INOC REACTION IN GIBBERELLIN SYNTHESIS—— A PRACTICAL SYNTHESIS OF THE KEY INTERMEDIATE FOR GIBBERELLIN A_{12}

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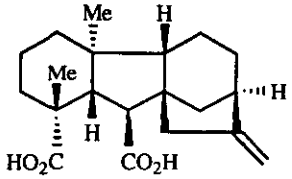
Abstract——The isoxazoline (**10**), a possible key intermediate for gibberellin A_{12} (**1**), has been synthesized in 91% yield by means of intramolecular nitrile oxide cycloaddition (INOC) reaction of the oxime (**9**).

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*.[1] The simplest member of this family of compounds is gibberellin A_{12} (**1**),[2] and its syntheses were reported independently by Mori[3] and by Tahara[4] and their colleagues.



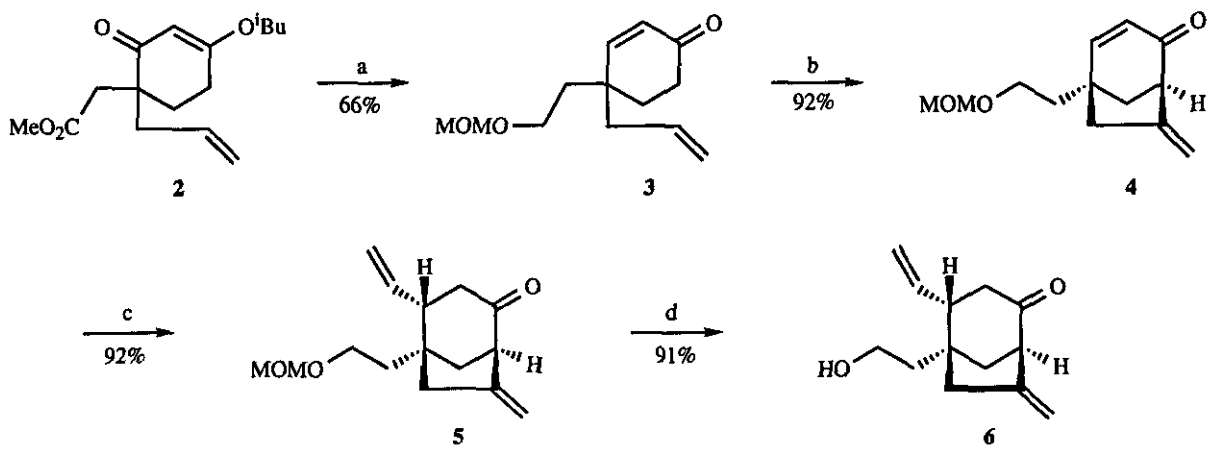
Gibberellin A_{12} (**1**)

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

Conversion of the enone (**2**)[5] 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.[6] Highly stereoselective 1,4-addition of a vinyl group was accomplished by the Kuwajima's protocol.[7] 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".[6,8] The stereochemistry of **5**[9] was made clearly apparent through combined 2-D ^{1}H-^{1}H COSY study and NOE measurements. The relevant NOE data for **5** are presented

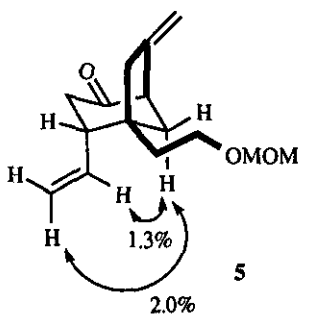
by arrows in **Figure I**. Deprotection of the MOM group of **5** was conducted to give rise to the alcohol (**6**) in 91% yield.

Scheme I



Reagents and Conditions: (a) LAH, Et_2O, *reflux*; MOMCl, DIPEA, CH_2Cl_2, 0 °C→room temperature; 10% HCl, THF, 0 °C. (b) LDA, THF, -78 °C; TMSCl, -78 °C→ room temperature; $Pd(OAc)_2$, MeCN, room temperature. (c) CH_2=CHMgBr, CuBr·SMe_2, TMSCl, HMPA, THF, -78 °C; 10% HCl, -78 °C→0 °C. (d) 35% $HClO_4$, THF, 40-45 °C.

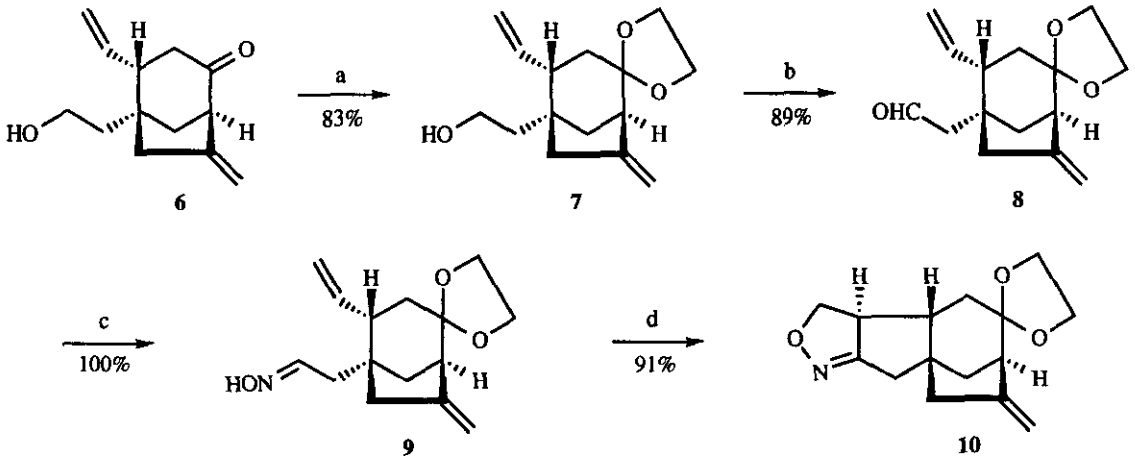
Figure I



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

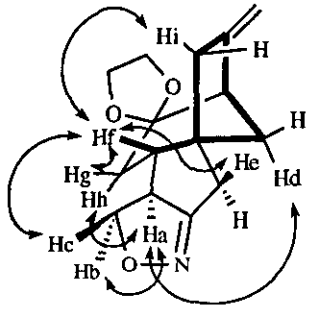
With *convenient access to* **9** *secure, the stage was now set for* INOC reaction.[11] On exposure of the oxime (**9**) to 1.15 equivalent of sodium hypochlorite in methylene chloride (0 °C→room temperature), the isoxazoline (**10**)[9] was produced in 91% yield as a single product. The stereochemical assignment to **10** was conclusively established by a combination of *difference* NOE and 2-D ^1H-^{13}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_6H_6, reflux. (b) SO_3·Py, DMSO, Et_3N, room temperature. (c) NH_2OH·HCl, pyridine, room temperature. (d) 8.5% NaClO, CH_2Cl_2, 0 °C→room temperature.

Figure II



This strategy will be used in the total synthesis of gibberellin A_{12} (**1**) in the near future.

REFERENCES AND NOTES

1. A recent review: L. N. Mander, *Chem. Rev.*, 1992, **92**, 573.
2. B. E. Cross and K. Norton, *J. Chem. Soc.*, 1965, 1570.
3. K. Mori, I. Takemoto, and M. Matsui, *Tetrahedron*, 1976, **32**,1497.
4. T. Nakata and A. Tahara, *Tetrahedron Lett.*, 1976, 1515.
5. P. A. Zoretic, C. Bhakta, and R. H. Khan, *Tetrahedron Lett.*, 1983, **24**, 1125.
6. Recent examples: M. Toyota, T. Wada, Y. Nishikawa, K. Yanai, and K. Fukumoto, *Synlett*, 1994, 597, and refs cited therein.
7. Y. Horiguchi, S. Matsuzawa, E. Nakamura, and I. Kuwajima, *Tetrahedron Lett.*, 1986, **27**, 4025.
8. A. S. Cieplak, *J. Am. Chem. Soc.*, 1981, **103**, 4540.

9. Satisfactory analytical data were obtained for all new compounds. Selected data are as follows. *Compound* (**5**); ir νmax (neat): 1710 cm^{-1}; ^1H nmr ($CDCl_3$): δ 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}C nmr ($CDCl_3$): δ 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 $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.73; H, 8.91. *Compound* (**10**); ^1H nmr ($CDCl_3$): δ 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}C nmr: δ 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 $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.68; H, 7.30; N, 5.37.
10. J. R. Parikh and W. E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505.
11. Recent reviews: (a) D. P. Curren, "Advances in Cycloaddition", JAI Press Inc, Greenwich, Connecticut, London, 1988, **1**, 129, (b) A. Padwa and A. M. Schoffstall, *ibid.*, 1990, **2**, 1, (c) A. Padwa, "Comprehensive Organic Synthesis", Pergamon Press, Oxford, New York, Seoul, Tokyo, 1991, **4**, 1069.

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