past decades, the radical chemistry has witnessed tremendous progress.[1] Initially, through simple 5-*exo-trig* cyclizations,[2] and more recently, on using cyclizations in tandem[3] and in cascades,[4] the synthetic chemists have been able to construct a very diverse palette of natural or unnatural molecular architectures. The accurate determination of the kinetics of the majority of radical reactions[5] has largely contributed to this successful evolution, notably for the development of radical reactions in cascades, i.e., how to successfully sequence radical cyclizations and intermolecular events. Moreover, the design of radical translocations on organic substrates mainly through hydrogen transfers has emerged as an important tool in radical chemistry. Extending the seminal works relying on very reactive heteroatomic radicals[6] to promote hydrogen transfers, Curran has focused on radical translocations between carbon centers and has set useful guidelines.[7] Recent studies[8] of reactivity and applications in synthesis have confirmed this interest and have allowed a better understanding of the hydrogen transfer reaction.

Some of our recent work has addressed the problem of mixing hydrogen transfers and radical cyclizations in cascade reactions,[4b,9] aiming at enlarging the repertoire of radical synthesis. Notably, we wanted to exploit the recently reported 5-*endo-trig* radical cyclization of bromomethyldimethylsilyl ethers[9b] in the construction of polycyclic frameworks. Precursor **1** was therefore prepared in order to check if intermediate radical **3**, originating from the 5-*endo-trig* ring closure, could be trapped in a 6-*exo-dig* manner. However, when submitted to radical cyclization conditions, precursor **1** followed a completely different pathway and bicyclo[3.1.1]heptane **5a** was obtained after treatment with methyllithium in 85% yield and as a single diastereomer (Scheme 1).[10] The structure and the stereochemistry of the bicyclo[3.1.1]-heptane derivative were fully established by an X-ray analysis of **5b**, obtained after Tamao oxidation. This reaction that consumes the two acetylenic partners and gives birth to a strained four-membered ring is intriguing and its mechanism has been determined on modifying the substituents at four locations: the acetylenic partner, the alkyl chain, the propargyl position, and the unsaturated partner (alkene or alkyne) (Figure 1).

Results and Discussion

Preparation of the Radical Cyclizations Precursors. This synthesis began with the efficient monosi-

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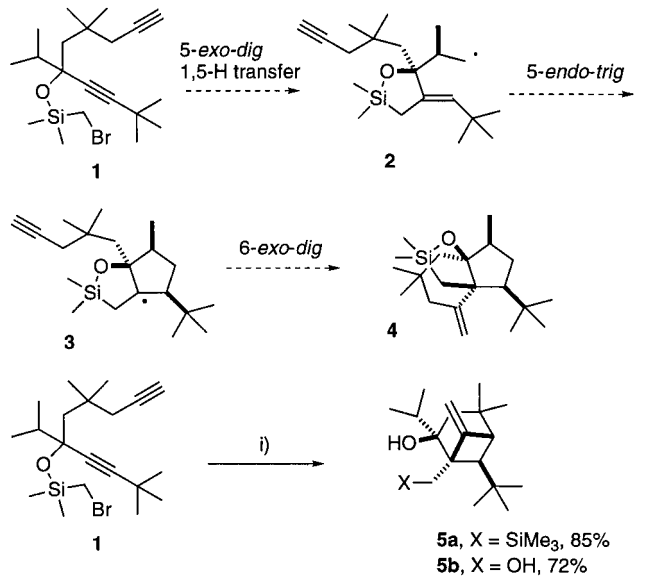
Scheme 1



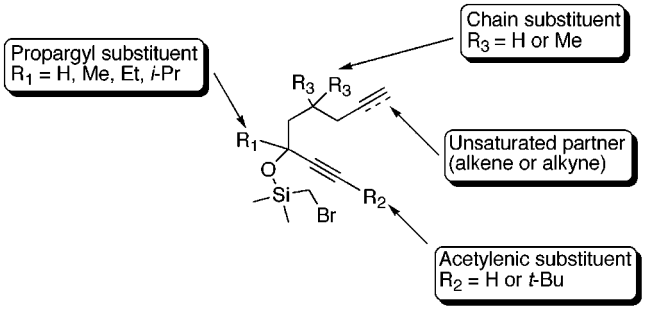


Figure 1.

lylation[11] of 3,3-dimethylpentane-1,5-diol (**6**) (Scheme 2). The resulting monoalcohol **7** was then oxidized to an aldehyde, which was directly engaged in a Corey−Fuchs[12] reaction to form dibromoolefin **8** in 87% overall yield. Subsequent treatment with butyllithium and a O-desilylation furnished alcohol **9**. Alternatively, the intermediate alkynyllithium could be trapped with trimethylsilyl chloride, and after a similar O-desilylation step, C-silylated alcohol **10** was obtained in satisfactory overall yield. Aldehyde **11** was obtained through a Swern oxidation of **9** and was condensed on isopropylmagnesium chloride, methylmagnesium bromide, lithium *tert*-butylacetylide, and lithium (trimethylsilyl)acetylide, to respectively provide alcohols **12**−**16** (after desilylation of **15**). Secondary alcohols **12** and **13** were further oxidized to ketones, which upon addition of lithium *tert*-butylacetylide, gave tertiary alcohols **17** and **18**. In the same fashion, alcohol **10** was oxidized to silylated aldehyde **19**. Treatment of **19** with ethylmagnesium bromide gave secondary alcohol **20**. Then, tertiary alcohol **21** was prepared in 70% overall yield through a three-step process involving a Swern oxidation, an addition of lithium *tert*-butyl acetylide and a C-desilylation. Finally, on using similar chemistry, alcohols **24** and **27** were obtained (Scheme 3), starting from readily available hexynal **22**[13] and aldehyde **25**.[14] Alcohols **14**, **16**, **17**, **18**, **21**, **24**, and **27** were silylated in yields higher than 90% with (bromomethyl)dimethylchlorosilane in DMF in the presence of imidazole (Scheme 4), which proved to be the method of choice for the silylation of these sterically encumbered tertiary alcohols.

A Proposed Mechanism for the Cascade. Following an expected 5-*exo*-*dig* cyclization,[15] vinyl radical **34** would translocate in a 1,6-H manner to generate radical **35** (Scheme 5). Although generally entropically[16] and here statistically more favorable,[9b] no 1,5-H transfer involving a methyl of the isopropyl group would take place. Rather, weaker bond dissociation energies to generate a highly stabilized propargyl radical[17] could be responsible for this exclusive 1,6-H transfer. Propargyl radical **35** then cyclizes in a 6-*endo*-*trig* manner to form cyclohexyl radical **36**β**ax**. At this stage, no intermolecular reduction (*syn* to a *tert*-butyl group or an isopropyl group) is possible so that radical **36**β**ax** follows an unprecedented 4-*exo*-*dig* cyclization,[18] which affords bicyclo[3.1.1] structure **5a** after treatment with methyllithium. The reversibility of the formation of α-cyclobutyl radicals is well established[19] and has been usually overcome using electronic effects,[20] often mixed with Thorpe−Ingold effects,[21] or by introducing a fast irreversible step such as fragmentation or intermolecular trapping.[22] We were therefore very puzzled by this finding until we realized, on using tributyltin deuteride, that no deuterium was incorporated on the *exo*-methylene moiety and that an additional 1,6-H transfer from the vinyl radical **37** occurred to give stabilized α-silyl radical **38**.[23] This final hydrogen transfer would therefore constitute a sufficient driving force to assemble the very strained four-membered ring. *The concept of translocating a radical to ensure an unfavorable cyclization process has to the best of our knowledge never been really reported and it may find here one of its first illustrations*. Moreover, it should be mentioned that the use of propargyl radical in organic synthesis is quite rare.[24] More recently, a variant involving cobalt-complexed propargyl radicals has been reported.[25]

One point remained to be elucidated: how does the

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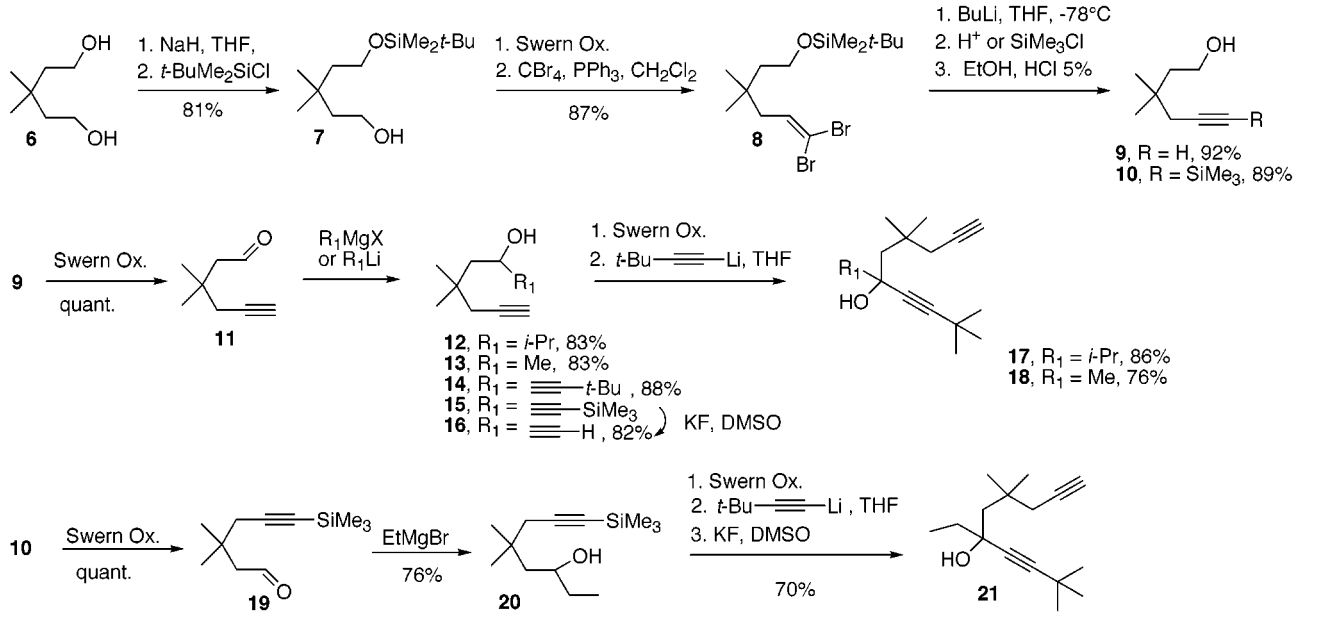
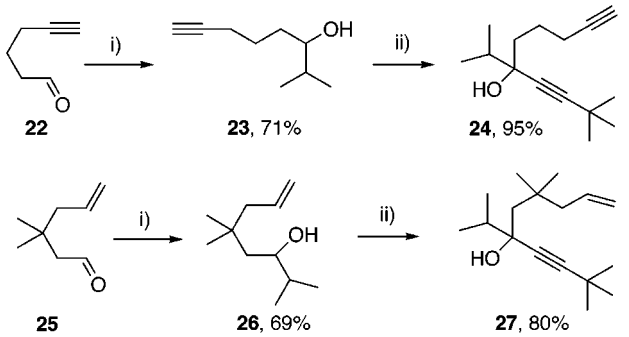
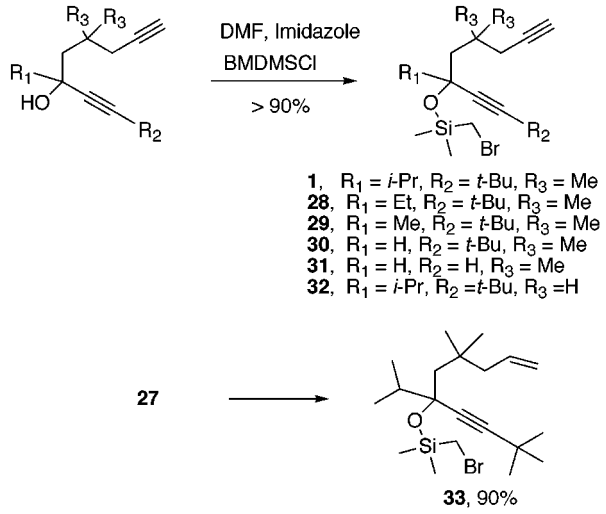
Scheme 2



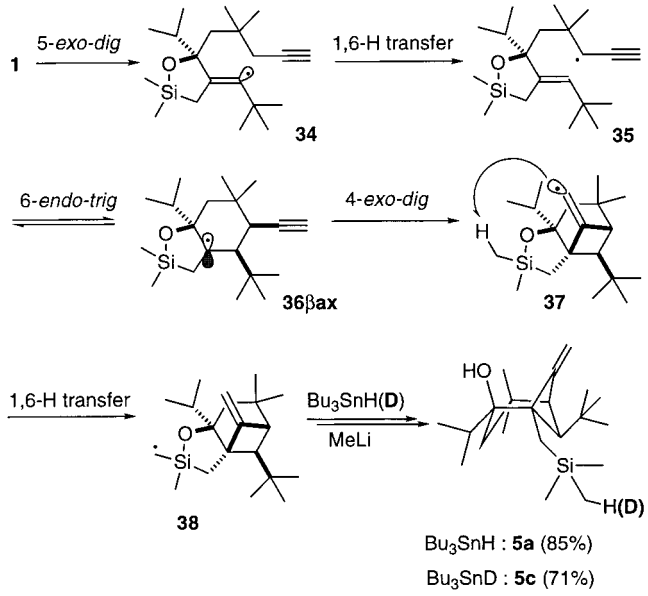
Scheme 3



Scheme 4



Scheme 5



6-*endo-trig* cyclization work, notably in terms of diastereoselectivity? An examination of Dreiding models showed that there was no satisfactory approach for a 5-*exo-trig* ring closure,[26] and the four transition states depicted in Scheme 6 must be considered for the 6-*endo-trig* cyclization. For R_1 = *i*-Pr, only an attack of the propargyl radical, from the β face, as in pseudoboats **35**β is possible because of large 1,3-interactions between the R_1 and the axial methyl groups on **35**α**ax** and **35**α**eq**. This attack presumably takes place with the acetylenic chain in a pseudoequatorial position on the less occupied convex face. However, as mentioned previously, no intermolecular reduction is possible on **36**β**eq**, and in this case no 4-*exo-dig* cyclization placing the *tert*-butyl group in an axial position seems possible. Rather, equilibration to **36**β**ax** via **35**β**eq** would place the acetylenic partner in a particularly favorable position for the 4-*exo-dig* cycliza-

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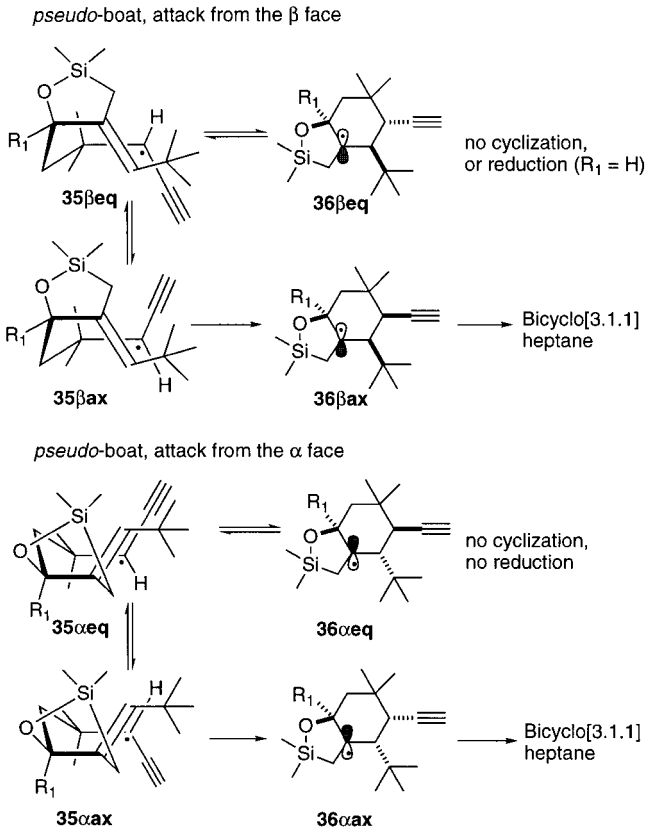
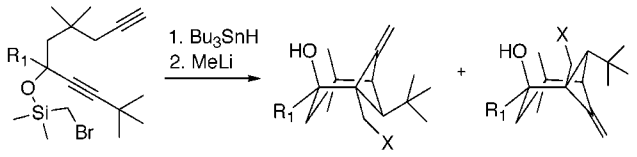
Scheme 6



tion. The reversibility of this 6-*endo*-*trig* cyclization may be ascribed to the stabilized nature of the propargyl radical and will be confirmed by further findings. From this, it also appears that the substitution at the propargyl position is a key factor for directing the 6-*endo*-*trig* cyclization from the α face or the *β* face.

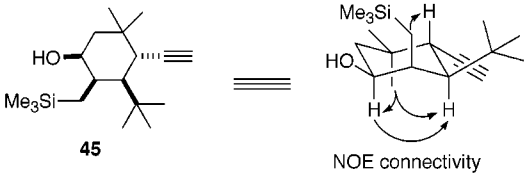
Role of the Propargyl Substituent. We next examined precursors **28**−**30**, which possess less sterically demanding groups than an isopropyl group. As expected, replacing the isopropyl group by an ethyl group reduced the diastereoselectivity of the cascade reaction (entry 1, Table 1). Major diastereomer **39** presumably results from the identical pathway that gives **5a**. Minor diastereomer **40** would originate from the 6-*endo*-*trig* cyclization from the α face. Examination of molecular models indeed reveals that a weaker interaction between the ethyl and the *gem*-dimethyl groups on intermediates **35**α**eq** and **35**α**ax** now authorizes this mode of cyclization. The cyclization from the α face must be reversible too. Intermediate **36**α**eq** is not productive. Cyclization placing the *tert*-butyl group in an axial position and reduction *syn* to the R_1 and the *tert*-butyl groups, or *syn* to the C−O bond, are not possible. So only **36**α**ax** bearing the acetylenic chain in a pseudoaxial position can evolve to the bicyclo[3.1.1] framework. No diastereoselectivity is observed in the cyclization of **29** (R_1 = Me). Both pathways from the α and the *β* faces are now identical and provide bicyclic products **37** and **38** in an equimolar ratio. The radical cyclization of **30** produced three compounds, the two diastereomers **43** and **44** in a 1:1 ratio, and a similar amount of cyclohexane **45**, whose relative stereochemistry has been determined by NOE analysis. Thus, the cascade is now less efficient. The formation of **45** may be rationalized by the stannane reduction of **36***β***eq** *anti* to the *tert*-butyl group. This,

Table 1.



entry	R_1	yield %, X	products	ratio
1	Et, **28**	67, $SiMe_3$	**39** : **40**	63 : 37
2	Me, **29**	75%, OH	**41** : **42**	50 : 50
3	H, **30**	46%[a], $SiMe_3$	**43** : **44**	50 : 50

[a] In addition, cyclohexane **45** (42%) was isolated.

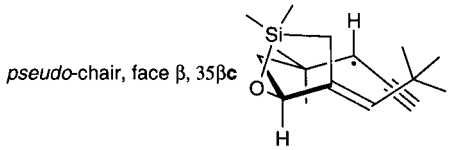


therefore, confirms our initial hypothesis that the 6-*endo*-*trig* cyclization probably proceeds more easily, when it places the acetylenic moiety in the pseudoequatorial position on the less occupied convex face (as in **35***β***eq** to **36***β***eq**).[27] The formation of cyclohexane **45** should not be included in a measurement of the diastereoselectivity of the 6-*endo*-*trig* cyclization. It simply reflects that an intermolecular way out via stannane reduction, which alters the equilibrium of the reversible 6-*endo*-*trig* cyclization, is available in this case. Thus, it appears that the substitution at the propargyl position is critical not only for the diastereoselectivity of the cascade but also for its efficiency by controlling the premature intervention of intermolecular reductions.

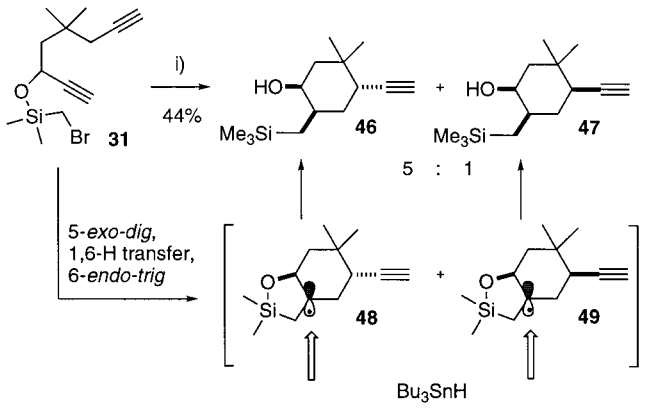
Role of the Acetylenic Substituent. We studied the behavior of precursor **31**, with no acetylenic substituent. The radical cyclization of **31** furnished a complex mixture, presenting no compound bearing an *exo*-methylene moiety and from which the inseparable mixture of cyclohexanes **46** and **47** could be isolated (Scheme 7). A 5-*exo*-*dig*−1,6-H transfer−6-*endo*-*trig* sequence gives birth to cyclohexyl intermediates **48** and **49**, which can be intermolecularly reduced *anti* to the C−O bond of the heterocycle. A NOE analysis performed on the mixture of **46** and **47** showed that the major diastereomer **46** originates from a 6-*endo*-*trig* cyclization with the acetylenic chain occupying the convex face of the incipient bicyclic compound, thus confirming our previous findings. Moreover, the steric bulk around radical **36** appears critical for the occurrence of the 4-*exo*-*dig* cyclization, probably through protecting the radical species from an intermolecular reduction.

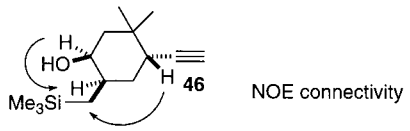
Role of the Chain Substituent. Aiming at testing the efficiency of this intriguing 1,6-H transfer, we inves-

(27) It should be also noted that when R_1 = H, the cyclization from the *β* face may also proceed via the pseudochair transition state **35***β***c**, which now displays no 1,3-diaxial interaction between the R_1 and the axial methyl groups.

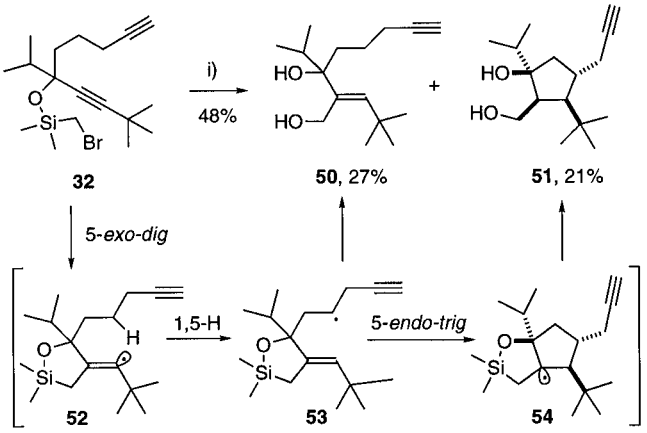


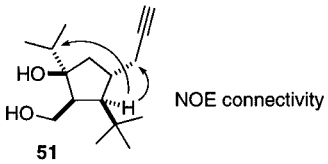
Scheme 7





Scheme 8





tigated the behavior of precursor **32** in radical cyclization conditions. After Tamao oxidation, olefin **50** and cyclopentanol **51** were isolated in modest yields (Scheme 8). The vinyl radical **52** now follows a completely chemoselective 1,5-H transfer, in favor of the most stable 4-pentenyl radical **53**.[28] This radical can be reduced by tin hydride to furnish olefin **50**. After a diastereoselective 5-*endo-trig* cyclization, heterodiquinane **54** is reduced *syn* to the isopropyl group and then oxidized to **51**. Interestingly, trapping of radical **54** in a 5-*exo-dig* manner is not observed. The relative stereochemistry of **51** has been determined through NOE analysis and shows that the cyclization proceeds, here also, with the acetylenic chain in the convex face. The isopropyl and the *tert*-butyl groups probably, to some extent, prevent the stannane intermolecular reduction from occurring. A β-hydrogen abstraction, as in previous studies,[9b] could give rise to a vinylsilane intermediate, which then would decompose in the Tamao oxidation and would explain the low yield of this cyclization.

Role of the Unsaturated Partner. Precursor **33** looks very much like silyl ether **1**. Only one unsaturated partner has been changed. However, the outcome from the radical cyclization of **33** was quite different from the one obtained with **1** (Scheme 9). No cyclic product was observed. All the products formed in this reaction originate from the allyl radical **59**,[29] produced through a 1,6-H transfer from the vinyl radical **58**. Direct reduction of **59** gives **55**. Alternatively, isomerization of **59** to **60** gives either reduction or dimerization to **56** or **57**, respectively. The product of a 6-*endo-trig*/4-*exo-trig* sequence from **59** was not observed. Even if allyl radicals are slightly more stabilized than propargyl radicals,[17] allyl radical **59** should undergo the 6-*endo-trig* cyclization. We suspect that it is the 4-*exo-trig* cyclization that does not work here. The 4-*exo-trig* cyclization would give birth to the diastereomeric mixture of cyclobutyl adducts **61** and **62** (Chart 1). Examination of Dreiding models shows that in both cases the resulting methylene radical confronts some severe steric interactions: a 1,3 interaction with a methyl group in the case of **61** and a 1,3 interaction with a *tert*-butyl group in the case of **62**. Furthermore, the approaches for a less enthalpically favorable alkyl to alkyl 1,6-H transfer from radical **61** or **62** with a methylsilane appear more difficult than for **37**. These large steric interactions as well as the lack of obvious driving force is probably sufficient to preclude the 4-*exo-trig* cyclization and thus prevent the irreversibility of the 6-*endo-trig* cyclization. Indeed, no intermediate intermolecular reduction of the cyclohexyl radical resulting from the 6-*endo-trig* cyclization would be possible here too, and only at the stage of the allyl radical **59** does the intermolecular reduction intervene to provide **55** and **56**.

Conclusion

A new type of radical cascade mixing hydrogen transfers and leading to the very strained bicyclo[3.1.1] framework is disclosed. When no external reduction is possible, the reversible 6-*endo-trig* cyclization of a propargyl radical is followed by an unprecedented 4-*exo-dig* cyclization. It was established that the driving force of this reversible four-membered ring closure is a 1,6-H transfer involving a methylsilane and a vinyl radical. The use of an allyl precursor in this sequence gave no cyclic adduct, probabaly because of a much more reversible 4-*exo-trig* cyclization. The role of the propargyl substituent to ensure the efficiency and the diastereoselectivity of the 6-*endo-trig* was evidenced. Even if our results are probably a reflection of a particularly crowded starting material, the possibility of ensuring unfavorable cyclization processes through hydrogen transfers is very appealing and is under investigation in our laboratory on simpler systems. Application of this chemistry toward the synthesis of relevant bicyclo[3.1.1] systems is also underway.

(28) In a general study of the 5-*endo-trig* cyclization, we have shown that vinyl radicals of type **52** are completely reduced in an intramolecular fashion through a chemoselective 1,5-H transfer: Bogen, S.; Fensterbank, L.; Malacria, M. To be published.

(29) We cannot rule out that **55** directly originates from vinyl radical **58**. However, previous work in our laboratory suggests that vinyl radical of type **58** is highly protected against intermolecular reduction (see also note 28).

Scheme 9

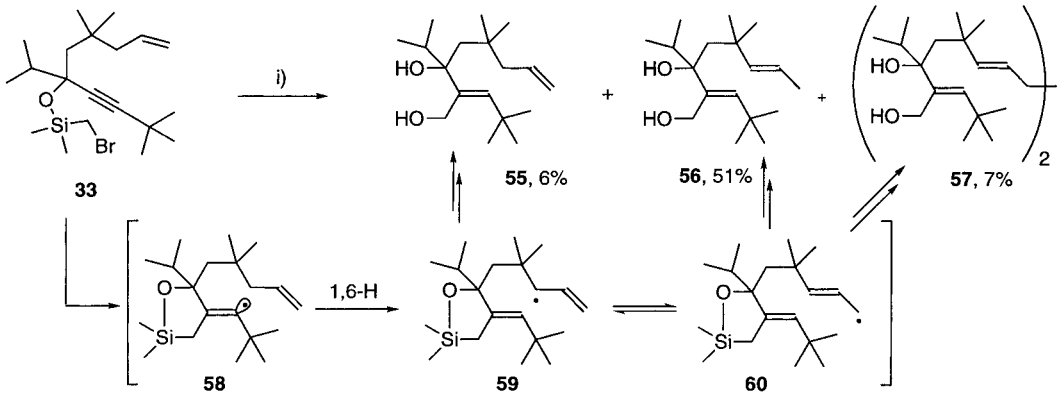
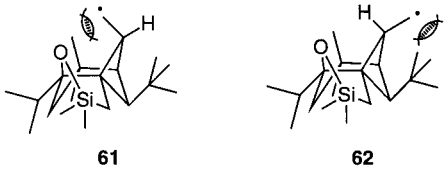


Chart 1



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.[30]

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

Typical Procedure for the Radical Cyclization of (Bromomethyl)dimethylsilyl Propargyl Ethers. A benzene solution (13.5 mL) of Bu_3SnH (360 μL, 1.34 mmol) containing 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. Methyllithium (3.0 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 and filtered over Celite, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel.

6-*tert*-Butyl-2-isopropyl-4,4-dimethyl-1-[(trimethylsilyl)methyl]-7-methylidenebicyclo[3.1.1]heptan-2-ol (5a). After the methyllithium treatment, chromatography (PE:EE, 99:1) afforded 286 mg (85%) of pure oil: R_f = 0.28 (PE:EE, 99:01); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.78 (s, 1H), 2.20 (s, 1H), 2.01 (sept, J = 7.4 Hz, 1H), 1.77 (d, J = 1.0 Hz, 1H), 1.73−1.24 (m_{AB}, 2H), 1.19−1.11 (m_{AB}, 2H), 1.08 (s, 3H), 1.00 (s, 9H), 0.98 (d, J = 7.4 Hz, 3H), 0.94 (s, 3H), 0.92 (d, J = 7.4 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 104.2, 82.5, 62.9, 55.2, 51.2, 40.5, 35.5, 34.5, 33.6, 30.0, 29.0 (3C), 28.9, 20.6, 19.3, 17.1, 3.0 (3C); IR (neat) 3550, 2960, 1660, 1040 cm^{-1}. Anal. Calcd for $C_{21}H_{40}OSi$: C, 74.93; H, 11.98. Found: C, 74.91; H, 11.94.

6-*tert*-Butyl-2-hydroxy-2-isopropyl-4,4-dimethyl-7-methylidenebicyclo[3.1.1]heptan-2-ol (5b). After the Tamao oxidation, chromatography afforded 201 mg (72%) of white solid: mp 160−162 °C; R_f = 0.28 (PE:EE, 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 4.83 (s, 1H), 4.16 (m, 2H), 2.20 (s, 1H), 2.13 (sept, J = 7.1 Hz, 1H), 1.75 (s, 1H), 1.74−1.20 (m_{AB}, 2H), 1.11 (s, 3H), 1.02 (d, J = 7.1 Hz, 3H), 0.98 (d, J = 7.1 Hz, 3H), 0.94 (s, 3H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 104.8, 84.1, 64.3, 60.2, 55.4, 50.4, 40.2, 36.0, 35.7, 33.2, 29.9, 29.1 (3C), 28.8, 19.2, 17.4; IR ($CHCl_3$) 3450, 2950, 1680, 1080 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 77.03; H, 11.51.

6-*tert*-Butyl-2-isopropyl-4,4-dimethyl-1-[[(deuteriomethyl)dimethylsilyl]methyl]-7-methylidenebicyclo[3.1.1]heptan-2-ol (5c). After the methyllithium treatment, chromatography afforded 240 mg (71%) of pure oil: R_f = 0.42 (PE:CH_2Cl_2, 92:08); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.78 (s, 1H), 2.20 (s, 1H), 2.01 (sept, J = 7.4 Hz, 1H), 1.77 (d, J = 1.0 Hz, 1H), 1.74−1.24 (m_{AB}, 2H), 1.19−1.11 (m_{AB}, 2H), 1.08 (s, 3H), 1.00 (s, 9H), 0,99 (d, J = 7.4 Hz, 3H), 0.95 (s, 3H), 0.93 (d, J = 7.4 Hz, 3H), 0.20−0.11 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 104.2, 82.5, 63.0, 55.3, 51.2, 40.5, 34.6, 35.5, 33.7, 30.1, 29.1 (3C), 29.0, 20.7, 19.4, 17.1, 3.1 (3C), 2.8 (t, J = 20 Hz, CH_2D); IR (neat) 3550, 2960, 1660, 1240, 1040 cm^{-1}; CIMS NH_3 m/z (rel int) 320 ($MH^+ - H_2O$, 100).

6-*tert*-Butyl-2-ethyl-4,4-dimethyl-1-[(trimethylsilyl)methyl]-7-methylidenebicyclo[3.1.1]heptan-2-ol (39). After the methyllithium treatment, chromatography (PE:CH_2Cl_2, 90:10) afforded 55 mg (17%) of pure oil: R_f = 0.40 (PE:CH_2Cl_2, 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (s, 1H), 4.77 (s, 1H), 2.20 (s, 1H), 1.72−1.44 (m_{AB}, 2H), 1.70−1.62 (m, 1H), 1.58 (d, J = 1.6 Hz, 1H), 1.40−1.36 (m, 1H), 1.08−0.96 (m_{AB}, 2H), 1.06 (s, 3H), 0.99 (s, 9H), 0.98−0.94 (m, 3H), 0.93 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 102.4, 80.0, 61.4, 54.1, 50.6, 45.8, 34.3, 31.6, 28.6, 27.8, 27.5, 27.4 (3C), 19.3, 6.1, 1.2 (3C); IR (neat) 3560, 1670, 1240, 1160 cm^{-1}; CIMS NH_3 m/z (rel int) 305 ($MH^+ - H_2O$, 100), 323 (MH^+, 4). Anal. Calcd for $C_{20}H_{38}OSi$: C, 74.46; H, 11.87. Found: C, 74.54; H, 11.93.

6-*tert*-Butyl-2-ethyl-4,4-dimethyl-1-[(trimethylsilyl)methyl]-7-methylidenebicyclo[3.1.1]heptan-2-ol (40). The second fraction of the chromatography consisted in 161 mg (50%) of a 1:1 mixture of **39** and **40** as a clear oil: R_f = 0.38 (PE:CH_2Cl_2, 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96−4.94 (m, 2H), 4.77−4.75 (m, 2H), 2.52−2.50 (m, 2H), 2.20 (s, 1H), 1.87−1.65 (m_{AB}, 2H), 1.73−1.44 (m_{AB}, 2H), 1.72−1.65 (m, 1H), 1.63−1.54 (m, 1H), 1.58 (d, J = 1.6 Hz, 1H), 1.40−1.36 (m, 2H), 1.10−0.93 (m, 40H), 0.11 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), obtained by comparing **39** and **39** + **40** (1:1), δ 148.8, 140.8, 84.5, 62.3, 59.7, 51.0, 36.6, 31.8, 31.4, 28.6, 28.4 (3C), 27.8, 15.5, 7.5, 0.0 (3C); IR (neat) 3560, 2950, 1670, 1240 cm^{-1}. Anal. Calcd for $C_{20}H_{38}OSi$: C, 74.46; H, 11.87. Found: C, 74.59; H, 11.95.

(30) Still, W.; Kahn, M.; Mittra, A. *J. Org. Chem.* **1978**, *43*, 2923.

6-*tert*-Butyl-2-ethyl-1-(hydroxymethyl)-2,4,4-trimethyl-7-methylidenebicyclo[3.1.1]heptan-2-ol (41 and 42). After the Tamao oxidation, chromatography (PE:EE, 60:40) afforded 190 mg (75%) of an inseparable 1:1 mixture of **41** and **42** as a clear oil: $R_f = 0.18$ (PE:EE, 60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (d, $J = 1.5$ Hz, 1H), 4.93 (t, $J = 2.5$ Hz, 1H), 4.76 (s, 1H), 4.74 (dd, $J = 3.0$, 1.5 Hz, 1H), 4.07−4.00 (m_{AB}, 2H), 4.06−3.92 (m_{AB}, 2H), 2.72 (t, $J = 2.5$ Hz, 1H), 2.50−2.47 (m_{AB}, 1H), 2.19 (s, 1H), 1.48 (d, $J = 1.0$ Hz, 1H), 1.93−1.53 (m_{AB}, 2H), 1.67−1.35 (m_{AB}, 2H), 1.28 (s, 3H), 1.27 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.95 (s, 9H), 0.94 (s, 3H), 0.85 (s, 3H), 0.84 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 149.4, 108.1, 104.4, 86.0, 81.3, 64.2, 60.7, 60.4, 60.0, 59.5, 58.4, 56.2, 55.8, 51.1, 50.0, 38.7, 36.1, 33.5, 32.6, 31.4, 30.4 (3C), 29.9 (3C), 29.8, 28.4, 28.1, 25.0 (2C); IR (neat) 3350, 2970, 1660, 1250 cm^{-1}; CIMS NH_3 *m/z* (rel int) 235 ($MH^+ - H_2O$, 100), 252 ($MNH_4^+ - H_2O$, 35), 253 (MNH_4^+, 30). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.13; H, 11.18. Found: C, 76.08; H, 11.19.

6-*tert*-Butyl-2-ethyl-4,4-dimethyl-1-[(trimethylsilyl)-methyl]-7-methylidenebicyclo[3.1.1]heptan-2-ol (43). After the methyllithium treatment, chromatography (PE:EE, 95:05) afforded 71 mg (24%) of pure oil: $R_f = 0.20$ (PE:EE, 95:05); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82−4.80 (m, 2H), 4.02 (dd, $J = 10.7$, 6.6 Hz, 1H), 2.31 (s, 1H), 1.89−1.31 (m_{AB}, 2H), 1.72 (d, $J = 1.0$ Hz, 1H), 1.18−1.07 (m_{AB}, 2H), 1.07 (s, 3H), 0.98 (s, 9H), 0.95 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 101.2, 76.2, 57.0, 55.6, 50.5, 41.3, 35.6, 32.0, 28.2, 28.0 (4C), 17.8, 0.1 (3C); IR (neat) 3600, 2960, 1650, 1250 cm^{-1}; CIMS NH_3 *m/z* (rel int) 295 (MH^+, 55), 312 (MNH_4^+, 85). Anal. Calcd for $C_{18}H_{34}OSi$: C, 73.41; H, 11.64. Found: C, 73.48; H, 11.63.

6-*tert*-Butyl-2-ethyl-4,4-dimethyl-1-[(trimethylsilyl)-methyl]-7-methylidenebicyclo[3.1.1]heptan-2-ol (44): 65 mg (22%) of oil; $R_f = 0.26$ (PE:EE, 95:05); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (s, 1H), 4.75 (s, 1H), 3.94 (d, $J = 5.1$ Hz, 1H), 2.47 (s, 1H), 2.35−2.33 (m, 1H), 2.24−1.66 (m_{ABX}, 2H), 1.24 (s, 3H), 1.13−1.09 (m, 2H), 1.05 (s, 9H), 1.01 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 105.9, 81.4, 63.4, 61.1, 57.6, 50.2, 40.6, 33.4, 32.9, 29.1 (3C), 27.8, 17.7, 1.5 (3C); IR (neat): 3550, 2960, 1660, 1250 cm^{-1}; CIMS NH_3 *m/z* (rel int) 295 (MH^+, 10), 312 (MNH_4^+, 15).

3-*tert*-Butyl-4-(1-ethynyl)-2-[(trimethylsilyl)methyl]-5,5-dimethylcyclohexan-1-ol (45): 124 mg (42%) of white solid; mp = 74−76 °C; $R_f = 0.36$ (PE:EE, 95:05); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85−3.81 (m, 1H), 2.42−2.41 (m, 1H), 2.38 (dd, $J = 11.2$, 2.5 Hz, 1H), 2.13 (d, $J = 2.5$ Hz, 1H), 1.52−1.40 (m, 3H), 1.17 (s, 9H), 1.14 (s, 3H), 1.05 (s, 3H), 0.58 (d, $J = 6$,6 Hz, 2H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.9, 72.5, 70.0, 47.1, 41.7, 39.3, 36.2, 34.5, 32.7, 30.6, 29.9 (3C), 21.7, 8.9, −0.3 (3C); IR ($CHCl_3$) 3580, 2920, 2100, 1230 cm^{-1}; CIMS NH_3 *m/z* (rel int) 295 ($MH^+ - H_2O$, 40), 312 (MNH_4^+, 85). Anal. Calcd for $C_{18}H_{34}OSi$: C, 73.41; H, 11.64. Found: C, 73.52; H, 11.68.

4-(1-Ethynyl)-2-[(trimethylsilyl)methyl]-5,5-dimethylcyclohexan-1-ol (46 and 47). After the methyllithium treatment, chromatography (PE:EE, 80:20) afforded 105 mg (44%) of 5:1 mixture of **46** and **47**: $R_f = 0.20$ (PE:EE, 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87−3.83 (m, *1H*), 3.35−3.28 (m, 1H), 2.37−2.32 (m, *1H*); 2.22−2.18 (m, 1H), 2.15−2.05 (m, *1H* + 1H), 2.04 (d, $J = 2.8$ Hz, *1H*), 1.90 (m, 1H), 1.80 (dt, $J = 13.6$, 4.4 Hz, *1H*), 1.70−1.63 (m, *1H* + 1H), 1.60−1.53 (m, *1H*), 1.45 (dd, $J = 12.8$, 9.2 Hz, *1H*), 1.30−1.22 (m, 2H), 1.15−1.05 (m, 2H), 1.10 (s, *3H*), 1.07 (s, 3H), 1.03 (s, *3H*), 1.00 (s, 3H), 0.62 (dd, $J = 14.7$, 3.6 Hz, 1H), 0.42 (dd, $J = 14.7$, 10.7 Hz, *1H*), 0.25 (dd, $J = 14.7$, 9.6 Hz, 1H), 0.05 (*9H* + 9H, s); IR (neat) 3400, 3300, 2100, 1240, 1045 cm^{-1}; CIMS NH_3 *m/z* (rel int) 221 ($MH^+ - H_2O$, 45), 256 (MNH_4^+, 100). Anal. Calcd for $C_{14}H_{26}OSi$: C, 70.59; H, 10.92. Found: C, 70.55; H, 10.97.

2-(2,2-Dimethyl-(*E*)-propylidene)-3-(1-methylethyl)oct-7-yne-1,3-diol (50). After the Tamao oxidation, chromatography (PE:EE, 40:60) afforded 68 mg (27%) of clear oil: $R_f = 0.23$ (PE:EE, 40:60); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (s, 1H), 4.31−4.17 (m_{AB} 2H), 2.16−2.11 (m, 2H), 1.88 (t, $J = 2.5$ Hz, 1H), 1.75 (sept, $J = 6.6$ Hz, 1H), 1.65−1.38 (m, 4H), 1.11 (s, 9H), 0.84 (d, $J = 6.6$ Hz, 3H), 0.81 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 141.6, 140.8, 86.5, 82.8, 70.4, 60.7, 39.9, 39.4, 34.5, 33.9 (3C), 24.6, 20.6, 19.1, 18.6; IR (neat) 3480, 3300, 2950, 2100, 1000 cm^{-1}.

3-*tert*-Butyl-2-(hydroxymethyl)-1-isopropyl-4-(2-propynyl)-1-cyclopentanol (51). The second fraction of the chromatography consisted of 53 mg (21%) of pure oil. $R_f = 0.14$ (PE:EE, 40:60); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99−3.89 (m_{ABX}, 2H), 2.48 (dt, $J = 16.8$, 2.5 Hz, 1H), 2.34−2.28 (m, 2H), 2.20 (ddd, $J = 16.8$, 7.6, 2.5 Hz, 1H), 1.98 (t, $J = 2.5$ Hz, 1H), 1.88 (d, $J = 8.6$ Hz, 2H), 1.74 (sept, $J = 6.6$ Hz, 1H), 1.54 (dd, $J = 11.2$, 6.6 Hz, 1H), 1.02 (s, 9H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.2, 82.6, 70.0, 61.8, 54.5, 51.2, 44.6, 37.8, 36.8, 32.2, 29.9 (3C), 23.8, 17.4, 16.5; IR (neat) 3450, 2920, 2110, 1230 cm^{-1}; Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.12. Found: C, 76.07; H, 11.10.

2-(2,2-Dimethyl-(*E*)-propylidene)-3-(1-isopropyl)-5,5-dimethyloct-7-ene-1,3-diol (55) and 2-(2,2-Dimethyl-(*E*)-propylidene)-3-(1-isopropyl)-5,5-dimethyloct-6-ene-1,3-diol (56). After the Tamao oxidation, chromatography (PE:EtOAc, 90:10) afforded 163 mg (57%) of a 1:9 mixture of **55** and **56** as a clear oil. **56**: $R_f = 0.30$ (PE:EtOAc, 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (dq, $J = 15.8$, 1 Hz, 1H), 5.41 (m, 2 H), 4.32 (d, $J = 11.8$ Hz, 1 H), 4.18 (d, $J = 11.8$ Hz, 1H), 1.77 (m_{AB}, 2H), 1.72 (m, 1H), 1.67 (dd, $J = 6.6$, 1.1 Hz, 3H), 1.20 (s, 9H), 1.05 (s, 3H), 1.02 (s, 3H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.82 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 139.9, 139.0, 122.2, 81.2, 59.1, 48.7, 38.9, 36.4, 32.8, 31.9, 31.8 (3C), 28.1, 18.3, 17.4, 17.1; IR (neat) 3500, 3020, 2950, 1360 cm^{-1}. Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found: C, 76.43; H, 12.18.

The second fraction of the chromatography consisted of 40 mg of **57** (7%) as a pure oil. **57**: $R_f = 0.10$ (PE:EtOAc, 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (d, $J = 15.7$, 1 Hz, 2H), 5.37 (m, 4H), 4.36 (d, $J = 12.0$ Hz, 2H), 4.20 (d, $J = 12.0$ Hz, 2H), 2.08 (m, 4H), 1.80 (m_{AB}, 4H), 1.70 (m, 2H), 1.19 (s, 18H), 1.07 (s, 6H), 1.01 (s, 6H), 0.88 (d, $J = 6.6$ Hz, 6H), 0.83 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 139.8, 126.7, 81.4, 59.1, 48.8, 39.2, 36.5, 32.8, 32.9, 32.8 (6C), 32.5, 31.8, 27.7, 17.4, 17.2; IR (neat) 3400, 3020, 2950, 1470, 1000 cm^{-1}; CIMS NH_3 *m/z* (rel int) 563 (MH^+, 45), 545 ($MH^+ - H_2O$, 35).

Supporting Information Available: The synthesis of precursors (**1**, **7**−**14**, **16**−**21**, **23**, **24**, **26**−**33**) and their characterization data are given (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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