

SYNTHESIS OF GIBBERELLIN A₁₂ FROM l-ABIETIC ACID¹⁾

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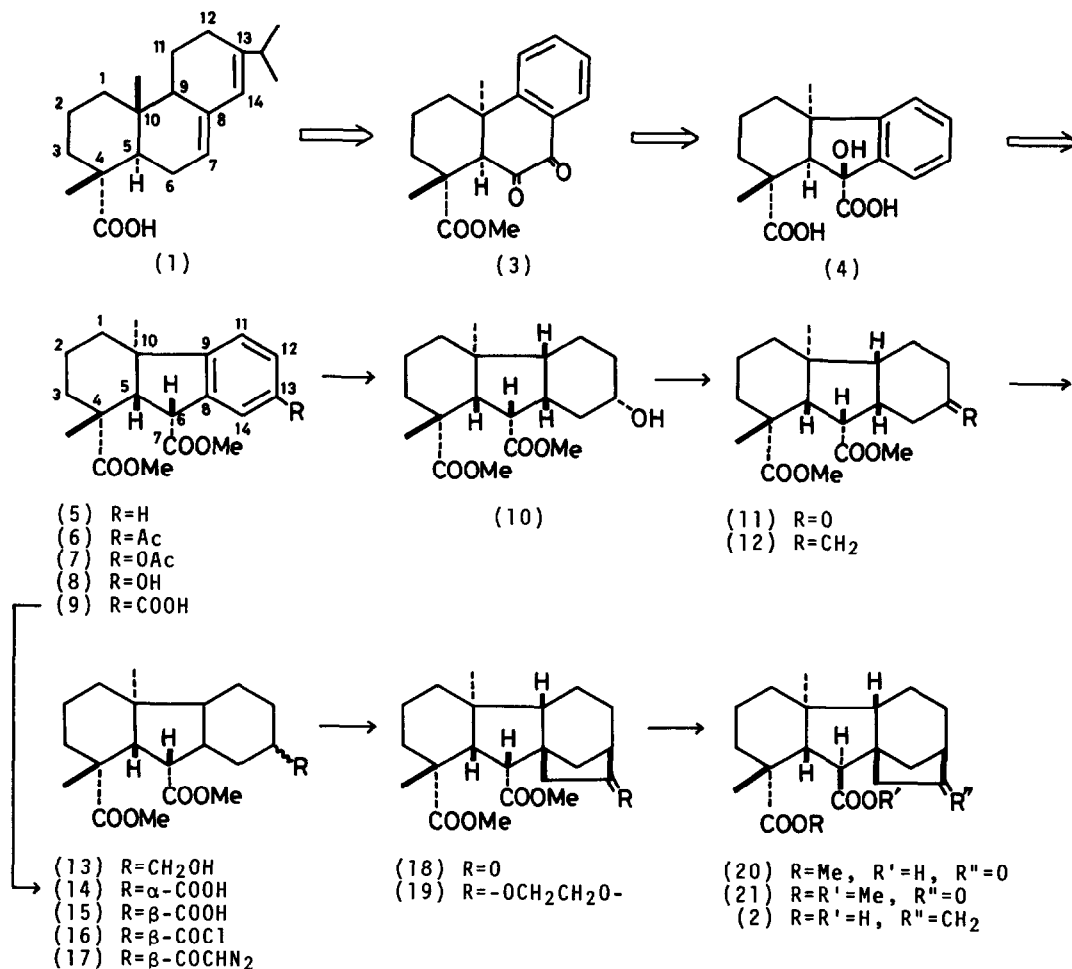
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Chemical conversion of l-abietic acid (1), a major component of pine rosin, to biologically active natural products has been carried out in our laboratory. We now wish to report the synthesis of gibberellin A₁₂²⁾(2), a minor metabolite of Gibberella fujikuroi, from l-abietic acid (1).

In our previous studies,³⁾ A/B-trans hydrofluorene compound (5) was synthesized via a benzilic acid rearrangement⁴⁾ of a dioxo ester (3) derived from 1. The Friedel-Crafts acylation of the diester (5) with AcCl and AlCl₃ (10 mol eq.) in CS₂ gave regioselectively a 13-acetyl diester (6)[mp 121-123°; IR ν_{\max}^{KBr} : 1741, 1721, 1681 cm⁻¹; NMR (CDCl₃) δ : 2.61 (s, 3H; Ac)] in 100% yield.⁵⁾ The Baeyer-Villiger oxidation of 6 with m-chloroperbenzoic acid in CH₂Cl₂ afforded a 13-acetoxy diester (7)[mp 145-146°; IR ν_{\max}^{KBr} : 1753, 1721 cm⁻¹; NMR (CDCl₃) δ : 2.26 (s, 3H; OAc)] in 96% yield, which was hydrolyzed with conc. H₂SO₄-MeOH to give a 13-hydroxy diester⁶⁾(8)[mp 140-143°] in 99% yield. Catalytic hydrogenation of 8 over RuO₂ in EtOH at 100 atmospheric pressure of hydrogen afforded a 13 α -hydroxy diester (10)[mp 161-162.5°; IR ν_{\max}^{KBr} : 3525, 1737, 1715 cm⁻¹] in 78% yield. Because of the steric hindrance of both 6 α -methoxycarbonyl and 10 α -methyl groups, hydrogen was expected to attack from the β -side. Oxidation of 10 with the Jones reagent gave a 13-oxo diester (11)[mp 98-99.5°; IR ν_{\max}^{KBr} : 1731, 1715 cm⁻¹; NMR (CDCl₃) δ : 1.79 (d, 1H, $J=8$; 5 β -H), 3.34 (t, 1H, $J=8$; 6 β -H); ORD (MeOH): a positive Cotton effect (308 nm)] in 100% yield. Since the 13-oxo diester (11)



showed a positive Cotton effect, 8-H clearly has a β -configuration, then 9-H should also have a β -one, same as β 8-H; *i.e.*, the configuration of 8-H and 9-H is the same as that of natural gibberellin. The Wittig reaction of 11 with triphenylmethylphosphonium iodide and NaH in DMSO gave a 13-methylidene diester (12)[oil; NMR (CDCl₃) δ : 4.70 (m, 2H; =CH₂)] in 99% yield. Hydroboration of 12 with diborane in THF gave a 13-hydroxymethyl diester (13)[oil; IR $\nu_{\text{max}}^{\text{CCl}_4}$: 3650, 1741, 1732 cm⁻¹] in 96% yield, which was oxidized with the Jones reagent to give

a 1:1 mixture of two isomeric carboxylic acids; (14)[mp 117-119.5°; IR ν_{\max}^{KBr} : 1730, 1720, 1700 cm^{-1}] and (15)[oil; IR $\nu_{\max}^{\text{CCl}_4}$: 1737, 1705 cm^{-1}], separable by preparative thin-layer chromatography on silica gel. One isomeric carboxylic acid (14) was identical (mp, mixed mp, and IR spectrum) with the 13 α -carboxylic acid (14), obtained by catalytic hydrogenation (PtO₂, AcOH, 130-H₂ atom) of the 13-carboxy diester (9)[mp 257-260.5°; IR ν_{\max}^{KBr} : 3600, 1737, 1716 cm^{-1}], which was derived from 6 by the King reaction⁷⁾(iodide-pyridine, and then 1N NaOH). Accordingly, the other carboxylic acid (15) must be a 13 β -carboxy diester. This 13 β -carboxy diester (15) was converted with SOCl₂ and followed with CH₂N₂ into a 13 β -diazoketone (17)[IR $\nu_{\max}^{\text{CCl}_4}$: 2100, 1725, 1640 cm^{-1}] via an acid chloride (16). Intramolecular carbene insertion of 17 with CuSO₄ in benzene under reflux with a 300-W tungsten lamp⁸⁾ produced a diester (18)[mp 87-89°; IR $\nu_{\max}^{\text{CCl}_4}$: 1744, 1737 cm^{-1} ; NMR (CCl₄) δ : 0.95 (s, 3H; 10 α -Me), 1.30 (s, 3H; 4 β -Me), 1.71 (d, 1H, \underline{J} =8.5; 5 β -H), 3.16 (d, 1H, \underline{J} =8.5; 6 β -H), 3.56, 3.60 (each s, 3H; COOMe)] in 40% yield. IR spectrum showed that the diester (18) has a 5-membered ring ketone, and its NMR spectrum indicated that position of the 5-membered ring is at C-8, since 5 β -H and 6 β -H are each split into a doublet. After ketalization of 18, partial alkaline hydrolysis of the ketal diester (19) in KOH-H₂O-ethylene glycol gave a half acid (20)[IR $\nu_{\max}^{\text{CCl}_4}$: 1747, 1732, 1705 cm^{-1}], which was methylated with CH₂N₂ to give a diester (21)[mp 132-134.5°; IR ν_{\max}^{KBr} : 1747, 1735, 1725 cm^{-1} ; NMR (CCl₄) δ : 0.69 (s, 3H; 10 α -Me), 1.04 (s, 3H; 4 β -Me), 3.27 (d, 1H, \underline{J} =12.5; 6 α -H)], identical (mp, mixed mp, and IR and NMR spectra) with gibberellin A₁, nor-ketone dimethyl ester (21) derived from natural gibberellin A₁₂ (2). The half acid (20) had already been converted to ¹⁴C-gibberellin A₁₂ by the Wittig reaction (¹⁴CH₂=PPh₃), followed by demethylation (Li-liq. NH₃) during studies on the biosynthesis of the gibberellins by Cross, et al.⁹⁾

As the total synthesis of l-abietic acid (1) had been accomplished,¹⁰⁾ the chemical conversion of l-abietic acid (1) to gibberellin A₁₂(2) can be regarded as the total synthesis of gibberellin A₁₂.

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References and Notes

- 1) This work was presented at the 19th Symposium on the Chemistry of Natural Products at Hiroshima, October 25, 1975. As the hydrofluorene compounds in this work were obtained from 1-abietic acid (1), the usual numbering for diterpene was used for the hydrofluorene derivatives.
- 2) B. E. Cross and K. Norton, J. Chem. Soc., 1570 (1965).
- 3) A. Tahara and Y. Ohtsuka, J. Chem. Soc. (Perkin I), 320 (1972).
- 4) a) J. F. Grove and B. J. Riley, J. Chem. Soc., 1105 (1961).
b) A. Tahara, Chem. Pharm. Bull. (Tokyo), 9, 252 (1961).
- 5) The Friedel-Crafts acylation of several hydrofluorene compounds derived from 1-abietic acid (1) will be published in detail.
- 6) The 13-hydroxy diester (8) had also been synthesized via nitration of the A/B-trans diester (5). [A. Tahara and Y. Ohtsuka, Chem. Pharm. Bull. (Tokyo), 20, 1637 (1972)].
- 7) L. C. King, J. Am. Chem. Soc., 66, 894 (1944).
- 8) Cf. M. Kitadani, K. Ito, and A. Yoshikoahi, Bull. Chem. Soc. Japan, 44, 3431 (1971).
- 9) B. E. Cross, K. Norton, and J. C. Stewart, J. Chem. Soc. (C), 1054 (1968).
- 10) a) G. Stork and J. W. Schulenberg, J. Am. Chem. Soc., 78, 250 (1956); ibid., 84, 284 (1962).
b) A. W. Burgstahler and L. R. Worden, J. Am. Chem. Soc., 83, 2587 (1961); ibid., 86, 96 (1964).
c) E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, J. Am. Chem. Soc., 86, 2038 (1964).