Pergamon

Tetrahedron 58 (2002) 9279–9287

TETRAHEDRON

Preparation of *gem*-dimethylcyclopropane-fused compounds through sigmatropic rearrangements. On/off-switching of the tautomerization of 3,4-homotropilidene by steric hindrance

Tohru Futagawa, Norio Nishiyama, Akira Tai, Tadashi Okuyama and Takashi Sugimura*

Graduate School of Science, Himeji Institute of Technology, 3-2-1 Kohto, Kamigori, Ako-gun, Hyogo 678-1297, Japan

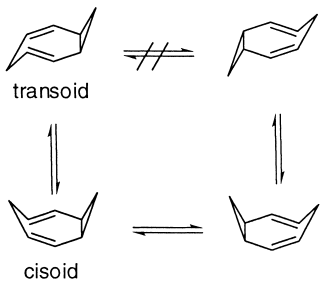
Received 23 July 2002; accepted 11 September 2002

Abstract—Cyclopropanation of 4,8,8-trimethylcycloheptatriene having an ether function at the 3-position by unsubstituted carbenoid addition resulted in a complex mixture mainly due to quick valence tautomerization of the produced 3,4-homotropilidene analogue during the reaction. Dihalocarbene addition to the same substrate proceeded exclusively at the 3,4-position to give an adduct, where the tautomerization process was interrupted by steric hindrance caused by the halogen substituents. Removal of the halogen atoms by reduction promotes the tautomerization to give a *gem*-dimethylcyclopropane-fused product. Stereospecificity of the tautomerization was also demonstrated by obtaining the product in an optically pure state.

1. Introduction

gem-Dimethylcyclopropane-fused carbocyclic compounds are common in natural terpenes produced by cationic cyclization of linear isoprenoids.[1] Although a variety of synthetic methods are available for cyclopropyl units,[2] application thereof to the preparation of a *gem*-dimethylcyclopropane is not always possible. For example, transformation of a cycloalkene to a *gem*-dimethylcyclopropane-fused cycloalkane by cycloaddition can be only possible for specific substrates by the two-step procedure of 1,3-dipole addition of 2-diazopropane and subsequent photolysis of the adduct.[3] We have assumed that *gem*-dimethylcyclopropane-fused cycloheptadiene, a key intermediate for various natural products, can be prepared by using valence tautomerization of bicyclo[5.1.0]octa-2,5-diene (3,4-homotropilidene), which consists of a quick thermal [3,3] sigmatropic rearrangement to convert the two cyclopropane-fused compounds each other.[4] This tautomerization should proceed much faster through *cisoid* conformers than through *transoid* conformers (Scheme 1), because of the maximum overlap of the frontier orbitals at the transition state.[5] Hence, the reaction is strongly suggested to be stereospecific, and is a potent useful tool for stereoselective synthesis of a cyclopropyl compound.

The tautomerization of 3,4-homotropilidene has been well studied for mechanistic interests, but has not been used for synthetic purposes. In this report, we would like to present a highly regio-controlled cyclopropanation of a cycloheptatriene at the 3,4-position under the kinetic interruption of the tautomerization by a steric fence. After the cyclopropanation, removal of the fence caused the tautomerization to give the desired *gem*-dimethylcyclopropane with a sufficiently large equilibrium constant. The stereospecificity of this rearrangement was also proved by obtaining an optically active product.[6]



Scheme 1.

2. Reaction design

Substrate **1** was designed for the synthesis of **3**, a key intermediate for dimethylcyclopropane-fused natural products such as ingenol.[7] The silyloxy substituent at the 3-position of **1** is expected to promote electrophilic cyclopropanation at the 3,4-position. Even if the cycloaddition to **1** proceeds with sufficiently high regioselectivity (including suppression of the reaction as a valence isomer

Keywords: electrocyclic reaction; stereospecificity; steric effects; cyclopropanes.

* Corresponding author. Tel.: +81-791-58-0168; fax: +81-791-58-0115; e-mail: sugimura@sci.himeji-tech.ac.jp

0040–4020/02/$ - see front matter
PII: S0040-4020(02)01193-6

Table 1. Calculated heats of formation (kcal/mol) for tautomers standardized by that of the *trans*-conformer of the reactant at the AM-1 level

Entry		Reactant	Tautomer	
		cisoid	*cisoid*	*transoid*
1	**2**	1.94	−12.44	−17.68
2	**5**	–[a]	–[a]	−9.23
3	**6**	(ca. 30)[a,b]	–[a]	−5.56
4	**7**	–[a]	–[a]	−9.78
5	**8**	2.33	−3.29	−16.23

[a] Energy minimum is not found for the conformer.
[b] Estimated energy using the structure of *cisoid*-**2**.

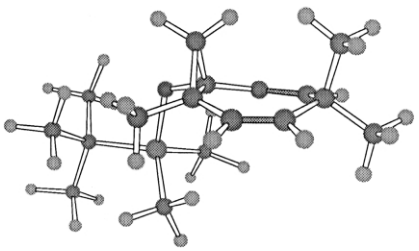


Figure 1. Structure of *cisoid*-**2** obtained by AM-1.

4), over-reactions leading to the second and third cyclopropanations as well as the decomposition of the product should also be considered. Under the cyclopropanation conditions, the unconjugated olefins of the produced **2** may be more reactive than the 3,4-position of **1**, and unconjugated enol ether of **3** must be much more reactive. Thus, the rapid tautomerization from **2** to **3** is a disadvantage in a sense for the chemoselective cyclopropanation of **1**, and should be interrupted during the cyclopropanation reaction.

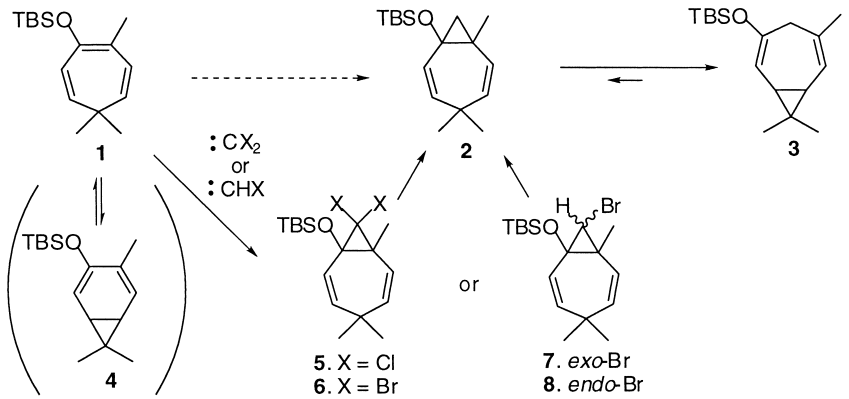
To prevent the tautomerization during the cyclopropanation reaction and to turn it on after the reaction, we introduced an on/off-switch by steric hindrance. Since the tautomerization should take place through *cisoid*-conformers, substitution of **2** at the *exo*-8-position (inner position of the bicyclo ring) to cause steric overlap with the *endo*-4-methyl in the transition state is expected to interfere with the tautomerization; removal of the substituent after the cyclopropanation will give **3**.

By ab initio MO calculations at the HF/6-31G level, 8,8-dimethylbicyclo[5.1.0]octa-2,5-diene (the parent form of **3**) is 3.72 kcal/mol more stable than the 4,4-dimethyl tautomer (the parent form of **2**). Thus, the basic reaction design is reasonable in the sense of thermodynamic control of the tautomerization. In the present case with **2**, the ether function cooperates the control. The tautomerization process from **2** to **3** is mimicked by a MO calculation at the AM-1 level of the conformational pairs of the two tautomers. Heats of formation for the process starting with *transoid*-**2** are calculated, and the relative values are given in Table 1 (entry 1) after standardization with that of *transoid*-**2**. The results suggest that the tautomerization of **2** to give **3** through their *cisoid*-conformers occurs readily. In contrast, when a halogen atom is placed at the *exo*-8-position of **2** (**5**–**7**), the *cisoid*-conformers of the reactant and rearranged compound are not even energy minimum structures. By applying the structure of *cisoid*-**2** skeleton (Fig. 1), the energy of *cisoid*-**6** of the dibromo-analogue is estimated to be ca. 30 kcal/mol higher than that of *transoid*-**6**. Thus, the tautomerization through the *cisoid*-conformer is expected to be inhibited unless the halogen substituent at the *exo*-8-position is removed (Scheme 2).

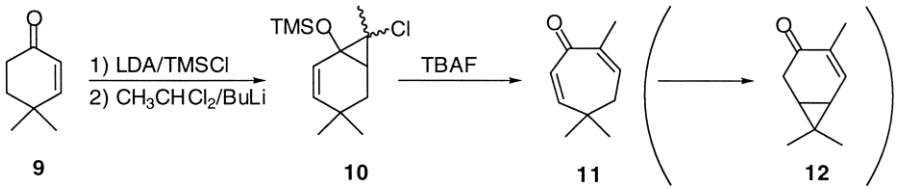
3. Results and discussion

3.1. Regioselective cyclopropanation of cycloheptatriene

Precursor **1** was prepared from **9** in four steps as shown in Scheme 3. Enol ether formation from **9** (94% yield) followed by chloromethylcarbenoid addition gave a diastereomeric mixture of **10** (72%) in a ratio of *exo*/*endo*=6/4 (the *exo*-isomer has the chlorine substituent at the inner position of the bicyclo ring). The ring expansion of **10** needs a comment because standard conditions[8] of the thermal reaction, refluxing methanol in the presence of triethylamine, afforded **11** only in 24% yield. The low yield is attributable both to the instability of **11**, which is further transformed to **12** and to the low reactivity of *endo*-**10**, the minor isomer. After several attempts, we have found that treatment of *exo*-**10** with tetrabutylammonium fluoride (TBAF) at room temperature under anhydrous conditions gives **11** in quantitative yield. Under the same conditions, *endo*-**10** can be converted to **11** in 50% yield, where simple de-silylation is the side reaction. When the diastereomeric mixture of **10** as obtained was treated with TBAF, **11** was obtained in 62% yield. Fixation of the enol form of **11** with



Scheme 2.



Scheme 3.

the *t*-butyldimethylsilyl (TBS) group gave cyclic triene **1** in 96% yield.

Cyclopropanation of **1** with an unsubstituted carbenoid resulted in a complex mixture consisting of poly-cyclopropanated compounds. For example, when **1** was treated with Et_2Zn and CH_2I_2 in ether at room temperate, more than five products were formed. The reactions with other reagents, $Zn–Cu/CH_2I_2$, Sm/CH_2I_2, $Sm/CH_2Cl_2/HgCl_2$, or $AlMe_3/CH_2I_2$, also resulted in a complex mixture or recovery of the reactant.

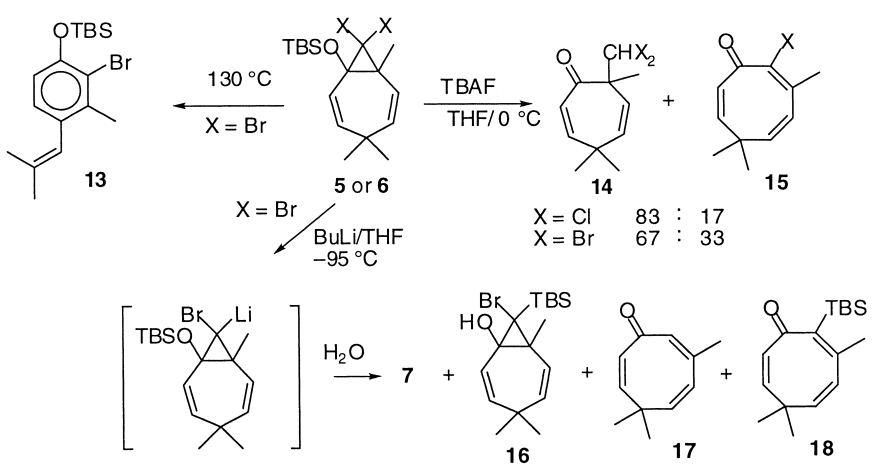
In contrast, the reaction of **1** with dihalocarbene proceeded smoothly. Under the conventional procedure for a generation of dichlorocarbene (aqueous NaOH solution and benzlytriethylammonium chloride catalyst with $CHCl_3$), adduct **5** was obtained in 98% isolated yield. Use of bromoform instead of chloroform gave adduct **6** in 98% yield. These high yields with no side products are quite satisfactory from a synthetic point of view. The reaction of zinc mono-bromocarbenoid by the treatment of **1** with Et_2Zn and $CHBr_3$ under dry air gave adduct **7** in 26% yield. Interestingly, **7** was stereochemically pure, and its diastereomer **8** was not found in the reaction mixture. This apparent stereoselectivity could be due to the over-reaction of the *endo*-bromo-isomer **8** through its tautomerization, and as a result, unreactive *exo*-isomer **7** remains.

The thermal stability of adducts **5** and **6** were enough to handle them at ambient temperature, and they are stable even at 100°C. When a benzene-d_6 solution of **6** in a sealed NMR tube was heated at 130°C, **6** was converted to **13** with a half-life of 6 h (ca. 70% yield). In the presence of tetramethylethylenediamine, the reaction to give **13** became faster ($t_{1/2}$=3.3 h, quantitative yield). Treatment of **5** or **6** with TBAF in anhydrous THF to result in de-silylation should proceed via an oxy-anion intermediate, which is expected to enhance the rate of the tautomerization.[9] Under these conditions, the obtained products did not include the dimethylcyclopropane skeleton, but were **14** and **15**.

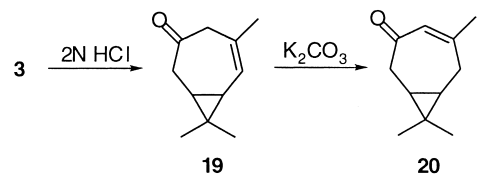
3.2. Tautomerization by removing the steric fence

Now, the steric fence inhibiting the tautomerization of **5**–**7** is removed by replacing a halogen atom at the inner-*exo*-position with a hydrogen. Dehalogenation of **5** and **6** was performed by reduction with metallic sodium and methanol in ether at 0°C. During the reaction, only one product was detected by TLC analysis, and was assigned as **3**. However, extraction and purification by silica gel chromatography promoted decomposition of **3** to reduce its isolated yield. The highest isolated yield of **3** was 33% from **5** and 29% from **6** after purification. The major side product did not contain the TBS group, and was identified as **20**, which is derived from **3**. If the recovered amount of **5** (10–30% in most cases) is considered, the combined yield of **3** and **20** is very high. Reduction of **5** or **6** with metallic lithium in liquid ammonia gave a similar result to that with sodium, but the isolated yield of **3** is somewhat lower; 28% from **5** and 26% from **6**.

Dehalogenation of **6** is also possible by metalation at the 8-position and subsequent protonation. When **6** was treated with a 1 equiv. of butyllithium at −95°C followed by the treatment with water at the same temperature, unreacted **6** and product **7** was obtained in a 1 to 1 ratio (ca. 60% yield for the mixture). This procedure is not recommended for practical synthesis of **7** due to the difficulty in the separation of **6** and **7**. When the amount of butyllithium was increased to 2.5 equiv., yields of both **6** and **7** were decreased (6% as a 1 to 1 mixture). Under these conditions, the major products were **16** (29.3%) and **17** (20.5%). When the reaction mixture



Scheme 4.



Scheme 5.

with 1 equiv. of butyllithium was warmed up to 0°C before the protonation, the product was sharply switched to **18** (36.2%). Other isolated compounds from this reaction were **6** and **7** (isolated as a 1 to 1 mixture, ca. 10%). All products in this series of reactions can be understood by the reaction from a lithiated intermediate shown in Scheme 4 and a carbene produced from it; thus, there is no evidence that tautomerization occurred during the reaction. However, when **7** was treated with *sec*-butyllithium (ca. 1 equiv.) in ether at −70°C, **3** was obtained (ca. 30% yield) after treatment with water at the same temperature. Increase of the reagent drastically decreased the yield of **3** and gave a complex mixture. Radical reduction, such as tributyltin hydride with azobisisobutyronitrile, can also replace a halogen atom with a hydrogen atom, but reaction of **7** with these reagents only induced decomposition.

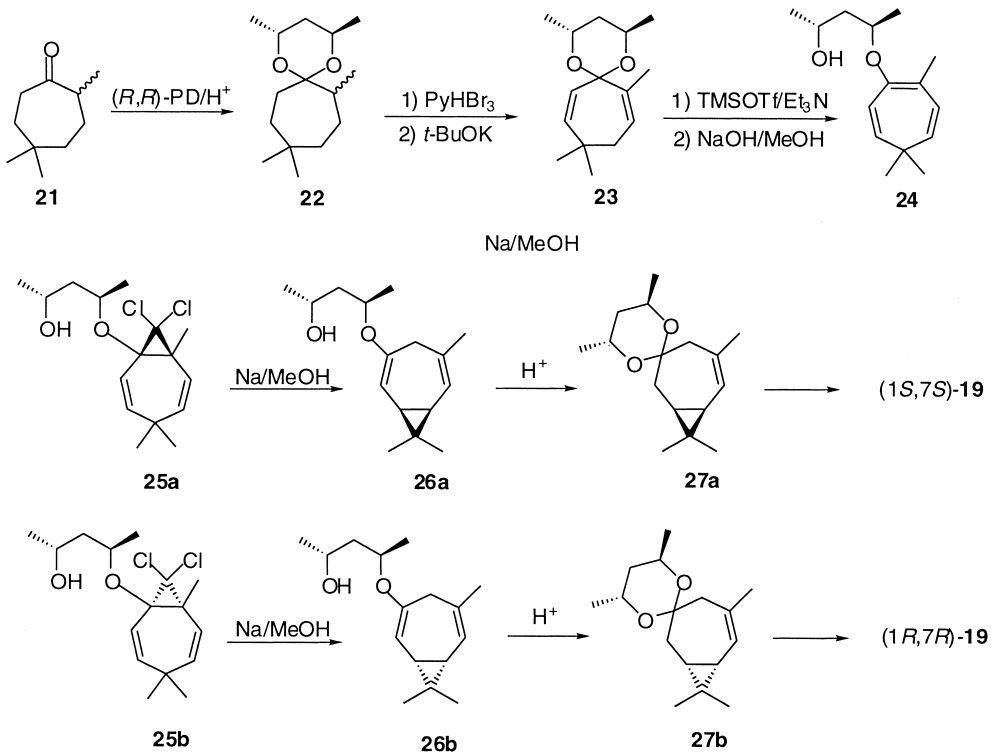
The formation of **3** by the reductive dehalogenations with metallic sodium or lithium must be a result of the formation and the rapid tautomerization of **2**. The ^{1}H NMR of **3** was not changed until −95°C. The spectrum was also unchanged up to 100°C for several hours. By these experiments, the tautomerization from **2** to **3** is confirmed to be quick, but practically irreversible as expected from the MO calculations. By conventional methods, **3** was converted to two ketones, **19** and **20**, in high yields. The ^{1}H and ^{13}C spectra of obtained **20** were identical with reported ones (Scheme 5).[7]

3.3. Chiral approach for the synthesis of optically active products

The results using an achiral substrate **1** suggest that the tautomerization only proceeds through *cisoid* conformers and should be stereospecific. To directly prove the stereospecificity of the tautomerization, optically active compounds corresponding to **5** were prepared. Acetal **22** was prepared from (2*R*,4*R*)-2,4-pentanediol and ketone **21**[10] (77.8%). Dibromination of **22** with excess pyridinium perbromide (87%) followed by debromination with potassium *t*-butoxide in DMSO afforded **23** (22%). The low yield of **23** is due to the formation of an *exo*-methylene product. Treatment of **23** with trimethylsilyl trifluoromethanesulfonate in the presence of triethylamine followed by de-silylation resulted in chiral starting material **24** (70%). Dichlorocarbene addition to **24** was again highly regioselective to give a diastereomeric mixture of **25** in a ratio of 2.3/1 (100%). Each diastereomer of **25** was isolated and reduced with sodium/methanol to give **26a** or **26b** in 33–36% yield. Each isomer of **26** and their derivative **27** are over 97% diastereomerically pure deduced from their ^{1}H NMR spectra. Thus, stereospecificity of the tautomerization of 3,4-homotropilidene has been for the first time experimentally established. From **27a**, optically active **19**, **20** and their dihydro derivative were obtained. Since the stereochemistries of **20** and its dihydro derivative are known, structures of the present products can be assigned as shown in Scheme 6.

4. Conclusions

The present study demonstrates synthetic use of the tautomerization of 3,4-homotropilidene. The results display



Scheme 6.

that the kinetic control of the tautomerization is indispensable for achievement of a highly selective synthesis of the desired product by cyclopropanation. Stereoselective cyclopropanation of **24** with zinc carbenoid[11] would be difficult to obtain a singly cyclopropanated product deduced from the result of the reaction with **1**. Actually, the second cyclopropanation could not be interrupted even under well-optimized conditions for an analogue of **24**.[12] Development of a proper method for the stereoselective cyclopropanation inhibiting over-reactions will enhance the versatility of the present system.

5. Experimental

5.1. General

All temperatures are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL GX-400 spectrometer. IR spectra were obtained on a JASCO FT/IR-410 spectrometer. Mass spectra were obtained on a JEOL JMS-AX-505HA. Optical rotations were measured on a Perkin–Elmer 243B polarimeter. Analytical GLC was conducted with a Shimadzu gas chromatograph GC-17A using a capillary column. The MPLC was carried out using an FMI pump (10 mL/min) and a Lobar column (MERCK Si-60 type B). (2*R*,4*R*)-Pentanediol was obtained by the hydrogenation of 2,4-pentanedione over (*R*,*R*)-tartaric acid-modified Raney nickel followed by three recrystallizations (>99.6% ee).[13] All solvents were purified by distillation. Reactions were carried out under a dry nitrogen atmosphere. Energy minimization was performed on a PC using MOPAC93 with Gaussian 98W.

5.1.1. Preparation of 10. A solution of LDA was prepared from diisopropylamine (54.5 mL, 389 mmol) and butyllithium (1.59 M in hexane, 225 mL, 258 mmol) in THF (780 mL) at −78°C. To this solution, 4,4-dimethylcyclohex-2-en-1-one (**9**) (40.04 g, 322 mmol) in THF (32 mL) was added in 20 min. After 1 h, freshly distilled trimethylsilyl chloride (70 mL, 552 mmol) was added in 10 min; then the resulting solution was allowed to warm up to room temperature. After concentration of the reaction mixture under vacuum, the residue was suspended in pentane and filtered through Celite. The filter cake was washed twice with pentane (100 mL). Evaporation of the combined filtrate gave 68.72 g of a yellow oil. Distillation of the oil gave 59.45 g of the enol silyl ether as a colorless oil (64–65°C/6 Torr, 93.9% yield). IR (neat) 3050, 2950, 1660, 1400, 1380, 1260, 1210, 900 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.55 (m, 2H), 4.79 (t, J=4.9 Hz, 1H), 2.12 (d, J=4.9 Hz, 2H), 1.01 (s, 6H), 0.19 (s, 9H). Anal. calcd for $C_{11}H_{20}OSi$ C: 67.29, H: 10.27, found C: 67.42, H: 10.30. A mixture of the enol silyl ether (20.92 g, 107 mmol) and 1,1-dichloroethane (28.7 mL, 341 mmol) in dry ether (41 mL) was cooled to −40°C. To this solution, a solution of butyllithium (1.59 M in hexane, 134 mL, 213 mmol) was added for 2.5 h. The reaction mixture was allowed to warm up to 0°C, and then, 100 mL of water was added. Extraction with ether (200 mL×3), washing with water (100 mL×2), drying (Na_2SO_4), and concentration gave a mixture of crude **10** as a diastereomeric mixture. The isomer ratio of **10** was determined by GLC to be *exo*/*endo*=6/4 (PEG 20 M, 25 m, 100°C; *endo*-**10**, 6.59 min, *exo*-**10**, 5.44 min). A part of the mixture was purified by silica gel chromatography (hexane). *endo*-**10** (first eluate): IR (neat) 2950, 2930, 2860, 1460, 1470, 1400, 1250, 1220, 1180, 1140, 1090 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.67–5.66 (m, 2H), 1.93 (dd, J=14.7, 10.8 Hz, 1H), 1.54 (ddd, J=10.8, 4.9, 1.5 Hz, 1H), 1.44 (s, 3H), 1.41 (dd, J=14.7, 4.9 Hz, 1H), 1.10 (s, 3H), 0.92 (s, 3H), 0.20 (s, 9H). ^{13}C NMR δ 142.12, 123.50, 59.02, 52.39, 35.42, 30.63, 30.48, 30.15, 28.53, 18.82, 1.19. High-MS calcd for $C_{13}H_{23}OClSi$ 258.1207, observed 258.1205. *exo*-**10** (second eluate): IR (neat) 2950, 2930, 2860, 1460, 1400, 1380, 1250, 1200, 1110, 1070 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.66–5.65 (m, 2H), 1.92 (dd, J=15.1, 10.3 Hz, 1H), 1.69 (s, 3H), 1.66 (dd, J=15.1, 4.4 Hz, 1H), 1.19 (ddd, J=10.3, 4.4, 1.5 Hz, 1H), 1.11 (s, 3H), 0.96 (s, 3H), 0.17 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 141.39, 123.54, 60.46, 56.16, 35.95, 30.42, 30.19, 30.03, 27.70, 23.92, 1.31. High-MS calcd for $C_{13}H_{23}OClSi$ 258.1207, observed 258.1205. The reaction mixture was employed for the next step after passing through a silica gel pad eluted with hexane.

5.1.2. Preparation of dienone 11. To a solution of **10** (a diastereomeric mixture, 2.11 g, 9.31 mmol) in dry THF (42 mL) was added K_2CO_3 (1.41 g, 10.25 mmol) and tetrabutylammonium fluoride (0.28 M in THF, 43.7 mL, 12.2 mmol) at room temperature. After 1.5 h, the reaction mixture was extracted with ether (400 mL×2) and washed with water (400 mL×2). Drying over Na_2SO_4 and silica gel column chromatography (elution with 3% ethyl acetate in hexane) gave **11** as a colorless oil (868 mg, 62.0% yield) and de-silylated product from *endo*-**10** (280 mg). Data for **11**: IR (neat) 2950, 2930, 2870, 1660, 1640, 1620, 1470, 1450, 1410, 1380, 1360, 1230, 1080 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.36 (m, 1H), 6.24 (dm, J=12.2 Hz, 1H), 5.92 (d, J=12.2 Hz, 1H), 2.42–2.40 (m, 2H), 1.90 (m, 3H), 1.14 (s, 6H). Anal. calcd for $C_{10}H_{14}O$ C: 79.96, H: 9.39, found C: 79.30, H: 9.50. Data for the de-silylated product from *endo*-**10**: IR (neat) 3400, 2950, 2930, 2860, 1470, 1380, 1360, 1180, 1120, 1090 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.80 (dd, J=9.8, 1.0 Hz, 1H), 5.65 (dd, J=9.8, 1.5 Hz, 1H), 1.94 (ddd, J=14.7, 10.3, 1.0 Hz, 1H), 1.54 (ddd, J=10.3, 5.4, 2.0 Hz, 1H), 1.51 (s, 3H), 1.40 (dd, J=14.7, 5.4 Hz, 1H), 1.12 (s, 3H), 0.94 (s, 3H).

5.1.3. Preparation of triene 1. To a mixture of **11** (1.00 g, 6.65 mmol) and triethylamine (1.21 mL, 8.71 mmol) in dry CH_2Cl_2 (17 mL) was added *t*-butyldimetylsilyl trifluoromethanesulfonate (1.64 mL, 7.16 mmol) at 0°C. After 1 h, cold saturated aqueous $NaHCO_3$ solution was added to the reaction mixture. Extraction with CH_2Cl_2 (50 mL×2), washing with water (30 mL×2), drying over Na_2SO_4, and silica gel column chromatography (elution with hexane) gave **1** as a colorless oil (1.72 g, 96.2% yield). IR (neat) 2960, 2930, 2900, 2860, 1630, 1550, 1480, 1400, 1380, 1260, 1220, 1180 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.89 (d, J=10.3 Hz, 1H), 5.84 (d, J=10.7 Hz, 1H), 5.14 (d, J=10.7 Hz, 1H), 5.00 (d, J=10.3 Hz, 1H), 1.93 (s, 3H), 1.00 (s, 6H), 0.98 (s, 9H), 0.12 (s, 6H). Anal. calcd for $C_{16}H_{28}OSi$ C: 72.66, H: 10.67, found C: 72.12, H: 10.80.

5.1.4. Dichlorocarbene addition to 1 to give 5. To a solution of **1** (305 mg, 1.14 mmol) in chloroform (9 mL) was added benzyltriethylammonium chloride (75 mg) at

0°C. To this solution, cold 50% aqueous NaOH (8.5 g) was added in 5 min under sufficient stirring. After 1 h at 0°C and then 2 h at room temperature, the mixture was diluted with water (20 mL), and then extracted with CH_2Cl_2 (50 mL×4). The organic layer was washed with water (50 mL×2), dried over Na_2SO_4, and then concentrated. Purification of the crude product by silica gel column chromatography (elution with hexane) gave 397 mg of **5** as a colorless oil (99.1% yield). IR (neat) 2960, 2930, 2850, 1480, 1470, 1260, 1200, 1180, 1140, 1110, 1100, 900 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.85 (dd, J=10.7, 1.0 Hz, 1H), 5.69 (d, J=10.7 Hz, 1H), 5.64 (dd, J=10.3, 1.0 Hz), 5.43 (d, J=10.3 Hz, 1H), 1.38 (s, 3H), 1.32 (s, 3H), 1.17 (s, 3H), 0.97 (s, 9H), 0.24 (s, 3H), 0.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 145.02, 141.39, 127.93, 125.16, 70.14, 64.87, 39.32, 35.67, 32.09, 30.93, 25.94, 18.67, 17.80, −2.69, −3.14. Anal. calcd for $C_{17}H_{28}OCl_2Si$ C: 58.78, H: 8.12, found C: 58.39, H: 8.20.

5.1.5. Dibromocarbene addition to 1 to give 6. To a solution of **1** (322 mg, 1.20 mmol) in bromoform (10 mL) was added benzyltriethylammonium chloride (114 mg) at 0°C. To this solution, cold 50% aqueous NaOH (8.5 g) was added in 3 min under sufficient stirring. After stirring 1 h at room temperature, the mixture was diluted with water (10 mL), and then extracted with CH_2Cl_2 (50 mL×4). The organic layer was washed with water (50 mL×2), dried over Na_2SO_4, and then concentrated. Purification of the crude product by silica gel column chromatography (elution with hexane) gave 514 mg of **6** as a pale yellow oil (97.2% yield). IR (neat) 2960, 2930, 2850, 1480, 1470, 1260, 1200, 1170, 1140, 1110, 1100, 890, 860 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.83 (dd, J=11.0, 1.2 Hz, 1H), 5.65 (d, J=10.5 Hz, 1H), 5.64 (dd, J=11.0, 1.2 Hz), 5.37 (d, J=10.5 Hz, 1H), 1.41 (s, 3H), 1.31 (s, 3H), 1.17 (s, 3H), 0.92 (s, 9H), 0.29 (s, 3H), 0.20 (s, 3H). High-MS calcd for $C_{17}H_{28}OBr_2Si$ 434.0276, observed 434.0277.

5.1.6. Monobromocarbenoid addition to 1 to give 7. To a solution of **1** (216 mg, 0.82 mmol) in dry hexane (2 mL) was added diethylzinc (1.0 M in hexane, 1.7 mL, 1.7 mmol). To the mixture after cooling it to 0°C, bromoform (0.22 mL, 2.5 mmol) was added under bubbling of dry air. After 5 min, the mixture was allowed to warm up to room temperature, stirred for 20 min, and then treated with saturated aqueous ammonium chloride (10 mL). Extraction with ether (10 mL×3), drying over Na_2SO_4, and purification by MLPC (elution with hexane) afforded **7** as a colorless oil (74.7 mg, 26.4% yield). IR (neat) 2950, 2930, 2900, 2850, 1460, 1260, 1130, 860, 840, 780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.78 (dd, J=10.8, 1.0 Hz, 1H), 5.67 (dd, J=10.5, 1.0 Hz, 1H), 5.52 (d, J=10.8 Hz, 1H), 5.23 (d, J=10.5 Hz, 1H), 2.89 (s, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.16 (s, 3H), 0.88 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H). High-MS calcd for $C_{17}H_{29}OBrSi$ 356.1171, observed 356.1177.

5.1.7. Thermolysis of 6. A solution of **6** (ca. 20 mg) in benzene-d_6 (0.5 mL) was sealed in an NMR tube, and the tube was heated in an oil bath at 130°C. Reactant **6** was completely converted to **13** after 17 h monitored by the ^1H NMR spectrometer. IR (neat) 2950, 2930, 2850, 1590, 1480, 1300, 1260, 1040 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.90 (d, J=8.3 Hz, 1H), 6.68 (d, J=8.3 Hz, 1H), 6.16 (8s, 1H), 2.32 (s, 3H), 1.88 (s, 3H), 1.63 (s, 3H), 1.05 (8s, 9H), 0.25 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 150.97, 137.83, 135.39, 132.31, 128.70, 124.19, 118.65, 110.95, 26.24, 25.86, 20.71, 19.20, 18.44, −3.76. High-MS calcd for $C_{17}H_{27}OBrSi$ 354.10145, observed 354.10160.

5.1.8. Reaction of 5 and 6 with TBAF. Dihalocarbene adduct, **5** or **6**, was treated with 5–7 equiv. of tetrabutylammonium fluoride (TBAF) in dry THF at 0°C for 30 min. The mixture was extracted with ether, washed with water, and dried over Na_2SO_4. A ratio of produced **14** and **15** was determined by GLC analysis (PEG 20 M, 50 m, 160°C, 18.8 min for **14** (X=Cl), 23.3 min for **15** (X=Cl), 26.8 min for **14** (X=Br), and 53.9 min for **15** (X=Br)). The products were isolated by preparative GLC (OV-101, 200°C). Compound **14** (X=Cl): IR 3030, 2970, 2870, 1760, 1700, 1660, 1470, 1460, 1380, 1300, 1220, 1170 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.19 (s, 1H), 6.15 (dd, J=12.9, 2.2 Hz, 1H), 5.97 (d, J=12.9 Hz, 1H), 5.69 (dd, J=12.2, 2.2 Hz, 1H), 5.39 (d, J=12.2 Hz, 1H), 1.48 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 195.73, 149.38, 140.09, 125.27, 125.04, 78.79, 41.58, 40.53, 31.67, 29.55, 19.47. High-MS calcd for $C_{11}H_{14}OCl_2$ 232.0423, observed 232.0421. Compound **15** (X=Cl): IR 3000, 2970, 2930, 2870, 1660, 1470, 1380, 1240, 1130, 780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.38 (d, J=12.2 Hz, 1H), 6.08 (d, J=12.2 Hz, 1H), 5.86 (dd, J=11.2, 0.7 Hz, 1H), 5.49 (d, J=12.2 Hz, 1H), 2.01 (d, J=0.7 Hz, 1H), 1.31 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 154.82, 140.48, 137.57, 129.31, 127.75, 124.90, 38.49, 28.94, 19.89. High-MS calcd for $C_{11}H_{13}OCl$ 196.0656, observed 196.0644. Compound **14** (X=Br): IR 3030, 2970, 2930, 2870, 1760, 1700, 1660, 1470, 1450, 1380, 1290, 1200, 1160 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.13 (dd, J=12.9, 2.2 Hz, 1H), 6.07 (s, 1H), 5.99 (d, J=12.9 Hz, 1H), 5.70 (dd, J=12.0, 2.2 Hz, 1H), 5.39 (d, J=12.0 Hz, 1H), 1.54 (s, 3H), 1.31 (s, 3H), 1.23 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 198.37, 148.62, 140.39, 126.72, 124.82, 124.60, 54.32, 41.72, 31.13, 30.94, 29.06. High-MS calcd for $C_{11}H_{14}OBr_2$ 319.9411, observed 319.9405. Compound **15** (X=Br): IR 3000, 2960, 2930, 2870, 1660, 1470, 1380, 1230, 1130, 770 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.34 (d, J=12.0 Hz, 1H), 6.03 (d, J=12.0 Hz, 1H), 5.86 (dd, J=11.2, 0.7 Hz, 1H), 5.44 (d, J=12.2 Hz, 1H), 2.00 (d, J=0.7 Hz, 1H), 1.30 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 154.12, 140.09, 136.44, 128.43, 128.12, 114.25, 38.59, 29.07, 21.71. High-MS calcd for $C_{11}H_{13}OBr$ 240.0150, observed 240.0117.

5.1.9. Reduction of 5 (6) with sodium/methanol. A solution of **5** (69.2 mg, 0.197 mmol) in ether (4 mL) was cooled with ice-water bath. To this solution was added a piece of sodium metal (195 mg, 8.48 mmol) followed by dropwise addition of a mixture of methanol and water (2.5 mL, 100/3.3) in 30 min. After 1 h, the mixture was diluted with water (20 mL) and extracted with ether (20 mL×4). Drying and evaporation under vacuum resulted in a colorless oil (54.4 mg). Purification by MPLC on silica gel (elution with hexane) gave **3** (18.3 mg, 32.9%) and **20** (13.8 mg, 42.6%) in addition to some recovered **5** (ca. 10%). Reduction of **6** by this method proceeded similarly. Data for **3**: IR (neat) 2960, 2930, 2860, 1670, 1480, 1470, 1340, 1260, 1230, 1200, 1140, 1130 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.36 (m, 1H), 4.82 (m, 1H), 3.58 (dm, J=16.8 Hz, 1H), 2.10 (dm, J=16.8 Hz, 1H), 1.73–1.72 (m, 3H), 1.24–1.17 (m, 2H), 1.09 (s, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H). ^{13}C

NMR ($CDCl_3$) δ 152.62, 134.82, 121.89, 103.98, 39.09, 28.47, 27.63, 26.13, 25.76, 25.52, 19.25, 17.98, 16.51, −4.26, −4.52, High-MS calcd for $C_{17}H_{30}OSi$ 278.2066, observed 278.2066.

5.1.10. Reduction of 5 (6) with lithium in ammonia. A solution of lithium was prepared by addition of lithium (32 mg, 4.63 mmol) to a mixture of ammonia (ca. 10 mL) and dry ether (2 mL) at −78°C. A solution of **5** (244 mg, 0.693 mmol) in dry ether (2 mL) was added to this solution over 5 min. After 30 min, sodium benzoate (1.01 g, 70.1 mmol) and pentane (15 mL) was added, and then, ammonia was removed by warming the mixture to room temperature. The resulting mixture was extracted with ether (30 mL×5), washed with aqueous sodium bicarbonate solution, dried over Na_2SO_4, and purified by column chromatography on silica gel (elution with hexane). The first eluate was further purified by MPLC (hexane) to give **3** (54.2 mg, 27.7%), and the second eluate was purified by MPLC (10% ethyl acetate in hexane) to give **20** (40.8 mg, 35.8%). Reduction of **6** by this method proceeded similarly.

5.1.11. Reaction of 6 with butyllithium. To a solution of **6** (200–400 mg) in dry THF (5–10 mL) was added butyllithium (1.5 M hexane solution, 1.06 or 2.5 equiv.) in 15 min at −95°C. After stirring for 2.5 h at the same temperature (or after warming to 0°C for 2 h), a mixture of THF-water (10/1, 5 mL) was added to the reaction mixture. The crude product obtained by the extraction procedure was purified by MPLC (elution with 6% ethyl acetate). The isolated yields of **7** and **16**–**18** are shown in the text. Data for **16**: IR (neat) 2960, 2930, 2870, 2850, 1460, 1390, 1230, 1080, 1040 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.72 (dd, J=11.0, 1.2 Hz, 1H), 5.63 (d, J=11.0 Hz, 1H), 5.50 (dd, J=10.7, 1.2 Hz, 1H), 5.32 (d, J=10.7 Hz, 1H), 1.81 (s, 1H), 1.48 (s, 3H), 1.29 (s, 3H), 1.16 (s, 3H), 1.06 (s, 9H), 0.27 (s, 3H), 0.26 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 142.55, 138.94, 131.93, 127.69, 124.90, 67.40, 40.64, 38.62, 35.50, 32.24, 31.80, 28.62, 18.38, −0.72, −1.25. High MS calcd for $C_{17}H_{29}$-OSiBr 356.1171, observed 356.1150. Data for **17**: IR (neat) 2960, 2870, 1640, 1600, 1380, 1320, 1250, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.21 (d, J=12.5 Hz, 1H), 6.19 (s, 1H), 6.07 (dd, J=12.5, 0.5 Hz, 1H), 5.86 (d, J=12.0 Hz, H), 5.76 (d, J=12.0 Hz, 1H), 2.05 (s, 3H), 1.32 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 192.46, 152.39, 145.32, 144.80, 131.54, 131.13, 128.10, 37.49, 36.68, 27.62, 26.74. High MS calcd for $C_{11}H_{14}O$ 162.10447, observed 162.10443. Data for **18**: IR (neat) 2960, 2940, 2900, 2850, 1660, 1600, 1260, 1220, 1130 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.00 (d, J=12.0 Hz, 1H), 5.99 (dd, J=11.5, 0.7 Hz, 1H), 5.82 (d, J=12.0 Hz, 1H), 5.19 (d, J=11.5 Hz, 1H), 1.91 (d, J=0.7 Hz, 3H), 1.27 (s, 6H), 0.97 (s, 9H), 0.11 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 304.98, 148.54, 145.68, 142.72, 136.09, 134.10, 130.07, 38.66, 29.00, 27.34, 22.46, 19.14, −3.71. High MS calcd for $C_{17}H_{28}OSi$ 276.19094, observed 279.19099.

5.1.12. Preparation of 19 from 3. Treatment of **3** (12.0 mg) in a mixture of THF (1 mL) and 2N HCl (0.3 mL) for 30 min at room temperature followed by extraction with ether gave 7.1 mg of **19** (100% yield); the ^1H NMR spectrum did not show any detectable signals except for those of **19**. The product was further purified by preparative TLC (silica gel, elution with 10% ethyl acetate in hexane). IR (neat) 2950, 2930, 2860, 1720, 1460, 1380, 1270, 1250, 1200 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.51 (m, 1H), 3.57 (dm, J=16.1 Hz, 1H), 2.57 (d, J=16.1 Hz, 1H), 2.51 (dd, J=15.4, 6.6 Hz, 1H), 2.28 (dd, J=15.4, 10.5 Hz, 1H), 1.74–1.73 (m, 3H), 1.30 (ddm, J=8.6, 2.2 Hz, 1H), 1.09 (s, 3H), 1.00 (s, 3H), 0.91 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 209.41, 134.18, 123.35, 48.46, 38.52, 27.59, 25.74, 24.76, 22.78, 17.46, 15.79. High-MS calcd for $C_{11}H_{16}O$ 164.1202, observed 164.1190.

5.1.13. Preparation of 20 from 19. A mixture of **19** (10.2 mg) and K_2CO_3 (5 mg) in methanol–water (10/1, 1 mL) was stirred for 1 h at room temperature. Extraction of the mixture with ether (5 mL ×3) gave essentially pure **20** (9.6 mg, 95%). The product was further purified by a short silica gel column (elution with 10% ethyl acetate in hexane). IR (neat) 2980, 2950, 1660, 1650, 1620, 1460, 1440, 1380, 1290, 1200 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.87 (m, 1H), 2.71 (ddd, J=13.9, 7.1, 5.4 Hz, 1H), 2.41–2.29 (m, 3H), 2.02 (m, 3H), 1.18 (s, 3H), 1.14 (ddd, J=11.0, 9.0, 6.1 Hz, 1H), 1.08 (s, 3H), 0.74 (ddd, J=12.0, 9.0, 5.4 Hz, 1H). MS (EI) 164 (M+, 30%), 149 (10%), 121 (10%), 82 (100%). Anal. calcd for $C_{11}H_{16}O$, C: 80.44, H: 9.82, found C: 80.12, H: 9.96.

5.1.14. Preparation of acetal 22. A solution of 2,5,5-trimethylcyclohexan-2-en-1-one (12.03 g, 79.0 mmol) in ethyl acetate (170 mL) was stirred with Pd–C (5%, 700 mg) under a hydrogen atmosphere for 10 h. Filtration and concentration of the mixture gave essentially pure **21** (12.00 g, 98.6%). A mixture of **21** (1.22 g, 7.89 mmol), (2*R*,4*R*)-2,4-pentanediol (>99.6% pure, 1.07 g, 10.3 mmol), and pyridinium *p*-toluenesulfonate (32 mg) was dissolved in benzene (80 mL). The solution was heated to boiling in a flask fitted with a Dean–Stark trap for 68 h. After cooling, triethylamine (1 mL) and then aqueous saturated $NaHCO_3$ (80 mL) was added to the mixture. Extraction with ether (70 mL×4), drying over $MgSO_4$, and concentration resulted in a yellow oil (1.76 g), which was purified by silica gel column chromatography (elution with 3% ethyl acetate in hexane) to give a colorless oil (1.29 g, 68.0%, a diastereomeric mixture in a ratio of 2/3). Bp 80–88°C/7 Torr. IR (neat) 2950, 2870, 1380, 1160, 1080, 1060 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.05–3.90 (m, 2H), 1.94 (m, 0.6H), 1.82 (m, 0.4H), 1.66–1.22 (m, 10H), 1.20 (d, J=6.4 Hz, 1.2H), 1.19 (d, J=6.3 Hz, 1.8H), 1.16 (d, J=6.3 Hz, 1.8H), 1.14 (d, J=6.4 Hz, 1.2H), 0.85 (d, J=6.8 Hz, 1.2H), 0.92 (d, J=7.1 Hz, 1.8H), 0.87 (s, 1.8H), 0.86 (s, 1.8H), 1.86 (s, 1.2H), 0.84 (s, 1.2H). Anal. calcd for $C_{15}H_{28}O_2$ C: 74.85, H: 11.74, found C: 74.53, H: 11.84.

5.1.15. Preparation of 23 from 22. To a solution of **22** (800 mg, 3.32 mmol) in THF (20 mL) was added pyridinium perbromide (2.72 g, 8.50 mmol) at −78°C. The reaction mixture was warmed up to room temperature over 2.5 h. Pyridine (0.9 mL), and then an aqueous solution of $NaHCO_3$ (10%, 75 mL) containing Na_2SO_3 (100 mg) were added to the mixture. The resulting solution was extracted with ether (25 mL×3), washed with water, dried over Na_2SO_4, and then concentrated to give a yellow oil (2.11 g). Purification of this by silica gel column chromatography (elution with 1% ethyl acetate in hexane) gave a diastereomeric mixture of the dibromoacetal as a colorless oil (1.10 g, 86.9%).

Potassium *t*-butoxide (1.04 g, 9.27 mmol) was placed in a flask, and was dissolved in dry DMSO (20 mL) at 50°C. After cooling, a solution of the dibromoacetal (1.68 g, 4.23 mmol) in dry DMSO (15 mL) was added to the flask, and the mixture stirred for 45 h. After the addition of water (50 mL), the mixture was extracted with ether (80 mL×4), dried over Na_2SO_4, concentrated, and purified by MPLC on silica gel (elution with 1% ethyl acetate in hexane) to give **23** (221.6 mg, 22.2%) and its *exo*-regioisomer (238.6 mg, 23.9% yield). Data for **23**: $[\alpha]_D^{25}$=5.40 (*c* 1.1, methanol). IR (neat) 2970, 2940, 2900, 2870, 1380, 1360, 1160, 1110, 1060, 1010 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.64 (d, *J*=12.2 Hz, 1H), 5.62 (m, 1H), 5.33 (d, *J*=12.2 Hz, 1H), 4.04 (ddm, *J*=7.8, 6.1 Hz, 1H), 3.88 (ddm, *J*=7.6, 6.3 Hz, 1H), 2.50 (dd, *J*=13.4, 7.6 Hz, 1H), 2.32 (dd, *J*=13.4, 7.8 Hz, 1H), 1.84 (m, 3H), 1.63 (t, *J*=7.6 Hz, 2H), 1.20 (d, *J*=6.1 Hz, 3H), 1.20 (d, *J*=6.3 Hz, 3H), 0.98 (s, 3H), 0.96 (s, 3H). High-MS calcd for $C_{15}H_{24}O_2$ 236.1777, observed 236.1765.

5.1.16. Preparation of 24 from 23. To a solution of **23** (214 mg, 0.91 mmol) and triethylamine (0.25 mL, 0.91 mmol) in dry CH_2Cl_2, trimethylsilyl trifluoromethanesulfonate (0.27 mL, 1.4 mmol) was added in 5 min at 0°C. The same amounts of triethylamine and trimethylsilyl trifluoromethanesulfonate were added three more times at 6, 12, and 18 h; then the mixture was poured onto saturated aqueous $NaHCO_3$ (20 mL). Extraction with CH_2Cl_2 (20 mL×3) and purification by column chromatography on alumina (10% water, elution with hexane) gave the enol trimethylsilyl ether (272.5 mg, 97.5% yield). IR (neat) 2950, 1380, 1260, 1180, 1120, 1060, 840 cm^{-1}. ^1H NMR (C_6D_6) δ 6.24 (d, *J*=10.5 Hz, 1H), 6.00 (d, *J*=10.3 Hz, 1H), 5.25 (dm, *J*=10.5 Hz, 1H), 5.15 (dm, *J*=10.3 Hz, 1H), 4.44 (m, 1H), 4.23 (m, 1H), 2.12 (s, 3H), 1.79 (ddd, *J*=13.9, 8.8, 3.3 Hz, 1H), 1.64 (ddd, *J*=13.9, 9.0, 3.4 Hz, 1H), 1.17 (s, 3H), 1.16 (d, *J*=6.1 Hz, 3H), 1.14 (d, *J*=6.1 Hz, 3H), 0.98 (s, 3H), 0.20 (s, 9H). A solution of this compound (272.6 mg, 0.88 mmol) in methanol (15 mL) was stirred with NaOH (as pellets, ca. 60 mg) for 20 h at room temperature. Addition of water (30 mL), extraction with ether (40 mL×4), drying over Na_2SO_4, concentration, and purification by MPLC on silica gel afforded **24** as a colorless oil (145.7 mg, 69.8%). $[\alpha]_D^{20}$=−45.1 (*c* 0.8, methanol). IR (neat) 3400, 3000, 2900, 1380, 1220, 1180, 1120, 740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.98 (d, *J*=10.5 Hz, 1H), 5.90 (d, *J*=10.3 Hz, 1H), 5.27 (dm, *J*=10.5 Hz, 1H), 5.02 (dm, *J*=10.3 Hz, 1H), 4.33 (m, 1H). 4.17 (m, 1H), 2.32 (brs, 1H, −OH), 1.95 (s, 3H), 1.80–1.67 (m, 2H), 1.24 (d, *J*=6.4 Hz, 3H), 1.17 (d, *J*=6.1 Hz, 3H), 1.17 (s, 3H), 0.83 (s, 3H). High-MS calcd for $C_{15}H_{24}O_2$ 236.1777, observed 236.1780.

5.1.17. Dichlorocarbene addition of 24 to give 25a and 25b. To a solution of **24** (87.8 mg, 0.37 mmol) in chloroform (190 mL) was added aqueous 50% NaOH (1.69 g, 21.12 mmol) and then benzyltriethylammonium chloride (9.8 mg) at 0°C. After 4 h, the mixture was diluted with water (30 mL), extracted with chloroform (30 mL×3), and concentrated. Purification of the residue by MPLC on silica gel (elution with 10% ethyl acetate in hexane) gave a colorless oil (120.5 mg, 100%). This material contains **25a** and **25b** in a ratio of 2.3/1 deduced from the ^1H NMR spectrum. Further purification by preparative HPLC on ODS (elution with 20% water in methanol) gave **25a** (41.5 mg, 35%) and **25b** (20.3 mg, 17.1%). Data for **25a**: $[\alpha]_D^{25}$=−10.3 (*c* 1.0, methanol). IR (neat) 3400, 2950, 1380, 1120, 760 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.89 (dd, *J*=11.5, 1.5 Hz, 1H), 5.70 (d, *J*=11.5 Hz, 1H), 5.57 (dd, *J*=11.0, 1.5 Hz, 1H), 5.35 (d, *J*=11.0 Hz, 1H), 4.31 (m, 1H), 4.17 (m, 1H), 2.90 (brs, 1H, OH), 1.85 (ddd, *J*=14.4, 9.3, 4.9 Hz, 1H), 1.62 (ddd, *J*=14.4, 5.1, 2.5 Hz, 1H), 1.40 (s, 3H), 1.27 (s, 3H), 1.26 (d, *J*=6.4 Hz, 3H), 1.20 (d, *J*=6.4 Hz, 3H), 1.18 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 145.74, 140.75, 126.43, 122.58, 77.41, 72.14, 68.26, 64.37, 45.02, 40.51, 36.64, 32.23, 31.35, 23.71, 20.48, 18.94. EI-MS (*m/e*) 318 (M+, 0.5%), 283 (1.7%), 232 (40%), 217 (15%), and 197 (100%). High MS calcd for $C_{16}H_{24}Cl_2O_2$ 318.1153, observed 318.1180. Data for **25b**: mp 71.0–72.0°C. $[\alpha]_D^{25}$=−31.6 (*c* 0.7, methanol). IR (neat) 3400, 2950, 1460, 1380, 1120, 1040, 900, 760 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.01 (dd, *J*=11.0, 1.2 Hz, 1H), 5.75 (d, *J*=11.0 Hz, 1H), 5.66 (dd, *J*=10.7, 1.2 Hz, 1H), 5.41 (d, *J*=10.7 Hz, 1H), 4.30 (m, 1H), 4.13 (m, 1H), 2.67 (brs, 1H, OH), 1.76 (ddd, *J*=14.5, 9.0, 3.9 Hz, 1H), 1.63 (ddd, *J*=14.5, 6.1, 2.7 Hz, 1H), 1.42 (s, 3H), 1.36 (d, *J*=6.3 Hz, 3H), 1.34 (s, 3H), 1.19 (s, 3H), 1.18 (d, *J*=6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 147.57, 141.37, 127.78, 122.53, 77.30, 71.09, 66.92, 64.47, 45.06, 39.31, 35.72, 32.15, 31.13, 23.51, 20.49, 18.09. Anal. calcd for $C_{16}H_{24}O_2Cl_2$ C: 60.19, H: 7.58, found C: 59.87, H: 7.60.

5.1.18. Preparation of 26a and 26b by sodium/methanol reduction. To a solution of **25a** (42.3 mg, 0.13 mmol) in ether (20 mL) was added a piece of sodium (ca. 300 mg) and methanol (1.2 mL, 3.3% water) at 0°C. After 28 h, the remaining sodium metal was removed from the flask, and the reaction mixture was diluted with water (30 mL). Extraction with ether (35 mL ×5), drying over Na_2SO_4, and concentration gave a yellow oil (32.0 mg). Purification by column chromatography on alumina (elution with 3% ethyl acetate in hexane) gave **26a** as a colorless oil (11.8 mg, 35.6%). Data for **26a**: $[\alpha]_D^{25}$=−59.2 (*c* 0.6, methanol). IR (neat) 3400, 2950, 1660, 1380, 1220, 1120 cm^{-1}. ^1H NMR (C_6D_6) δ 5.43 (brs, 1H), 4.63 (brs, 1H), 4.25 (m, 1H), 3.91 (m, 1H), 3.83 (d, *J*=15.2 Hz, 1H), 2.18 (ddd, *J*=15.2, 2.0, 1.0 Hz, 1H), 1.75 (m, 3H, 5-Me), 1.59 (ddd, *J*=14.2, 8.1, 3.2 Hz, 1H), 1.50–1.32 (m, 4H), 1.16 (d, *J*=6.1 Hz, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.05 (d, *J*=6.4 Hz, 3H). High-MS of the acetate calcd for $C_{18}H_{28}O_3$ 292.2038, observed 292.2052. By the same procedure, **25b** was converted to **26b** (33%). Data for **26b**: $[\alpha]_D^{25}$=−25.8 (*c* 0.2, methanol). IR (neat) 3400, 2950, 1660, 1380, 1220, 1180, 1120 cm^{-1}. ^1H NMR (C_6D_6) δ 5.44 (s, 1H), 4.59 (s, 1H), 4.30 (m, 1H), 3.94 (m, 1H), 3.84 (d, *J*=15.2 Hz, 1H), 2.18 (dd, *J*=15.2, 0.9 Hz, 1H), 1.72 (m, 3H), 1.62–1.30 (m, 5H), 1.13 (s, 3H), 1.12 (d, *J*=5.9 Hz, 3H), 1.10 (s, 3H), 1.07 (d, *J*=6.1 Hz, 3H). High-MS of the acetate calcd for $C_{18}H_{28}O_3$ 292.2038, observed 292.2048.

5.1.19. Formation of 27a and 27b. By the treatment of **26** with pyridinium *p*-toluenesulfonate in benzene, **27** was obtained in quantitative yield. Further purification was performed by column chromatography on silica gel (elution with 3% ethyl acetate in hexane). Data for **27a**: $[\alpha]_D^{25}$=65.8 (*c* 0.3, methanol). IR (neat) 2950, 1380, 1160, 1100 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.17 (s, 1H), 4.05–3.47 (m, 2H), 2.78 (d, *J*=13.4 Hz, 1H), 2.20 (d, *J*=13.4 Hz, 1H), 2.14 (dd, *J*=14.4, 4.9 Hz, 1H), 1.70 (brs, 3H), 1.63–1.58 (m, 4H),

1.21 (d, J=6.1 Hz, 3H), 1.17 (d, J=6.4 Hz, 3H), 1.04 (s, 3H), 0.95 (s, 3H), 0.74 (ddd, J=12.7, 8.5, 4.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 137.90, 121.96, 102.73, 62.58, 62.20, 42.32, 38.20, 30.55, 28.12, 25.75, 24.64, 22.21, 21.78, 21.62, 18.53, 16.14. High-MS calcd for $C_{11}H_{26}O_2$ 250.1934, observed 250.1930. Data for **27b**: $[\alpha]_D^{25}=-59.0$ (c 0.2, methanol). IR (neat) 2950, 1380, 1150, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.26 (s, 1H), 4.09–3.97 (m, 2H), 2.93 (d, J=13.0 Hz, 1H), 2.20 (d, J=13.0 Hz, 1H), 2.15 (dd, J=14.2, 5.1 Hz, 1H), 1.73 (brs, 3H), 1.63–1.57 (m, 4H), 1.22 (d, J=6.3 Hz, 3H), 1.15 (d, J=6.3 Hz, 3H), 1.03 (s, 3H), 0.94 (s, 3H), 0.86 (m, 1H). High-MS calcd for $C_{16}H_{26}O_2$ 250.1934, observed 250.1945.

5.1.20. Preparation and reaction of optically active 19 and its dihydroderivative. Treatment of **26** or **27** with a catalytic amount of pyridinium *p*-toluenesulfonate in wet benzene for 4 h at room temperature gave **19** as the sole product. Spectroscopic data of **19** obtained was identical with that from racemic mixture. Conjugated compound **20** was also obtained as the optically active compound. (1*S*,7*S*)-**19** (obtained from **27a**): $[\alpha]_D^{25}=426$ (c 1.1, methanol). (1*R*,7*R*)-**19** (obtained from **27b**): $[\alpha]_D^{25}=-390$ (c 0.5, methanol). (1*S*,7*R*)-**20**: $[\alpha]_D^{25}=178$ (c 0.4, methanol). Hydrogenation of (1*S*,7*R*)-**20** in ethyl acetate in the presence of Pd–C (5%) afforded (1*S*,5*R*,7*R*)-5,8,8-trimethylbicyclo-[5.1.0]octan-3-one, whose data are identical with the reported ones. $[\alpha]_D^{25}=195.1$ (c 0.76, $CHCl_3$), (lit.[7] 215 (c 2.9, $CHCl_3$)). IR (neat) 2950, 1710, 1460, 1380, 1290, 1160, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.62–2.54 (m, 2H), 2.32 (dd, J=11.4, 5.7 Hz, 1H), 2.19–2.09 (m, 2H), 1.81 (ddd, J=14.8, 5.4, 3.5 Hz, 1H), 1.26 (m, 1H), 1.10 (s, 3H), 1.05 (d, J=6.8 Hz, 3H), 1.01 (s, 3H), 0.81 (ddd, J=11.4, 8.8, 5.4 Hz, 1H), 0.72 (dd, J=9.5, 8.1 Hz, 1H). High-MS calcd for $C_{11}H_{18}O$ 166.1358, observed 166.1350.

Acknowledgements

The authors thank Mr Katsuhiro Hashimoto of Sumitomo Pharmaceutical Co. for help with the MO calculations. The present work was partially supported by a Grant-in-Aid for Scientific Research No. 03740279.

References

1. Cane, D. E. *Comprehensive Natural Products Chemistry*, Elsevier: Amsterdam, 1999; Vol. 2.
2. *The Chemistry of the Cyclopropyl Group*, Rappoport, Z., Ed.; Wiley: Chichester, 1987; Part 1 and 2.
3. Newmann, M. F. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 65–67.
4. (a) Doering, W. E.; Roth, W. R. *Tetrahedron* **1963**, *19*, 715–737. (b) Günther, H.; Pawliczek, J. B.; Ulmen, J.; Grimme, W. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 517–518. (c) Bicker, R.; Kessler, H.; Steigel, A.; Stohrer, W. *Chem. Ber.* **1975**, *108*, 2708–2721. (d) Günther, H.; Ulmen, J. *Chem. Ber.* **1975**, *108*, 3132–3140. (e) Günther, H.; Pawliczek, J.; Ulmen, J.; Grimme, W. *Chem. Ber.* **1975**, *108*, 3141–3150. (f) Bicke, R.; Kessler, H.; Ott, W. *Chem. Ber.* **1975**, *108*, 3151–3158. (g) Kessler, H.; Ott, W. *J. Am. Chem. Soc.* **1976**, *98*, 5014–5016. (h) Fühlhuber, H. D.; Gousetis, C.; Troll, T.; Sauer, J. *Tetrahedron Lett.* **1978**, 3903–3906. (i) Dyllick-Brenziger, R.; Oto, J. F. M.; Fühlhuber, H. D.; Gousetis, C.; Troll, T.; Sauer, J. *Tetrahedron Lett.* **1978**, 3907–3910. (j) Kessler, H.; Ott, W.; Lindner, H. J.; Schnering, H. G.; Peters, E.; Peters, K. *Chem. Ber.* **1980**, *113*, 90–103. (k) Maas, G.; Kettenring, J. K. *Chem. Ber.* **1982**, *115*, 627–644. (l) Maas, G.; Kettenring, J. K. *Chem. Ber.* **1984**, *117*, 575–584. (m) Kettenring, J. K.; Maas, G. *Tetrahedron* **1984**, *40*, 391–403.
5. (a) Simonetta, M.; Favini, G.; Mariani, C.; Gramaccioni, P. *J. Am. Chem. Soc.* **1968**, *90*, 1280–1289. (b) Schneider, M. P.; Rau, A. *J. Am. Chem. Soc.* **1979**, *101*, 4426–4427.
6. For a preliminary communication, see: Sugimura, T.; Futagawa, T.; Katagiri, T.; Nishiyama, N.; Tai, A. *Tetrahedron Lett.* **1996**, *37*, 7303–7306.
7. Satoh, T.; Kaneko, Y.; Okuda, T.; Uwaya, S.; Yamakawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 3452–3460.
8. Blanco, L.; Amice, P.; Conia, J. M. *Synthesis* **1981**, 289.
9. Wilson, S. R. *Organic Reactions*, Wiley: New York, 1993; Vol. 43. pp 93–250.
10. (a) Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073–2074. (b) Paquette, L. A.; Ham, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 3025–3036.
11. (a) Sugimura, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett.* **1988**, *29*, 5775–5778. (b) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955–5966. (c) Sugimura, T.; Yoshikawa, M.; Mizuguchi, M.; Tai, A. *Chem. Lett.* **1999**, 831–832. (d) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Katagiri, T.; Miyashige, R.; Mizuguchi, M.; Nagano, S.; Sugimori, S.; Tai, A.; Tei, T.; Okuyama, T. *Tetrahedron* **2001**, *57*, 7495–7499.
12. Tei, T.; Sugimura, T.; Katagiri, T.; Tai, A.; Okuyama, T. *Tetrahedron: Asymmetry* **2001**, *12*, 2727–2730.
13. Tai, A.; Kikukawa, T.; Sugimura, T.; Inoue, Y.; Abe, S.; Osawa, T.; Harada, T. *Bull. Chem. Soc. Jpn* **1994**, *67*, 2473–2477.