A Total Synthesis of ($\pm$)-Gibberellin A₁₂ via Methyl ($\pm$)-7,16-dioxo-17-norkauran-19-oate

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The gibberellins are known to be biosynthesized from geranylgeranyl pyrophosphate (A) by cyclization to kaurene via a tricyclic intermediate (B) followed by oxidation to C and its ring contraction to give C₂₀-gibberellins such as gibberellin A₁₂ (1).^{1~3)} The existing total syntheses of both the C₁₉-gibberellins⁴⁾ and a C₂₀-gibberellin (gibberellin A₁₅),⁵⁾ however, were not carried out along this biosyn-

mp 119 ~ 120°C; UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 235 (18000). This was reduced with sodium borohydride to give a hydroxy ester (4). Hydroboration-oxidation followed by chromic acid oxidation of 4 gave a diketo ester (5), mp 141 ~ 142°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1725, 1715, 1225, 1165; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.93 (3H, s), 1.22 (3H, s), 3.73 (3H, s); 27% overall yield from 2. Reaction of 5 with *p*-tolylloxymethylene triphenylphosphorane⁷⁾ afforded an enol ether (6), mp 198 ~ 199°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1725, 1705, 1620, 1245, 1230, 820; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.88 (3H, s), 1.20 (3H, s), 2.36 (3H, s), 3.76 (3H, s), 6.19 (1H, s), 6.80 ~ 7.14 (4H). The enol ether (6) was hydrolyzed to give a keto aldehyde (7), (4.5% overall yield from 5), mp 125 ~ 126°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 2720, 1735, 1720, 1710, 1160; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.90 (3H, s), 1.20 (3H, s), 3.76 (3H, s), 9.69 (1H, s). Since 7 was recovered unchanged when treated with sodium methoxide in methanol, an equatorial conformation was assigned to its formyl group. The Wittig methylenation of the keto aldehyde (7) afforded the desired keto olefin (8) in 60% yield, mp 79 ~ 79.5°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3080, 1730, 1710, 1640, 1220, 1160, 990, 900; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.90 (3H, s), 1.18 (3H, s), 3.76 (3H, s), 4.9 ~ 5.2 (2H, m), 5.6 ~ 6.1 (1H, m). The keto olefin (8) corresponds to the tricyclic intermediate (B) in

thetic pathway. In continuation of our works on the gibberellins, we focused our attention to the synthesis of gibberellin A₁₂ (1) mimicking the biogenetical pattern.

The starting enone (2)⁶⁾ was treated with acetyl chloride to give an enol acetate (3);

tion of the keto aldehyde (7) afforded the desired keto olefin (8) in 60% yield, mp 79 ~ 79.5°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3080, 1730, 1710, 1640, 1220, 1160, 990, 900; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.90 (3H, s), 1.18 (3H, s), 3.76 (3H, s), 4.9 ~ 5.2 (2H, m), 5.6 ~ 6.1 (1H, m). The keto olefin (8) corresponds to the tricyclic intermediate (B) in

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the biosynthetic scheme.

Our strategy was to effect the intramolecular alkylation at C-8 as the key step. The keto olefin (**8**) was converted into the corresponding bromohydrin (**9a**) by treatment with N-bromo-succinimide in aqueous dimethoxyethane. Protection of the hydroxyl group as tetrahydropyranyl ether gave **9b** as a gummy mixture of two stereoisomers at C-15. This was heated with sodium hydride in xylene to effect cyclization, followed by treatment with *p*-toluenesulfonic acid in methanol to remove the tetrahydropyranyl protecting group. The resulting tetracyclic alcohol was oxidized with the Jones chromic acid. Purification of the product by preparative TLC afforded crystalline diketone ester (**10**) in 16% yield from **8**, mp 132~133°C; IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1751 (s), 1715 (vs), 1701 (vs), 1224 (m), 1152 (m), (cf. The optically active **10**: IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1740 (vs), 1715 (s), 1698 (vs), 1224 (m), 1153 (m)); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1740, 1722, 1705; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.8~1.3 (2H), 1.08 (3H, s), 1.18 (3H, s), 1.3~2.1 (11H), 2.1~2.6 (3H), 2.6~2.9 (1H), 2.9~3.3 (2H), 3.68 (3H, s); MS *m/e*: 332 (M⁺, 62%), 272 (42%), 149 (35%), 109 (100%); GLC (SE-30, at 230°C with N₂, 0.7 kg/cm²): Rt 4.4 min. The recrystallized racemic diketone (**10**) was identical with the optically active authentic sample (**10**)⁸ in its spectral (IR, NMR and MS) and chromato-

graphic (TLC and GLC) properties. This diketone ester (**10**) corresponds to the tetracyclic intermediate (C) in the biosynthetic scheme.

The remaining steps to gibberellin A₁₂ were previously investigated by British workers in their efforts to convert *ent*-kaurenolides into gibberellins. They converted the optically active diketone (**10**) into 7,16-diketone lactone (**11**).⁹ On the other hand *ent*-7-oxokaurenolide (**12**) was converted to gibberellin A₁₂ (**1**).¹⁰ Therefore the only remaining step to complete the formal total synthesis of gibberellin A₁₂ was the regioselective methylenation of the diketone lactone (**11**) to *ent*-7-oxokaurenolide (**12**). In order to achieve this goal, we prepared **11** from *ent*-7 β ,18-dihydroxykaurenolide (**13**) by modification of the published procedures.¹¹ The Wittig reaction between **11** and methylene triphenylphosphorane afforded *ent*-7-oxokaurenolide (**12**)^{8,12} in 55% yield, mp 265~266°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1780, 1705, 1660, 1110, 885; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.70 (3H, s), 1.30 (3H, s), 4.86 (1H, d, *J*=7 Hz), 4.88 (1H, m), 5.06 (1H, m); MS *m/e*: 314 (M⁺, 84%), 278 (42%), 277 (58%), 137 (100%); GLC (SE-30, at 220°C with N₂, 0.8 kg/cm²) Rt 5.5 min. This was identical with an authentic sample on the basis of IR, NMR, MS, GLC, TLC and mmp (265~266°C). This completed the formal total synthesis of ($\pm$)-gibberellin A₁₂.

in view of the omission of the optical resolution of the racemic diketone (**10**).

Details will soon be published in *Tetrahedron*.

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