

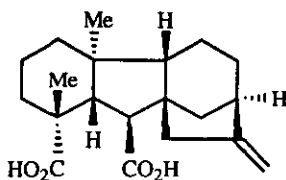
## INOC REACTION IN GIBBERELLIN SYNTHESIS— A PRACTICAL SYNTHESIS OF THE KEY INTERMEDIATE FOR GIBBERELLIN A<sub>12</sub>

Masahiro Toyota, Toshihiro Wada, and Keiichiro Fukumoto\*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

**Abstract**—The isoxazoline (10), a possible key intermediate for gibberellin A<sub>12</sub> (1), has been synthesized in 91% yield by means of intramolecular nitrile oxide cycloaddition (INOC) reaction of the oxime (9).

Nature provides synthetic chemists with a plethora of architecturally diverse diterpenes, many of which have significant biological properties. Gibberellins, mostly tetra- or pentacyclic diterpenoids, are important plant growth hormones which control cell elongation and were discovered in Japan in an investigation of the "baka-nae" disease of rice attributed to the fungus *Gibberella fujikuroi*.<sup>1</sup> The simplest member of this family of compounds is gibberellin A<sub>12</sub> (1),<sup>2</sup> and its syntheses were reported independently by Mori<sup>3</sup> and by Tahara<sup>4</sup> and their colleagues.



Gibberellin A<sub>12</sub> (1)

Herein we disclose an alternative approach to 1 by using INOC reaction.

Conversion of the enone (2)<sup>5</sup> into the keto alcohol (6) was achieved *via* the reaction sequence summarized in Scheme I. Namely, successive LAH reduction of 2, dietherification of the resulting diol with MOMCl in the presence of diisopropylethylamine (DIPEA) and acidic treatment provided the enone (3) in 66% overall yield. Upon treatment of the silyl enol ether of 3 with palladium(II) acetate in MeCN, the desired enone (4) was obtained in 92% yield.<sup>6</sup> Highly stereoselective 1,4-addition of a vinyl group was accomplished by the Kuwajima's protocol.<sup>7</sup> The high preference for the Grignard reagent to add to 4 from *exo*-face can be explained by both the steric interaction and the "Cieplak effect".<sup>6,8</sup> The stereochemistry of 5<sup>9</sup> was made clearly apparent through combined 2-D <sup>1</sup>H-<sup>1</sup>H COSY study and NOE measurements. The relevant NOE data for 5 are presented

by arrows in Figure I. Deprotection of the MOM group of 5 was conducted to give rise to the alcohol (6) in 91% yield.

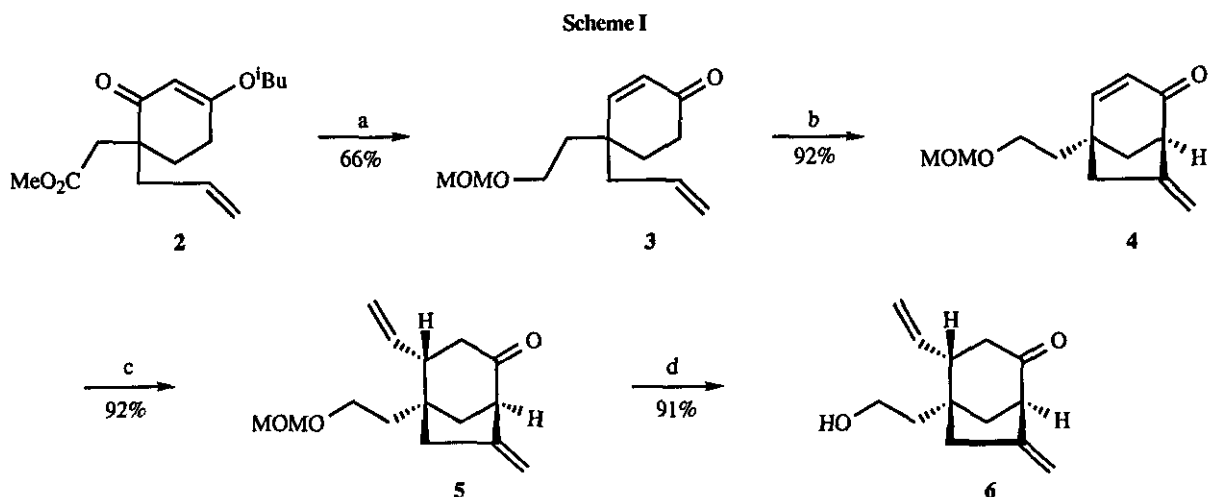
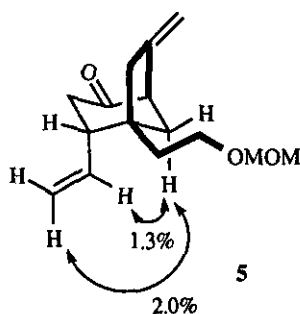


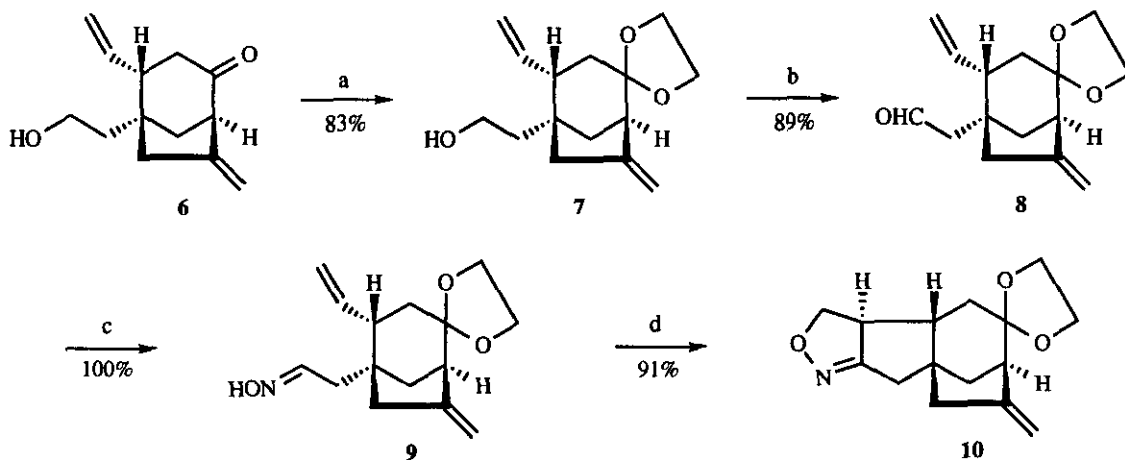
Figure I



Preparation of the isoxazoline (10) from 6 is shown in Scheme II. Ketalization (83%) followed by Parikh modified Moffatt oxidation<sup>10</sup> (89%) afforded the aldehyde (8). 8 was quantitatively converted to its oxime (9) by treatment with hydroxylamine hydrochloride in pyridine.

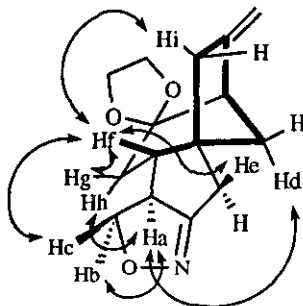
With convenient access to 9 secure, the stage was now set for INOC reaction.<sup>11</sup> On exposure of the oxime (9) to 1.15 equivalent of sodium hypochlorite in methylene chloride (0 °C → room temperature), the isoxazoline (10)<sup>9</sup> was produced in 91% yield as a single product. The stereochemical assignment to 10 was conclusively established by a combination of difference NOE and 2-D <sup>1</sup>H-<sup>13</sup>C COSY nmr experiments. Enhancements between Ha-Hb, Ha-Hd, Ha-Hh, Hf-Hc, Hf-He, Hf-Hg, and Hf-Hi were proofs of the proposed structure (Figure II).

Scheme II



**Reagents and Conditions:** (a) ethylene glycol, PPTS, C<sub>6</sub>H<sub>6</sub>, reflux. (b) SO<sub>3</sub>·Py, DMSO, Et<sub>3</sub>N, room temperature. (c) NH<sub>2</sub>OH·HCl, pyridine, room temperature. (d) 8.5% NaClO, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C → room temperature.

Figure II



This strategy will be used in the total synthesis of gibberellin A<sub>12</sub> (1) in the near future.

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9. Satisfactory analytical data were obtained for all new compounds. Selected data are as follows. *Compound (5)*; ir  $\nu_{\max}$  (neat): 1710  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ ):  $\delta$  1.59 (1H, ddd,  $J = 7.0, 8.0$  and  $14.5$  Hz), 1.65 (1H, ddd,  $J = 2.0, 5.5$  and  $12.5$  Hz), 1.92 (1H, ddd,  $J = 6.0, 8.0$  and  $14.5$  Hz), 2.01 (1H, dd,  $J = 1.0$  and  $12.5$  Hz), 2.12 (1H, d,  $J = 15.8$  Hz), 2.55 - 2.59 (2H, m), 2.68 (1H, br dt,  $J = 2.0$  and  $8.1$  Hz), 2.76 (1H, dd,  $J = 8.1$  and  $15.8$  Hz), 3.17 (1H, d,  $J = 5.5$  Hz), 3.34 (3H, s), 3.56 (1H, ddd,  $J = 7.0, 8.0$  and  $10.0$  Hz), 3.63 (1H, ddd,  $J = 6.0, 8.0$  and  $10.0$  Hz), 4.59 (2H, s), 4.90 (1H, s), 5.01 (1H, t,  $J = 2.5$  Hz), 5.06 (1H, dt,  $J = 1.0$  and  $17.2$  Hz), 5.10 - 5.14 (1H, m) and 5.86 (1H, ddd,  $J = 8.1, 10.6$  and  $17.2$  Hz);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ ):  $\delta$  36.43, 39.25, 39.83, 42.37, 44.10, 47.03, 54.92, 59.60, 64.09, 96.11, 108.10, 116.56, 138.15, 148.69 and 208.75. *Anal. Calcd for  $\text{C}_{15}\text{H}_{22}\text{O}_3$* : C, 71.97; H, 8.86. Found: C, 71.73; H, 8.91.
- Compound (10)*;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ ):  $\delta$  1.57 (1H, ddd,  $J = 1.3, 5.5$  and  $12.0$  Hz), 1.58 (1H, br d,  $J = 15.0$  Hz), 1.81 (1H, br dd,  $J = 8.3$  and  $11.7$  Hz), 1.99 (1H, dd,  $J = 8.3$  and  $15.0$  Hz), 2.29 (1H, dd,  $J = 2.8$  and  $12.0$  Hz), 2.36 (1H, br dd,  $J = 1.5$  and  $16.2$  Hz), 2.42 (1H, dd,  $J = 1.0$  and  $18.0$  Hz), 2.51 (1H, dt,  $J = 2.9$  and  $16.2$  Hz), 2.55 (1H, dd,  $J = 2.0$  and  $18.0$  Hz), 2.58 (1H, br d,  $J = 5.5$  Hz), 3.76 (1H, dd,  $J = 7.9$  and  $12.4$  Hz), 3.89 - 3.98 (4H, m), 3.98 - 4.05 (1H, m), 4.54 (1H, dd,  $J = 7.9$  and  $9.2$  Hz), 5.00 - 5.02 (1H, m), 5.10 - 5.13 (1H, m),  $^{13}\text{C}$  nmr:  $\delta$  30.97, 31.20, 38.74, 42.06, 48.15, 49.64, 53.68, 57.76, 63.86, 64.71, 73.62, 109.90, 110.14, 148.20 and 169.94. *Anal. Calcd for  $\text{C}_{15}\text{H}_{19}\text{NO}_3$* : C, 68.94; H, 7.33; N, 5.36. Found: C, 68.68; H, 7.30; N, 5.37.
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