Application of Palladium-Catalyzed Cycloalkenylation Reaction to C_{20} Gibberellin Synthesis: Formal Syntheses of GA_{12}, GA_{111}, and GA_{112}

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Received May 19, 2000

The gibberellins (GAs), discovered in Japan in an investigation of the "baka-nae" disease of rice attributed to the fungus *Gibberella fujikuroi*, have been implicated in various crucial aspects of plant growth, for example, seed germination, breaking of winter dormancy, enzyme synthesis, reversal of dwarfism, induction of stem growth, induction of flowering, modification of flower sex expression, parthenocarpic development of fruit, fruit enlargement, inhibition of senescence, and so on.[1] The gibberellins are divided into two groups, the larger of which is C_{19} gibberellins [gibberellic acid: GA_3 (**1**); a typical representative], and most of the remaining have 20 carbons. The latter possess the *ent*-gibberellane carbon skeleton. GA_{12} (**2**), GA_{111} (**3**), and GA_{112} (**4**) belong to C_{20} gibberellins, and **2** is presumed to be a common intermediate in the biosynthesis of all gibberellins. Eight (seven in **2**) stereogenic centers, of which three are quaternary, of C_{20} gibberellins such as **3** and **4** are spread over the A, B, C, and D ring systems. The AB ring of *ent*-gibberellane skeleton comprises *trans*-hydrindane structure and the CD ring consists of bicyclo[3.2.1]octane ring system. A significant array of biological activities and structural complexity have made gibberellins popular targets for total synthesis.[2] Although GA_3 (**1**) is produced commercially by the large-scale fermentation of the fungus *G. fujikuroi*, most of the C_{20} gibberellin syntheses have been achieved through many functional group manipulations, despite starting with tricyclic compounds or natural gibberellins.[3] Therefore, the question of how to establish practical methodologies for the construction of C_{20} gibberellins is still open. An efficient synthetic route to C_{20} gibberellins would make it possible to confirm tentative new structures and to explore their biological activities. Herein we would like to present a practical synthetic route to C_{20} gibberellins by a combination of palladium-catalyzed cycloalkenylation reaction and reverse electron demand intramolecular Diels−Alder reaction (Figure 1).

Since the efficient synthesis of the desired bicyclo[3.2.1]octane derivative **6** employing palladium-catalyzed cycloalkenylation of **5** has already been developed by us,[4] the synthesis started with the alcohol **7**. What needs to be emphasized at this juncture is that the compound **6** has a carbonyl function at the C-2 position, convertible to the C-12 hydroxyl group of **3** and **4**, and the transformation of **6** into **7** has been achieved in a stereoselective

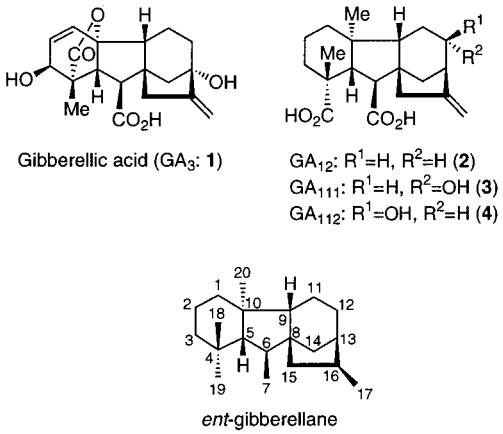
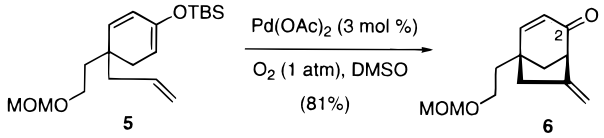


Figure 1.

Scheme 1



manner in good yield.[4] To introduce a C_1 carbon unit (C-7 carboxyl group-to-be in GAs) to the alcohol **7**, the transformation of **7** into the ester **8** was accomplished in 85% overall yield in the usual way. Alkylation of **8** was next conducted with benzyl chloromethyl ether in the presence of LDA and HMPA to afford **9** and **20** (87% yield) as about a 2:1 mixture of stereoisomers. After separation of the mixture by recrystallization from acetone, the desired single stereoisomer **9** was subjected to DIBAH reduction, followed by Parikh−Doering[5] oxidation and Wadsworth−Emmons olefination[6] to give the α,β-unsaturated esters **10** and **11** as a 11:8 separable mixture. It should be added that **20** was easily converted to **22** (DIBAH reduction product of **9**) in good overall yield,[7] and in this way could be melded into the sequence shown in Scheme 2. The diene moiety of **12** was constructed by means of DIBAH reduction of **10**, followed by oxidation and Wittig reaction. After carboethoxylation of **12**, reverse electron demand intramolecular Diels−Alder reaction

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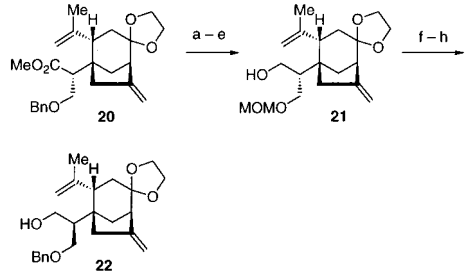
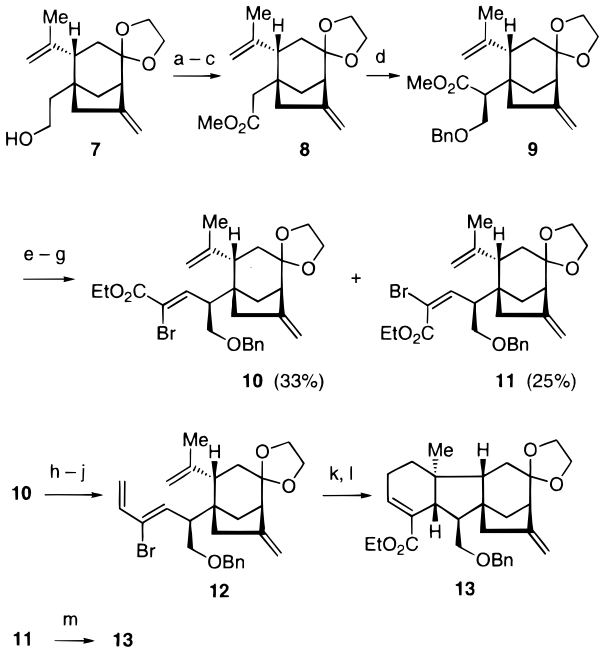
(7) The stereoisomer **20** was converted to the alcohol **22** as follows. Thus, DIBAH reduction of **20** followed by protection of the resulting primary alcohol gave the corresponding TBS ether, which was subjected to Birch reduction followed by etherification and desilylation to produce the alcohol **21**. After benzylation of **21**, the methoxymethyl ether moiety was hydrolyzed. Finally, the carbonyl group, partially hydrolyzed, was reprotected to afford **22**.



Reagents and Conditions: a. DIBAH, toluene, −78 °C (93%): b. TBDMSCl, imidazole, DMF (100%): c. liq. NH_3, Li, −78 °C (90%): d. MOMCl, *i*-Pr_2NEt, CH_2Cl_2 (99%): e. TBAF, THF (94%): f. NaH, DMF, BnBr, THF (70%): g. 35% $HClO_4$, THF (86%): h. ethylene glycol, PPTS, benzene, reflux (74%).

10.1021/ja0017413 CCC: $19.00
Published on Web 08/30/2000

Scheme 2



Reagents and Conditions: a. SO_3·Py, DMSO, Et_3N: b. $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*-BuOH−H_2O: c. MeI, DBU, MeCN (85% for 3 steps): d. LDA, THF, −78 °C; BOMCl, HMPA (87%): e. DIBAH, toluene, −78 °C (97%): f. SO_3·Py, DMSO, *i*-Pr_2NEt, CH_2Cl_2 (95%): g. NaH, $(EtO)_2P(O)CHBrCO_2Et$, toluene (58%): h. DIBAH, toluene −78 °C (75%): i. SO_3·Py, *i*-Pr_2NEt, CH_2Cl_2 (69%): j. Ph_3PMeBr, BuLi (86%): k. *t*-BuLi; $ClCO_2Et$, HMPA, THF, −78 to 0 °C: l. toluene, reflux (35% for 2 steps): m. $Pd(PPh_3)_4$, CH_2=CHSnBu_3, toluene, reflux (91%).

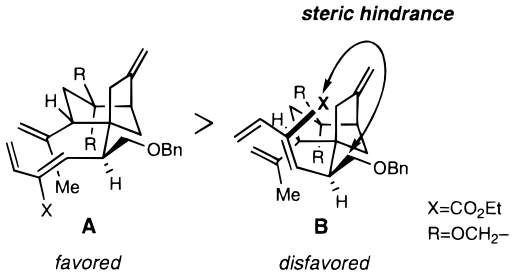


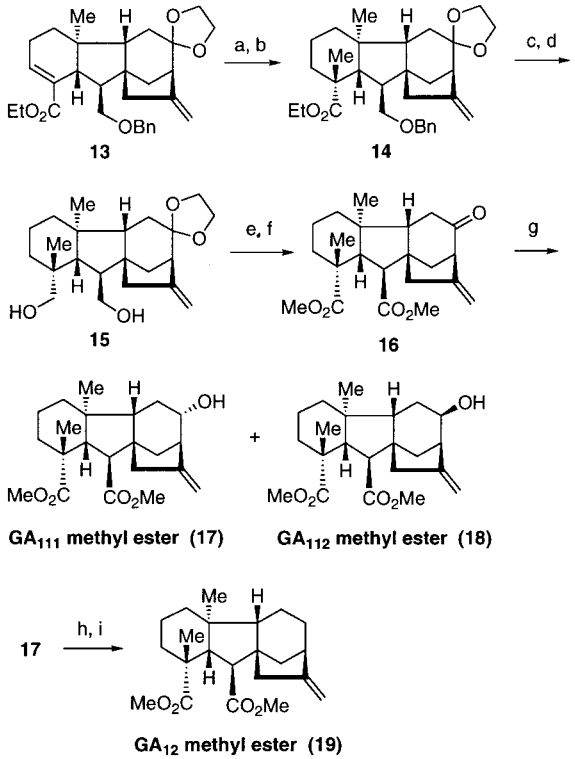
Figure 2.

proceeded smoothly, leading to the desired pentacyclic α,β-unsaturated ester **13** as a sole product. On the other hand, the geometrical isomer **11** was directly transformed into **13** (91% yield) upon Stille coupling[8] with tributylvinylstannane. An important advantage of the present synthetic route is that each isomer **10** and **11**, resulting from **9**, could be efficiently converted to the same compound **13**.

The high selectivity of the present cycloaddition may be attributed to the interactions of the carboethoxy group with hydrogens of the methylene in the conformer **B**. This interaction is absent in the conformer **A**, which gives rise to the desired cycloadduct **13** (Figure 2).

Having assembled the requisite skeletal framework, our synthetic efforts were focused on the functional group adjustments of **13**. Successive conjugate reduction[9] of **13** and stereoselective methylation furnished the ester **14**, which was submitted to DIBAH reduction, followed by debenzylation under Birch reduction conditions to yield the diol **15**. Jones oxidation of **15** was carried out to generate the corresponding keto diacid, which was allowed to react with trimethylsilyldiazomethane, producing the

Scheme 3



Reagents and Conditions: a. Mg, MeOH (82%): b, LDA, THF, −78 °C; MeI, HMPA (95%): c. DIABH, toluene, −78 °C (93%): d. liq. NH_3, Li, −78 °C (79%): e. Jones Reagent, acetone: f. $TMSCHN_2$, (61% for 2 steps): g. (*i*-PrO)$_3$Al, *i*-PrOH, reflux (78%): h. TsCl, Py (71%): i. $NaBH_4$, HMPA (68%).

keto diester **16**.[3c] Although hydride reduction of the ketone at the C-12 position of **16** gave GA_{112} methyl ester (**18**) as a single product, formation of α-alcohol at the same location proved to be more difficult than expected. Ultimately, Meerwein−Ponndorf reduction[10] was adopted to afford GA_{112} (**18**)[11] and GA_{111} methyl ester (**17**)[11] in a ratio of 3:1. Transformation of **18** into GA_{12} methyl ester (**19**)[12] was performed by tosylation followed by $NaBH_4$ reduction. Each ^{1}H NMR spectral property of our synthetic **17** and **18** was identical with authentic data provided by Mander see Scheme 3).[3c]

In conclusion, highly stereoselective formal syntheses of GA_{12}, GA_{111}, and GA_{112} were achieved from a common intermediate by a combination of palladium-catalyzed cycloalkenylation reaction and reverse electron demand intramolecular Diels−Alder reaction. The most important aspect of the present synthesis is that all stereoisomers produced were used, and most of the reaction yields were good. The present syntheses would provide some perspectives both on the determination of tentative new structures and on the exploration of their bioactivities.

Acknowledgment. We thank Professor L. N. Mander for providing us with the spectral data of **16**, GA_{111}, and GA_{112} methyl ester.

Supporting Information Available: Experimental Procedures for **12**, **13**, **17**, and **18**, and ^{1}H and ^{13}C NMR spectra for **12** and **13** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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