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Remarkable template effect of a Lewis acid receptor in the intramolecular radical cyclization: control of reaction pathway as well as stereochemistry

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Abstract—A remarkable template effect in the intramolecular radical cyclization process has been observed by the successful utilization of Lewis acid receptor, aluminum tris(2,6-diphenylphenoxide) (ATPH). The origin of this efficient template effect by ATPH would be ascribable to the well-defined reaction environment created in front of the aluminum coordination center; this enables appropriate proximity of initially generated carbon radical to unsaturated carbon–carbon bond in the transition state for smooth cyclization and hence completely suppresses the undesired intermolecular reduction pathway. Moreover, such conformational restriction provided by the unique cavity of ATPH alters the stereoselectivity of the cyclization.

During the last 15 years, radical chemistry has been extensively investigated and a great deal of success in the development of new methods has appeared in the literature, dramatically changing the common sense about free radical reactions.[1] Along with this stream, intramolecular radical additions to multiple bonds, i.e. radical cyclization, has been visualized as a powerful new methodology for ring construction via C–C bond forming process and it actually serves as one of the most reliable tools in organic synthesis.[2] Although the chemo-, regio-, and stereoselectivities of many classes of radical cyclizations are well understood and the preparative importance has been growing at an incredible rate, the full potential of this reaction including stereochemical control at the newly created carbon centers is yet to be realized; hence only limited structural types of cyclization products have been accessible by this reaction.[3] In this context, we have been interested in the development of a conceptually new method for obtaining hitherto unattainable reactivity and selectivity in the intramolecular radical additions to multiple bonds by the successful utilization of rationally designed Lewis acids.[4] Aluminum tris(2,6-diphenylphenoxide) (ATPH),[5] a structurally well-defined Lewis acid receptor possessing a unique bowl-shaped reaction cavity created by three phenyl substituents in front of the highly oxygenophilic aluminum center, certainly appeared to be ideal for our purpose, and we envisaged that oxygen-containing substrates such as halo ethers of type **1** could adopt the chair-like conformation by precomplexation with ATPH. This conformational restriction within the cavity, upon subsequent exposure to the radical reaction conditions, would play a crucial role in allowing an appropriate proximity of initially generated carbon radical to triple bond in the transition state, thereby smoothly facilitating the desired cyclization process and yet altering the stereoselectivity as illustrated in Scheme 1.[6]

First, we examined intramolecular radical cyclization of 2-iodoethyl 3-phenylpropynyl ether (**1**, n=1) under several representative radical reaction conditions and the results are summarized in Table 1. The reaction of **1** (n=1) with Bu_3SnH and catalytic amount of AIBN in refluxing benzene for 1 h gave rise to an *E*/*Z* mixture of cyclic ether, 3-benzylidenetetrahydrofuran (**2**) in 96% yield (*E*/*Z*=50:50) (entry 1). Use of catalytic Et_3B as radical initiator allowed the cyclization to be conducted at −78°C, which brought slightly higher stereoselectivity (*E*/*Z*=61:39) (entry 2).[7] In contrast, however, initial complexation of **1** (n=1) with ATPH (2 equiv.) in toluene and subsequent addition of Bu_3SnH (1.5 equiv.) and catalytic Et_3B (0.2 equiv.) afforded **2** quantitatively with totally opposite preference of olefin geometry (*E*/*Z*=14:86) (entry 3). Since the geometry of the newly formed double bond is likely to be determined in the hydrogen abstraction process,[8] the observed (*Z*)-selectivity can be accounted for by the preferable approach of Bu_3SnH from the less hindered site to trap the ATPH-coordinated vinyl radical (**B**), avoiding the steric repulsion with 2,6-diphenylphenoxy ligand of ATPH (**A**). This argument is strongly supported by the fact that the

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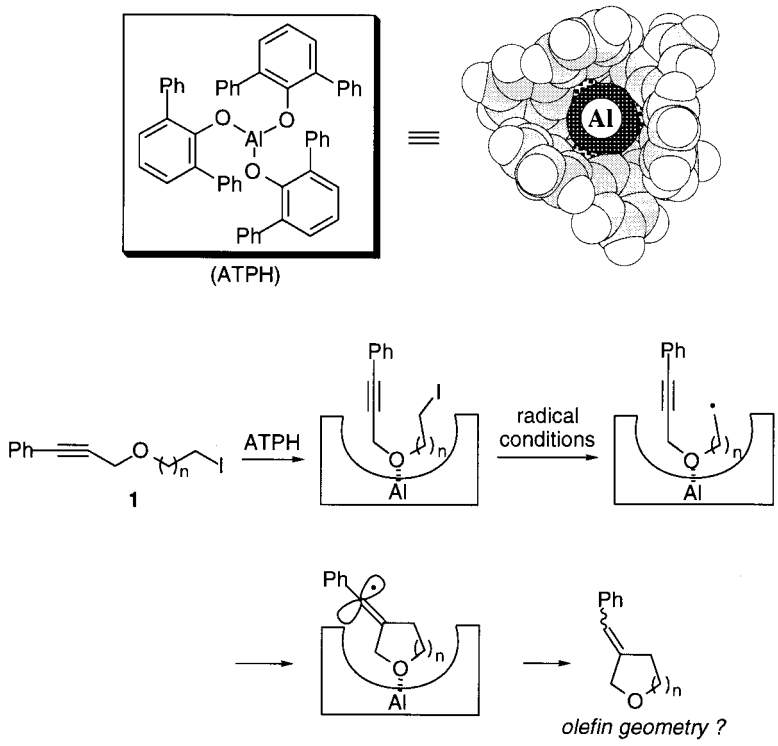
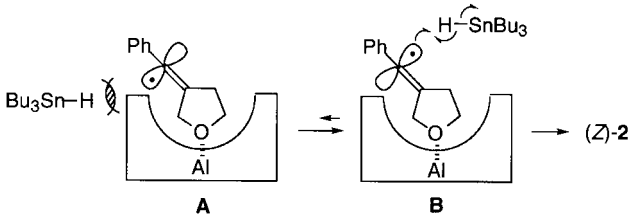


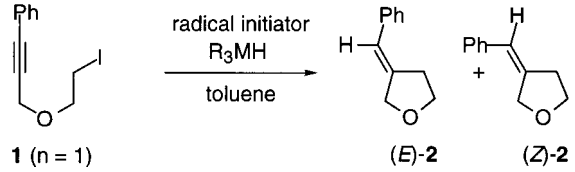
Scheme 1.

stereoselectivity was further improved by the use of $(Me_3Si)_3SiH$[9] instead of Bu_3SnH (entry 4).



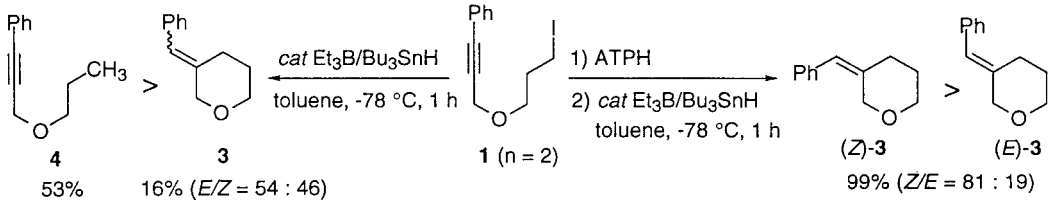
Based on the results, intramolecular cyclization of one-carbon elongated halo ether, 3-iodopropyl 3-phenylpropynyl ether (**1**, n=2), which can be categorized as heptynyl radical cyclization, was also examined. Here, commonly expected 6-*exo* cyclizations are usually slower than related 5-*exo* cyclizations, and therefore simple reduction of alkyl iodide rather than relatively unfamiliar 7-*endo* cyclization can often compete, which obviously diminishes the synthetic utility of this type of reaction. Indeed, treatment of **1** (n=2) with Bu_3SnH and catalytic Et_3B in toluene at −78°C for 1 h resulted in predominant formation of the reduction product **4** and the desirable cyclic ether **3** was obtained in only 16% yield. In marked contrast, radical cyclization of **1** (n=2) under the influence of ATPH under otherwise similar reaction conditions afforded **3** as the sole isolable product quantitatively, demonstrating a remarkable template effect of ATPH for acceleration of the otherwise disfavored 6-*exo* cyclization (Scheme 2). It should be emphasized that the *E*/*Z* selectivity in the cyclization

Table 1. Intramolecular radical cyclization of 2-iodoethyl 3-phenylpropynyl ether (**1**, n=1) under various conditions (unless otherwise specified, the radical cyclization was carried out in toluene with 1.2 equiv. of reagent and catalytic amount of radical initiator under the given reaction conditions)



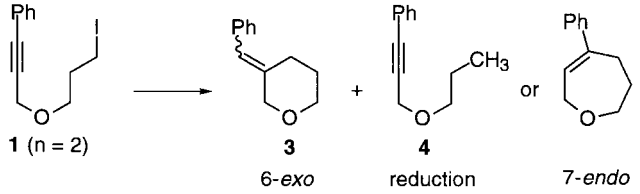
Entry	Reagent (R_3MH)	Initiator	Condition	% Yield[a] (*E*/*Z* ratio)[b]
1	Bu_3SnH	AIBN	80°C, 1 h	96 (50:50)[c]
2	Bu_3SnH	Et_3B	−78°C, 1 h	94 (61:39)
3	ATPH[d]/Bu_3SnH	Et_3B	−78°C, 1 h	99 (14:86)
4	ATPH[d]/$(Me_3Si)_3SiH$	Et_3B	−78°C, 1 h	99 (<1:>99)

[a] Isolated yield.
[b] Determined by ^1H NMR analysis.
[c] Use of benzene as solvent.
[d] 2 equiv. of ATPH was used.



Scheme 2.

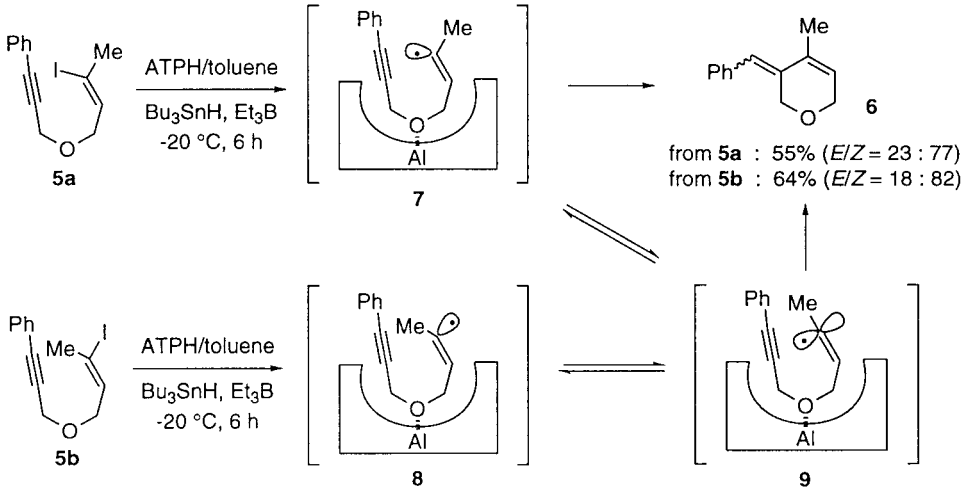
products **3** is again opposite in the presence or absence of ATPH and nearly perfect *Z* selectivity was also obtained with $(Me_3Si)_3SiH$,[9] despite the significant rate retardation under similar reaction conditions [30% yield of **3**; *E*/*Z*=<1:>99 and 70% recovery of **1** (*n*=2)].



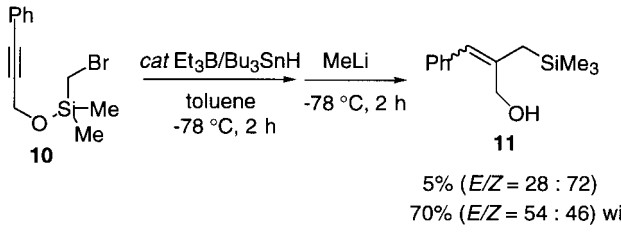
In the examples described above the reaction was terminated by the hydrogen abstraction of vinyl radicals which are considered to have linear structure as reported by Giese.[8] However, it seemed difficult to rule out the possibility that the vinyl radicals exist in a nonlinear configuration capable of extremely facile isomeric interconversion.[10] This thought stimulated our interest in the effect of the stereochemistry of vinyl radicals on cyclization processes and eventually led us to compare the reactivity of stereochemically defined (*Z*)- and (*E*)-3-iodo-2-butenyl 3-phenylpropynyl ethers (**5a**, **b**) in the ATPH-assisted intramolecular radical cyclization. The reaction of **5a** with Bu_3SnH (1.2 equiv.) and Et_3B (0.6 equiv.) under the influence of ATPH in toluene at −20°C for 6 h gave rise to the cyclization product **6** in 55% yield with the *E*/*Z* ratio of 23:77. Interestingly, the cyclization of **5b** under similar reaction conditions reached the almost identical result with the slight difference of the stereoselectivity, suggesting that the initially generated two configurationally isomeric vinyl radicals **7** and **8** with bent structure experienced rapid isomerization through linear structure **9**, and either **7** or **9** underwent smooth cyclization to furnish the corresponding hydropyrane derivative **6** (Scheme 3).

Our approach has been successfully applied to the radical cyclization of (bromomethyl)dimethylsilyl propargyl ethers, which is usually carried out in refluxing benzene with catalytic amount of AIBN by slow addition of R_3SnH (R=Ph or Bu) with a syringe pump to avoid undesired reduction of the relatively stable α-silyl radical.[11] Actually, the reaction initiated by the addition of catalytic Et_3B to the premixed toluene solution of (bromomethyl)dimethylsilyl ether of 3-phenyl-1-propynol (**10**) and Bu_3SnH at −78°C resulted in formation of allylic alcohol **11** in only 5% yield (*E*/*Z*=28:72) after the treatment with MeLi (3 equiv.) at −78°C. Surprisingly, the reaction with ATPH under otherwise identical reaction conditions gave rise to **11** in 70% yield with the opposite preference of olefin geometry (*E*/*Z*=54:46). Here, template effect of ATPH did not seem enough to achieve high stereochemical control probably due to the steric and electronic demand of silyl substituents upon complexation, resulting a rather weak aluminum–oxygen coordination bond (Scheme 4).

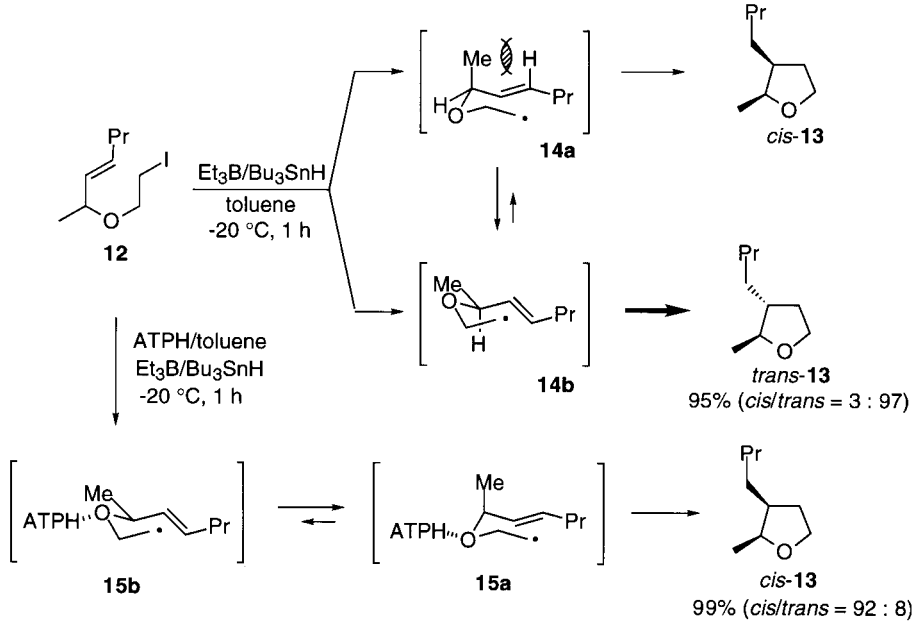
Typically, 4-substituted hexenyl radicals cyclize with a high level of selectivity and closure of the 4-methylhexenyl radical is known to provide predominantly the *trans* isomer, as expected from the Beckwith–Houk model.[12] For instance, radical cyclization of 2-iodoethyl *trans*-1-methyl-2-hexenyl ether (**12**) proceeded in toluene at −20°C with catalytic Et_3B/Bu_3SnH to furnish tetrahydrofuran **13** in 95% yield with a *cis*/*trans* ratio of 3:97. Examination of the two chairlike transition state conformations as illustrated in



Scheme 3.

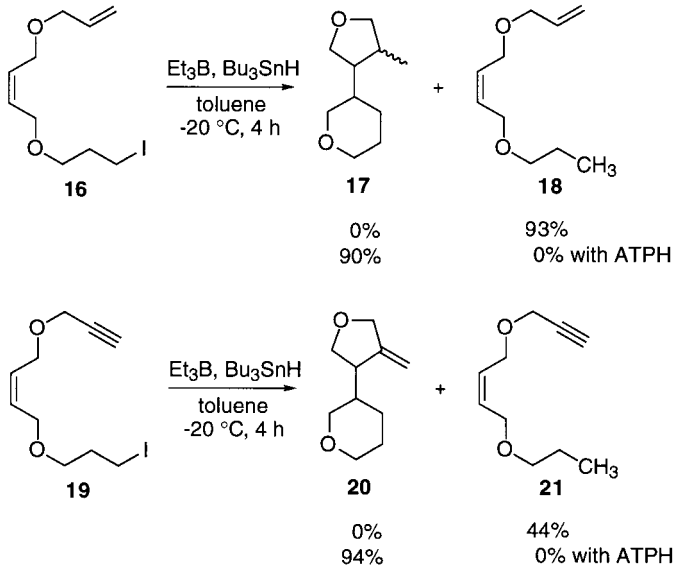


Scheme 4.



Scheme 5.

Scheme 5 can reveal why such excellent diastereoselectivity was observed. Conformation **14b**, with the methyl group equatorial, can minimize the allylic strain leading to *trans* isomer, whereas less likely conformation **14a**, with the methyl group axial, leads to *cis* isomer. As easily expected, the participation of the conformation would be dramatically decreased in the cyclization of the substrates possessing either bulky 4-substituent or *cis* double bond, which consequently manifest the difficulty in attaining the *cis* selectivity. Here, the template effect of ATPH was found to be greatly



Scheme 6.

appreciated, altering the transition state structure of the present cyclization; i.e. initial treatment of **12** with ATPH followed by the addition of catalytic Et_3B/Bu_3SnH at −20°C resulted in formation of **13** almost quantitatively with totally opposite diastereoselectivity (*cis*/*trans*=92:8). Apparently, steric requirement for fitting inside the cavity of ATPH through Lewis acid–base complexation made the less likely conformation **15a** more favorable than **15b**, leading to the preferential formation of *cis* tetrahydrofuran (Scheme 5).

Further, we applied the unique property of ATPH as a Lewis acid receptor to the tandem intramolecular radical cyclizations of halo ethers **16** based on our recent finding of the encapsulation of 1,4-carbonyl guests by ATPH through Lewis acid–base interaction.[5g] The bis-ether **16** can be prepared from *cis*-2-buten-1,4-diol and reaction of **16** with Bu_3SnH (1.2 equiv.) and Et_3B (0.5 equiv.) in toluene at −20°C for 4 h gave rise to the simple reduction product **18** in 93% yield. In marked contrast, however, initial complexation of **16** with ATPH (2.4 equiv.) and the subsequent treatment with Et_3B/Bu_3SnH at −20°C for 4 h resulted in the formation of the corresponding tandem cyclization product **17** in 90% yield as a mixture of diastereomers and none of reduction product **18** was obtained as shown in Scheme 6. Noteworthy is the fact that use of 1.2 equiv. of ATPH significantly diminished the chemical yield of **17** (38%), suggesting the importance of simultaneous coordination of ATPH on both the oxygen atoms of **16** to smoothly facilitate the present tandem cyclization process. A similar tendency was observed in the intramolecular radical cyclization of **19**, exhibiting completely opposite product distribution with or without ATPH as included in Scheme 6.

1. Experimental

1.1. General

Infrared (IR) spectra were recorded on Shimadzu FT-IR 8200A spectrometer. ^{1}H NMR spectra were measured on Varian Gemini-300 (300 MHz) spectrometer. Analytical gas–liquid phase chromatography (GLC) was performed on Shimadzu GC-14B instrument equipped with a flame ionization detector and a capillary column of PEG-HT (0.25×25,000 mm) using nitrogen as carrier gas. Analytical gas–liquid phase chromatography-mass spectrometer (GC-MS) was performed on Shimadzu GC-17A instrument equipped with a EI-detector and a capillary column of DB-1 (J&W SCIENTIFIC, 0.25×30,000 mm) using helium as carrier gas, and GCMS-QP5000. All experiments were carried out under an atmosphere of dry argon. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385). Microanalyses were accomplished at the Center for Instrumental Analysis, Hokkaido University. The high-resolution mass spectra (HRMS) were conducted at the School of Agriculture, Hokkaido University and the School of Engineering, Kyoto University.

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Kanto Chemical Co., Inc. as 'Dehydrated'. Hexane and toluene were dried over sodium metal. Dichloromethane, DMF and hexamethylphosphoric triamide (HMPA) were stored over 4 Å molecular sieves. Pyridine was stored over KOH pellets. Trimethylaluminum (Me_3Al) and triethylborane (Et_3B) were kindly supplied from Toso-Akzo Chem. Co. Ltd., Japan. Other simple chemicals were purchased and used as such.

1.2. General procedure for the preparation of iodoalkyl ethers

1.2.1. Preparation of 2-iodoethyl 3-phenylpropynyl ether (1, *n*=1) To a solution of 3-phenyl-2-propyn-1-ol (1.15 g, 8.7 mmol) in ether (15 mL) was added some drops of pyridine and phosphorous tribromide (0.33 mL, 3.48 mmol) at 0°C under argon and the reaction mixture was stirred for 4 h. The resulting mixture was then poured into saturated $NaHCO_3$ and extracted with ether. The organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel (ether/pentane=1:50 as eluent) gave 3-bromo-1-phenyl-1-propyne as a colorless oil (1.57 g, 8.7 mmol) quantitatively: ^{1}H NMR ($CDCl_3$) δ 7.27–7.48 (5H, m, Ph), 4.17 (2H, s, CH_2Br).

To a suspension of sodium hydride (65% assay, 359 mg, 9.7 mmol) in THF (20 mL) was added 1,2-ethanediol (4.5 mL) at 0°C under argon and the bromide obtained above (8.7 mmol) was introduced at 0°C. After the addition of hexamethylphosphoric triamide (HMPA, 4 mL), the reaction mixture was allowed to warm to room temperature and stirred for additional 6 h. The mixture was then poured into brine and extracted with ether. The organic extracts were dried over Na_2SO_4. Evaporation of solvent and purification of the residual oil by column chromatography on silica gel (ether/hexane=1:1 as eluent) furnished 3-oxa-6-phenyl-6-hexyn-1-ol as a colorless oil (1.34 g, 7.6 mmol, 94%): ^{1}H NMR ($CDCl_3$) δ 7.42–7.48 (2H, m, Ph), 7.27–7.35 (3H, m, Ph), 4.42 (2H, s, C≡CCH_2O), 3.81 (2H, m, CH_2OH), 3.74 (2H, m, O–CH_2), 2.02 (1H, t, J=6.2 Hz, OH).

This alcohol (7.6 mmol) was dissolved into dichloromethane (20 mL) and pyridine (2.5 mL, 31 mmol) and triphenylphosphine (2.2 g, 8.4 mmol) were added at 0°C under argon. After being stirred for 30 min, iodine (2.2 g, 8.4 mmol) was added portionwise and stirring was continued for 1 h at 0°C. The mixture was treated with saturated Na_2SO_3 until the color turned into yellow. Then the whole mixture was poured into saturated $NaHCO_3$ and extracted with ether. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (ether/hexane=1:30 as eluent) to give **1** (*n*=1) as a colorless oil (1.97 g, 6.9 mmol, 91%): ^{1}H NMR ($CDCl_3$) δ 7.27–7.50 (5H, m, Ph), 4.45 (2H, s, C≡CCH_2O), 3.88 (2H, t, J=6.9 Hz, O–CH_2), 3.32 (2H, t, J=6.9 Hz, CH_2I); IR (liquid film) 3058, 2848, 2239, 1489, 1443, 1354, 1256, 1190, 1168, 1109, 1085, 1029, 964, 918, 758, 690 cm^{-1}. MS: 286 (M^+), 173, 155, 145, 131, 115 (100%), 103. Anal. Calcd for $C_{11}H_{11}IO$: C, 46.18; H, 3.88; I, 44.35. Found: C, 46.42; H, 3.89; I, 44.17.

1.2.2. 3-Iodopropyl 3-phenylpropynyl ether (1, n=2). ^{1}H NMR ($CDCl_3$) δ 7.28–7.51 (5H, m, Ph), 4.38 (2H, s, C≡CCH_2O), 3.66 (2H, t, J=6.0 Hz, O–CH_2), 3.31 (2H, t, J=6.9 Hz, CH_2I), 2.12 (2H, tt, J=6.0, 6.9 Hz, CH_2CI); IR (liquid film) 3053, 2943, 2860, 1489, 1443, 1360, 1258, 1182, 1101, 1069, 1028, 758, 691 cm^{-1}. MS: 300 (M^+), 243, 155, 145, 129, 115 (100%), 103. Anal. Calcd for $C_{12}H_{13}IO$: C, 48.02; H, 4.37; I, 42.28. Found: C, 48.14; H, 4.39; I, 42.39.

1.2.3. Preparation of 3-iodo-(2*Z*)-butenyl 3-phenylpropynyl ether (5a). To a solution of sodium iodide (2.69 g, 18 mmol) in trifluoroacetic acid (5 mL) was added ethyl tetrolate (1.68 g, 15 mmol) dropwise at 0°C under argon. The mixture was then heated to 80°C and stirred for 5 h. After the resulting mixture was cooled to room temperature, it was poured into water and extracted with ether. The ethereal extracts were neutralized by saturated $NaHCO_3$, washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane=1:30 then 1:10 as eluent) gave ethyl β-iodocrotonate as a colorless oil (*E*-isomer: 576 mg, 2.4 mmol; *Z*-isomer: 2.52 g, 10.5 mmol, 86% combined yield): ^{1}H NMR ($CDCl_3$) *E*-isomer: δ 6.63 (1H, s, IC=CH), 4.15 (2H, q, J=6.9 Hz, OCH_2CH$_3$), 2.98 (3H, s, CH_3C=C), 1.28 (3H, t, J=6.9 Hz, OCH$_2$CH_3); *Z*-isomer: δ 6.29 (1H, s, IC=CH), 4.22 (2H, q, J=6.9 Hz, OCH_2CH$_3$), 2.73 (3H, s, CH_3C=C), 1.30 (3H, t, J=6.9 Hz, OCH$_2$CH_3).

Aluminum chloride (1.40 g, 10.5 mmol) was treated with lithium aluminum hydride (1.20 g, 31.5 mmol) in ether (100 mL) at 0°C for 30 min and the (*Z*)-β-iodocrotonate (10.5 mmol) was added dropwise. The mixture was stirred for 1 h and the excess aluminum hydride was quenched by the addition of 1N HCl at 0°C. The whole mixture was poured into saturated $NaHCO_3$ and extracted with ether. The organic extracts were dried over Na_2SO_4 and concentrated. The crude (*Z*)-β-iodocrotyl alcohol was converted without any purification to the corresponding bromide by PBr_3 and *cat.* pyridine in ether.

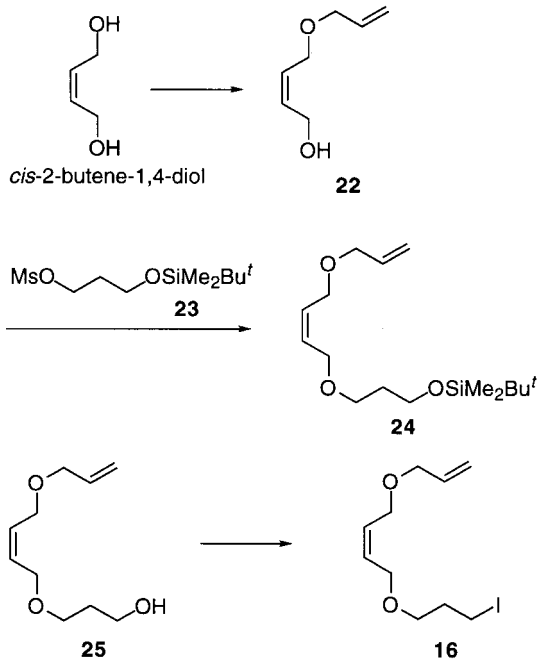
To a suspension of sodium hydride (385 mg, 10.4 mmol) in THF (10 mL) was added 3-phenyl-2-propyn-1-ol (1.15 g, 8.7 mmol) at 0°C under argon. After stirring for 15 min, the bromide obtained above was added. The mixture was allowed to warm to room temperature and stirred for 3 h. It was then poured into brine and extracted with ether. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (ether/hexane=1:1 as eluent) to furnish 3-iodo-(2*Z*)-butenyl 3-phenylpropynyl ether (**5a**) as a colorless oil (1.64 g, 5.3 mmol, 50% in three steps): ^{1}H NMR ($CDCl_3$) δ 7.41–7.50 (2H, m, Ph), 7.28–7.36 (3H, m, Ph), 5.76 (1H, t, J=5.7 Hz, IC=CH), 4.38 (2H, s, C≡CCH_2O), 4.18 (2H, d, J=5.7 Hz, OCH$_2$C=CI), 2.56 (3H, s, CH_3C=C); IR (liquid film) 3057, 2849, 1654, 1599, 1489, 1443, 1352, 1256, 1078, 1028, 964, 918, 758, 691 cm^{-1}. MS: 312 (M^+), 184, 155, 141, 131, 115 (100%), 91. HRMS Calcd for $C_{13}H_{13}IO$: 311.9970 (M^+). Found: 312.0013 (M^+).

1.2.4. 3-Iodo-(2*E*)-butenyl 3-phenylpropynyl ether (5b). The title compound was prepared in exactly the same way described above from the (*E*)-β-iodocrotonate: ^{1}H NMR ($CDCl_3$) δ 7.40–7.48 (2H, m, Ph), 7.28–7.36 (3H, m, Ph), 6.39 (1H, t, J=6.9 Hz, IC=CH), 4.37 (2H, s, C≡CCH_2O), 4.09 (2H, d, J=6.9 Hz, OCH_2C=CI), 2.50 (3H, s, CH_3C=C); IR (liquid film) 3057, 2954, 2847, 2359, 1638, 1489, 1443, 1354, 1256, 1084, 1055, 962, 927, 758, 690 cm^{-1}.

1.2.5. Preparation of (bromomethyl)dimethylsilyl 3-phenylpropynyl ether (10). To a solution of 3-phenyl-2-propyn-1-ol (661 mg, 5.0 mmol) in DMF (10 mL) was added imidazole (681 mg, 10.0 mmol) and bromomethyldimethylchlorosilane (1.13 g, 6.0 mmol) sequentially at 0°C under argon. The mixture was stirred for 3 h and poured into saturated $NaHCO_3$. Extractive workup was performed with ether and the organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane=1:50 as eluent) gave **10** as a colorless oil (1.04 g, 3.7 mmol, 74%): ^{1}H NMR ($CDCl_3$) δ 7.40–7.47 (2H, m, Ph), 7.29–7.37 (3H, m, Ph), 4.59 (2H, s, C≡CCH_2O), 2.91 (1H, s, CHBr), 2.59 (1H, s, CHBr), 0.37 (3H, s, $SiCH_3$), 0.35 (3H, s, $SiCH_3$); IR (liquid film) 3058, 2963, 2864, 2362, 1491, 1369, 1258, 1084, 999, 964, 847, 758, 691 cm^{-1}. MS: 284 ($[M+2]^+$), 282 (M^+), 239, 237, 203, 189, 159 (100%), 115. HRMS Calcd for $C_{12}H_{15}BrOSi$: 282.0075 (M^+). Found: 282.0080 (M^+).

1.2.6. Preparation of 2-iodoethyl *trans*-1-methyl-2-hexenyl ether (12). The two-neck flask equipped with reflux condenser and Dean Stark trap was charged with a solution of 3-hepten-2-one (2.24 g, 20 mmol) in hexane (10 mL), *p*-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol) and 1,2-ethanediol (1.2 mL). The solution was heated to reflux and stirred for 2 h with continuous removal of water. After cooled to room temperature, the mixture was concentrated and the residual oil was purified by column chromatography on silica gel (ether/pentane=1:30 as eluent) to give the corresponding acetal as a colorless oil (1.26 g, 8.0 mmol, 40%): ^{1}H NMR ($CDCl_3$) δ 5.80 (1H, dt, J=6.9, 15.2 Hz, $CH_3(CH_2)_2$CH=C), 5.42 (1H, d, J=15.2 Hz, C=CHC(CH_3)O), 3.84–3.99 (4H, m, 2(CH_2O)), 2.02 (2H, q, J=6.9 Hz, CH_2C=C), 1.46 (3H, s, CH_3C–O), 1.41 (2H, sex, J=7.5 Hz, $CH_3CH_2CH_2$), 0.90 (3H, t, J=7.5 Hz, CH_3(CH_2)$_2$).

DIBAH (3.0 mL, 16.8 mmol) was added dropwise to a solution of the acetal obtained above (8.0 mmol) in dichloromethane (20 mL) at −78°C under argon and the mixture was stirred for 1 h. The reaction was quenched by the careful addition of 1N HCl at 0°C. The whole mixture was then poured into water and extracted with ether. The ethereal extracts were dried over Na_2SO_4 and concentrated. Purification of the residual oil by column chromatography on silica gel (ether/hexane=1:1 as eluent) furnished 3-oxa-4-methyl-5-nonan-1-ol as a colorless oil (1.16 g, 7.3 mmol, 91%): ^{1}H NMR ($CDCl_3$) δ 5.60 (1H, dt, J=6.9, 15.2 Hz, $CH_3(CH_2)_2$CH=C), 5.34 (1H, dd, J=6.9, 15.2 Hz, C=CHC(CH_3)O), 3.82 (1H, quint, J=6.9 Hz, CH(CH_3)O), 3.70 (2H, m, CH_2OH), 3.58 (1H, m, CH–O), 3.40 (1H, m, CH–O), 2.02 (1H, s, OH), 2.01 (2H, q, J=6.9 Hz, CH_2C=C), 1.40 (2H, sex, J=7.5 Hz, $CH_3CH_2CH_2$), 1.25 (3H, d, J=6.9 Hz, CH_3C–O), 0.90 (3H, t, J=7.5 Hz, CH_3(CH_2)$_2$).



Scheme 7.

The alcohol (7.3 mmol) was dissolved into dichloromethane (20 mL) and pyridine (2.4 mL, 30 mmol) and triphenylphosphine (2.31 g, 8.8 mmol) were added at 0°C under argon. After being stirred for 30 min, iodine (2.23 g, 8.8 mmol) was added portionwise and stirring was continued at 0°C for additional 1 h. The resulting mixture was treated with saturated Na_2SO_3 to reduce excess iodine and then poured into saturated $NaHCO_3$. Extractive workup was conducted with ether and the organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane=1:30 as eluent) yielded **12** as a colorless oil (1.45 g, 5.42 mmol, 74%): ^{1}H NMR ($CDCl_3$) δ 5.60 (1H, dt, J=6.6, 15.3 Hz, $CH_3(CH_2)_2CH$=C), 5.34 (1H, dd, J=7.8, 15.3 Hz, C=CHC(CH_3)O), 3.85 (1H, quint, J=6.3 Hz, CH(CH_3)O), 3.69 (1H, dt, J=6.9, 10.8 Hz, CH–O), 3.56 (1H, dt, J=6.9, 10.8 Hz, CH–O), 3.22 (2H, t, J=6.9 Hz, CH_2I), 2.01 (2H, q, J=6.6 Hz, CH_2C=C), 1.40 (2H, sex, J=7.5 Hz, $CH_3CH_2CH_2$), 1.24 (3H, d, J=6.3 Hz, CH_3C–O), 0.91 (3H, t, J=7.5 Hz, $CH_3(CH_2)_2$); IR (liquid film) 2961, 2930, 2872, 2370, 1458, 1369, 1317, 1261, 1109, 1076, 972 cm^{-1}. MS: 268 (M^+), 253, 225, 212, 199, 155 (100%), 141, 113, 97. Anal. Calcd for $C_9H_{17}IO$: C, 40.31; H, 6.39; I, 47.33. Found: C, 40.31; H, 6.33; I, 47.30.

1.2.7. Preparation of *cis*-4,9-dioxa-12-iodo-1,6-dodecadiene (16). To a suspension of sodium hydride (65% assay, 554 mg, 15 mmol) in THF (20 mL) was added *cis*-2-butene-1,4-diol (3 mL) at 0°C under argon. After being stirred for 15 min, allyl bromide (1.81 g, 15 mmol) was introduced dropwise at 0°C. The mixture was warmed to room temperature and stirred there for 3 h. It was then poured into brine and extracted with ether. The ethereal extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (ether/hexane=1:1 as eluent) to afford 5-oxa-2,7-octadiene-1-ol (**22**) as a colorless oil (1.54 g, 12.0 mmol, 80%): ^{1}H NMR ($CDCl_3$) δ 5.92 (1H, ddt, J=5.7, 10.4, 17.2 Hz, CH=C), 5.67–5.87 (2H, m, O–CCH=CHC–O), 5.29 (1H, d, J=17.2 Hz, O–CC=CH), 5.20 (1H, d, J=10.4 Hz, O–CC=CH), 4.21 (2H, t, J=5.6 Hz, C=CCH_2OH), 4.07 (2H, d, J=6.0 Hz, C=CCH_2O), 4.00 (2H, d, J=5.7 Hz, OCH_2C=C), 1.84 (1H, t, J=5.6 Hz, OH) (Scheme 7).

Sodium hydride (65% assay, 532 mg, 14.4 mmol) was suspended in THF (20 mL) and **22** obtained above (12.0 mmol) was added at 0°C under argon. The mixture was stirred for 15 min and the mesylate **23** (4.03 g, 15 mmol), prepared from 1,3-propanediol by the silylation–mesylation sequence (70% in two steps), was introduced. After the addition of hexamethylphosphoric triamide (HMPA, 4 mL), the mixture was warmed to room temperature and stirred for 5 h. The reaction was quenched with brine and extracted with ether. The organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel (ether/hexane=1:1 as eluent) furnished **24** as a colorless oil (2.49 g, 8.4 mmol, 70%): ^{1}H NMR ($CDCl_3$) δ 5.92 (1H, ddt, J=5.7, 10.5, 17.1 Hz, CH=C), 5.72 (2H, m, O–CCH=CHC–O), 5.29 (1H, d, J=17.1 Hz, O–CC=CH), 5.20 (1H, d, J=10.5 Hz, O–CC=CH), 4.06 (2H, d, J=4.5 Hz, OCH_2C=CC), 4.03 (2H, d, J=4.5 Hz, OCH_2C=CC), 3.97 (2H, d, J=5.7 Hz, OCH_2C=C), 3.69 (2H, t, J=6.3 Hz, CH_2OSi), 3.50 (2H, t, J=6.3 Hz, O–CH_2), 1.78 (2H, quint, J=6.3 Hz, CH_2), 0.88 (9H, s, *t*-Bu), 0.04 (6H, s, $2CH_3$).

The *tert*-butyldimethylsilyl ether (**24**) was cleaved quantitatively by the treatment with TBAF in THF. To a solution of the alcohol **25** (8.4 mmol) in dichloromethane (10 mL) was added pyridine (2.7 mL, 33.6 mmol) and triphenylphosphine (2.62 g, 10.0 mmol) at 0°C under argon. After stirring for 30 min, iodine (2.53 g, 10.0 mmol) was added portionwise and the resulting mixture was stirred for additional 1 h at 0°C. The excess iodine was reduced by the addition of saturated Na_2SO_3 and the whole mixture was poured into saturated $NaHCO_3$. Extractive workup was performed with ether and the ethereal extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane=1:30 as eluent) gave **16** as a colorless oil (1.74 g, 5.88 mmol, 70% in two steps): ^{1}H NMR ($CDCl_3$) δ 5.92 (1H, ddt, J=5.7, 10.5, 17.1 Hz, CH=C), 5.67–5.79 (2H, m, O–CCH=CHC–O), 5.29 (1H, d, J=17.1 Hz, O–CC=CH), 5.20 (1H, d, J=10.5 Hz, O–CC=CH), 4.06 (4H, m, OCH_2C=CCH_2O), 3.98 (1H, d, J=5.7 Hz, OCH_2C=C), 3.48 (1H, t, J=5.4 Hz, O–CH_2), 3.28 (2H, t, J=6.9 Hz, CH_2I), 2.05 (2H, tt, J=5.4, 6.9 Hz, CH_2CI); IR (liquid film) 3022, 2860, 1474, 1420, 1329, 1236, 1182, 1105, 1012, 929 cm^{-1}. MS: 296 (M^+), 238, 186, 169 (100%), 141, 128, 110. Anal. Calcd for $C_{10}H_{17}IO_2$: C, 40.56; H, 5.79; I, 42.85. Found: C, 40.59; H, 5.67; I, 43.19.

1.2.8. *cis*-4,9-Dioxa-12-iodo-6-dodecen-1-yne (19). ^{1}H NMR ($CDCl_3$) δ 5.67–5.81 (2H, m, O–CCH=CHC–O), 4.17 (2H, d, J=5.1 Hz, OCH_2C=CC), 4.16 (2H, s, OCH_2C≡C), 4.09 (2H, d, J=5.1 Hz, OCH_2C=CC), 3.50 (2H, t, J=5.7 Hz, OCH_2CCI), 3.28 (2H, t, J=6.7 Hz, CH_2I), 2.45 (1H, m, C≡CH), 2.06 (2H, tt, J=5.7, 6.7 Hz,

CH_2CI); IR (liquid film) 3294, 3026, 2860, 2116, 1474, 1439, 1354, 1331, 1269, 1236, 1182, 1099, 1028, 677 cm^{-1}. MS: 293 ($[M-H]^+$), 238, 225, 184, 169 (100%), 155, 141, 128, 107. Anal. Calcd for $C_{10}H_{15}IO_2$: C, 40.84; H, 5.14; I, 43.15. Found: C, 41.05; H, 5.19; I, 43.11.

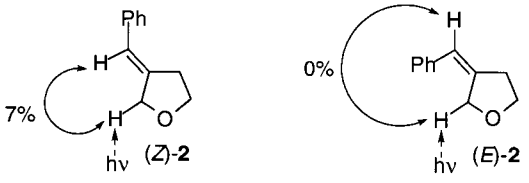
1.2.9. Preparation of ATPH. A solution of 2,6-diphenylphenol (739 mg, 3 mmol) in toluene (5 mL) was carefully degassed and a 2 M hexane solution of Me_3Al (0.5 mL, 1 mmol) was added at room temperature under argon. The methane gas evolved immediately. The resulting slightly yellow solution was stirred at room temperature for 30 min and used as a solution of ATPH in toluene without any purification.

1.3. General method for the intramolecular radical cyclizations with ATPH

To a solution of ATPH (1 mmol) in toluene (5 mL) was added iodoalkyl ether (0.5 mmol) at −78°C, and the resulting mixture was stirred for 10 min to generate ATPH–ether complex. Then tributyltin hydride (Bu_3SnH, 161 μL, 0.6 mmol) and Et_3B (100 μL, 0.1 mmol) were introduced sequentially at the same temperature. The reaction was monitored by TLC analysis. After the completion of the reaction, the resulting mixture was poured into saturated $NaHCO_3$ and extracted with ether. The organic extracts were dried over Na_2SO_4 and concentrated. Purification by column chromatography on silica gel (dichloromethane/hexane=1:4, then ether/hexane=1:10 as eluent) gave the corresponding cyclic ether as a colorless oil except **6** (light yellow oil).

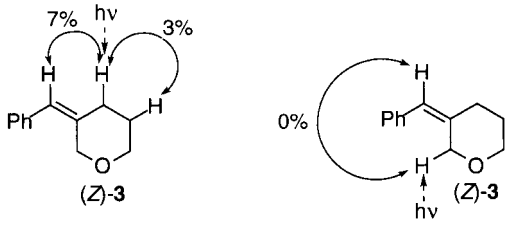
1.3.1. 3-Benzylidenetetrahydrofuran (2). ^1H NMR ($CDCl_3$) δ 7.10–7.40 (5H, m, Ph), 6.45 (1H, m, CH=C, *Z*-isomer), 6.37 (1H, m, CH=C, *E*-isomer), 4.58 (2H, m, C=CCH_2O, *Z*-isomer), 4.46 (2H, m, C=CCH_2O, *E*-isomer), 4.01 (2H, t, *J*=6.9 Hz, CH_2–O, *E*-isomer), 3.90 (2H, t, *J*=6.9 Hz, CH_2–O, *Z*-isomer), 2.82 (2H, m, CH_2C–O, *E*-isomer), 2.77 (2H, m, CH_2C–O, *Z*-isomer); IR (liquid film) 3024, 2953, 2852, 1603, 1491, 1448, 1317, 1142, 1072, 1053, 964, 922, 862, 752, 696 cm^{-1}. MS: 160 (M^+), 142, 131 (100%), 115, 104, 91. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.30; H, 7.71.

Stereochemical assignment of (*E*)- and (*Z*)-**2** was performed by the difference NOE spectra measurement. Irradiation of the α-proton of the furan ring resulted in a 7% NOE to the olefinic proton in the case of *Z*-isomer, while no NOE was observed between the α-proton and the olefinic proton with *E*-isomer as shown below.



1.3.2. 3-Benzylidenetetrahydropyran (3).[13] ^1H NMR ($CDCl_3$) δ 7.11–7.35 (5H, m, Ph), 6.37 (1H, s, CH=C), 4.33 (2H, s, C=CCH_2O, *Z*-isomer), 4.17 (2H, s, C=CCH_2O, *E*-isomer), 3.81 (2H, t, *J*=5.1 Hz, CH_2–O, *E*-isomer), 3.77 (2H, t, *J*=5.4 Hz, CH_2–O, *Z*-isomer), 2.59 (2H, dt, *J*=1.5, 6.3 Hz, CH_2C=C, *E*-isomer), 2.46 (2H, dt, *J*=1.5, 6.0 Hz, CH_2C=C, *Z*-isomer), 1.81 (2H, m, CH_2C–O, *Z*-isomer), 1.70 (2H, m, CH_2C–O, *E*-isomer); IR (liquid film) 3022, 2954, 2835, 1491, 1439, 1259, 1209, 1090, 1030, 951, 920, 880, 745, 700, 667 cm^{-1}. MS: 174 (M^+) (100%), 155, 145, 131, 115, 104.

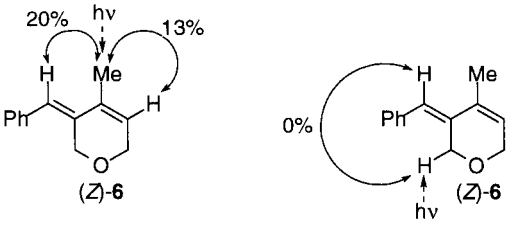
Stereochemistries were ascertained by conducting the difference NOE spectra measurement of (*Z*)-**3** in a similar manner as described above.



1.3.3. 3-Phenylpropynyl propyl ether (4).[14] ^1H NMR ($CDCl_3$) δ 7.42–7.48 (2H, m, Ph), 7.28–7.35 (3H, m, Ph), 4.37 (2H, s, C≡CCH_2O), 3.54 (2H, t, *J*=6.6 Hz, CH_2–O), 1.66 (2H, sex, *J*=7.5 Hz, CH_2C–O), 0.96 (2H, t, *J*=7.5 Hz, CH_3); IR (liquid film) 2963, 2937, 2877, 2189, 1663, 1599, 1491, 1443, 1358, 1256, 1097, 1045, 961, 916, 758, 692 cm^{-1}. MS: 174 (M^+), 159, 145, 131, 115 (100%), 103.

1.3.4. 3-Benzylidene-4-methyl-2*H*,6*H*-dihydropyran (6). ^1H NMR ($CDCl_3$) δ 7.13–7.36 (5H, m, Ph), 6.51 (1H, s, PhCH=C, *Z*-isomer), 6.41 (1H, s, PhCH=C, *E*-isomer), 5.78 (1H, m, C=CHC–O, *Z*-isomer), 5.57 (1H, m, C=CHC–O, *E*-isomer), 4.58 (2H, s, PhC=CCH_2O, *Z*-isomer), 4.31 (2H, m, OCH_2C=CCH_3, *E*-isomer), 4.25 (2H, m, OCH_2C=CCH_3, *Z*-isomer), 4.23 (2H, s, PhC=CCH_2O, *E*-isomer), 1.97 (3H, s, CH_3, *Z*-isomer), 1.49 (3H, s, CH_3, *E*-isomer); IR (liquid film) 3022, 2932, 2812, 2361, 1705, 1597, 1491, 1445, 1394, 1292, 1217, 1130, 1074, 1032, 968, 894, 864, 729, 698 cm^{-1}. MS: 186 (M^+), 171, 157, 142 (100%), 129, 115. HRMS Calcd for $C_{13}H_{14}O$: 186.1045 (M^+). Found: 186.1043 (M^+).

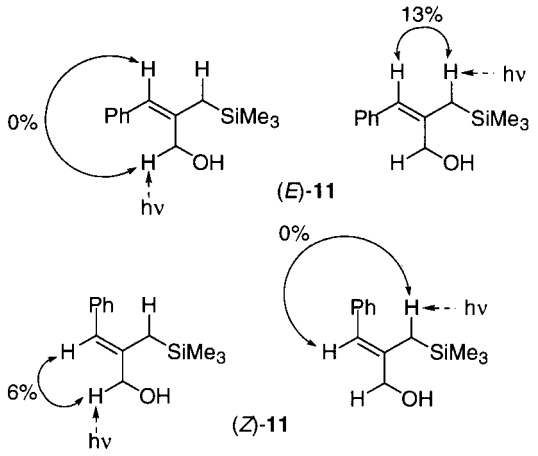
Stereochemistries were confirmed by the difference NOE spectra measurement of (*Z*)-**6** as shown below.



1.3.5. 3-Phenyl-2-trimethylsilylmethyl-2-propen-1-ol (11).[15] ^1H NMR ($CDCl_3$) δ 7.17–7.47 (5H, m, Ph), 6.43 (1H, s, PhCH=C, *Z*-isomer), 6.30 (1H, s, PhCH=C, *E*-isomer), 4.26 (2H, d, *J*=5.7 Hz, CH_2O, *E*-isomer), 4.15 (2H, d, *J*=6.3 Hz, CH_2O, *Z*-isomer), 1.92 (2H, s, C=CCH_2Si, *Z*-isomer), 1.83 (2H, s, C=CCH_2Si, *E*-isomer), 1.46 (1H, t, *J*=6.3 Hz, OH, *Z*-isomer), 1.31 (1H, t, *J*=5.7 Hz, OH,

E-isomer), 0.10 (9H, s, $3CH_3$, *E*-isomer), 0.00 (9H, s, $3CH_3$, *Z*-isomer); IR (liquid film) 3341, 2955, 2358, 1647, 1599, 1491, 1447, 1418, 1250, 1157, 1034, 853, 756, 698 cm^{-1}. MS: 220 (M^+), 205, 145, 131, 129 (100%), 115, 91.

Stereochemical assignment was carried out by measuring the difference NOE spectra of (*E*)- and (*Z*)-**11**.



1.3.6. *cis*-1-Butyl-2-methyltetrahydrofuran (*cis*-13).[16] ^1H NMR ($CDCl_3$) δ 4.06 (1H, quint, J=6.3 Hz, C*H*(CH_3)O), 3.91 (1H, dt, J=3.9, 8.4 Hz, CH–O), 3.68 (1H, dt, J=7.2, 8.4 Hz, CH–O), 2.03–2.14 (1H, m, C*H*C(CH_3)O), 1.93–2.04 (1H, m, CHC–O), 1.52–1.65 (1H, m, CHC–O), 1.19–1.47 (6H, m, $CH_3(CH_2)_3$), 1.06 (3H, d, J=6.3 Hz, CH_3C–O), 0.90 (3H, t, J=6.9 Hz, $CH_3(CH_2)_3$); IR (liquid film) 2961, 2930, 2860, 1460, 1379, 1101, 1076, 1043, 856, 734 cm^{-1}. MS: 141 ($[M-H]^+$), 127, 111, 97, 83 (100%).

1.3.7. *trans*-1-Butyl-2-methyltetrahydrofuran (*trans*-13).[16] ^1H NMR ($CDCl_3$) δ 3.84 (1H, dt, J=5.7, 8.1 Hz, CH–O), 3.78 (1H, dt, J=3.3, 8.1 Hz, CH–O), 3.47 (1H, quint, J=6.3 Hz, C*H*(CH_3)O), 2.05–2.18 (1H, m, CHC–O), 1.49–1.63 (1H, m, CHC–O), 1.40–1.49 (1H, m, C*H*C(CH_3)O), 1.16–1.38 (6H, m, $CH_3(CH_2)_3$), 1.23 (3H, d, J=6.3 Hz, CH_3C–O), 0.91 (3H, t, J=6.9 Hz, $CH_3(CH_2)_3$); IR (liquid film) 2963, 2926, 2860, 1456, 1381, 1111, 1086, 1032, 866, 733 cm^{-1}.

Stereochemistries of *cis*- and *trans*-**13** were determined by comparing their CH_3 signals of ^1H NMR spectra with those of (2α,3α)- and (2α,3β)-(±)-tetrahydro-2,3-dimethylfurans. The characteristic peaks were as follows; *cis*-**13**: δ 1.06 (3H, d, J=6.3 Hz, CH_3C–O); (2α,3α)-(±)-tetrahydro-2,3-dimethylfuran: δ 1.05 (3H, d, J=6 Hz, CH_3C–O); *trans*-**13**: δ 1.23 (3H, d, J=6.3 Hz, CH_3C–O); (2α,3β)-(±)-tetrahydro-2,3-dimethylfuran: δ 1.15 (3H, d, J=6 Hz, CH_3C–O).

1.3.8. 4-Methyl-3-(3-tetrahydropyranyl)tetrahydrofuran (17). ^1H NMR ($CDCl_3$) δ 3.80–4.00 (3H, m, 3(O–CH)), 3.29–3.80 (4H, m, 4(O–CH)), 3.08–3.19 (1H, m, O–CH), 2.01–2.34 (1H, m, O–CCH), 1.88–2.00 (1H, m, O–CCH), 1.45–1.71 (4H, m, O–CCHCH, 2(O–CCH)), 1.15–1.34 (1H, m, O–CCCH), 1.05 (0.6H, d, J=6.6 Hz, CH_3), 1.02 (0.3H, d, J=6.9 Hz, CH_3), 0.95 (0.7H, d, J=6.9 Hz, CH_3), 0.94 (1.4H, d, J=7.2 Hz, CH_3); IR (liquid film) 2932, 2851, 1458, 1387, 1281, 1221, 1180, 1096, 1030, 982, 910, 874, 850, 681 cm^{-1}. MS: 169 ($[M-H]^+$), 155, 143, 129, 117, 104, 83 (100%). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.72; H, 10.47.

1.3.9. *cis*-4,9-Dioxa-1,6-dodecadiene (18). ^1H NMR ($CDCl_3$) δ 5.92 (1H, ddt, J=5.7, 10.5, 17.1 Hz, CH=C), 5.71–5.74 (2H, m, O–CCH=CHC–O), 5.28 (1H, d, J=17.1 Hz, O–CC=CH), 5.20 (1H, d, J=10.5 Hz, O–CC=CH), 4.07 (2H, d, J=4.8 Hz, OCH_2C=CC), 4.04 (2H, d, J=4.8 Hz, OCH_2C=CC), 3.98 (2H, d, J=5.7 Hz, OCH_2C=C), 3.38 (2H, t, J=6.6 Hz, O*C*$H_2CH_2CH_3$), 1.60 (2H, sex, J=7.5 Hz, $CH_2CH_2CH_3$), 0.92 (3H, t, J=7.5 Hz, $(CH_2)_2CH_3$); IR (liquid film) 2964, 2932, 2855, 1650, 1456, 1329, 1269, 1099, 993, 926, 714, cm^{-1}. MS: 169 ($[M-H]^+$), 153, 145, 129, 112, 95, 83 (100%). HRMS Calcd for $C_{10}H_{17}O_2$ ($[M-H]^+$): 169.1228. Found: 169.1234.

1.3.10. 3-Methylene-4-(3-tetrahydropyranyl)tetrahydrofuran (20). ^1H NMR ($CDCl_3$) δ 5.03 (1H, s, C=CH), 4.97 (1H, m, C=CH), 4.26 (2H, br s, OCH_2C=C), 3.77–4.01 (4H, m, 4(O–CH)), 3.30–3.40 (1H, m, O–CH), 3.21 (0.6H, t, J=11.1 Hz, O–CH), 3.16 (0.4H, t, J=11.1 Hz, O–CH), 2.42–2.58 (1H, m, O–CCHC=C), 1.70–1.95 (2H, m, O–CCHCCH), 1.55–1.69 (2H, m, O–CCHCH), 1.19–1.37 (1H, m, O–CCH); IR (liquid film) 2936, 2847, 2364, 1665, 1466, 1450, 1281, 1205, 1178, 1093, 1064, 921, 893, 669 cm^{-1}. MS: 167 ($[M-H]^+$), 149, 121, 107, 93, 83 (100%). HRMS Calcd for $C_{10}H_{15}O_2$ ($[M-H]^+$): 167.1072. Found: 167.1039.

1.3.11. *cis*-4,9-Dioxa-6-dodecen-1-yne (21). ^1H NMR ($CDCl_3$) δ 5.65–5.83 (2H, m, O–CCH=CHC–O), 4.17 (2H, d, J=6.0 Hz, OCH_2C=CC), 4.15 (2H, s, OCH_2C≡C), 4.06 (2H, d, J=6.0 Hz, OCH_2C=CC), 3.39 (2H, t, J=6.6 Hz, O*C*$H_2CH_2CH_3$), 2.44 (1H, m, C≡CH), 1.62 (2H, sex, J=7.2 Hz, $CH_2CH_2CH_3$), 0.93 (3H, t, J=7.2 Hz, $(CH_2)_2CH_3$); IR (liquid film) 3296, 2963, 2936, 2862, 2359, 1464, 1360, 1331, 1267, 1096, 1045, 945, 669 cm^{-1}. MS: 168 (M^+), 153, 138, 125, 112 (100%), 107. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.59.

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