

Chiral Synthesis of the Intermediate of (-)-Gibberellin A₁₂

Xiao-Jiang HAO¹⁾, Manabu NODE²⁾ and Kaoru FUJI³⁾

1) Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204

2) Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607, Japan

3) Institute for Chemical Research, Kyoto University, Uji 611, Japan

Abstract: (-)-Dimethyl(1*R*,4*aS*)-1,4*a*-dimethyl-6-nitro-1,2,3,4,4*a*-pentahydrofluorene-1,9-dicarboxylate (**1**) was synthesized from (*R*)-(+)-2-methyl-2-(2'-nitrovinyl)- δ -valerolactone(**2**), which constitutes a formal total synthesis of (-)-gibberellin A₁₂.

In the previous papers, we reported total syntheses of diterpenoids of C-20 α series such as (+)-podocarpic acid⁽¹⁾, and calabar bean alkaloid (-)-physostigmine⁽²⁾ from (*S*)-(-)-2-methyl-2-(2'-nitrovinyl)- δ -valerolactone. Here we report a synthesis of the key intermediate (**1**) for (-)-gibberellin A₁₂ using (*R*)-(+)-2-methyl-2-(2'-nitrovinyl)- δ -valerolactone(**2**)⁽³⁾ as a chiral building block.

(*R*)-(+)-2-methyl-2-(2'-nitrovinyl)- δ -valerolactone(**2**) was synthesized according to literature method⁽³⁾ in 95% yield and 91% ee. The Michael addition of benzylmagnesium bromide to (*R*)-nitroolefin **2** afforded a diastereomeric mixture **3**(1:3) in 82% yield. Without separation, the mixture was directly treated with MeONa followed by methylation with MsCl-Et₃N, and substitution with NaI in acetone to give a mixture of iodide (**4**) in 83% overall yield. Intramolecular alkylation of iodide (**4**) with NaH in DMF provided a mixture of nitro cyclohexane compound (**5**). McMurry reaction⁽⁴⁾ of **5** afforded a mixture(2:1) of **6a** and **6b**, and **6b** was converted to **6a** in refluxing MeOH with *p*-TsOH. Grignard addition of **6a** with methylmagnesium iodide gave **7** quantitatively, which was treated with PPA provided tricyclic product **8**⁽⁵⁾. On oxidation with *t*-BuO₂H/Cr(CO)₆ in MeCN⁽⁶⁾, **8** was oxidized to keto ester (**9**) in 62% yield beside the recovery of 27% of starting material **8**. Addition of keto ester (**9**) with TMSCN and catalytic amount of *n*-BuLi⁽⁷⁾ afforded adduct **10** which was hydrolyzed with H₂SO₄-HOAc-H₂O(1:1:1) at 110°C for 4hr. followed by methylation with CH₂N₂ to provide conjugated amide **11**. Amide **11** was treated with NOBF₄⁽⁸⁾ at 50 °C overnight followed by methylation to provide (-)-dimethyl(1*R*,4*aS*)-1,4*a*-dimethyl-6-nitro-1,2,3,4,4*a*-pentahydrofluorene-1,9-dicarboxylate(**1**)(m.p. 168-170°C, [α]_D-88°(c 0.8, CHCl₃); lit.⁽⁹⁾ m.p.171-172.5°C) which was already found to be convertible to gibberellin A₁₂⁽¹⁰⁾.

References

- (1) a. M. Node, X-J. Hao, H. Nagasawa and K. Fuji, *Tetrahedron Lett.*, 1989, 30, 4141.
b. X-J Hao, M. Node and K. Fuji, *J. Chem. Soc., perkin Trans 1*, 1992, 1505.
- (2) a. M. Node, X-J. Hao and K. Fuji, *Chemistry Lett.*, 1991, 57.
b. M. Node, X-J. Hao, K. Nishide and K. Fuji, *Chem. Pharm. Bull.*, 1996, 44(4), 715.
- (3) a. K. Fuji, M. Node, H. Nagasawa, S. Terada, *J. Am. Chem. Soc.*, 1986, 108, 3885.

b. K. Fuji, M. Node, H. Nagasawa, Y. Naniwa, R. Taga, K. Machida and G. Snatzke, *J. Am. Chem. Soc.*, 1989, 111, 7921.

(4) J. E. McMurry and J. Melton, *J. Org. Chem.*, 1973, 38, 4367.

(5) Synthesis of di-8, see U. R. Ghatale, J. Chaleravarty and A. K. Banejeo, *Tetrahedron*, 1968, 24, 1577.

(6) A. J. Pearson and G. R. Han, *J. Org. Chem.*, 1985, 50, 2791.

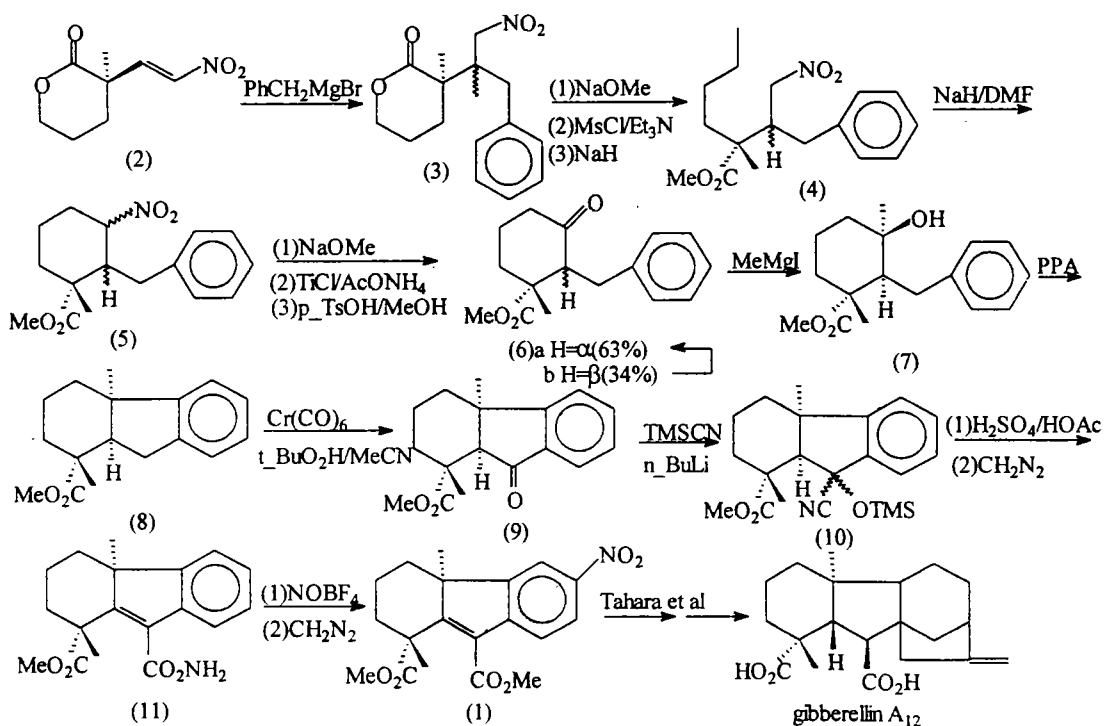
(7) S. Ohta, S. Hayaleawa and M. Okamoto, *Tetrahedron Lett.*, 1984, 25, 5681.

(8) G. A. Olah and J. A. Olah, *J. Org. Chem.*, 1965, 30, 2386.

(9) A. Tahara and Y. Ohtsuka, *Chem. Pharm. Bull.*, 1972, 20, 1637.

(10)a. T. Nakata and A. Tahara, *Tetrahedron Lett.*, 1976, 1515.

b. A. Tahara and Y. Ohtsuka, *Chem. Pharm. Bull.*, 1972, 20, 1637.



(Received 4 September 1997)