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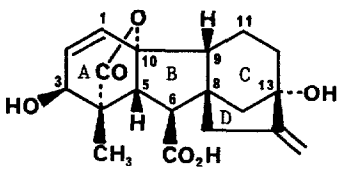
TOTAL SYNTHESIS OF (±)-GIBBERELLIC ACID

Hiroto Nagaoka, Masanao Shimano and Yasuji Yamada*
Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Summary: Total synthesis of (±)-gibberellic acid was accomplished *via* highly stereocontrolled route.

A number of synthetic efforts for C_{19}-gibberellin phytohormones have been made in recent years.[1] The total synthesis of gibberellic acid (gibberellin A_3, GA_3), a representative gibberellin, was completed first by Corey *et al.*[2] and then by Mander *et al.*[3] However, intensive work is still being made for the establishment of a more efficient method of the synthesis of C_{19}-gibberellins.[4] Here, we describe a highly stereocontrolled total synthesis of (±)-GA_3, in which tetrahydrofluorene derivative 2[5] previously synthesized was converted into enone 6 having the same C(9) configuration as in GA_3, then the D-ring system was constructed to form 11, and finally the functional groups at the A-ring were appropriately modified.

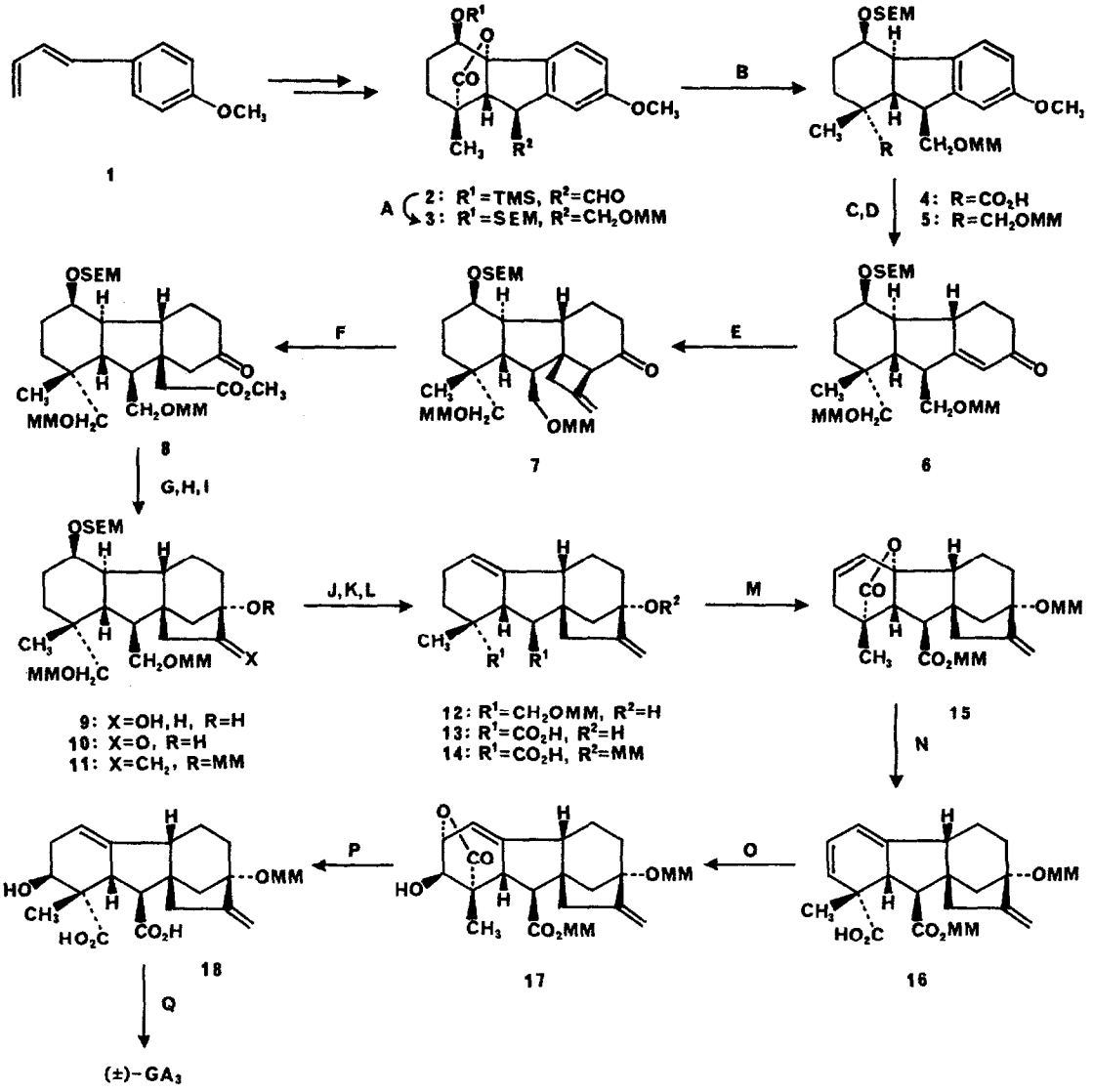


GA_3

The reduction of the formyl group of aldehyde 2 (stereoselectively prepared from diene 1 by eight step sequence),[5] methoxymethylation of the resulting hydroxyl group and replacement of the protection group of the hydroxyl at C(1)[6] gave trimethylsilylethoxymethyl (SEM) ether 3[7] in 93% overall yield (Scheme I). Then the oxygen at C(10) was selectively removed by hydrogenolysis, because direct Birch reduction of 3 removes not only the benzylic oxygen but also the oxygen function at C(1), which is necessary to construct the functional groups of A-ring in the final stage of this synthesis. Hydrogenation of 3 using 10% Pd-$BaSO_4$ in ethanol at 23°C gave exclusively carboxylic acid 4[8] with trans A/B juncture in 92% yield. Carboxylic acid 4 was then transformed into methoxymethyl ether 5 by two sequential reactions. Compound 5 thus obtained was reduced with sodium in a mixture of liquid ammonia, ethanol and THF (12:3:1), and subjected to careful acid hydrolysis of the enol ether and isomerization of the double bond with a base to give α,β-unsaturated enone 6 with the right C(9)-H configuration as a single isomer.[9]

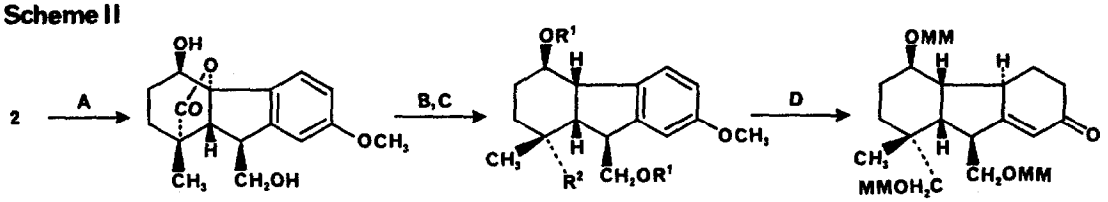
When diol 19, which was prepared from 2 by removal of trimethylsilyl group and reduction of the formyl group, was hydrogenated with 10% Pd-C as catalyst in methanol, it gave 20 with a cis-fused A/B ring system in quantitative yield (Scheme II),[10] which was then converted into methoxymethyl ether 21. However, Birch reduction of 21 and subsequent acid treatment and base treatment of the product gave enone 22 with the undesired C(9)-H configuration. To obtain

Scheme I



Reagents: (A) 1) $NaBH_4$, MeOH, 0°C, 98%; 2) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 24°C, 96%; 3) *n*-Bu_4NF, THF, 25°C; 4) $Me_3SiCH_2CH_2OCH_2Cl$, *i*-Pr_2NEt, CH_2ClCH_2Cl, 60°C, 98% (two steps); (B) H_2, 10% Pd-$BaSO_4$, EtOH, 23°C, 92%; (C) 1) $LiAlH_4$, THF, 0°C to 25°C; 2) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2ClCH_2Cl, 55°C, 98% (two steps); (D) 1) Na, liq.NH_3, EtOH, THF, -34°C; 2) AcOH-H_2O-THF (3:1:1), 25°C; 3) K_2CO_3, MeOH, -15°C, 87% from 5; (E) $CH_2{=}C{=}CH_2$, $h\nu$, CH_2Cl_2, -70°C, 69%(7) and 12%(stereoisomer of 7); (F) O_3, MeOH, $NaHCO_3$, -78°C then Me_2S, 86%; (G) K, liq.NH_3, $(NH_4)_2SO_4$, -34°C, 78%; (H) 1) $(COCl)_2$, Me_2SO, CH_2Cl_2, -78°C then Et_3N, 78%; 2) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2ClCH_2Cl, 50°C, 97%; (I) $Ph_3P{=}CH_2$, THF-HMPA, 60°C, 90%; (J) 1) *n*-Bu_4NF, THF, 40°C; 2) MsCl, pyridine, CH_2Cl_2, 0°C; 3) DBU, $PhCH_3$, 100°C, 57% from 11; (K) 1) c.HCl-MeOH (1:20), 25°C, 75%, 2) $(COCl)_2$, Me_2SO, CH_2Cl_2-THF, -78°C then Et_3N, 75%; 3) $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, *t*-BuOH-H_2O, 25°C, 83%; (L) 1) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2ClCH_2Cl, 65°C; 2) 1N KOH aq, THF, reflux; (M) 1) I_2, 5% $NaHCO_3$ aq, THF, 0°C; 2) DBU, PhH, 65°C; 3) $MeOCH_2Cl$, Et_3N, CH_2Cl_2, 25°C, 91% from 13; (N) LDA, THF, -55°C, 25 min, 100%; (O) MCPBA, CH_2Cl_2, -20°C, 84%; (P) 1) H_2O, THF, pyridine, 80°C, 10 h; 2) LDA, (2 equiv), THF, -78°C then Li, liq.NH_3, -65°C; (Q) 1) I_2, 5% $NaHCO_3$ aq, THF, 0°C; 2) c.HCl-MeOH (1:20), 25°C; 3) DBU, PhH, 65°C, 86% from 17.

Scheme II



19 20: R^1=H, R^2=CO_2H 21: R^1=MM, R^2=CH_2OMM 22

Reagents: (A) 1) TsOH, MeOH, 25°C; 2) $NaBH_4$, MeOH, 0°C; (B) H_2, 10% Pd-C, MeOH, 25°C; (C) 1) CH_2N_2, Et_2O-MeOH, 0°C, 97% from 2; 2) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2ClCH_2Cl, 70°C; 3) $LiAlH_4$, Et_2O, 0°C; 4) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2ClCH_2Cl, 65°C, 91% (three steps); (D) 1) Na, liq.NH_3, EtOH, -34°C; 2) AcOH-H_2O-THF (4:1:1), 23°C; 3) K_2CO_3, MeOH, 23°C, 71% from 21.

the right configuration at B/C ring juncture, the A/B ring system should be trans.

Stereoselective formation of D-ring was accomlished via photocycloadduct 7. Irradiation of a mixture of 6 and allene with Hanovia 100-W high pressure lamp (Pyrex filter, CH_2Cl_2, -70°C, 6 h) produced the desired photoadduct 7[11] in 69% yield together with its stereoisomer at C(8) and C(14) in 12% yield. Ozonolysis of 7 in methanol in the presence of sodium bicarbonate oxidized the exo-olefin group and cleave the cyclobutane ring[12] to give keto ester 8 in 86% yield. Reductive intramolecular cyclization of 8 with 10 equiv of potassium in liquid ammonia - THF (30:1) in the presence of 50 equiv of ammonium sulfate[4b] at -34°C gave diol 9 as a diastereomeric mixture (15:1) in 78% yield.[13] Without further purification, the product was subjected to Swern oxidation to give keto alcohol 10. After protecting the hydroxyl group in 10, it was treated with Wittig reagent to give 11 having a gibbane skeleton. Compound 11 thus obtained was converted into diacid 13 as follows: the SEM group in 11 was removed, the resulting hydroxyl groups were dehydrated, the methoxymethyl group was removed by acid hydrolysis, and primary hydroxyl group was stepwisely oxidized to give 13. The stereochemistry of 13 was confirmed by the comparison of the spectral data with those of optically active (+)-13 derived from natural GA_3.[14]

After protection of the tertiary hydroxyl group of 13 as methoxymethyl ether, the compound was treated with I_2 in the presence of sodium bicarbonate and then with DBU to give olefin lactone 15. Direct allylic oxidation failed to introduce oxygen at C(3) position of 15. However, this problem was successfully solved by the following procedure. The allylic lactone of A-ring of 15 was transformed into a homodiene system with 1.1 equiv of lithium diisopropylamide (LDA) in THF at -55°C for 25 min to give 16[16] in quantitative yield. Subsequent MCPBA oxidation of diene 16 at -20°C introduced C(3) oxygen and gave lactone 17.[17] After the hydrolysis of methoxymethyl ether in 17, the compound was treated with 2.0 equiv of LDA and then lithium in liquid ammonia at -65°C to give homoallylic alcohol 18. Without the LDA treatment, the liquid ammonia reduction reduced C(3) oxygen of 17 as well to give 14.

Finally, diacid 18 was led to (±)-GA_3 by following three successive reac-

tions: 1) iodolactonization; 2) acid hydrolysis of methoxymethyl ether; 3) DBU treatment. The ^{1}H-NMR, IR, mass spectra, and TLC behavior of (±)-GA_3 (mp 212-4°C)[18] thus prepared were identical with those of the natural GA_3 (mp 228°C)[18] in every respect.

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6) Numbering of compounds used here was in accordance with that for gibberellins.

7) Structural assignments for all stable synthetic intermediates were made by ^{1}H-NMR (400 MHz), IR, high resolution mass spectroscopy and/or combustion analysis.

8) The configuration at C(10) of 4 was determined by ^{1}H-NMR analysis of its methyl ester prepared by the treatment of 4 with CH_2N_2: a large coupling constant (J=12.3 Hz) between the methine protons at C(5) and C(10) indicates the trans arrangement of these protons.

9) The coupling constant (J=11.5 Hz) between the methine protons at C(9) and C(10) indicates the trans arrangement of these protons.

10) The configuration at C(10) in 20 was determined by ^{1}H-NMR analysis of its methyl ester: the coupling constant (J=9.8 Hz) between the protons at C(10) and C(5), that (J=6.7 Hz) between the protons at C(10) and C(1), and W-coupling (J=1.3 Hz) between the protons C(3) and C(5) were observed.

11) The configurations at C(4) and C(14) were estimated on the basis of attack of allene at the less screened face of the olefin.

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14) Compound (+)-13 was derived from optically active C(6) monomethyl ester of 14, which was prepared from GA_3 by Mander's procedure,[15] using two step sequence: 1) c.HCl-MeOH (1:20), 25°C; 2) 1N KOH aq., 100°C.

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16) This compound is comparable to Corey's synthetic intermediate for GA_3.[2,17]

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18) Recrystallization was made from ethyl acetate.

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