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Simple Design for the Construction of Complex Gibberellin Framework——Stereoselective Synthesis of a Possible Key Intermediate to GA_{12} *via* Pd^{2+}-Promoted Cycloalkenylation Reaction

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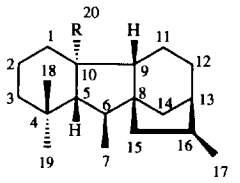
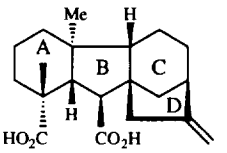
Abstract: A successful design for the construction of C_{20} gibberellin framework has been described. The key features of the synthesis are as follows: (a) Pd^{2+}-promoted cycloalkenylation reaction (**6**→**5**) and (b) intramolecular Diels-Alder reaction (**4**→**3**).

Introduction

The gibberellins, mostly tetra- or pentacyclic diterpenoids, are important plant-growth-regulator which control cell elongation and were discovered in Japan in an investigation of the "bakanae" disease of rice attributed to the fungus *Gibberella fujikuroi.*[1] One third of the group possesses the *ent*-gibberellane skeleton (**1**), with the level of oxidation of C-20 ranging from methyl through to carbonyl.



ent-Gibberellane Skeleton (**1**)



Gibberellin A_{12} (**2**)

The simplest member of this family of compounds is gibberellin A_{12} (GA_{12}) (**2**),[2] and its syntheses were reported independently by Mori[3] and by Tahara[4] and their colleagues.

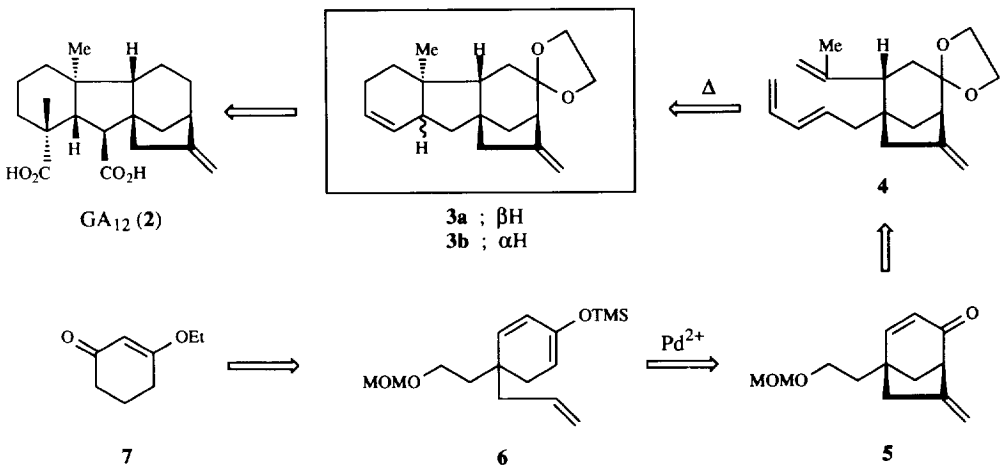
GA_{12} (**2**) incorporates three structural features which have posed long-standing synthetic problems: (i) a spiro fused bicyclo[3.2.1]octane moiety which comprises C and D rings, (ii) three quaternary stereogenic centers (C-4, C-8 and C10), and (iii) A, B-*trans* ring juncture.

We now report the details of our investigations in this area and successful synthesis of a possible synthetic key intermediate for GA_{12} (**2**).

Synthetic Plan

For preparing GA_{12} (**2**), the novel synthetic strategy shown in **Scheme I** was designed in which Pd^{2+}-promoted cycloalkenylation reaction and intramolecular Diels-Alder reaction were employed. We reasoned that the pentacyclic compounds (**3**) would admirably serve as key intermediates for the synthesis of **2**, and **3** become the initial targets of our synthetic undertaking.[5] Access to **3** is provided through the intramolecular Diels-Alder reaction of the tetraene (**4**), which is in turn available from stereoselective introduction of dienophile portion to the enone (**5**) followed by construction of diene portion. Pd^{2+}-promoted cycloalkenylation reaction of the cross-conjugated trimethylsilyl enol ether (**6**), obtainable from **7** by means of Stork-Danheiser's protocol, affords **5**.

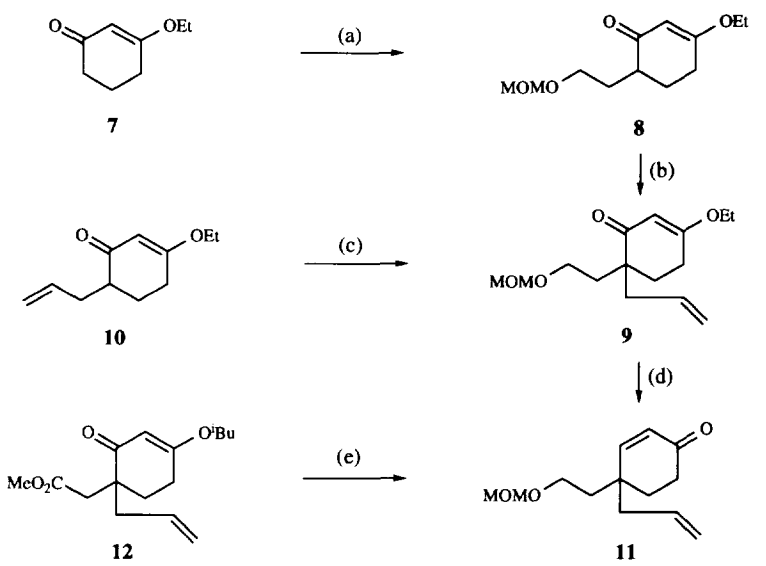
Scheme I



Results and Discussion

In order to explore feasibility of the designed synthetic strategy, Pd^{2+}-promoted cycloalkenylation reaction[6] was studied. In this connection, the establishment of efficient routes for the construction of highly functionalized bicyclo[3.2.1]octane ring systems continues to attract attention due to the wide variety of natural products containing this structural unit. The requisite enone (**11**) for the first key reaction was readily prepared by three different ways. First of all, we elected **7** by way of starting material. Monoalkylation of **7** under the kinetically controlled conditions (LDA, THF, HMPA, -30 °C) with iodoethanol derivative afforded, in 90% yield, the desired product (**8**), which was subjected to allylation [LDA, THF, -30 °C; allyl bromide, tetrakis-(triphenylphosphine)palladium (0),[7] THF, 98%] to furnish **9**. The compound (**9**) was also obtained from **10**.[8] Upon treatment of **10** with iodoethanol derivative in the presence of LDA and HMPA in THF at -30 °C, **9** was produced in 98% yield. The compound (**9**) was transformed into the desired enone (**11**) by sequential LAH reduction and acidic treatment (5% HCl, THF, 0 °C) in 64% overall yield. Furthermore, **11** was directly synthesized by using the ester (**12**)[9] as starting material. Namely, LAH reduction in Et_2O under reflux followed by protection (MOMCl, $^iPr_2NEt$, CH_2Cl_2) gave the corresponding dimethoxymethyl ether, which was converted into the enone (**11**) in 66% overall yield (**Scheme II**).

Scheme II



(a) LDA, THF, HMPA, -30 °C; ICH_2CH_2OMOM, (b) LDA, THF, -30 °C; $CH_2=CHCH_2Br$, $Pd(PPh_3)_4$, (c) LDA, THF, HMPA, -30 °C; ICH_2CH_2OMOM, (d) LAH, THF, 0 °C; 5% HCl, THF, 0 °C, (e) LAH, Et_2O, ref; MOMCl, $^iPr_2NEt$, CH_2Cl_2; 10% HCl, THF.

With convenient access to **11** secure, we then examined on Pd^{2+}-promoted cycloalkenylation reaction for the construction of C, D ring system of GA_{12} (**2**). Upon treatment of the silyl enol ether (**6**) with palladium(II) acetate in MeCN-CH_2Cl_2, the desired enone (**5**) was produced in 92% yield as a sole product. Interestingly, no *endo*-olefinic enone (**13**) was detected. In order to provide some understanding of the above result, the calculations have been performed on systems involving **5** and **13** by means of the semiempirical Hamiltonian PM3 in MOPAC 7.0.[10] As shown in **Figure I**, the *exo*-olefin (**5**), kinetic product, is more stable than the *endo*-olefin (**13**).

Figure I

5 ΔHf = -93.99 Kcal/mol

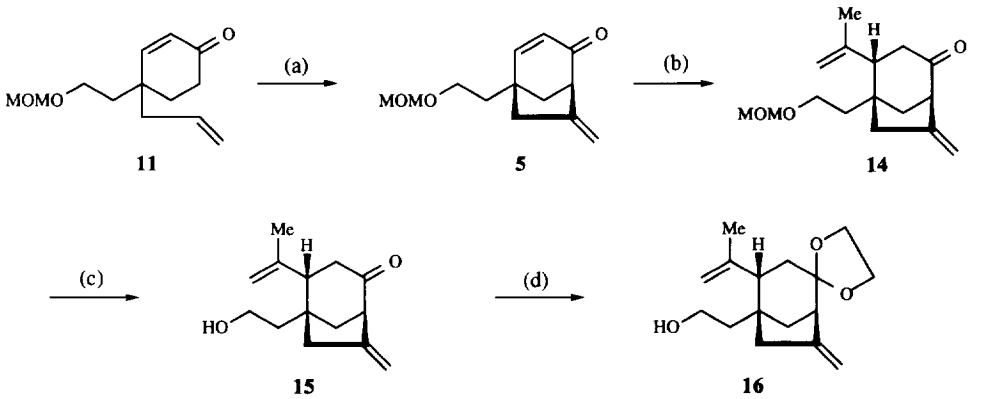
13 ΔHf = -92.61 Kcal/mol

(PM3 / MOPAC 7.0)

Our synthetic efforts were next focused on the stereoselective introduction of dienophile portion for the second key reaction. Highly stereoselective 1,4-addition (99%) of isopropenyl group was accomplished by the

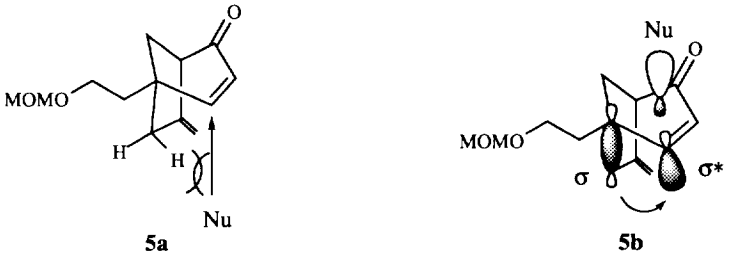
Kuwajima's method.[11] The high preference for the Grignard reagent to add to **5** from *exo*-face can be explained by both the steric interaction between the allylic hydrogen and a nucleophile in **5a**, and the "Cieplak effects"[12] by hyperconjugative stabilization of neighboring group electrons into the σ*-orbital of the incipient carbon-nucleophile bond in **5b** (**Figure II**). The stereochemistry of **14** was made clearly apparent through combined 2-D ^{1}H-^{1}H COSY study and NOE measurements. Irradiation of the methyl group in **14** produced an 11.5% NOE enhancement of the Ha hydrogen (δ 2.26, dd, J = 2.0 and 12.5 Hz). While, irradiation of the Ha hydrogen led to a 3.6% enhancement of the methyl group (**Figure III**). These data are in complete agreement with the assigned structure. For preparing the diene portion, the compound (**14**) was next subjected to acidic treatment (35% $HClO_4$, THF, 40 - 45 °C, 89%) and ketalization (ethylene glycol, PPTS, C_6H_6, reflux, 93%) to furnish the alcohol (**16**) (**Scheme III**).

Scheme III



(a) LDA, THF, -30 °C; TMSCl, -78 °C→room temperature; $Pd(OAc)_2$, MeCN, (b) CH_2=C(Me)MgBr, CuBr·SMe_2, THF, HMPA, TMSCl, -78 °C; 10% HCl, -78 °C→0 °C, (c) 35% $HClO_4$, THF, 40 - 45 °C, (d) ethylene glycol, PPTS, C_6H_6, reflux.

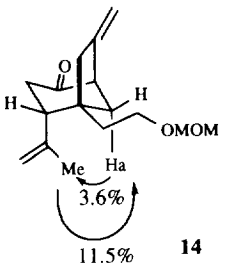
Figure II



5a (Steric effect)

5b (Cieplak effect)

Figure III

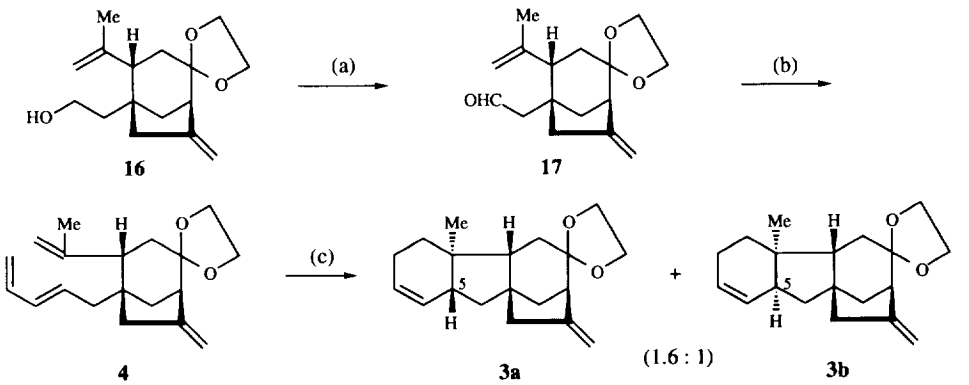


14

Conversion of **16** into the pentacyclic compounds (**3**) was achieved *via* the reaction sequence summarized in **Scheme IV**. Parikh modified Moffatt oxidation[13] (SO_3·Py, DMSO, Et_3N, 94%) of **16** was performed to furnish the aldehyde (**17**), which was subjected to Yamamoto's olefination reaction[14] to give rise to the tetraene (**4**) in 69% yield.

With the efficient synthesis of **4** realized, the stage was now set for the construction of gibberellin-type ring system. An intramolecular Diels-Alder reaction was conducted in toluene at 190 °C for 19 h in a sealed tube to afford the desired pentacyclic compounds (**3**) in 95% yield as a 1.6 : 1 mixture at C-5. Each epimer was easily separated by column chromatography (**Scheme IV**).

Scheme IV

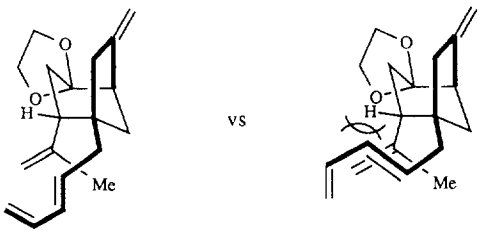


16 **17** **4** **3a** **3b**

(a)SO_3·Py, DMSO, Et_3N, (b) $Ph_2P(O)CH_2CH{=}CH_2$, n-BuLi, HMPA, THF, -78 °C→room temperature, (c) toluene, 190 °C, 19 h, sealed tube.

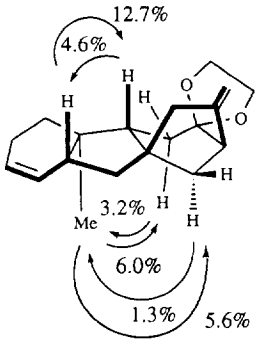
The stereochemistry of **3a** was deduced on the preference of the conformer (**4a**) in the transition state during the cycloaddition (**Figure IV**) and the spectral evidence; particularly due to the similarity of the halfband width (W h/2 = 1.10 Hz) of the angular methyl group with the proposed that of the methyl group possessing anticoplanar hydrogen.[15] The stereochemistry was made clearly apparent through combined 2D ^1H-^1H COSY study and NOE measurements. The relevant NOE data for **3a** are presented by arrows in **Figure V**. Furthermore, the structure of **3a** was determined by X-ray analysis (**Figure VI**).

Figure IV



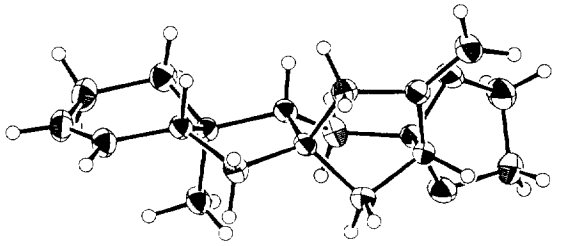
4a **4b**

Figure V



3a

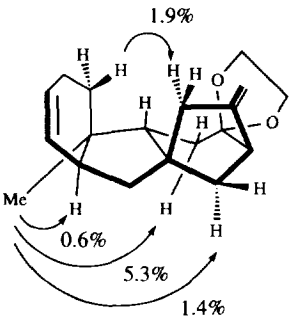
Figure VI



ORTEP Representation of **3a**

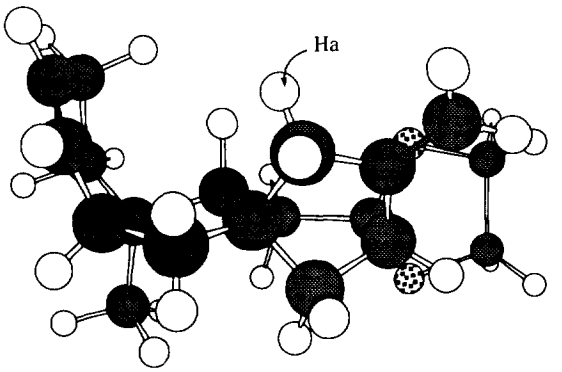
On the other hand, the stereochemistry of the minor Diels-Alder adduct (**3b**) was deduced from its ^{1}H-NMR spectra and NOE experiments (**Figure VII**). Particularly noteworthy is the shielding of the C-15 hydrogen Ha (δ 2.14, br d, J = 15.5 Hz) by the olefin moiety in A ring part in **3b**; in the major isomer (**3a**), this C-15 hydrogen resonance occurs at lower field (δ 2.26, br d, J = 15.5 Hz) (**Figure VIII**).

Figure VII



3b

Figure VIII



3b

Calculated lowest energy conformer of **3b**
(PM3 / MOPAC 7.0).

In conclusion, the work described here provides a strategy for the stereocontrolled synthesis of GA_{12} (**2**) with Pd^{2+}-promoted cycloalkenylation reaction and intramolecular Diels-Alder reaction. Further efforts will be directed toward fine tuning this protocol with a view to yield improvement and with synthesis of suitable functionalized pentacyclic compound for completion of the total synthesis.

Experimental Section

General: Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and Et_2O were distilled under argon from sodium benzophenone

immediately prior to use. Dichloromethane (CH_2Cl_2), acetonitrile (MeCN), dimethyl sulfoxide (DMSO), hexamethylphosphoramide (HMPA), diisopropylamine and diisopropylethylamine were distilled under argon from CaH_2 and used immediately. Toluene and benzene (C_6H_6) were distilled under argon from phosphorus pentoxide (P_2O_5). The concentration of commercially available n-butyllithium in n-hexane was checked by titration by using diphenylacetic acid.[16] All reactions involving organometallic reagents or strong bases (e.g. LDA) were conducted under an argon atmosphere in dry flasks. Unless otherwise noted, reagents and solvents were added by syringe, and organic extracts were dried by being stirred over anhydrous $MgSO_4$, filtered through Celite®, and concentrated under reduced pressure (aspirator) with the aid of a rotary evaporator. Chromatography was carried out by using Merck 60 (230 - 400 mesh) silica gel according to the procedure described by Still.[17] Reactions and chromatography fractions were analyzed by using precoated silica gel 60 F_{254} plates (Merck). IR spectra were recorded as films on NaCl plates unless otherwise noted. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 Hz, respectively, for solutions in $CDCl_3$. COSY spectra were obtained 500 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane or relative internal $CHCl_3$, J values are in hertz.

(±)-3-Ethoxy-6-(2-methoxymethoxyethyl)cyclohex-2-en-1-one (8)

To a stirred solution of LDA [from diisopropylamine (0.38 mL, 2.71 mmol) and 1.6 M n-hexane solution of n-butyllithium (1.67 mL, 2.67 mmol)] in THF (10.0 mL) cooled to -30 °C was added dropwise a solution of **7** (289 mg, 2.06 mmol) in THF (1.0 mL). After 0.5 h, HMPA (0.46 mL, 2.64 mmol) was added followed by 2-methoxymethoxy-1-iodoethane (535 mg, 2.48 mmol) at the same temperature, whereupon the resulting mixture was allowed to warm to room temperature. Stirring was continued for 8 h, then saturated aqueous NH_4Cl was added and the reaction mixture was diluted with Et_2O, washed with water, saturated aqueous $NaHCO_3$, saturated aqueous NaCl and then dried. Removal of the solvent and chromatography of the residue on silica gel with n-hexane-EtOAc (2 : 3 v/v) as eluent afforded the compound (**8**) (197 mg, 42%, 90% based on recovered **7**) as a colorless oil followed by unreacted **7** (154 mg). IR: 1650 and 1610 cm^{-1}. ^1H NMR: δ 1.36 (3H, t, J = 7.1), 1.57 (1H, dt, J = 6.5 and 12.5), 1.66 - 1.88 (1H, m), 2.06 - 2.29 (2H, m), 2.30 - 2.49 (3H, m), 3.36 (3H, s), 3.65 (2H, t, J = 6.5), 3.89 (2H, dq, J = 1.5 and 7.1), 4.62 (2H, s) and 5.32 (1H, s). ^{13}C NMR: δ 14.25, 26.91, 28.42, 29.78, 42.46, 55.29, 64.26, 65.86, 96.46, 102.27, 176.70 and 201.01. EI-MS *m/z* 229 (M^+ +H). *Anal.* Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.10; H, 8.88.

(±)-4-Ethoxy-6-(2-methoxymethoxyethyl)-6-(2-propenyl)cyclohex-2-en-1-one (9)

(i) To a stirred solution of LDA [from diisopropylamine (0.22 mL, 1.57 mmol) and 1.6 M n-hexane solution of n-butyllithium (0.95 mL, 1.52 mmol)] in THF (9.0 mL) cooled to -30 °C was added dropwise a solution of **8** (230 mg, 1.01 mmol) in THF (2.0 mL). After 20 min, tetrakis(triphenylphosphine)palladium (0) (63.0 mg, 0.05 mmol) was added followed by allyl bromide (0.10 mL, 1.16 mmol) at the same temperature, whereupon the resulting mixture was continued to stir at -30 °C for 0.5 h. Furthermore, the mixture was allowed to warm to room temperature and 3 N aqueous HCl was added at 0 °C and the mixture was extracted with Et_2O. The ethereal layer was washed with saturated aqueous $NaHCO_3$, water, dried, and filtered through a Florisil® short column. The filtrate was concentrated and chromatographed on silica gel. Elution with n-hexane-EtOAc (1 : 1 v/v) yielded **9** (265 mg, 98%) as a colorless oil. IR: 1645 and 1605 cm^{-1}. ^1H NMR: δ 1.36 (3H, t, J = 7.3), 1.76 (1H, ddd, J = 6.0, 8.5 and 14.0), 1.90 (2H, t, J = 6.3), 1.95 (1H, ddd, J = 6.5, 8.5 and 14.0), 2.23 (1H,

dd, J = 7.5 and 14.0), 2.39 (1H, dd, J = 7.0 and 14.0), 2.44 (2H, t, J = 6.3), 3.34 (3H, s), 3.51 (1H, dt, J = 6.0 and 8.5), 3.60 (1H, dt, J = 6.5 and 8.5), 3.89 (2H, q, J = 7.3), 4.57 (2H, s), 5.02 - 5.12 (2H, m), 5.27 (1H, s) and 5.67 - 5.84 (1H, m). ^{13}C NMR: δ 14.24, 25.89, 29.66, 34.31, 39.85, 45.49, 55.29, 64.16, 64.24, 96.46, 101.71, 118.18, 134.08, 175.75 and 202.07. EI-MS *m/z* 269 (M^+ +H). *Anal.* Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.94; H, 8.86.

(ii) To a stirred solution of LDA [from diisopropylamine (8.0 mL, 57.2 mmol) and 10% n-hexane solution of n-butyllithium (33.4 mL, 52.1 mmol)] in THF (160 mL) cooled to -30 °C was added dropwise a solution of **10** (8.0 g, 43.4 mmol) in THF (20 mL). After being stirred at the same temperature for 50 min, HMPA (9.1 mL, 52.1 mmol) and 2-methoxymethoxy-1-iodoethane (13.1 g, 60.8 mmol) were added at the same temperature, whereupon the resulting mixture was allowed to warm to room temperature over a period of 6 h. After separation, the aqueous layer was further extracted with EtOAc. The combined organic layers were washed with H_2O and saturated aqueous $NaHCO_3$. All the aqueous layers were combined and back-extracted with C_6H_6. The organic layers were similarly combined and dried. Removal of the solvent and chromatography of the residue on silica gel with n-hexane-EtOAc (3 : 1 v/v) as eluent gave rise to unreacted **10** (4.08 g) followed by the compound (**9**) (5.47 g, 47%, 98% based on recovered **10**) as an oil. Characteristics are identical to those given above.

(±)-4-(2-Methoxymethoxyethyl)-4-(2-propenyl)cyclohex-2-en-1-one (11)

(i) To a suspension of LAH (330 mg, 8.70 mmol) in THF (60 mL) at 0 °C was added dropwise a solution of the compound (**9**) (2.32 g, 8.66 mmol) in THF (10 mL). After 0.5 h at 0 °C, the reaction mixture was allowed to stir at room temperature for 0.5 h. The solution was then cooled to 0 °C, and water (0.33 mL) was cautiously added followed by 15% aqueous NaOH (0.33 mL) and then water (0.99 mL). After 0.5 h, $MgSO_4$ (1.50 g) was added, whereupon the resulting suspension was filtered through Celite. The filtered solids were washed with Et_2O several times, then the combined filtrates were concentrated. The crude product (2.12 g) was used in the following reaction without further purification.

To a stirred solution of the above allylic alcohol (2.12 g, 7.85 mmol) in THF (30 mL) was added 5% HCl (5 mL) at 0 °C. After 10 min, the mixture was neutralized with saturated aqueous $NaHCO_3$ at 0 °C, and extracted with Et_2O. The ethereal layer was dried and concentrated to afford an oil, which was subjected to column chromatography on silica gel. Elution with n-hexane-EtOAc (10 : 3 v/v) to furnish **11** (1.24 g, 64%) as a colorless oil. A small amount was distilled (Kugelrohr): 145 °C / 0.6 mmHg. IR: 1675 and 1635 cm^{-1}. ^1H NMR: δ 1.81 (2H, dt, J = 3.3 and 7.0), 1.90 - 1.98 (2H, m), 2.29 (2H, br d, J = 7.3), 2.41 - 2.46 (2H, m), 3.35 (3H, s), 3.62 (2H, dt, J = 1.8 and 7.0), 4.60 (2H, s), 5.13 (1H, dd, J = 2.0 and 17.5), 5.15 (1H, dt, J = 1.0 and 10.5), 5.78 (1H, ddt, J = 7.3, 10.5 and 17.5), 5.94 (1H, d, J = 10.3) and 6.76 (1H, d, J = 10.3). ^{13}C NMR: δ 31.17, 33.67, 37.12, 37.65, 42.55, 55.06, 63.65, 96.23, 118.65, 127.90, 133.02, 157.05 and 198.66. EI-MS *m/z* 224 (M^+). *Anal.* Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.53; H, 9.00.

(ii) To a suspension of LAH (2.53 g, 66.7 mmol) in Et_2O (300 mL) at ambient temperature was added dropwise a solution of the ester (**12**) (17.0 g, 66.6 mmol) in Et_2O (25 mL). After 0.5 h of gentle reflux, the reaction mixture was cooled to 0 °C, and then water (2.5 mL) was cautiously added followed by 15% aqueous NaOH (2.5 mL) and water (7.5 mL). The mixture was diluted with n-hexane (150 mL) and then the resulting mixture was continued to stir at room temperature for 1.5 h. $MgSO_4$ (4.5 g) was added at 0 °C, then the suspension was filtered through Celite. The filtered solids were washed with Et_2O several times, and then the

combined filtrates were concentrated to give the crude diol, which was dissolved in CH_2Cl_2 (160 mL) and treated with diisopropylethylamine (160 mL, 896 mmol) and chloromethyl methyl ether (46.0 mL, 606 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h and then at room temperature for 10 h. After removal of the solvent, water (250 mL) was added and then the resulting mixture was extracted with Et_2O several times. The combined ethereal layers were washed with water, 50% AcOH, saturated aqueous $NaHCO_3$, and then dried. After removal of the solvent and the residue was dissolved into THF (160 mL), then 10% HCl (26 mL) was added at 0 °C and the mixture was allowed to stand for 10 min. The mixture was neutralized with saturated aqueous $NaHCO_3$ at 0 °C. After extraction with Et_2O, the aqueous layer was further extracted with Et_2O. The combined organic layers were washed with saturated aqueous NaCl and dried. Removal of the solvent and chromatography on silica gel of the residue with n-hexane-EtOAc (3 : 1 v/v) as eluent furnished the enone (**11**) (9.60 g, 66%) as a colorless oil. Characteristics are identical to those given above.

(±)-5-(2-Methoxymethoxyethyl)-7-methylidene-cis-bicyclo[3.2.1]oct-3-en-2-one (5)

To a stirred solution of LDA [from diisopropylamine (0.83 mL, 5.92 mmol) and 1.6 M n-hexane solution of n-butyllithium (3.66 mL, 5.86 mmol)] in THF (30 mL) cooled to -30 °C was added dropwise a solution of **11** (1.01 g, 4.51 mmol) in THF (2 mL). After 0.5 h, chlorotrimethylsilane (0.86 mL, 6.78 mmol) was added at -30 °C, whereupon the resulting mixture was allowed to warm to room temperature. After removal of the solvent, a solution of the silyl enol ether dissolved in MeCN-CH_2Cl_2 (25 mL, 3 : 2) was added dropwise to a stirred solution of $Pd(OAc)_2$ (1.01 g, 4.51 mmol) dissolved in MeCN (15 mL) at room temperature. The resulting mixture was continued to stir at the same temperature for 16 h. The reaction mixture was filtered through an Al_2O_3 short column. The filtrate was concentrated and the residue was chromatographed on silica gel. Elution with n-hexane-EtOAc (3 : 1 v/v) gave rise to **5** (922 mg, 92%) as a colorless oil. A small amount was distilled (Kugelrohr): 150 °C / 0.4 mmHg. IR: 1680 and 1650 cm^{-1}. ^1H NMR (500 MHz): δ 1.79 (1H, ddd, J = 1.8, 5.0 and 11.4), 1.84 - 2.09 (2H, m), 2.17 (1H, br d, J = 11.4), 2.40 - 2.47 (2H, m), 3.36 (3H, s), 3.46 (1H, br d, J = 5.0), 3.67 (2H, dt, J = 1.1 and 6.6), 4.62 (2H, s), 5.05 (1H, br s), 5.27 (1H, br s), 5.80 (1H, dd, J = 1.5 and 9.9) and 7.14 (1H, dd, J = 1.8 and 9.9). ^{13}C NMR: δ 36.66, 41.92, 44.39, 44.87, 54.52, 58.14, 64.24, 95.77, 111.12, 125.35, 144.98, 157.61 and 197.12. EI-MS *m/z* 222 (M^+). *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.03; H, 8.22.

(1R*,4S*,5S*)-5-(2-Methoxymethoxyethyl)-4-methylethenyl-7-methylidenebicyclo[3.2.1]-octan-2-one (14)

To a stirred solution of isopropenylmagnesium bromide [from isopropenyl bromide (0.21 mL, 2.36 mmol) and Mg (43.0 mg, 1.77 mmol)] in THF (10.0 mL) cooled to -78 °C was added dropwise HMPA (0.61 mL, 3.51 mmol). After 5 min, copper(I) bromide-dimethyl sulfide complex (31.0 mg, 0.149 mmol) was added. After being stirred for 5 min at -78 °C, a solution of the compound (**5**) (326 mg, 1.47 mmol) and chlorotrimethylsilane (0.41 mL, 3.23 mmol) in THF (2.0 mL) was added dropwise at the same temperature. After 0.5 h, 10% HCl was added at -78 °C, whereupon the resulting mixture was allowed to warm to 0 °C with stirring. After dilution of the mixture with Et_2O followed by separation, the aqueous layer was further extracted with Et_2O. The combined organic layers were washed with water to remove HMPA, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, and dried. Removal of the solvent and chromatography of the residue on silica gel with n-hexane-EtOAc (4 : 1 v/v) as eluent yielded **14** (384 mg, 99%) as a colorless oil. A small amount

was distilled (Kugelrohr): 170 °C / 0.6 mmHg. IR: 1710 cm^{-1}.^{1}H NMR: δ 1.64 (1H, ddd, *J* = 6.5, 9.0 and 14.0), 1.70 (1H, ddd, *J* = 1.8, 5.5 and 12.5), 1.75 (3H, s), 1.88 (1H, ddd, *J* = 5.5, 9.0 and 14.0), 2.08 (1H, br d, *J* = 16.5), 2.26 (1H, dd, *J* = 2.0 and 12.5), 2.46 (1H, br dd, *J* = 1.8 and 17.0), 2.60 (1H, dt, *J* = 2.5 and 17.0), 2.68 (1H, dd, *J* = 1.8 and 9.2), 2.78 (1H, dd, *J* = 9.2 and 16.5), 3.21 (1H, br d, *J* = 5.5), 3.33 (3H, s), 3.56 (1H, dt, *J* = 6.5 and 9.0), 3.67 (1H, dt, *J* = 5.5 and 9.0), 4.58 (2H, s), 4.69 (1H, s), 4.85 - 4.87 (1H, m), 4.90 (1H, br s) and 5.02 (1H, m). ^{13}C NMR: δ 23.01, 36.75, 39.31, 40.69, 43.54, 44.43, 51.30, 55.04, 59.62, 64.47, 96.25, 108.25, 114.89, 147.26, 148.57 and 209.85. EI-MS *m/z* 264 (M^+). *Anal.* Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.69; H, 9.21.

(1R*,4S*,5S*)-5-(2-Hydroxyethyl)-4-methylethenyl-7-methylidenebicyclo[3.2.1]octan-2-one (15)

To a stirred solution of the MOM ether (**14**) (797 mg, 3.02 mmol) in THF (34.0 mL) was added dropwise 35% aqueous $HClO_4$ (34.0 mL) at room temperature. The temperature of the resulting mixture went up to 47 °C. After being stirred for 10 min at 40 - 45 °C, the mixture was cooled to 0 °C, and then neutralized with saturated aqueous $NaHCO_3$. Following dilution with Et_2O and separation, the aqueous layer was extracted with EtOAc (× 2). The combined organic layers were washed with saturated aqueous NaCl and dried. Removal of the solvent and chromatography of the residue on silica gel with n-hexane-EtOAc (5 : 3 v/v) as eluent afforded the alcohol (**15**) (595 mg, 89%) as a colorless oil. IR: 3400 and 1710 cm^{-1}. ^{1}H NMR: δ 1.25 (1H, br s), 1.58 - 1.80 (5H, m), 1.90 (1H, ddd, *J* = 4.5, 7.5 and 11.0), 2.10 (1H, br d, *J* = 13.5), 2.30 (1H, dd, *J* = 1.5 and 10.0), 2.51 (1H, br dd, *J* = 1.5 and 14.0), 2.63 (1H, dt, *J* = 2.0 and 14.0), 2.71 (1H, dd, *J* = 1.5 and 8.0), 2.82 (1H, dd, *J* = 8.0 and 13.5), 3.24 (1H, d, *J* = 5.5), 3.67 - 3.93 (2H, m), 4.73 (1H, d, *J* = 0.8), 4.89 (1H, t, *J* = 0.8), 4.94 (1H, br s), and 5.05 (1H, br t, *J* = 2.5). ^{13}C NMR: δ 23.13, 39.57, 40.15, 40.89, 43.86, 44.64, 51.55, 59.68, 59.74, 108.60, 115.10, 147.45, 148.58 and 210.59. HRMS calcd for $C_{14}H_{22}O_2$: 220.1463, found: 220.1469.

(R*,4S*,5S*)-5-(2-Hydroxyethyl)-4-methylethenyl-7-methylidenebicyclo[3.2.1]octan-2-one 2-Etylene Acetal (16)

A solution of **15** (18.0 mg, 0.082 mmol), ethylene glycol (0.05 mL, 0.90 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (3.0 mg, 0.012 mmol) in C_6H_6 (2.0 mL) was refluxed under a Dean-Stark water separator for 1 h. The solution was cooled to room temperature and then water was added. Following dilution with Et_2O and separation, the combined organic layers were washed with saturated aqueous $NaHCO_3$, water, saturated aqueous NaCl, and dried. Removal of the solvent and chromatography of the residue on silica gel with n-hexane-EtOAc (10 : 3 v/v) as eluent furnished the ketal (**16**) (20.0 mg, 93%) as a white solid. An analytical sample was obtained by recrystallization of the solid from Et_2O-n-hexane as colorless prisms: mp 86.5 - 88.0 °C. IR: 3400 cm^{-1}. ^{1}H NMR: δ 1.19 (1H, br s), 1.39 (1H, ddd, *J* = 1.5, 5.5 and 12.5), 1.46 - 1.64 (3H, m), 1.84 - 1.98 (4H, m), 2.08 (1H, dd, *J* = 9.0 and 15.0), 2.24 - 2.44 (3H, m), 2.57 (1H, br d, *J* = 5.5), 3.58 - 3.82 (2H, m), 3.86 - 4.06 (4H, m), 4.79 (1H, br s), 4.85 - 4.95 (2H, m) and 5.03 (1H, br s). ^{13}C NMR: δ 22.78, 35.10, 37.26, 41.18, 43.54, 45.10, 50.39, 50.88, 60.31, 63.84, 64.67, 107.98, 114.23, 149.00 and 150.22. EI-MS *m/z* 264 (M^+). *Anal.* Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.53; H, 9.21.

(1R*,4S*,5S*)-4-Methylethenyl-7-methylidene-5-(2-oxoethyl)bicyclo[3.2.1]octan-2-one 2-Ethylene Acetal (17)

To a stirred solution of **16** (486 mg, 1.84 mmol) and Et_3N (4.0 mL, 28.7 mmol) in DMSO (10.0 mL) was added sulfur trioxide pyridine complex (1.37 g, 8.46 mmol) at ambient temperature. After 20 min, water was added and the mixture was extracted with Et_2O. The ethereal layer was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, water, saturated aqueous NaCl, and then dried. Removal of the solvent and chromatography of the residue on silica gel with n-hexane-EtOAc (8 : 1 v/v) as eluent gave rise to the aldehyde (**17**) (453 mg, 94%) as a colorless oil along with the methylthiomethyl ether of **16** (20.4 mg, 3%; colorless oil). ***Compound (17)***; IR: 1720 cm^{-1}. ^1H NMR: δ 1.45 (1H, ddd, *J* = 1.5, 5.5 and 12.0), 1.60 (1H, br dd, *J* = 1.5 and 15.5), 1.89 (3H, s), 2.12 (1H, dd, *J* = 8.5 and 15.5), 2.29 (1H, dd, *J* = 1.8 and 17.0), 2.34 - 2.45 (2H, m), 2.54 - 2.67 (3H, m), 2.72 (1H, dd, *J* = 1.8 and 17.0), 3.87 - 4.03 (4H, m), 4.76 - 4.83 (1H, m), 4.88 - 4.97 (2H, m), 5.03 - 5.09 (1H, m), 9.78 (1H, t, *J* = 1.8). HRMS calcd for $C_{16}H_{22}O_3$: 262.1569, found: 262.1546. ***MTM ether of 16***; ^1H NMR: δ 1.40 (1H, ddd, *J* = 1.5, 5.5 and 12.0), 1.50 - 1.62 (2H, m), 1.82 - 1.93 (1H, m), 1.93 (3H, s), 2.08 (1H, dd, *J* = 9.5 and 15.0), 2.14 (3H, s), 2.20 - 2.45 (4H, m), 2.57 (1H, br d, *J* = 5.5), 3.51 (1H, dt, *J* = 6.5 and 9.0), 3.62 (1H, dt, *J* = 5.5 and 9.0), 3.82 - 4.05 (4H, m), 4.79 (2H, s), 4.76 - 4.82 (1H, m), 4.87 - 4.96 (2H, m) and 5.00 - 5.05 (1H, m). HRMS calcd for $C_{18}H_{28}O_3S$: 324.1759, found: 324.1735.

(1R*,4S*,5S*)-Methylethenyl-7-methylidene-5-[(2E)-2,4-pentadienyl]bicyclo[3.2.1]octan-2-one 2-Ethylene Acetal (4)

To a stirred solution of allyldiphenylphosphine oxide (12.0 mg, 0.050 mmol) in THF (2.0 mL) was added HMPA (0.013 mL, 0.048 mmol), whereupon the mixture was cooled to -78 °C. 1.6 M n-hexane solution of n-butyllithium (0.03 mL, 0.048 mmol) was added dropwise. The colorless solution turned red. After 10 min, a solution of the aldehyde (**17**) (8.0 mg, 0.031 mmol) in THF (1.0 mL) was added dropwise at -78 °C. After being stirred for 10 min at the same temperature, the resulting mixture was allowed to warm to 0 °C over a period of 10 min. After 10 min, the reaction was quenched with saturated aqueous NH_4Cl, and then the mixture was extracted with Et_2O. The organic layer was washed with water to remove HMPA, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, and dried. Evaporation and chromatography of the residue on silica gel with n-hexane-EtOAc (10 : 1 v/v) as eluent afforded the tetraene (**4**) (6.0 mg, 69%) as a colorless oil. ^1H NMR: δ 1.40 (1H, ddd, *J* = 1.8, 5.5 and 12.0), 1.58 (1H, dd, *J* = 1.5 and 15.0), 1.91 (3H, s), 1.96 - 2.42 (7H, m), 2.58 (1H, br d, *J* = 5.5), 3.85 - 4.04 (4H, m), 4.80 (1H, br s), 4.89 (1H, br s), 4.93 (1H, br d, *J* = 1.8), 4.96 (1H, br d, *J* = 11.0), 5.09 (1H, br d, *J* = 17.0), 5.10 (1H, br s), 5.70 (1H, dt, *J* = 7.0 and 15.0), 6.03 (1H, dd, *J* = 10.0 and 15.0) and 6.29 (1H, dt, *J* = 10.0 and 12.0). ^{13}C NMR: δ 23.25, 35.12, 35.78, 40.72, 44.30, 45.23, 50.83, 51.34, 63.81, 64.62, 107.85, 110.55, 114.15, 115.12, 131.77, 133.57, 137.19, 148.61 and 150.29.

(±)-7,18,19-Trinorgibberella-3,16-dien-12-one 12-Ethylene Acetal (3a) and (±)-(5βH)-7,18,19-Trinorgibberella-3,16-dien-12-one 12-Ethylene Acetal (3b)

A solution of the tetraene (**4**) (303 mg, 1.06 mmol) in toluene (30.0 mL) was heated at 190 °C in a sealed tube for 19 h. After removal of the solvent, the residue was filtered through a silica gel short column. The filtrate was concentrated to give the cycloaduct (**3**) (287 mg, 95%) as a colorless oil [1.6 : 1 mixture of β-H: α-H at C-5 of **3**, as determined by the angular methyl group in the ^1H NMR]. Chromatography on silica gel with n-hexane-

EtOAc (25 : 2 v/v) furnished first, the apolar oil (later assigned **3b**) followed by the polar solids (later assigned **3a**). Recrystallization of the latter from CH_2Cl_2-MeOH afforded colorless prisms, mp 95.0 - 97.0 °C, suitable for a single-crystal X-ray structural determination. ***Compound (3a)***; ^{1}H NMR (500 MHz): δ 0.72 (3H, s), 1.25 (1H, dd, *J* = 6.0 and 13.0), 1.39 (1H, br dt, *J* = 7.5 and 11.5), 1.50 - 1.59 (2H, m) 1.60 - 1.70 (3H, m), 1.73 (1H, dd, *J* = 3.0 and 11.5), 1.84 (1H, dd, *J* = 13.0 and 14.0), 2.00 - 2.12 (2H, m), 2.17 (1H, dt, *J* = 2.5 and 15.5), 2.26 (1H, br d, *J* = 15.5), 2.60 (1H, br d, *J* = 5.0), 3.82 - 4.04 (4H, m), 4.98 - 5.02 (2H, m), 5.50 - 5.56 (1H, m) and 5.63 (1H, dq, *J* = 2.5 and 10.0). ^{13}C NMR: δ 14.00, 24.18, 32.24, 36.04, 36.97, 37.53, 43.75, 46.23, 47.43, 50.08, 51.64, 52.36, 63.42, 64.87, 110.52, 111.77, 127.07, 127.76 and 149.38. MS *m/z* 286 (M^+). *Anal* Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.61; H, 9.07. ***X-ray data***; the compound (**3a**) crystallizes in the triclinic P_{-1} (No. 2) space group with a = 10.531 (2), b = 12.304 (2), c = 6.361 (1) Å, α = 101.88 (1), β = 98.40 (1), γ = 100.55 (1) °, V = 778.4 (3) Å^3, and Z = 2. The final coordinates were solved by direct methods and refined by fullmatrix least-squares methods with R = 0.054, Rw = 0.055. Final crystallographic coordinates are deposited in Cambridge Crystallographic Data Centre. ***Compound (3b)***; ^{1}H NMR (500 MHz): δ 0.92 (3H, s), 1.31 - 1.43 (3H, m), 1.45 - 1.55 (2H, m), 1.65 (1H, dd, *J* = 7.5 and 14.0), 1.75 (1H, dd, *J* = 9.5 and 14.0), 1.86 - 1.91 (2H, m), 1.93 - 1.98 (2H, m), 2.11 - 2.17 (1H, m), 2.14 (1H, br d, *J* = 15.5), 2.23 (1H, dt, *J* = 2.5 and 15.5), 2.56 (1H, br d, *J* = 5.5), 3.86 - 3.99 (4H, m), 4.95 (1H, br s), 4.98 - 5.00 (1H, m) and 5.55 - 5.62 (1H, m). ^{13}C NMR: δ 22.44, 22.89, 31.60, 33.27, 37.91, 41.08, 41.95, 46.38, 47.74, 48.68, 49.99, 50.91, 63.71, 64.55, 109.76, 111.58, 125.50, 130.80 and 150.14. HRMS calcd for $C_{19}H_{26}O_2$: 286.1933, found: 286.1966.

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