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# 1,3-Asymmetric Induction in the Intramolecular [2+2] Cycloaddition of Alkene-keteniminium Salts. Synthesis of (+)-Gibberellic Acid Key Intermediate+

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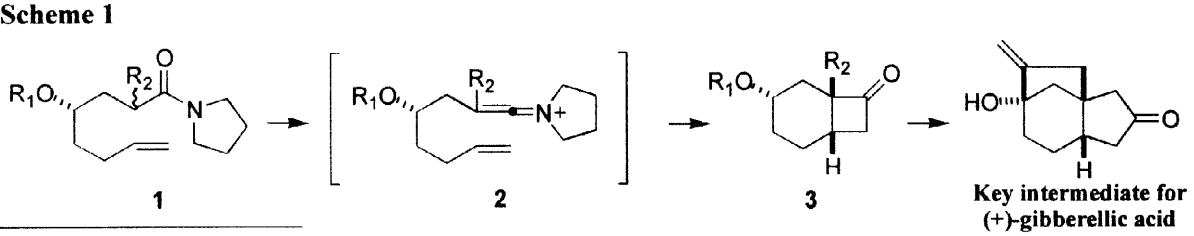
**Abstract**

Optically active bicyclo[4.2.0]octan-7-ones were synthesized by stereoselective intramolecular [2+2] cycloaddition of alkene-keteniminium salt derived from L-glutamic acid, based on 1,3-asymmetric induction. Synthetic application toward (+)-gibberellic acid key intermediate was also described.

*Key words:* Asymmetric induction; Bicyclic aliphatic compounds; Cycloadditions; Cyclobutanones.

The intramolecular [2+2] cycloaddition of keteniminium salt to alkene, an attractive alternative to ketene, serves as an important and efficient route for the synthesis of a variety of cyclobutanones fused to carbo- and heterocycles[1]. In view of cyclobutanone's chemical reactivity and selectivity[2], asymmetric version of this reaction might offer powerful methods for the synthesis of optically active polycyclic compounds. However, despite Ghosez's pioneering work using chiral keteniminium salts in this field[3], synthetic applications of this reaction are very rare and limited to 1,2-asymmetric induction[4-6]. The major obstacles to its general use may presumably have been originated from the difficulties obtaining a chiral auxiliary, which is destined to be removed after the reaction, or chiral synthon for the asymmetric induction. Now, we wish to report a practical asymmetric [2+2] cycloaddition reaction of keteniminium salt derived from L-glutamic acid, which is based on 1,3-asymmetric induction. Furthermore, the potential of our method is demonstrated by a concise synthesis of a key intermediate toward (+)-gibberellic acid (Scheme 1).

**Scheme 1**




1 2 3 **Key intermediate for (+)-gibberellic acid**

+ This paper is dedicated to Prof. Kenji Koga on the occasion of his retirement from the University of Tokyo.

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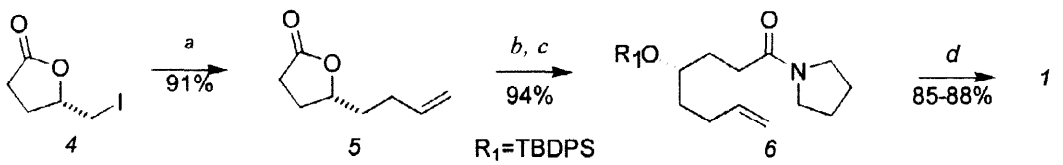
The synthesis of **1**, a suitable precursor for our planned [2+2] cycloaddition, was straightforward and gave a high yield as shown in Scheme 2. Lactone **4** was prepared *via* 4 steps from L-glutamic acid according to the literature method[7-8], then it was converted to **5** by radical allylation in 91% yield[9]. Conversion of **5** to **6** was accomplished simply by refluxing with pyrrolidine and TEA, followed by protecting hydroxyl group with pivaloyl chloride or *tert*-butyldiphenylsilyl chloride. Alkylation of **6** using LDA chemistry produced the corresponding α-substituted unsaturated amides **1**.

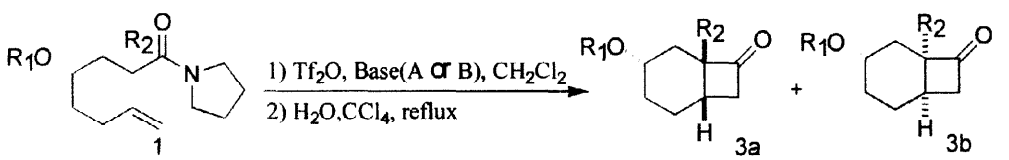
**Scheme 2**




*a*) allyltributyltin, AIBN, toluene, 80°C. *b*) pyrrolidine, TEA, reflux. *c*) TBDPSCl, imidazole, DMF, 60°C. *d*) LDA, THF, -78°C; RX, -78~-30°C.

The feasibility of 1,3-asymmetric induction in this [2+2] cycloaddition was examined towards several different amide precursors **1**. The keteniminum salts **2** were generated by treating amide **1** with base and triflic anhydride in dichloromethane at indicated temperature and underwent cyclization followed by hydrolysis to give **3a** and **3b**. The results obtained are shown in Table 1.

**Table 1.**
Diastereoselective intramolecular [2+2] cyclization of **1** *via* keteniminium salt

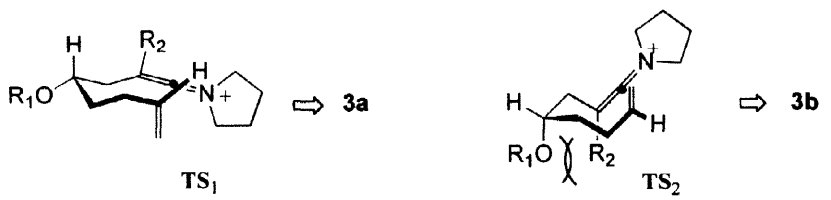



| Entry | $R_1$ | $R_2$ | base[a] | temp.(°C) | **3a**/**3b**[b] | yield[c] |
|---|---|---|---|---|---|---|
| 1 | Pv | H | A | 40 | 1.2:1 | 27(47) |
| 2 | TBDPS | H | A | 40 | 1.5:1 | 57(98) |
| 3 | TBDPS | H | A | 4 | 2.2:1 | 34(87) |
| 4 | TBDPS | Me | B | 40 | 5.2:1 | 33(59) |
| 5 | TBDPS | $PhCH_2$ | B | 40 | 7.1:1 | 31(45) |

[a] A: 2,4,6-collidine B: 2,6-di-*tert*-butyl-4-methylpyridine. [b] Ratios were determined by GLC (entries 1-3) or $^1$H-NMR analysis (entries 4 and 5). [c] Isolated yield: yields in parentheses are conversion yields.

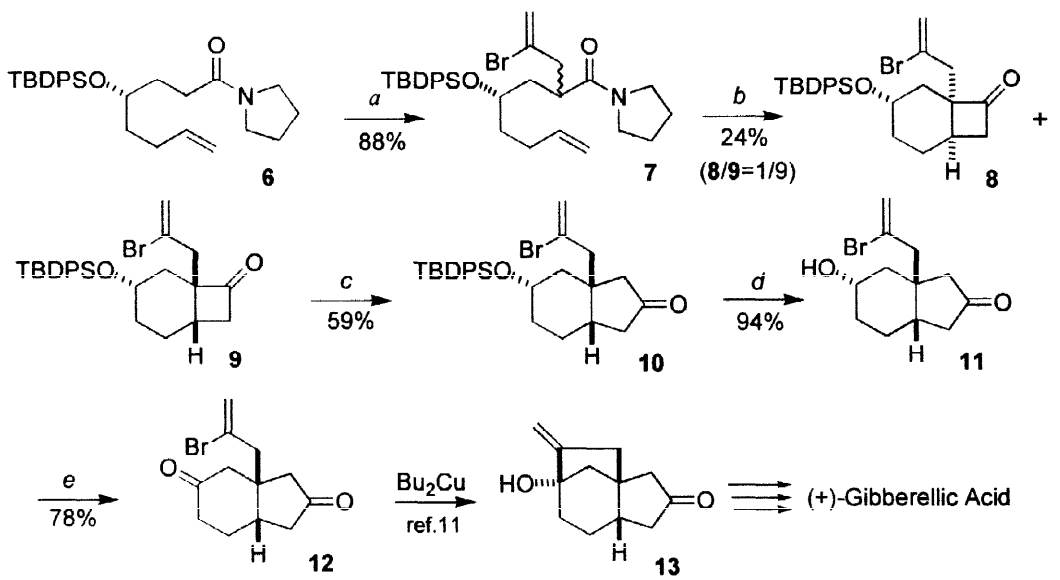
The relative and absolute configurations of newly created stereogenic centers were firmly established by measuring 2D-NOESY. It is noteworthy that chemical shift of the proton on C4($CHOR_1$) of **3a** always appears at higher field than that of **3b** in $^1$H NMR spectra. As shown in Table 1, the preferential formation of **3a** over **3b** was observed in all cases, and the ratio is seen to be highly dependent on $R_2$ group as well as the reaction temperature and $R_1$ group. Bulkiness of $R_2$ group seems to be directly correlated to stereoselectivity, but inversely to chemical yield. The selectivity ratio reaches up to 7 when $R_1$ and $R_2$ are TBDPS and benzyl

group, respectively. The result of this 1,3-asymmetric induction can be rationalized by considering the following chair-like transition-state models based on the stepwise mechanism[10], in which $TS_1$ leading to **3a** is favored over $TS_2$ leading to **3b** for steric reason.




Encouraged with this result, we applied the present method to the synthesis of optically active gibberellic acid key intermediate. Although much attention has been paid to the synthesis of tricyclic ketone (±)-**13**[11-14], the synthesis of optically active **12** or **13** has not been reported yet. It was anticipated that **13** or its well-known precursor **12** could be synthesized from **9**, which is readily obtainable from **7** using our method. Synthesis of the requisite bicyclic ketone **12** was accomplished as outlined in Scheme 3.

**Scheme 3**




*a)* LDA/THF, 2,3-dibromopropene,-78~-30°C; *b)* 2,6-di-*tert*-butyl-4-methylpyridine/$CH_2Cl_2$; $Tf_2O$; reflux, then $H_2O/CCl_4$, reflux; *c)* $CH_2N_2$/MeOH, rt. *d)* TBAF/THF, rt. *e)* $(COCl)_2/CH_2Cl_2$, DMSO, TEA, -78°C~rt.

Treatment of **6** with LDA, followed by addition of 2,3-dibromopropene (4 equiv), produced **7** as a 4:1 inseparable mixture of epimers in 88% isolated yield. Inability to separate this mixture was not important since this newly introduced stereogenic center would be rendered planar during subsequent keteniminium salt formation. With **7** in hand, our special attention was drawn to the level of 1,3-asymmetric induction in the course of cyclization from **7** to **8/9**. Performing the intramolecular [2+2] cyclization of **7** with triflic anhydride (1.2 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (1.3 equiv) in refluxing dichloromethane for 1.5 days, followed by hydrolysis gave a 1:9 ratio of **8** and **9**, isolated in 2.4% and 22.0% yields, respectively (96% combined yield based on recovered substrate **7**). On the basis of 2D-NOESY experiments, the

absolute configuration of major diastereomer **9**[1] was assigned to be 1*S*, 4*S* and 6*R*, as illustrated in Scheme 3. Subsequent ring enlargement of cyclobutanone **9** was accomplished with diazomethane to give cyclopentanone **10** and its regioisomer in 59% and 37% yields, respectively[15]. However, a detectable amount of *trans*-epimer of **10** was not found during the rearrangement, indicating that the cyclobutyl carbon migrated with retention of its stereochemistry[16]. The TBDPS group of **10** was removed by TBAF to yield the alcohol **11**[2], which was then converted to the known diketone **12** with $[\alpha]_D^{21}$ –72.6° (*c* 0.3, $CHCl_3$) by Swern oxidation in 73% overall yield. IR, $^1H$ NMR, and $^{13}C$ NMR data of **12** were identical with those of racemate previously reported[17]. Since (±)-**12** had already been converted to (±)-**13** by Corey[11], the formal synthesis of **13** was completed at this stage.

In summary, we have found an efficient 1,3-asymmetric induction process for the stereoselective construction of optically active bicyclo[4.2.0]octan-7-ones. The following features are notable. (1) Based on 1,3-asymmetric induction, which has been rarely reported previously, the stereoselectivity ratio of up to 9 was achieved. (2) The method is very practical since it employed L-glutamic acid as an inexpensive, enantiopure chiral source as well as a four-carbon synthon. (3) Considering the chemistry of hydroxyl group, cycloadduct of this study might hold a great potential as a bicyclic chiral synthon with a wide range of synthetic applications. (4) We have accomplished the asymmetric synthesis of a key intermediate for (+)-gibberellic acid for the first time.

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[17] See the supplementary material of reference 11.

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1 **9**: Colorless oil; $^1H$ NMR(500MHz/$CDCl_3$) δ 7.65(m, 4H), 7.43-7.33(m, 6H), 5.33(d, 1H, J=0.8Hz), 5.23(d, 1H, J=0.8Hz), 3.69(m, 1H), 3.19(dd, 1H, J=5.5, 10.2Hz), 2.87(dd, 1H, J=5.5, 10.2Hz), 2.56(d, 1H, J=8.9Hz), 2.54-2.47(m, 1H), 2.29(d, 1H, J=8.9Hz), 1.80-1.69(m, 4H), 1.61-1.58(m, 2H), 1.05(s, 9H); $^{13}C$ NMR(125MHz, $CDCl_3$) δ 209.2, 135.8, 135.7, 134.3, 134.1, 129.7, 129.6, 128.7, 127.6, 120.5, 68.2, 62.8, 47.1, 45.7, 36.3, 29.8, 27.2, 26.9, 24.0, 19.0; IR(film) $cm^{-1}$ 3080, 2990,1780, 1620; HRMS(EI) *m/e* calcd for $C_{23}H_{24}O_2BrSi(M^+-C_4H_9)$ 439.0729, found 439.0752; $[\alpha]_D^{23}$ +3.0° (*c* 1.0, $CHCl_3$).

2 **11**: Colorless oil; $^1H$ NMR(500MHz/$CDCl_3$) δ 5.55(d, 1H, J=1.8Hz), 5.54(d, 1H, 1.8Hz), 3.73(m, 1H), 2.83(d, 1H, J=14.6Hz), 2.45(d, 1H, J=14.6Hz), 2.37(d, 1H, J=18.2Hz), 2.32(d, 1H, J=18.2Hz), 2.25(dd, 1H, J=11.5, 18.4Hz), 2.18(dd, 1H, J=8.3, 18.4Hz), 2.13(m, 1H), 1.90-1.65(m, 5H), 1.34(m, 1H), 1.08(dd, 1H, J=11.2, 13.5Hz); $^{13}C$ NMR (125MHz, $CDCl_3$) δ 217.2, 129.1, 121.2, 66.5, 53.5, 48.2, 43.2, 39.7, 39.0, 38.7, 28.9, 22.2; IR (film) $cm^{-1}$ 3400, 2920, 1740, 1610; HRMS(EI) *m/e* calcd for $C_{12}H_{17}O_2(M^+-Br)$ 193.1228, found 193.1228; $[\alpha]_D^{18}$ –63.0° (*c* 0.4, $CHCl_3$).