Regular Article

Synthesis of α -Methylene- γ -lactone Structure by Cyclization of ω -Formylallylsilane in WaterHiroki Fukushima,^a Daisuke Ikegami,^a Chiaki Kuroda,^{*a} and Kenichi Kobayashi^b^aDepartment of Chemistry, Rikkyo University; Nishi-Ikebukuro, Toshima-ku, Tokyo 171–8501, Japan; and ^bGraduate School of Pharmaceutical Sciences, Meiji Pharmaceutical University; 2–522–1 Noshio, Kiyose, Tokyo 204–8588, Japan.

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Surfactant-type protonic acid-promoted intramolecular cyclization of functionalized allylsilanes was studied in water for the synthesis of α -methylene- γ -lactone compounds. ω -Formyl- β -(acetoxymethyl)allylsilane afforded carbocyclic compounds in good yields, while the cyclization product was not obtained from the corresponding β -ethoxycarbonyl derivative. It was found that (*Z*)- β -(acetoxymethyl)allylsilane predominantly afforded the *cis*-product, while (*E*)- β -(acetoxymethyl)allylsilane afforded both *cis*- and *trans*-products at a ratio of almost 1:1. The stereoselectivity of the cyclization reaction was almost the same as a protonic acid-promoted reaction in CH_2Cl_2 and was explained by an interaction between the C(Si)–C(alkene) bond and the carbonyl moiety. The cyclization products were converted to α -methylene- γ -lactone compounds.

Key words aqueous organic reaction; allylsilane; α -methylene- γ -lactone; stereochemistry

α -Methylene- γ -lactone (4,5-dihydro-3-methylene-2(3*H*)-furanone) structures fused to various carbocycles are often found in natural terpenoids, such as germacranolides, guaianolides, and eudesmanolides, and some of them have biological activities including anti-inflammatory, anti-bacterial, and cytotoxic properties.^{1–3} The two rings, carbocycle and α -methylene- γ -lactone, can be synthesized at once by acid- or fluoride-promoted intramolecular cyclization of β -(ethoxycarbonyl)allylsilane with aldehyde^{4,5} (Chart 1). During the 1990s, we^{6–9} and Nishitani's group^{10–14} independently synthesized various α -methylene- γ -lactone compounds by this method. A non-conjugated moiety, β -(acetoxymethyl)-allylsilane, was also used to synthesize large-size ring compounds.¹⁵ β -(Ethoxycarbonyl)allylsilane and its derivatives are carbon-1,3-dipole equivalents; that is, the γ -carbon of allylsilane acts as a nucleophile and the carbonyl carbon as an electrophile. A variety of carbon 1,3-dipole compounds are known to be versatile building blocks in organic synthesis.^{16–18} We prepared some related compounds, such as bicyclo[4.3.0]-nonanes,^{19,20} spiro[4.5]decanes,^{21,22} and cycloundecanes^{23,24} by related reactions, such as carbobicyclization, Nazarov reaction, and homo-Cope reaction, respectively.

Organic reactions in water, in which the use of harmful organic solvents can be avoided, have recently been extensively developed.^{25–29} Among them, C–C bond formation in water is especially important because many common reactions, such as Grignard and Wittig reactions, utilize various carbanions or their equivalents, but carbanions are not stable in water. Allylsilanes are water-stable carbanion equivalents. Thus, it is

useful to study the above carbocyclization reactions in water. In organic solvents, the cyclization reactions have largely been carried out under aprotic conditions using TiCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$, and other Lewis acid catalysts.^{8–15,19–22} These common Lewis acids are not applicable for use in water. Instead, surfactant-type protonic acids such as dodecylbenzenesulfonic acid (DBSA) are useful.^{26,28,30} Here, we report that the cyclization reaction proceeds in good yield using DBSA as a surfactant-type protonic acid catalyst.

Results and Discussion

We initially studied the cyclization of **1**, which is known to cyclize by treatment with a Lewis acid in organic solvents in good yields.^{10,11} Compound **1** was prepared as a mixture of *Z*- and *E*-isomers (ratio *ca.* 2:1) from 1,6-hexanediol according to previous reports^{10,11,19} with a slight modification (Chart 2). Namely, monoprotection of 1,6-hexanediol with tetrahydropyranyl (THP) group followed by Swern oxidation produced **2**. The β -(ethoxycarbonyl)allylsilane moiety was introduced by Horner–Wadsworth–Emmons reaction to afford **3**, which was converted to **1** by deprotection and oxidation. When **1** was treated with DBSA in water, only a complex mixture was obtained. HBF_4 /sodium dodecyl sulfate³¹ was also employed instead of DBSA but the reaction proved unsuccessful. We previously obtained cyclization products from related compounds by protonic acid treatment in acetone.^{6,7} Thus, *p*-toluenesulfonic acid (*p*-TsOH) was used as a protonic acid in tetrahydrofuran (THF)/ H_2O (9:1) or acetone/ H_2O (9:1) but again, no cyclization product was afforded. Scandium and ytterbium trifluoromethanesulfonate ($\text{Sc}(\text{OTf})_3$ and $\text{Yb}(\text{OTf})_3$) are often used as Lewis acid catalysts in aqueous organic reactions.^{32,33} However, the expected cyclization reaction did not occur when **1** was treated with these Lewis acids.

The reaction was also studied using thioester, which is a good electrophile in aqueous organic reactions. Thioesters are often found in biological compounds such as acetyl CoA. Thus, the aldehyde group in **1** was oxidized to carboxylic

Chart 1. Intramolecular Cyclization of ω -Formyl- β -(ethoxycarbonyl)-allylsilane

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Chart 2. Synthesis of ω -Formyl- β -(ethoxycarbonyl)allylsilane **1** Chart 3. Synthesis of Thioester Derivative **5** Chart 4. Synthesis and Cyclization Reaction of Allylsilane **8** Chart 5. Synthesis of ω -Formyl- β -(acetoxymethyl)allylsilane **14**

acid **4** (79% yield) followed by thioesterification³⁴⁾ to afford **5** (65%) (Chart 3). However, aqueous cyclization of **5** was unsuccessful; namely, when **5** was treated with DBSA in water, only a hydrolysis product (**4**) was afforded.

From these results, we thought that the nucleophilicity of the allylsilane moiety in both **1** and **5** was lower than H_2O due to the presence of a conjugated ethoxycarbonyl group. As a model study, we prepared a simple allylsilane **8** and studied its cyclization reaction. Compound **8** was prepared from **2** by analogous methods, namely, Wittig reaction (**6**, 93%), hydrolysis (**7**, 91%), and oxidation (**8**, 93%) (Chart 4). When **8** was treated with 1 eq of DBSA in water (0.3M), the expected cyclization reaction occurred. However, the cyclization product **9** was too volatile to isolate. Then, the product was obtained as benzoate **10** in 74% yield by treatment of **9** with benzoyl chloride (BzCl). The cyclization reaction was also carried out

in 0.07 and 0.03M solutions to obtain **10** in almost the same yield (73 to 74%).

After the success of the cyclization of the non-conjugated allylsilane compound, β -(acetoxymethyl)allylsilane **14** was designed to synthesize the α -methylene- γ -lactone compound. We previously reported that cyclization of ω -formyl- β -(acetoxymethyl)allylsilane proceeded in better yields than that of the β -ethoxycarbonyl derivative in the synthesis of large rings.¹⁵⁾ Compound **14** was synthesized from **3** via a diisobutylaluminum hydride (DIBAL-H) reduction (**11**, 88%), acetylation (**12**, 91%), removal of the THP group (**13**, 93%), and Dess–Martin oxidation (**14**, 84%) (Chart 5).

DBSA-promoted intramolecular cyclization reactions of **14** were examined (Table 1 and Chart 6). The expected cyclization products (**15a** and **15b**) were obtained together with acetyl-migrated products (**16a** and **16b**) and hydrolyzed

Chart 6. Cyclization Reaction of **14**Table 1. DBSA Promoted Cyclization of **14** in Water under Various Conditions^{a)}

Entry	Conc. of DBSA (M) ^{b)}	Time (h)	Yield (%) ^{c)}		
			15a, b	16a, b	17a, b
1	0.01	1	49	20	0
2	0.01	1.5	51	25	3
3	0.01	24	18	20	56
4	0.02	24	15	6	13
5	0.1	95	— ^{d)}	— ^{d)}	— ^{d)}
6	0.25	20	— ^{d)}	— ^{d)}	— ^{d)}

a) **14z**:**14e**=ca. 2:1. b) 1 eq of DBSA was used. c) The ratio was determined from the ¹H-NMR data of the reaction mixture. d) Only a complex mixture was afforded.

Table 2. Cyclization of **14** with Various *Z/E* Ratios^{a)}

Entry	Substrate ratio (14z : 14e)	Product ratio (<i>cis</i> : <i>trans</i>) ^{b),c)}
1	95:5	83:17
2	75:25	80:20
3	69:31	72:28
4	57:43	67:33
5	34:66	60:40

a) Conditions: 0.01 M DBSA in water, r.t., 24 h. b) *cis*-products=**15a**, **16a**, and **17a**; *trans*-products=**15b**, **16b**, and **17b**. c) The ratio was determined from the ¹H-NMR data of the reaction mixture. Total yields were 87–93%.

products (**17a** and **17b**). When the reaction was carried out in 0.01 M DBSA solution for 24 h, the products were obtained in 94% total yield (entry 3). The hydrolyzed products (**17a** and **17b**) were not obtained with shorter reaction times (entries 1 and 2), indicating that hydrolysis occurred after cyclization. In 0.02 M solution, the products were obtained in lower yield with some by-products (entry 4), and only complex mixtures were afforded in 0.1 and 0.25 M solutions (entries 5 and 6). The stereoselectivity of the reaction was then studied. Although it was difficult to isolate each **14z** and **14e** in pure form, mixtures at various ratios were obtained and their cyclization reactions were examined (Table 2). From the data, it was determined that **14z** and **14e** afforded the *cis*-products (**15a**, **16a**, and **17a**) and *trans*-products (**15b**, **16b**, and **17b**) at ratios of 86:14 and 46:54, respectively; that is, the cyclization of **14z** was *cis*-selective, while that of **14e** was non-stereoselective.

In the previous study, Lewis acid- or protonic acid-promoted cyclization reactions of both (*Z*)- and (*E*)- β -(ethoxycarbonyl)-allylsilanes in organic solvent were stereoselective, affording *cis*- and *trans*-products, respectively.^{6,7,10,11} Nishitani *et al.* explained the stereoselectivity of the cyclization of (*Z*)- and (*E*)-**1** in terms of “secondary orbital overlapping” between the trimethylsilyl-bearing carbon and the carbonyl oxygen in the conformers **ZA** and **EB** (Fig. 1, R=COOEt).¹¹ In

Fig. 1. Conformation of the Cyclization Reaction

Dotted lines indicate interaction¹¹⁾ and arrows indicate antiparallel electron flow³⁵⁾ (**14**: R=CH₂OAc).

their case and in our previous case,⁷⁾ the conformers **ZC**, **ZD**, **EC**, and **ED** were not considered because the bulky β -(ethoxycarbonyl)allylsilane moiety takes an axial orientation with respect to the newly forming cyclohexane ring. Later, Schlosser *et al.* explained the phenomenon in terms of “antiparallel electron flow” between the C(Si)–C(alkene) bond and the acid-activated C=O bond.³⁵⁾ In their case, the conformers **ZC**, **ZD**, **EC**, and **ED** were considered because of the absence of bulky substituents (Fig. 1, R=H, Me). As reported by Schlosser *et al.*, only **ZA** has the benefit of “antiparallel electron flow” in the *Z*-precursor (the C(Si)–C(alkene) and C=O bonds are parallel only in **ZA**), while both **EB** and **EC** are favorable conformers in the *E*-precursor (Fig. 1). The stereoselectivity of the cyclization of **14** can also be explained by the contribution of **ZA** to **14z**, and **EB** and **EC** to **14e** (Fig. 1, R=CH₂OAc).³⁶⁾ Although DBSA may have formed micelles under the present reaction conditions (critical micelle concentration of DBSA=ca. 5×10^{-4} M³⁷⁾), it is not clear whether the reaction occurred in the micelles or in the bulk water solution.

Reactivity of organic compounds in water is sometimes different from that in organic solvents due to the hydrophobic effect.^{38,39)} Thus, as a reference, we also studied the acid-promoted cyclization of **14** in organic solvent. The reactions were carried out in CH₂Cl₂ at room temperature (r.t.) using camphorsulfonic acid (CSA) or BF₃·OEt₂ as a protonic acid or Lewis acid catalyst, respectively; the results are shown in Table 3. From these data, stereoselectivity of each **14z** and **14e** was calculated. The CSA-promoted reaction of **14z** was *cis*-selective (*cis*:*trans*=93:7) and that of **14e** was non-stereoselective (*cis*:*trans*=43:57) (entries 1 and 2), as in the case of water solvent, but the yields were lower than in water. In contrast, both **14z** and **14e** afforded *cis*- and *trans*-products in almost the same ratio in BF₃·OEt₂-promoted cyclization (*cis*:*trans*=ca. 3:7 for both **14z** and **14e**, respectively) (entries 3 and 4).⁴⁰⁾ These results indicated that the stereochemistry of

Table 3. Acid Promoted Cyclization of **14** in CH₂Cl₂^{a)}

Entry	Substrate ratio (14z : 14e)	Acid ^{b)}	Product ratio (<i>cis</i> : <i>trans</i>) ^{c)}	Yield (%)
1	95:5	CSA	90:10	68
2	69:31	CSA	77:23	51
3	95:5	BF ₃ ·OEt ₂	28:72	74
4	69:31	BF ₃ ·OEt ₂	29:71	80

a) Conditions: the reactions were carried out at r.t. b) About 1.2eq of acid was used. c) *cis*-products=**15a**, **16a**, and **17a**; *trans*-products=**15b**, **16b**, and **17b**.

Chart 7. Lactonization Reaction

cyclization depends on the catalyst, protonic acid, or Lewis acid.

Finally, lactonization reactions were performed. A mixture of **15a**, **15b**, **16a**, and **16b** was hydrolyzed to obtain **17a** and **17b**, which were then separated. When **17a** was treated with MnO₂, the desired lactone **18** was obtained in 55% yield (Chart 7). However, **17b** did not afford the corresponding lactone **20** and yielded only aldehyde **19**. The lactone **20** was finally obtained by a Nishiyama's method using MnO₂ and NaCN.⁴¹⁾

Conclusion

Intramolecular cyclization of ω -formyl- β -(acetoxymethyl)-allylsilane **14** successfully proceeded in aqueous media to afford the corresponding carbocyclic compounds in good yield. The stereoselectivity of the cyclization reaction was almost the same as the CSA-promoted reaction in CH₂Cl₂. Thus, it was proved that aprotic organic solvents could be effectively replaced by water in cyclization reactions of allylsilanes.

Experimental

General Procedures ¹H-NMR spectra were measured on a JEOL ECX-400 (400MHz) spectrometer in CDCl₃ as the solvent. The chemical shifts are expressed in ppm downfield from either tetramethylsilane (δ =0.00) added as an internal standard, or CHCl₃ (δ =7.26). ¹³C-NMR spectra were measured at 100MHz. The chemical shifts are reported in ppm, relative to tetramethylsilane (δ =0.0) or the central line of a triplet at 77.0ppm for CDCl₃. IR spectra were measured on a JASCO FT/IR-230 spectrometer. High-resolution (HR) MS were obtained using a JEOL JMS 700 instrument with a direct inlet system. Column chromatography was carried out on silica gel (Wakogel C-200 or C-300). Analytical TLC was performed on precoated TLC plates (Kieselgel 60 F254, layer thickness 0.2mm). Anhydrous Na₂SO₄ or MgSO₄ was used as the drying agents for the extracted organic layers.

7-Ethoxycarbonyl-8-(trimethylsilyl)oct-6-enoic Acid (**4**)

Compound **1** (627mg, 2.32mmol) was dissolved in THF (90mL), and *t*-BuOH (90mL), 2-methyl-2-butene (9.9mL), and a solution of NaClO₂ (845.2mg) and NaH₂PO₄·2H₂O (1.45g) in water (30mL) were added successively at r.t. with stirring. After further stirring for 1d, 6M HCl aq. was added, and the mixture was extracted with CH₂Cl₂ and dried. Evaporation of the solvent followed by silica gel (20g) column chromatography using hexane/EtOAc (96:4) as the eluent afforded a crude product. To remove by-products, the crude product was dissolved in EtOAc, and extracted with Na₂CO₃ aq. The aqueous layer was acidified by the addition of 2M HCl aq. and extracted with CH₂Cl₂. After drying and removal of the solvent, the residue was chromatographed on silica gel (20g), as above, to yield **4** (526.5mg, 79%) as an oil; ¹H-NMR (CDCl₃) δ : -0.02 (9H×1/3, s), -0.01 (9H×2/3, s), 1.29 (3H×2/3, t, *J*=7.1Hz), 1.30 (3H×1/3, t, *J*=7.1Hz), 1.41–1.54 (2H, m), 1.62–1.73 (2H, m), 1.73 (2H×1/3, s), 1.80 (2H×2/3, s), 2.12 (2H×2/3, q, *J*=7.3Hz), 2.37 (2H, t, *J*=6.9Hz), 2.42 (2H×1/3, q, *J*=7.4Hz), 4.17 (2H×2/3, q, *J*=7.1Hz), 4.17 (2H×1/3, q, *J*=7.1Hz), 5.64 (1H×1/3, t, *J*=7.4Hz), 6.57 (1H×2/3, t, *J*=7.3Hz); ¹³C-NMR (CDCl₃) assigned for the *Z*-isomer δ : -1.1 (3C), 14.3, 24.3, 24.4, 28.2, 28.7, 33.6, 60.5, 129.9, 137.5, 168.3, 178.5; IR (neat/NaCl) cm⁻¹: 1713, 1636, 853; MS electron ionization (EI) *m/z*: 286 (M⁺, 14%), 271 (21), 185 (100), 73 (72); HR-EI-MS *m/z*: 286.1594 (M⁺) (Calcd for C₁₄H₂₆O₄Si: 286.1600).

2-[7-Ethoxycarbonyl-1-oxo-8-(trimethylsilyl)oct-6-en-1-ylthiol]propanoic Acid (5**)** To a stirred solution of **4** (217.9mg, 0.762mmol) in dry CH₂Cl₂ (2.8mL), (COCl)₂ (190 μ L) was added at once, and the mixture was stirred at 50°C for 3h. The mixture was evaporated to dryness and dry CH₂Cl₂ (1.5mL) was added. A solution of HS(CH₂)₂COOH (70 μ L) and Et₃N (0.22mL) in CH₂Cl₂ (1.6mL) was added at once at 0°C, and the mixture was stirred at r.t. for 1.5h. An aqueous solution of NH₄Cl was added, and the mixture was extracted with CH₂Cl₂ (5M HCl aq. and NaCl aq. were also added during the extraction process) and dried. Evaporation of the solvent followed by silica gel (5.4g) column chromatography using hexane/EtOAc (8:2) afforded **5** (185.8mg, 65%) as an oil; ¹H-NMR (CDCl₃) δ : -0.01 (9H×1/3, s), 0.00 (9H×2/3, s), 1.30 (3H×2/3, t, *J*=7.0Hz), 1.31 (3H×1/3, t, *J*=7.0Hz), 1.40–1.52 (2H, m), 1.65–1.75 (2H, m), 1.74 (2H×1/3, s), 1.81 (2H×2/3, s), 2.11 (2H×2/3, q, *J*=7.2Hz), 2.42 (2H×1/3, q, *J*=7.4Hz), 2.58 (2H, t-like, *J*=7.3Hz), 2.67–2.72 (2H, m), 3.09–3.16 (2H, m), 4.18 (2H×2/3, q, *J*=7.0Hz), 4.18 (2H×1/3, q, *J*=7.0Hz), 5.64 (1H×1/3, t, *J*=7.4Hz), 6.57 (1H×2/3, t, *J*=7.1Hz); ¹³C-NMR (CDCl₃) assigned for the *Z*-isomer δ : -1.1 (3C), 14.3, 23.5, 24.1, 25.3, 28.0, 28.7, 34.1, 43.8, 60.5, 130.5, 137.5, 168.4, 177.0, 198.9; IR (neat/NaCl) cm⁻¹: 3000 (broad), 1726, 1711, 1636, 853; MS (EI) *m/z*: 359 (M⁺-Me, 27%), 223 (36), 185 (52), 151 (100), 73 (81); HR-EI-MS *m/z*: 374.1582 (M⁺) (Calcd for C₁₇H₃₀O₅Si: 374.1583).

1-(Tetrahydro-2H-pyran-2-yl)oxy-8-(trimethylsilyl)oct-6-ene (6**)** *n*-BuLi (2.6mL, 1.41M solution in hexane) was added to a stirred solution of Ph₃P⁺CH₂CH₂SiMe₃ I⁻ (1.802g) in dry THF (30mL) at -78°C, and the mixture was stirred at 0°C for 1.5h. The flask was cooled to -78°C, a solution of **2** (363.2mg, 1.816mmol) in THF (15mL) was added, and stirring was continued at 0°C for 18h. An aqueous solution of NH₄Cl was added, and the mixture was extracted with Et₂O and dried. After removal of the solvent, the residue was subjected to silica gel (20g) column chromatography using

hexane/EtOAc (97:3) to afford **6** (477.9 mg, 93%) as an oil; $^1\text{H-NMR}$ (CDCl_3) δ : -0.01 (9H, s), 1.32–1.41 (4H, m), 1.45 (2H, brd, $J=8.4\text{ Hz}$), 1.48–1.88 (8H, m), 1.95–2.02 (2H, m), 3.39 (1H, dt, $J=9.5, 6.7\text{ Hz}$), 3.46–3.54 (1H, m), 3.73 (1H, dt, $J=9.5, 6.9\text{ Hz}$), 3.83–3.90 (1H, m), 4.57 (1H, dd, $J=4.3, 2.7\text{ Hz}$), 5.21–5.29 (1H, m), 5.33–5.42 (1H, m); $^{13}\text{C-NMR}$ (CDCl_3) δ : -1.8 (3C), 18.4, 19.7, 25.5, 26.0, 27.0, 29.6, 29.7, 30.8, 62.3, 67.6, 98.8, 125.4, 127.5; IR (neat/ NaCl) cm^{-1} : 1248, 858; MS (EI) m/z : 284 (M^+ , 5%), 85 (100), 73 (63); HR-EI-MS m/z : 284.2173 (M^+) (Calcd for $\text{C}_{16}\text{H}_{32}\text{O}_2\text{Si}$: 284.2172).

8-(Trimethylsilyl)oct-6-en-1-ol (7) H_2O (3.8 mL) and *p*-TsOH monohydrate (26.1 mg) were added successively to a stirred solution of **6** (292.7 mg, 1.03 mmol) in MeOH (7.6 mL), and the mixture was refluxed for 4 h. After cooling to r.t., NaHCO_3 aq. was added, and the mixture was extracted with EtOAc and dried. Evaporation of the solvent followed by silica gel (5 g) column chromatography using hexane/EtOAc (95:5) as the eluent afforded **7**^{35,42} (186.7 mg, 91%).

8-(Trimethylsilyl)oct-6-enal (8) A solution of (COCl_2)₂ (260 μL) in CH_2Cl_2 (27 mL) was cooled to -78°C , and a solution of dimethylsulfoxide (0.3 mL) in CH_2Cl_2 (1 mL) was added. After stirring for 15 min, a solution of **7** (272.4 mg, 1.36 mmol) in CH_2Cl_2 (4 mL) was added, and stirring was continued for an additional 30 min. Et_3N (1.2 mL) was added, and the mixture was stirred at r.t. for 2 h. After the addition of NH_4Cl aq., the mixture was extracted with CH_2Cl_2 and dried. Evaporation of the solvent afforded an oily residue, which was chromatographed on neutral alumina (30 g, containing 10% water) using hexane as the eluent to afford **8**³⁵ (251.0 mg, 93%).

2-Vinylcyclohexan-1-yl Benzoate (10) A solution of DBSA (54.8 mg, 0.17 mmol) in water (0.6 mL) was prepared at r.t. with stirring, and **8** (31.4 mg, 0.16 mmol) was dissolved in this solution. After stirring at r.t. for 1 d, NaHCO_3 aq. was added, and the mixture was extracted with CH_2Cl_2 and dried. The solvent was evaporated off carefully, and the crude product **9** was dissolved in CH_2Cl_2 (25 mL). Pyridine (640 μL) and benzoyl chloride (925 μL) were added successively with stirring, and stirring was continued for 2 d. NH_4Cl aq. was added, and the mixture was extracted with CH_2Cl_2 and dried. Evaporation of the solvent followed by silica gel (55 g) column chromatography using hexane/EtOAc (98:2) as the eluent afforded **10**⁴³ (27.0 mg, 74%).

8-(Tetrahydro-2H-pyran-2-yl)oxy-2-(trimethylsilylmethyl)oct-2-en-1-ol (11) DIBAL-H (12.0 mL, 1.0 M in toluene) was added to a stirred solution of **3** (1129.6 mg, 3.17 mmol) in dry CH_2Cl_2 (60 mL), and the solution was stirred at -50°C for 3 d. The reaction was quenched by the addition of MeOH, and a saturated solution of Rochelle salt was added. The mixture was extracted with CH_2Cl_2 , dried, and the solvent was evaporated off. The resultant residue was chromatographed on silica gel (27 g) using hexane/EtOAc (83:17) as the eluent to afford crude product **11** (879.5 mg, 88%), which was used in the next step without further purification. An oil; $^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H $\times$ 1/3, s), 0.02 (9H $\times$ 2/3, s), 1.31–1.88 (13H, m), 1.57 (2H $\times$ 2/3, s), 1.59 (2H $\times$ 1/3, s), 1.92–2.11 (2H, m), 3.34–3.42 (1H, m), 3.46–3.53 (1H, m), 3.68–3.90 (2H, m), 3.95 (2H $\times$ 2/3, s), 4.06 (2H $\times$ 1/3, s), 4.55–4.59 (1H, m), 5.11 (1H $\times$ 1/3, t, $J=7.5\text{ Hz}$), 5.29 (1H $\times$ 2/3, t, $J=6.8\text{ Hz}$).

8-(Tetrahydro-2H-pyran-2-yl)oxy-2-(trimethylsilylmethyl)oct-2-en-1-yl Acetate (12) Compound **11** (1190.3 mg, 3.79 mmol),

a solution of dimethylaminopyridine (DMAP) (48.4 mg) in Et_3N (8.7 mL), and Ac_2O (430 μL) were mixed together at r.t. After stirring for 1 h, the mixture was extracted with $\text{AcOEt}/1\text{ M HCl aq.}$ The organic layer was washed with 1 M HCl aq. and dried. Evaporation of the solvent followed by silica gel (25 g) column chromatography using hexane/EtOAc (95:5) as the eluent afforded **12** (1225.2 mg, 91%) as an oil; $^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H $\times$ 1/3, s), 0.03 (9H $\times$ 2/3, s), 1.33–1.87 (12H, m), 1.53 (2H $\times$ 1/3, s), 1.54 (2H $\times$ 2/3, s), 1.93–2.11 (2H, m), 2.06 (3H $\times$ 1/3, s), 2.07 (3H $\times$ 2/3, s), 3.37 (1H $\times$ 1/3, dt, $J=9.4, 6.5\text{ Hz}$), 3.38 (1H $\times$ 2/3, dt, $J=9.4, 6.5\text{ Hz}$), 3.46–3.53 (1H, m), 3.72 (1H $\times$ 1/3, dt, $J=9.4, 6.5\text{ Hz}$), 3.73 (1H $\times$ 2/3, dt, $J=9.4, 6.5\text{ Hz}$), 3.83–3.90 (1H, m), 4.40 (2H $\times$ 2/3, s), 4.51 (2H $\times$ 1/3, s), 4.55–4.59 (1H, m), 5.24 (1H $\times$ 1/3, t, $J=7.4\text{ Hz}$), 5.32 (1H $\times$ 2/3, t, $J=6.9\text{ Hz}$); $^{13}\text{C-NMR}$ (CDCl_3) assigned for the *Z*-isomer δ : -0.7 (3C), 19.2, 19.7, 21.1, 25.5, 26.1, 28.2, 29.3, 29.7, 30.8, 62.4, 63.4, 67.6, 98.9, 127.0, 131.8, 171.0; assigned for the *E*-isomer δ : -1.3 (3C), 19.2, 19.7, 21.0, 25.0, 25.9, 27.8, 29.6, 30.0, 30.8, 62.3, 63.4, 67.5, 98.8, 129.0, 131.2, 171.2; IR (neat/ NaCl) cm^{-1} : 1738, 1248, 851; MS (FAB) m/z : 357 ($[\text{M}+\text{H}]^+$, 4%), 307 (15), 154 (62), 136 (49), 85 (100); HR-(FAB)-MS m/z : 357.2453 ($[\text{M}+\text{H}]^+$) (Calcd for $\text{C}_{19}\text{H}_{37}\text{O}_4\text{Si}$: 357.2461).

8-Hydroxy-2-(trimethylsilylmethyl)oct-2-en-1-yl Acetate (13) Pyridinium *p*-toluenesulfonate (86.9 mg) was added to a stirred solution of **12** (1225.3 mg, 3.44 mmol) in EtOH (3.5 mL), and the mixture was stirred at 55°C for 11 h. An aqueous solution of NaHCO_3 was added, and the aqueous mixture was extracted with EtOAc, dried, and the solvent was evaporated. The residual oil was subjected to silica gel (26 g) column chromatography using hexane/EtOAc (78:22) to afford **13** (748.4 mg, 80%) as an oil; $^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H $\times$ 1/3, s), 0.03 (9H $\times$ 2/3, s), 1.33–1.61 (7H, m), 1.54 (2H $\times$ 1/3, s), 1.55 (2H $\times$ 2/3, s), 1.96–2.10 (2H, m), 2.07 (3H $\times$ 1/3, s), 2.07 (3H $\times$ 2/3, s), 3.63 (2H $\times$ 1/3, t, $J=6.6\text{ Hz}$), 3.64 (2H $\times$ 2/3, t, $J=6.6\text{ Hz}$), 4.40 (2H $\times$ 2/3, s), 4.52 (2H $\times$ 1/3, s), 5.23 (1H $\times$ 1/3, t, $J=7.5\text{ Hz}$), 5.32 (1H $\times$ 2/3, t, $J=6.9\text{ Hz}$); $^{13}\text{C-NMR}$ (CDCl_3) assigned for the *Z*-isomer δ : -0.7 (3C), 19.2, 21.1, 25.5, 28.2, 29.2, 32.7, 62.9, 70.1, 126.8, 131.9, 171.0. assigned for the *E*-isomer δ : -1.3 (3C), 19.2, 21.0, 25.2, 27.8, 29.9, 32.6, 63.4, 70.1, 128.9, 131.4, 171.2; IR (neat/ NaCl) cm^{-1} : 1738, 1248, 845; MS (EI) m/z : 272 (M^+ , 0.2%), 212 (27), 133 (59), 117 (100); HR-EI-MS m/z : 272.1801 (M^+) (Calcd for $\text{C}_{14}\text{H}_{28}\text{O}_3\text{Si}$: 272.1808).

8-Oxo-2-(trimethylsilylmethyl)oct-2-en-1-yl Acetate (14) Pyridine (0.39 mL) and Dess–Martin periodinane (1047.2 mg) were added successively to a stirred solution of **13** (312.1 mg, 1.147 mmol) in CH_2Cl_2 (18 mL) at r.t. After further stirring for 15 min, Na_2SO_3 aq. and NaHCO_3 aq. were added, and the mixture was extracted with CH_2Cl_2 and dried. Evaporation of the solvent followed by silica gel (27 g) column chromatography using hexane/EtOAc (9:1) as the eluent afforded **14** (269.9 mg, 87%) as an oil; $^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H $\times$ 1/3, s), 0.03 (9H $\times$ 2/3, s), 1.33–1.44 (2H, m), 1.54 (2H, s), 1.57–1.71 (2H, m), 1.95–2.13 (2H, m), 2.06 (3H $\times$ 1/3, s), 2.07 (3H $\times$ 2/3, s), 2.42 (2H $\times$ 1/3, td, $J=7.2, 1.8\text{ Hz}$), 2.43 (2H $\times$ 2/3, td, $J=7.3, 1.8\text{ Hz}$), 4.40 (2H $\times$ 2/3, brs), 4.51 (2H $\times$ 1/3, s), 5.21 (1H $\times$ 1/3, t, $J=7.5\text{ Hz}$), 5.30 (1H $\times$ 2/3, t, $J=6.9\text{ Hz}$), 9.75 (1H $\times$ 1/3, t, $J=1.8\text{ Hz}$), 9.76 (1H $\times$ 2/3, t, $J=1.8\text{ Hz}$); $^{13}\text{C-NMR}$ assigned for the *Z*-isomer δ : -0.7 (3C), 19.3, 21.1, 21.8, 27.9, 29.0, 43.8, 69.9, 126.0, 132.4, 170.9, 202.6. assigned for the *E*-isomer δ :

−1.3 (3C), 19.3, 21.0, 21.6, 27.6, 29.6, 43.7, 63.3, 128.2, 131.9, 171.1, 202.5; IR (neat/NaCl) cm^{-1} : 1732, 1258, 758; MS (EI) m/z : 270 (M^+ , 0.6%), 210 (9), 133 (40), 117 (95), 73 (100); HR-EI-MS m/z : 270.1652 (M^+) (Calcd for $\text{C}_{14}\text{H}_{26}\text{O}_3\text{Si}$: 270.1651).

Cyclization Reaction Compound **14** (32.1 mg, 0.119 mmol, $Z:E=57:43$) was dissolved in a solution of DBSA in water (11.1 mL, 0.11 mmol; 0.01 M), and the mixture was stirred at r.t. for 24 h. An aqueous solution of NaHCO_3 was added, and the mixture was extracted with EtOAc, and dried. After evaporation of the solvent, the residue was subjected to silica gel (7 g) column chromatography using hexane/EtOAc (gradient) to obtain **15a** (3.1 mg, 13%), an inseparable mixture of **15b**, **16a**, and **16b** (7.5 mg, 32%, ratio 28:56:16), and a mixture of **17a** and **17b** (7.6 mg, 41%, ratio 66:34). From these data, the ratio of the *cis*-products (**15a**, **16a**, and **17a**) to the *trans*-products (**15b**, **16b**, and **17b**) was determined to be 67:33 (Table 2, entry 4).

2-[(1*SR*,2*SR*)-2-hydroxycyclohex-1-yl]prop-2-en-1-yl Acetate (**15a**): An oil; $^1\text{H-NMR}$ (CDCl_3) δ : 1.20–1.82 (8H, m), 1.91–1.98 (1H, m), 2.08 (3H, s), 2.13 (1H, brd, $J=13\text{ Hz}$), 3.97 (1H, brs), 4.52 (1H, d, $J=13.4\text{ Hz}$), 4.58 (1H, d, $J=13.4\text{ Hz}$), 5.04 (1H, s), 5.20 (1H, s); $^{13}\text{C-NMR}$ (CDCl_3) δ : 19.5, 20.9, 23.8, 25.9, 32.4, 45.2, 66.2, 66.6, 113.7, 145.8, 170.8; IR (neat/NaCl) cm^{-1} : 3480 (OH), 1732, 1649, 1244, 972; MS (EI) m/z : 198 (M^+ , 0.4%), 180 (1), 138 (47), 109 (100), 94 (91), 79 (75); HR-EI-MS m/z : 198.1248 (M^+) (Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3$: 198.1255).

2-[(1*SR*,2*RS*)-2-hydroxycyclohex-1-yl]prop-2-en-1-yl Acetate (**15b**), 2-[(1*SR*,2*SR*)-2-acetoxycyclohex-1-yl]prop-2-en-1-ol (**16a**), and 2-[(1*SR*,2*RS*)-2-acetoxycyclohex-1-yl]prop-2-en-1-ol (**16b**): $^1\text{H-NMR}$ (CDCl_3) assigned for **16a** δ : 1.21–1.94 (9H, m), 2.01 (3H, s), 2.24 (1H, brd, $J=12.4\text{ Hz}$), 4.11 (2H, brs), 4.88 (1H, s), 5.09 (1H, q, $J=1.2\text{ Hz}$), 5.29 (1H, brs); assigned for **15b** δ : 2.11 (3H, s), 4.57 (2H, brs), 5.11 (1H, s), 5.18 (1H, q, $J=1.3\text{ Hz}$); assigned for **16b** δ : 2.00 (3H, s), 4.90 (1H, s), 5.04 (1H, q, $J=1.4\text{ Hz}$).

2-[(1*SR*,2*SR*)-2-Hydroxycyclohex-1-yl]prop-2-en-1-ol (**17a**) and 2-[(1*SR*,2*RS*)-2-Hydroxycyclohex-1-yl]prop-2-en-1-ol (**17b**): A mixture of **15a**, **15b**, **16a**, and **16b** (10.6 mg, 0.054 mmol, ratio 29:20:40:11) was dissolved in MeOH (1 mL) to which an aqueous solution of K_2CO_3 (1 mL, 1 M) was added. After stirring at r.t. for 1 d, NH_4Cl aq. was added, and the mixture was extracted with EtOAc and dried. Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (7 g). Elution with hexane/EtOAc (3:2) afforded **17a**⁴⁴ (4.6 mg, 55%) and with hexane/EtOAc (1:1) afforded **17b**⁴⁴ (3.2 mg, 38%) as colorless oils.

(3a*SR*,7a*SR*)-3-Methylenhexahydro-2(3*H*)-benzofuranone (18) MnO_2 (291.0 mg) was added at once to a stirred solution of **17a** (14.0 mg, 0.090 mmol) in CH_2Cl_2 (4.2 mL), and the mixture was stirred at r.t. for 19 h. The solid material was filtered off through Celite[®], and the filtrate was concentrated. The resultant residue was chromatographed on silica gel (7 g) using hexane/EtOAc (85:15) as the eluent to afford **18**¹¹ (7.5 mg, 55%).

(3a*SR*,7a*RS*)-3-Methylenhexahydro-2(3*H*)-benzofuranone (20) Compound **17b** (25.3 mg, 0.16 mmol) was treated with MnO_2 (225.9 mg) as above to yield a crude product of **19** (24.6 mg), which was not purified. This was dissolved in dry THF (7.5 mL), and NaCN (43.1 mg), MnO_2 (291.4 mg), and 18-crown-6 (22.2 mg) were added successively at r.t. After stirring the mixture for 20 h, the solid materials were filtered

off through Celite[®], and the filtrate was dried. Evaporation of the solvent followed by silica gel (7 g) column chromatography using hexane/EtOAc (9:1) as the eluent afforded **20**¹¹ (7.2 mg, 29%).

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Conflict of Interest The authors declare no conflict of interest.

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