Remarkable Control of Radical Cyclization Processes of Cyclic Enyne: Total Syntheses of (±)-Methyl Gummiferolate, (±)-Methyl 7β-Hydroxykaurenoate, and (±)-Methyl 7-Oxokaurenoate and Formal Synthesis of (±)-Gibberellin A_{12} from a Common Synthetic Precursor

Masahiro Toyota,* Masahiro Yokota, and Masataka Ihara*

Contribution from the Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

Received September 29, 2000

Abstract: Total syntheses of (±)-methyl gummiferolate (**13b**), (±)-methyl 7β-hydroxykaurenoate (**14b**), and (±)-methyl 7-oxokaurenoate (**14d**) and a formal synthesis of (±)-gibberellin A_{12} (**15**) have been accomplished through the common synthetic precursor, (3a*R**,7a*R**)-3,3-dimethyl-7a-(2-propynyl)-3a,4,7,7a-tetrahydroisobenzofuranone (**16**). The homoallyl−homoallyl radical rearrangement reaction of the monocyclic enyne **25**, derived from **16** in two steps, afforded the bicyclo[2.2.2]octane compound **26**, which was converted to (±)-methyl gummiferolate (**13b**). In contrast, the radical cyclization of the bicyclic enyne **16** gave the tricyclic lactone **19**, leading to (±)-methyl 7β-hydroxykaurenoate (**14b**) and (±)-methyl 7-oxokaurenoate (**14d**). Transformation of **14d** into lactone **20** was carried out in a single step under bromination conditions. This constitutes a formal total synthesis of gibberellin A_{12} (**15**).

Introduction

Radical reactions have evolved as a powerful methodology for the synthesis of biologically active organic compounds during the last two decades, and many elegant total syntheses of structurally complicated natural products have been realized employing radical cyclizations and cascade radical reactions.[1] Some of the attractive features of the radical reactions include high functional group tolerance, mild reaction conditions, and regio- and stereoselectivity. To prepare moderately functionalized bicyclo[2.2.2]- or bicyclo[3.2.1]octane ring compounds, both of which are crucial carbon frameworks for many biologically active natural products, we envisioned novel synthetic routes to these bicyclic compounds from a common intermediate by using radical cyclizations. The synthetic design is depicted in Scheme 1; the initially generated vinyl radical **3** from acetylene **1** or vinyl halide **2** was expected to cyclize to afford the bicyclic radical **5**.[2] The resulting radical **5** would undergo *3-exo-trig* cyclization to give the unstable cyclopropylcarbinyl radical **7**, which would rearrange to the thermodynamically more stable homoally radical **8**.[3]

After extensive investigation, it was found that the homoallyl radical **10** with a methyl group in the R^2 position gave good selectivity for the bicyclo[2.2.2]octane since the *3-exo-trig* cyclization proceeds smoothly, probably due to the nonbonding interaction between the R^2 substituent and $Bu_3Sn^{\bullet}$.[4] In contrast, avoidance of strain of the furanone ring in **11** can be important in bringing about conformational inversion of the six-membered ring in **11**. Attack by tributyltin hydride on the less hindered convex face of the more abundant conformation **12** provided the tricyclic compound as a major product (Scheme 2).[5]

Having successfully developed a flexible methodology for the selective formation of bicyclo[2.2.2]octane or bicyclo[3.2.1]-octane derivatives, our efforts were next focused on the total synthesis of plant growth-regulators, such as gummiferolic acid (**13a**) and gibberellin A_{12} (**15**), from a common starting material.

Plant Growth-Regulators. Interestingly, some tetracyclic diterpenoids, which have bicyclo[2.2.2]octane or bicyclo[3.2.1]-octane ring systems as their CD rings, exhibit considerable plant growth-regulatory activity. Gummiferolic acid (**13a**), which was isolated from *Margotia gummifera* by Pinar et al.,[6] possesses six contiguous stereogenic centers and a bicyclo[2.2.2]octane ring system as the CD part. In addition, **13a** shows plant growth-regulatory activity similar to or greater than that displayed by gibberellic acid.[7] Although kaurenoic acid and its derivatives, such as **14**, are biosynthetic intermediates for gibberellins, grayanotoxins, and stevioside, little is known about activities worthy of special mention.[8] Gibberellin A_{12} (**15**), isolated from *Gibberella fujikuroi* and whose structure was elucidated by Cross et al.,[9] has a *trans*-hydrindane AB ring system and a spiro-fused bicyclo[3.2.1]octane moiety that comprises the C and D rings (Figure 1).

Synthetic Plans for Gummiferolic Acid and Gibberellin A_{12}. In an effort to synthesize structurally different plant growth-regulators, **13** and **15**, through the use of radical cyclization reactions, we envisaged (3a*R**,7a*R**)-3,3-dimethyl-7a-(2-propynyl)-3a,4,7,7a-tetrahydroisobenzofuranone (**16**) as a common

(1) (a) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301−856. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, New York, Basel, Cambridge, Tokyo, 1995.

(2) (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140−3157. (b) Yadav, V.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 3283−3286.

(3) (a) Beckwith, L, J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525−4528. (b) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529−4532.

(4) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Huter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067−4079.

(5) Toyota, M.; Yokota, M.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 1551−1554.

(6) Pinar, M.; Rodriguez, B.; Alemany, A. *Phytochemistry* **1978**, *17*, 1637−1640.

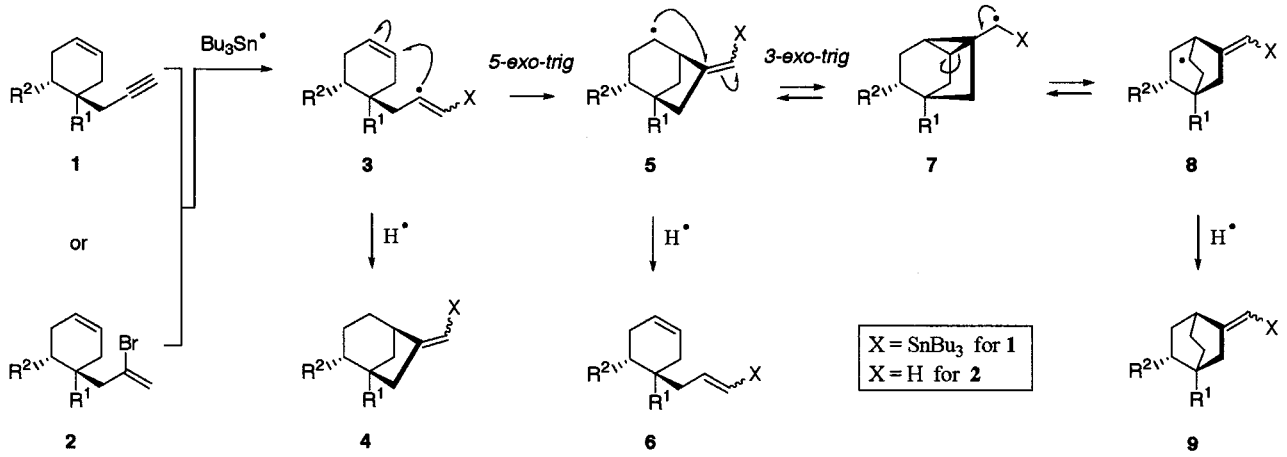
(7) Villalobos, N.; Martin, L.; Macias, M. J.; Mancheno, B.; Grande, M. *Phytochemistry* **1994**, *37*, 635−639.

(8) MacMillan, J. *Nat. Prod. Rep.* **1997**, *14*, 221−243.

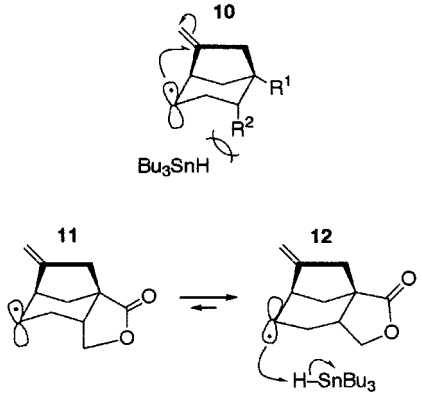
(9) Cross, B. E.; Norton, K. *J. Chem. Soc.* **1965**, 1570−1572.

10.1021/ja0035506 CCC: $20.00
Published on Web 02/10/2001

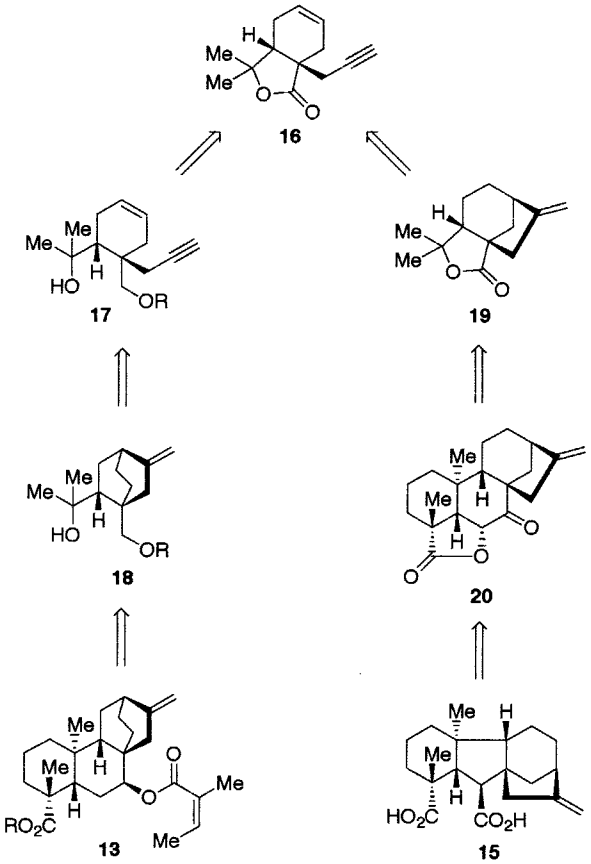
Scheme 1



Scheme 2



Scheme 3



intermediate. First, we planned to synthesize gummiferolic acid (**13a**) by means of homoallyl−homoallyl radical rearrangement. Thus, we designed the alcohol **17** as an appropriate precursor for vinyl radical assisted homoallyl−homoallyl radical rearrangement. Compound **17** has a tertiary alcohol, which should be bulky enough to control the radical cyclization and is easily convertible to isopropenyl group.[5] After construction of the bicyclo[2.2.2]octane compound **18**, the *trans*-decalin structure that corresponds to the AB ring system of gummiferolic acid (**13a**) could be prepared by an intramolecular Diels−Alder reaction.[10] On the other hand, the bicyclo[3.2.1]octane **19** would be synthesized through intramolecular vinyl radical-promoted cyclization. The *trans*-decalin part of the pentacyclic compound **20** could be prepared by intramolecular Diels−Alder reaction as described above. The lactone **20** had already been transformed into GA_{12}.[9,11,12]

Total Synthesis of (±)-Methyl Gummiferolate by Homoallyl−Homoallyl Radical Rearrangement. Since it was found that monocyclic enynes such as **1** and **2**, bearing bulky R^2 substituents, gave better selectivity for bicyclo[2.2.2]octanes in the preliminary studies,[5] substrates **24** and **25** were prepared as depicted in Scheme 4. Thus, commercially available *cis*-1,2,3,6-tetrahydrophthalic anhydride (**21**) was submitted to methanolysis to give the corresponding half ester, which was treated with excess methylmagnesium iodide to afford the lactone **22** in 76% overall yield from **21** after acid treatment. The vinyl bromide **24** was synthesized in three steps from **22** through alkylation (92%), $LiAlH_4$ reduction (82%) of the lactone moiety, followed by monoacetylation (93%) of the primary alcohol. Meanwhile, the cyclic enyne **25** was prepared in 84% overall yield in a manner similar to that described above.

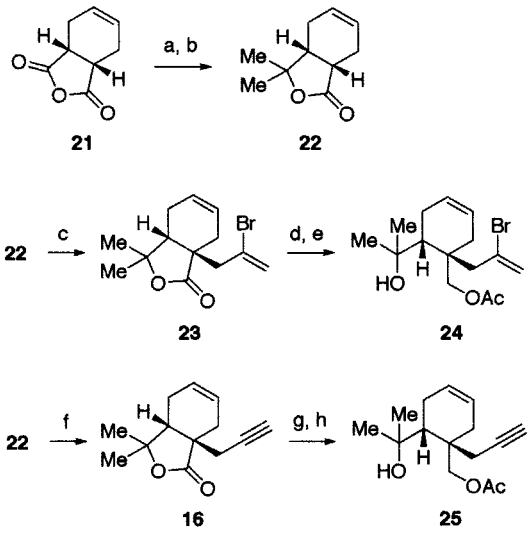
Refluxing a solution of **24** in benzene with tributyltin hydride and AIBN afforded the desired bicyclo[2.2.2]octane compound **26**. However, chromatographic purification of **26** was very difficult due to contamination by nonpolar byproducts. The isolation problem was solved by using acetylene **25** as a substrate for the key reaction. Thus, reaction of **25** under optimized conditions furnished the bicyclic acetate **26** (32%) together with the bicyclo[3.2.1]octane derivative **27** (50%).

(10) (a) Ciganek, E. *Org. React.* **1984**, *32*, 1−374. (b) Roush. W. R. *Advances in Cycloaddition*; JAI Press Inc.: Greenwich, CT, London, 1990; Vol. 2, pp 91−146. (c) Roush, W. R. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, New York, Seoul, Tokyo, 1991; Vol. 5, pp 513−550.

(11) (a) Cross, B, E.; Galt, R. H. B.; Hanson, J. R. *J. Chem. Soc. (C)* **1963**, 2944−2961. (b) Galt, R. H. B.; Hanson, J. R. *J. Chem. Soc. (C)* **1965**, 1565−1570.

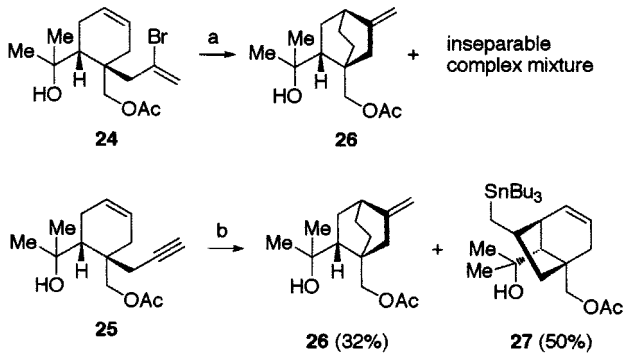
(12) Mori, K.; Takemoto, I.; Matsui, M. *Tetrahedron* **1976**, *32*, 1497−1502.

Scheme 4[a]



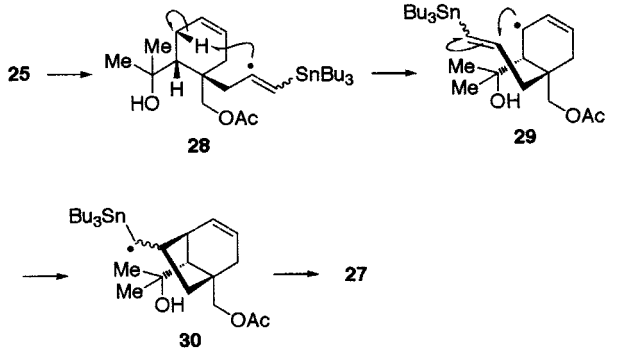
[a] Reagents and conditions: (a) MeOH, reflux, 100%. (b) MeMgI, Et_2O; H_2SO_4, 76%. (c) LDA, THF, −78 °C; HMPA, 2,3-dibromopropene, 92%. (d) LAH, Et_2O, 82%. (e) Ac_2O, pyridine, 93%. (f) LDA, THF, −78 °C; HMPA, propargyl bromide, 85%. (g) LAH, Et_2O, 99%. (h) Ac_2O, pyridine, 100%.

Scheme 5[a]



[a] Reagents and conditions: (a) Bu_3SnH, AIBN, benzene, reflux. (b) Bu_3SnH, AIBN, benzene, reflux; SiO_2, CH_2Cl_2.

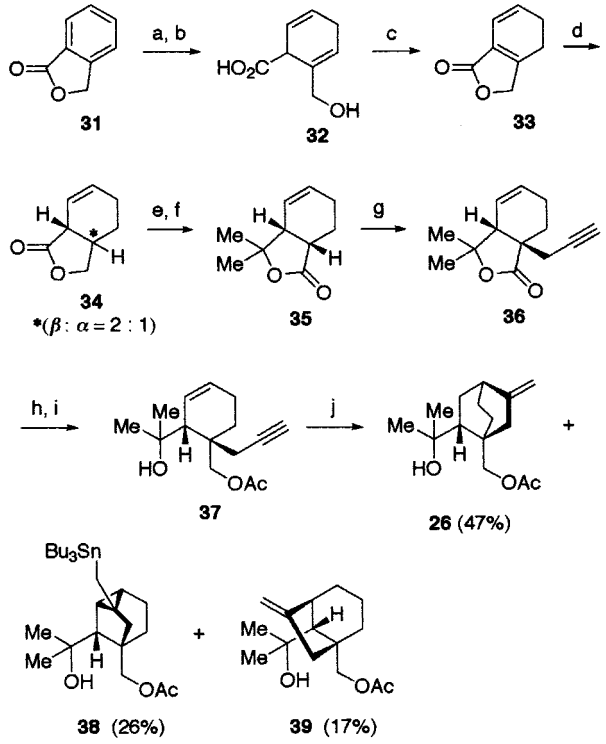
Scheme 6



Generation of **27** from **25** can be explained by 1,5-radical translocation (**28** → **29**) of the initially formed vinyl radical **28** followed by a 5-*exo-trig* cyclization process (**29** → **30**) as shown in Scheme 6. On the basis of our model studies,[5] the formation of the bicyclo[3.2.1]octane ring system was not anticipated.[13]

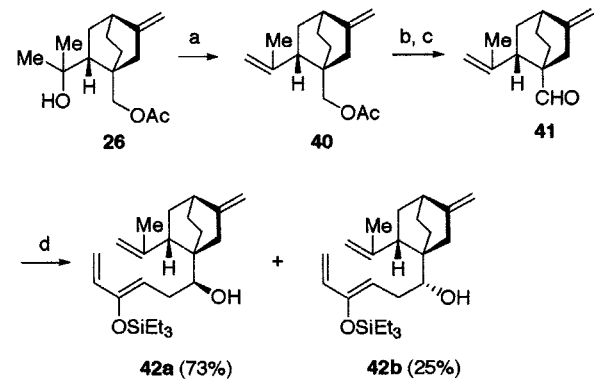
To overcome this drawback, many approaches were surveyed. The substrate **37** that eventually proved to be most amenable to large-scale synthesis was prepared from phthalide **31** as depicted in Scheme 7. Thus, hydrolysis of **31** followed by Birch reduction provided the cyclohexadiene derivative **32**, which was subjected to lactonization reaction by the use of the Steglich protocol[14] to afford the lactone **33** in 77% overall yield from **31**. Conjugate reduction with $NaBH_4$ furnished the tetrahydrophthalide **34** (92%) as a 2:1 mixture of diastereoisomers. Treatment of **34** with excess methylmagnesium iodide followed by PDC oxidation of the resulting diol produced lactone **35** as a single stereoisomer. After alkylation (67%) of **35**, the resulting lactone **36** was converted to the acetate **37** via $LiAlH_4$ reduction

Scheme 7[a]



[a] Reagents and conditions: (a) Aqueous NaOH, MeOH, reflux. (b) Liquid NH_3, Na; 10% HCl. (c) DCC, DMAP, CH_2Cl_2, 77% for 3 steps. (d) $NaBH_4$, MeOH. (e) MeMgI, Et_2O. (f) PDC, Florisil, CH_2Cl_2, 38% for 3 steps. (g) LDA, THF, −78 °C; HMPA; propargyl bromide, 67%. (h) LAH, Et_2O, 84%. (i) Ac_2O, pyridine, 100%. (j) Bu_3SnH, AIBN, benzene, reflux; SiO_2, Ch_2Cl_2.

Scheme 8[a]



[a] Reagents and conditions: (a) $POCl_3$, pyridine, 99%. (b) K_2CO_3, MeOH, 100%. (c) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, 97%. (d) *s*-BuLi, THF, 3-triethylsilyloxy-1,4-pentadiene, −78 °C.

(13) A part of this work was published as a preliminary communication: Toyota, M.; Yokota, M.; Ihara, M. *Org. Lett.* **1999**, *1*, 1627−1629.

(14) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522−524.

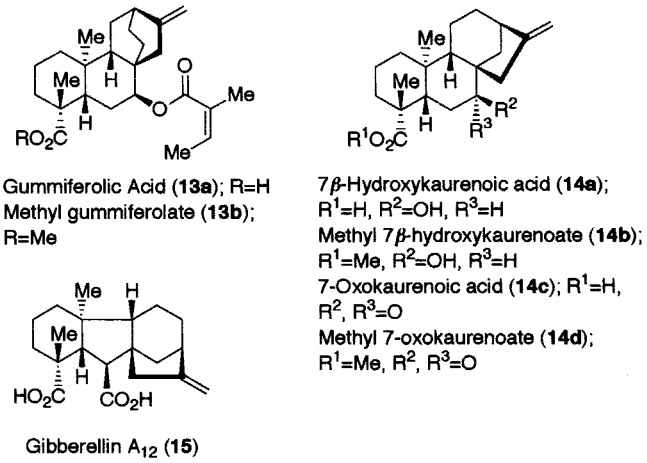


Figure 1.

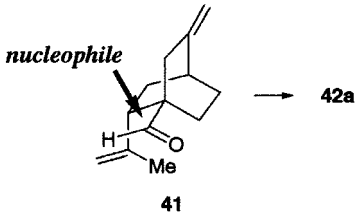


Figure 2.

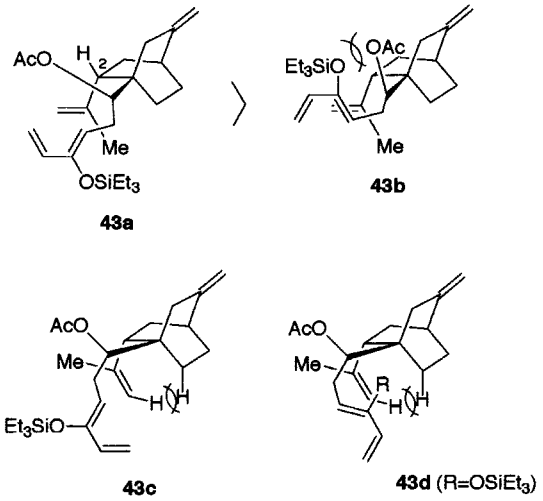
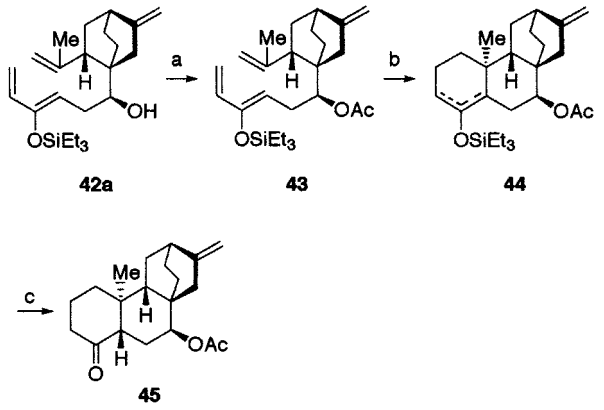


Figure 3.

(84%) and acetylation (100%). Homoallyl−homoallyl radical rearrangement of **37** was conducted under the same reaction conditions as described above to yield the crude products, which were submitted to protodestannylation[15] to lead to the desired acetate **26** in 47% overall yield as well as **38** (26%) and **39** (17%). The structures of **26**, **38**, and **39** were unambiguously determined by NMR spectroscopy.

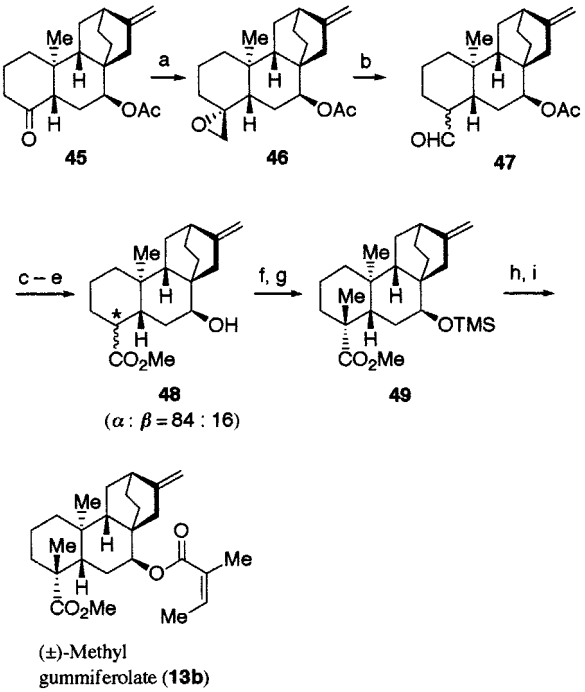
With the required bicyclo[2.2.2]octane compound **26** in hand, we turned to the next phase of our scheme. The tetraene **43** for intramolecular Diels−Alder reaction was constructed as depicted in Schemes 8 and 9. The isopropenyl group (dienophile) was prepared by the treatment of **26** with $POCl_3$ in pyridine, and the diene part was synthesized by hydrolysis of **40** followed by Parikh oxidation and alkylation with ((triethylsilyloxy)pentadienyl)lithium according to Oppolzer's method.[16] The stereoselectivity of this process could be explained by a Cram

Scheme 9[a]



[a] Reagents and conditions: (a) Ac_2O, DMAP, CH_2Cl_2, 99%. (b) toluene, 200 °C, sealed tube. (c) Bu_4NF, THF, 92% for 2 steps.

Scheme 10[a]



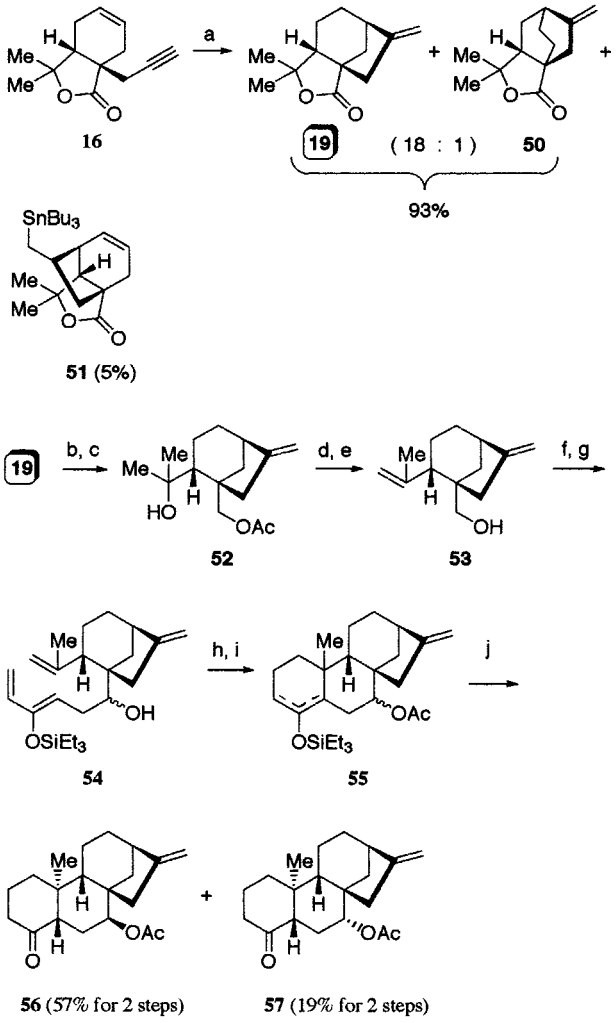
[a] Reagents and conditions: (a) $Me_3S^+OI^-$, NaH, DMSO, 50 °C, 73%. (b) $BF_3{\cdot}Et_2O$, toluene, -20 °C. (c) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH−H_2O. (d) DBU, MeI, MeCN. (e) K_2CO_3, MeOH, 50 °C, 65% for 4 steps. (f) TMSOTf, lutidine, CH_2Cl_2, 96%. (g) LDA, THF, −78 °C; HMPA; MeI, 94%. (h) Bu_4NF, THF, 94%. (i) angelic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, 80 °C, 55%.

model[17] (Figure 2). Finally, the alcohol **42a** was acetylated to furnish **43**.

Tetraene **43** was next subjected to intramolecular Diels−Alder reaction[10] to provide a 7.5:1 regioisomeric mixture of the tetracyclic silyl enol ethers **44** in quantitative yield. Although these regioisomers were not separable at this stage, ketone **45** was obtained as a sole product after treatment with tetrabutylammonium fluoride. Under such reaction conditions, the thermodynamically more stable **45** was isolated (Scheme 9). The high stereoselectivity observed for the present cycloaddition may be attributed to the fixed conformation of the isopropenyl group, in which 1,3-allylic strain[18] between the olefinic hydrogen

(15) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829−2831.
(16) Oppolzer, W.; Snowden, R. L.; Briner, P. H. *Helv. Chim. Acta* **1981**, *64*, 2002−2022.
(17) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828−5835.
(18) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

Scheme 11[a]



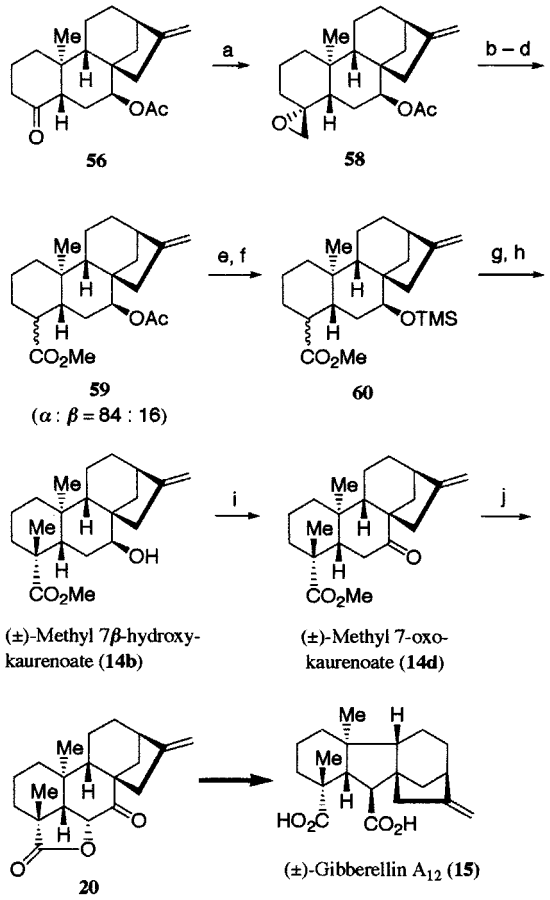
[a] Reagents and conditions: (a) Bu_3SnH, AIBN, benzene, reflux; SiO_2, CH_2Cl_2. (b) LAH, Et_2O, 97%. (c) Ac_2O, pyridine, 100%. (d) $POCl_3$, pyridine, 96%. (e) K_2CO_3, MeOH, 96%. (f) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, 99%. (g) *s*-BuLi, THF, 3-triethylsilyloxy-1,4-pentadiene, −78 °C, 96%. (h) Ac_2O, DMAP, CH_2Cl_2, 98%. (i) Toluene, 200 °C, sealed tube. (j) Bu_4NF, THF.

and C-2 hydrogen is minimun in both conformers **43a** and **43b**. However, the interaction of the silyloxy group of the diene part with the acetoxy group of the methylene would disfavor the conformer **43b**. In contrast, this interaction is absent in the conformer **43a**, which affords the desired cycloadduct **44.** On the other hand, conformers **43c** and **43d** suffer from severe interactions between the olefinic hydrogen and the ethano bridge as shown in Figure 3.

Introduction of a C_1 unit at the C-4 position of **45** proved to be rather difficult, and a variety of attempts to achieve the required homologation were unsuccessful. Ultimately, it was found that the Corey−Chaykovsky reaction[19] of ketone **45** gave rise to epoxide **46** in 73% yield as a single stereoisomer. This stereochemical outcome can be elucidated by nucleophilic attack from the face opposite to the angular methyl group at C-10. BF_3·Et_2O promoted rearrangement of the epoxide group of **46**, followed by oxidation of the resulting aldehyde **47**, esterification, and chemoselective hydrolysis of the acetyl group provided methyl ester **48** in 65% overall yield as an 84:16 mixture of stereoisomers. After protection of the hydroxyl group of **48**,

(19) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.

Scheme 12[a]



[a] Reagents and conditions: (a) $Me_3S^+OI^-$, NaH, DMSO, 50 °C, 72%. (b) BF_3·Et_2O, toluene, −20 °C. (c) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH−H_2O. (d) DBU, MeI, MeCN, 78% for 3 steps. (e) K_2CO_3, MeOH, 50 °C, 87%. (f) TMSOTf, 2,6-lutidine, CH_2Cl_2, 98%. (g) LDA, THF, −78 °C; HMPA; MeI, 81%. (h) Bu_4NF, THF, 100%. (i) PCC, Florisil, NaOAc, CH_2Cl_2, 100%. (j) $CuBr_2$, LiCl, DMF, reflux, 51%.

methylation followed by deprotection furnished the corresponding alcohol, which was finally transformed into (±)-methyl gummiferolate (**13b**). The synthetic **13b** thus obtained was spectroscopically identical with that reported.[6]

Total Syntheses of (±)-Methyl 7β-Hydroxykaurenoate and (±)-Methyl 7-Oxokaurenoate and Formal Synthesis of Gibberellin A_{12}. With the total synthesis of (±)-methyl gummiferolate (**13b**) accomplished, our attention turned to the synthesis of (±)-gibberellin A_{12} (**15**) from the same intermediate **16** by the route shown in Scheme 3. The pivotal radical cyclization reaction of **16** followed by protodestannylation led to the desired bicyclo[3.2.1]octane compound **19** and the bicyclo[2.2.2]octane derivative **50** in 93% yield as an 18:1 separable mixture. A small amount of **51** (5%) was also obtained. The structures of the cyclized products (**19**, **50**, and **51**) were determined by NMR spectroscopy. Furthermore, the structure of **50** was confirmed by the transformation of the bicyclic acetate **26** into **50** through hydrolysis followed by PCC oxidation. Successive treatment of **19** with $LiAlH_4$ and acetic anhydride in pyridine effected conversion to hydroxy acetate **52**, which was subjected to dehydration followed by hydrolysis to give rise to alcohol **53**. The diene moiety of **54** was installed in two steps by applying the same protocol described above for conversion of **41** to **42**. After protection of the hydroxyl group of **54**, the resulting tetraene was heated at 200 °C in a sealed tube to provide the tetracyclic silyl enol ether **55**, which was treated with tetrabu-

tylammonium fluoride to yield a chromatographically separable mixture of the 7β-acetoxy ketone **56** (57% overall yield from the tetraene acetate) together with the 7α-isomer **57** (19%). Functional group manipulation at the C-4 position in **56** was first carried out by using dimethyloxosulfonium methylide to give the epoxide **58** (72% yield). This intermediate was converted to an 84:16 mixture of stereoisomeric ester **59** in 78% overall yield via Lewis acid treatment, followed by oxidation and esterification. After changing the protective group of **59** from an acetate to a trimethysilyloxy group, the resulting compound **60** was successively submitted to methylation and desilylation to provide (±)-methyl 7β-hydroxykaurenoate (**14b**)[20] in 81% overall yield. Oxidation of **14b** afforded (±)-methyl 7-oxo-kaurenoate (**14d**)[21] in quantitative yield. The spectral data of both **14b** and **14d** were identical with those of the corresponding natural products. Intriguingly, keto lactone **20** was synthesized from **14d** by using bromination conditions. Thus, treatment of **14d** with copper(II) bromide in the presence of lithium chloride produced **20** in 51% yield. Since the keto lactone **20** has been transformed into gibberellin A_{12} (**15**),[9,11,12] the present work constitutes a formal total synthesis. In summary, total syntheses of (±)-methyl gummiferolate (**13b**), (±)-methyl 7β-hydroxykaurenoate (**14b**), and (±)-methyl 7-oxokaurenoate (**14d**) and a formal synthesis of (±)-gibberellin A_{12} (**15**) have been achieved via the common intermediate, (3a*R**,7a*R**)-3,3-dimethyl-7a-(2-propynyl)-3a,4,7,7a-tetrahydroisobenzofuranone (**16**). The salient steps include homoallyl−homoallyl radical rearrangement of monocyclic enyne derivatives, **25** and **37**, to generate the bicyclo[2.2.2]octane compound **26** and vinyl radical-promoted *5-exo-trig* cyclization of the bicyclic lactone **16** to form the bicyclo[3.2.1]octane framework **19**. The present synthetic design should be readily amenable to the construction of other polycyclic natural products that contain a bicyclo[2.2.2]-octane ring system or bicyclo[3.2.1]octane carbon framework.

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Experimental Section

See Supporting Information.

Acknowledgment. This work is supported by a Grant-in-Aid (No. 11672097) from the Ministry of Education, Science, Sports and Culture, Japan.

Supporting Information Available: Experimental details involving synthetic procedures and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0035506