

SYNTHESIS OF GIBBERELLIN A₁, A₅, A₅₅ AND A₆₀. METAL-AMMONIA REDUCTION OF GIBBERELIC 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 A₅₅ (10) and gibberellin A₁ (12) were synthesized. Without LDA treatment prior to Li-liquid ammonia reduction, 1 gave diacid 8 from which gibberellin A₆₀ (14) and gibberellin A₅ (17) were synthesized.

KEYWORDS gibberellic acid; Li-liquid ammonia reduction; C₁₉ gibberellin; gibberellin A₁; gibberellin A₅; gibberellin A₅₅; gibberellin A₆₀; 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 A₃, GA₃), (±)-1.²⁾ 3-Hydroxy diacid 5 and diacid 8, whose racemates were the synthetic intermediate in our GA₃ synthesis, will be useful synthetic precursors for various C₁₉ gibberellins having a 13-hydroxy group. Here we wish to report on an effective method for converting natural GA₃ (1) into the diacid 5 and 8, and an efficient synthesis of GA₁ (12), GA₅₅ (10), GA₆₀ (14) and GA₅ (17) from these diacids.

For the selective hydrogenolysis of the allylic C-O bond at the C₁₀ 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 (C₃ and C₁₀) to give diacid 8, $[\alpha]_D^{25} +42.3^\circ$ ($c=0.98$, EtOH), as a single product in 93% yield (Chart 1). The unusual reaction³⁾ probably proceeds *via* the diene 7 which can be formed by the initial hydrogenolysis of the C-O bond at the C₁₀ position in 1 leading to the carbanion 6 followed by dehydroxylation. The dehydroxylation at the C₃ 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⁾ $[\alpha]_D^{25} +155.7^\circ$ ($c=0.40$, EtOH), in 95% yield. Diacid 5, $[\alpha]_D^{25} +89.1^\circ$ ($c=0.22$, EtOH), was synthesized similarly in 96% yield from 13-O-methoxymethyl-GA₃ (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 C₃ with acetic anhydride and pyridine; (3) methoxymethylation of the tertiary hydroxyl group at C₁₃ 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, GA₅₅ (10) and GA₁ (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, $[\alpha]_D^{25} +101.5^\circ$ ($c=0.26$, EtOH), which was treated with 80% acetic acid at 65°C to afford GA₅₅

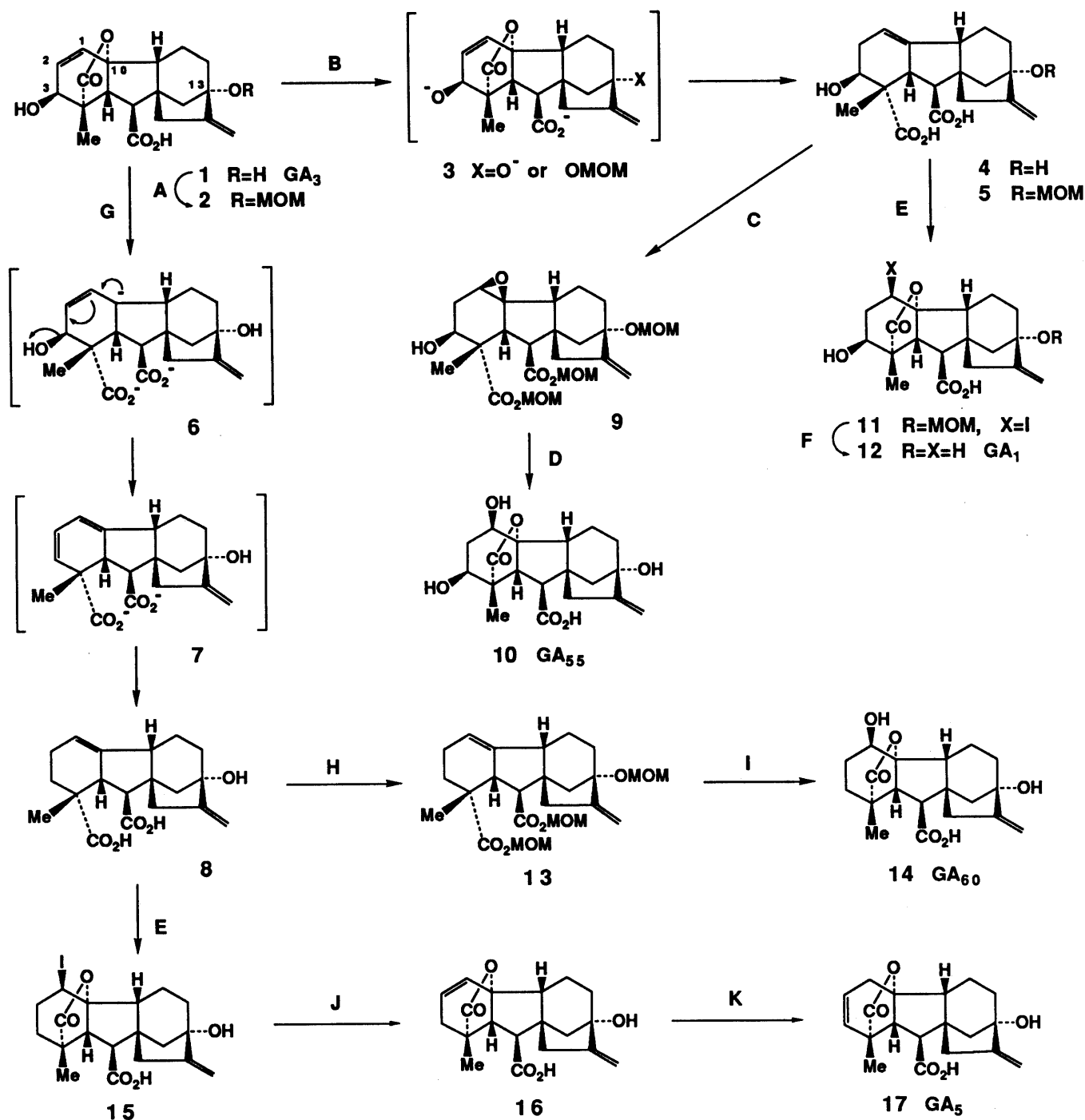


Chart 1

(10),⁶⁾ $[\alpha]_D^{25} +18.3^\circ$ ($c=0.48$, EtOH), in 81% overall yield. Direct lactonization of 4 and 5 with peracid to form GA₅₅ (10)⁷⁾ and 13-O-methoxymethyl-GA₅₅, 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 GA₁ (12), $[\alpha]_D^{25} +36.3^\circ$ ($c=0.10$, EtOH) (lit., $[\alpha]_D^{25} +35^\circ$ ($c=1.02$, EtOH))⁸⁾ (74%, over two steps).

GA₆₀⁹⁾ (3-dehydroxy-GA₅₅, 14), $[\alpha]_D^{25} +7.03^\circ$ ($c=0.73$, EtOH), was synthesized from the diacid 8 via dimethoxymethyl ester 13, $[\alpha]_D^{25} +86.1^\circ$ ($c=0.55$, EtOH), similar to the way 10 was synthesized. And GA₅ (17), $[\alpha]_D^{25} -77.2^\circ$ ($c=0.22$, EtOH) (lit., $[\alpha]_D^{25} -77^\circ$ ($c=0.5$, 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, $[\alpha]_D^{25} +37.6^\circ$ ($c=0.75$, 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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