SYNTHESIS OF GIBBERELLIN A_1, A_5, A_{55} AND A_{60}. METAL-AMMONIA REDUCTION OF GIBBERELLIC ACID AND ITS DERIVATIVE

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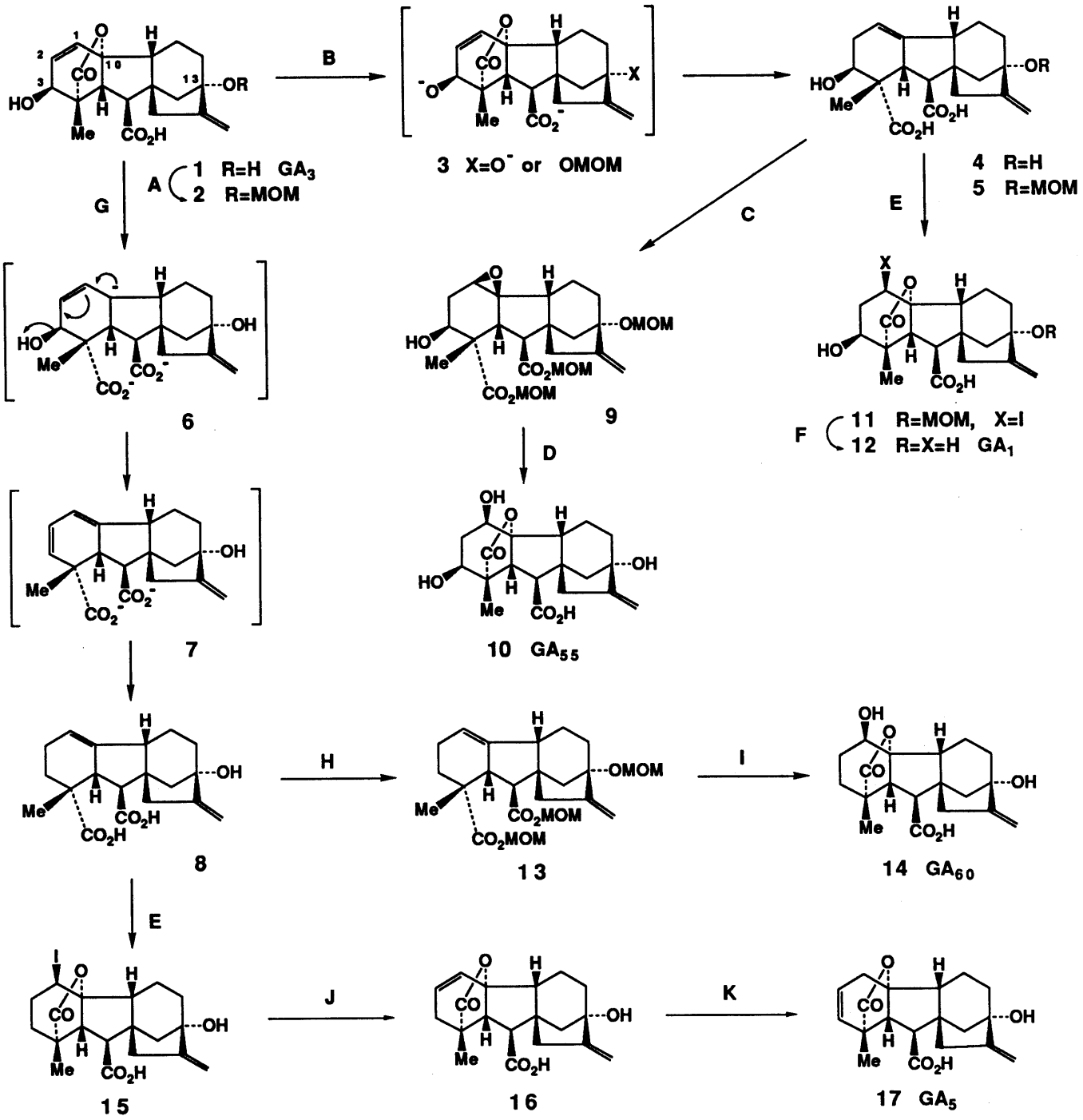
Treatment of gibberellic acid (**1**) and 13-O-methoxymethylgibberellic acid (**2**) with lithium diisopropylamide (LDA), and then with Li in liquid ammonia gave 3-hydroxy diacid **4** and **5**, respectively. From the diacid **5**, gibberellin A_{55} (**10**) and gibberellin A_1 (**12**) were synthesized. Without LDA treatment prior to Li-liquid ammonia reduction, **1** gave diacid **8** from which gibberellin A_{60} (**14**) and gibberellin A_5 (**17**) were synthesized.

KEYWORDS gibberellic acid; Li-liquid ammonia reduction; C_{19} gibberellin; gibberellin A_1; gibberellin A_5; gibberellin A_{55}; gibberellin A_{60}; synthesis

There have been a number of attempts to synthesize gibberellin phytohormones because of their biological importance and their structural interest.[1] Recently, we have accomplished the total synthesis of (±)-gibberellic acid (gibberellin A_3, GA_3), (±)-**1**.[2] 3-Hydroxy diacid **5** and diacid **8**, whose racemates were the synthetic intermediate in our GA_3 synthesis, will be useful synthetic precursors for various C_{19} gibberellins having a 13-hydroxy group. Here we wish to report on an effective method for converting natural GA_3 (**1**) into the diacid **5** and **8**, and an efficient synthesis of GA_1 (**12**), GA_{55} (**10**), GA_{60} (**14**) and GA_5 (**17**) from these diacids.

For the selective hydrogenolysis of the allylic C-O bond at the C_{10} position and the migration of the $C_{1,2}$ double bond in **1** leading to **4**, the metal-liquid ammonia reduction of **1** was carefully investigated. Direct treatment of **1** with lithium in a mixture of liquid ammonia and ethanol (8:1) at -78°C caused C-O bond fissions at both allylic positions (C_3 and C_{10}) to give diacid **8**, $[\alpha]_D^{25}$ +42.3° (c=0.98, EtOH), as a single product in 93% yield (Chart 1). The unusual reaction[3] probably proceeds *via* the diene **7** which can be formed by the initial hydrogenolysis of the C-O bond at the C_{10} position in **1** leading to the carbanion **6** followed by dehydroxylation. The dehydroxylation at the C_3 position was prevented by a devised reduction procedure, which involved (1) treatment of **1** with lithium diisopropylamide (LDA) prior to the reduction, and (2) metal-ammonia reduction of the resultant lithium alkoxide **3**. Solution of **1** in THF was treated with 3 equiv of LDA at -78°C for 20 min, diluted 6-fold with as much liquid ammonia as THF, then lithium metal was added to the mixture portionwise at -78°C until all of **1** reacted to afford the 3-hydroxy diacid **4**,[4] $[\alpha]_D^{25}$ +155.7° (c=0.40, EtOH), in 95% yield. Diacid **5**, $[\alpha]_D^{25}$ +89.1° (c=0.22, EtOH), was synthesized similarly in 96% yield from 13-O-methoxymethyl-GA_3 (**2**),[5] which was prepared from **1** in 85% overall yield by a five step sequence: (1) selective methoxymethylation of the carboxyl groups with chloromethylmethyl ether in the presence of triethylamine; (2) acetylation of the secondary hydroxyl group at C_3 with acetic anhydride and pyridine; (3) methoxymethylation of the tertiary hydroxyl group at C_{13} with chloromethylmethyl ether and diisopropylethylamine; (4) hydrolysis of the acetate with potassium carbonate in methanol; (5) hydrolysis of methoxymethyl ester with water and pyridine.

From the diacid **5**, GA_{55} (**10**) and GA_1 (**12**) were effectively synthesized by the following sequential reactions. Methoxymethylation of the carboxyl groups in **5** with an excess amount of chloromethylmethyl ether and triethylamine followed by careful treatment with MCPBA in methylenechloride at -15°C gave epoxide **9**, $[\alpha]_D^{25}$ +101.5° (c=0.26, EtOH), which was treated with 80% acetic acid at 65°C to afford GA_{55}



Reagents: (A) 1) $MeOCH_2Cl$ (1.2 eq), Et_3N (1.5 eq), CH_2Cl_2, 25°C, 6 h; 2) Ac_2O-pyridine-CH_2Cl_2 (6:7:20), 25°C, 12 h; 3) $MeOCH_2Cl$ (3 eq), i-Pr_2NEt (4 eq), CH_2ClCH_2Cl, 60°C, 3 h; 4) K_2CO_3, MeOH, -10°C, 30 min; 5) H_2O-THF-pyridine (40:24:1), 80°C, 20 h; (B) LDA (3 eq), THF then Li, liq NH_3-THF (6:1), -78°C; (C) 1) $MeOCH_2Cl$, Et_3N, CH_2Cl_2, 25°C, 80 min; 2) MCPBA, CH_2Cl_2, -15°C, 4.5 h; (D) AcOH-H_2O (4:1), 65°C, 30 h; (E) I_2, 5% $NaHCO_3$-THF (1:1), 0°C, 30 min; (F) 1) $NaBH_4$, DMSO, 75°C, 2 h; 2) AcOH-H_2O (4:1), 60°C, 35 h; (G) Li liq NH_3-EtOH (8:1), (H) $MeOCH_2Cl$, i-Pr_2NEt, CH_2ClCH_2Cl, 60°C, 3 h; (I) MCPBA, CH_2Cl_2, -25°C to -15°C, 5 h; 2) AcOH-H_2O (4:1), 65°C, 40 h; (J) DBU, THF, 65°C, 4 h; (K) $[Rh(Ph_3P)_3]Cl$, EtOH, 95°C to 100°C, 4 h.

Chart 1

(**10**),[6] $[\alpha]_D^{25}$ +18.3° (c=0.48, EtOH), in 81% overall yield. Direct lactonization of **4** and **5** with peracid to form GA_{55} (**10**)[7] and 13-O-methoxymethyl-GA_{55}, respectively, gave an unsatisfactory result. Iodolactonization of **5** with iodine in a mixture of 5% aqueous sodium bicarbonate and THF (1:1) at 0°C gave **11** in 95% and reduction of **11** with an excess amount of sodium borohydride in DMSO at 75°C followed by hydrolysis of methoxymethyl ether with 80% acetic acid at 60°C gave GA_1 (**12**), $[\alpha]_D^{25}$ +36.3° (c=0.10, EtOH) (lit., $[\alpha]_D^{25}$ +35° (c=1.02, EtOH))[8], (74%, over two steps).

GA_{60}[9] (3-dehydroxy-GA_{55}, **14**), $[\alpha]_D^{25}$ +7.03° (c=0.73, EtOH), was synthesized from the diacid **8** *via* dimethoxymethyl ester **13**, $[\alpha]_D^{25}$ +86.1° (c=0.55, EtOH), similar to the way **10**.was synthesized. And GA_5 (**17**), $[\alpha]_D^{25}$ -77.2° (c=0.22, EtOH) (lit., $[\alpha]_D^{25}$ -77° (c=0.5, EtOH))[8] was also synthesized from **8** by a three step sequence: (1) iodolactonization to form **15**; (2) dehydroiodination of **15** with DBU in THF at 65°C to give olefin **16**, $[\alpha]_D^{25}$ +37.6° (c=0.75, EtOH), in 96% yield from **8**; (3) isomerization of the $C_{1,2}$ double bond with tris(triphenylphosphine)rhodium(I) chloride in ethanol at 95°C to 100°C for 4 h in 85% yield.

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