Biomimetic Synthesis of a Leaf-opening Factor, Potassium Isolespedezate, by Direct Formation of Enol-glycoside

Takanori Sugimoto and Minoru Ueda*
Tohoku University, Department of Chemistry, Aoba-ku, Sendai 980-8578

(Received May 19, 2004; CL-040573)

Potassium isolespedezate (**1**) is a leaf-opening factor controlling the nyctinastic leaf-movement of leguminous plants. We carried out bioorganic studies on nyctinasty by using synthetic probes designed on the structure of **1** and its galactose analog (**2**). However, **1** was synthesized via an indirect route because of the difficulty of direct formation of the enol-glycosidic linkage. More efficiency is desired for the preparation of **1** and **2** which are necessary for the synthesis of probe compounds. In this paper, we report the biomimetic synthesis of **1** containing direct formation of an enol-glucosidic linkage. This efficient route makes it possible to prepare **1** and **2** in large quantity.

Most leguminous plants close their leaves in the evening, as if to sleep, and open them early in the morning according to the circadian rhythm controlled by the biological clock.[1] We have revealed that nyctinasty is controlled by a pair of leaf-movement factors: leaf-opening and leaf-closing substances.[1] Recently, we revealed the target cell[2] and potential receptor protein[3] of a leaf-opening substance, potassium isolespedezate (**1**),[4] by using synthetic probe compounds designed on the structure of **1** and its galactose analog (**2**).[5] Syntheses of probe compounds need a large amount of **1** and **2**, which are the core skeletons of the probes. However, **1** and **2** were synthesized via an indirect route because of the difficulty of direct formation of the enol–glycosidic linkage. The enol-glycosidic linkage was formed via 2 steps: glycosidation and following oxidative olefination. Besides its inefficiency, oxidative olefination incurs an experimental problem in the separation of the resulting coupling product from an excess amount of DDQ. Especially, this problem becomes serious in large-scale synthesis. Then, more efficiency is desired for the preparation of **1** and **2**, which are necessary for the development of probe compounds. In a biosynthetic pathway, **1** would be synthesized via direct formation of the enol-glucosidic linkage catalyzed by a glucosyltransferase. In this paper, we report a biomimetic synthesis of **1** and **2** via direct formation of the enol-glycosidic linkage.

For the direct enol-glycoside formation, aglycon (**3**) should be in a keto-enol equilibrium in dichloromethane (Figure 1), which is usually used as a solvent in Königs–Knorr reaction. However, no enol-glucoside was obtained under the usual Königs–Knorr glycosidation using **3** and **4**. The ^{1}H NMR spectrum of **1** in CD_2Cl_2 revealed that the ratio of keto to enol was $>99:1$, and almost no enol form of **1** existed in a nonpolar solvent such as dichloromethane.

S_N2-like glycosidation was studied by Rolando[6] and Danishefsky.[7] Only one example on the S_N2-type formation of enol-glycoside with enolate has been reported so far.[8] Then we examined S_N2-type glycosidation using enolate generated from aglycon **3** by using some bases. And we examined two electrophiles as a glycosyl donor: one is glucopyranosyl bromide and the other is epoxide (Figure 1).

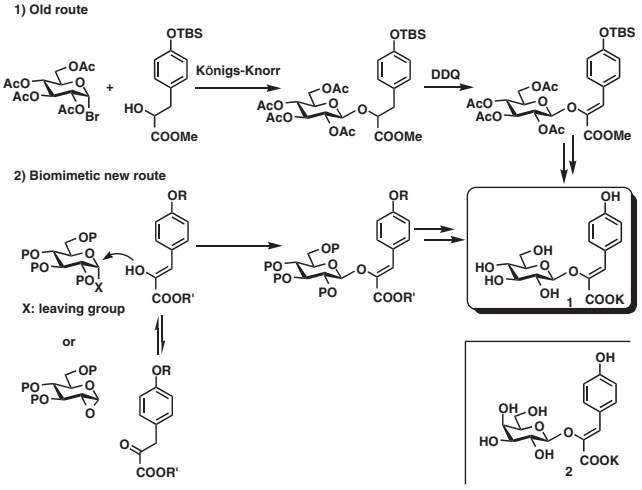


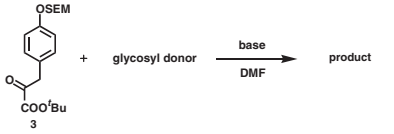
Figure 1. Old synthetic route and Biomimetic new route to **1**.

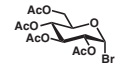
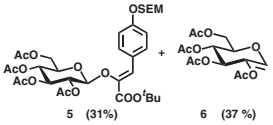
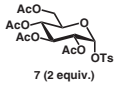
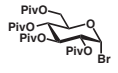
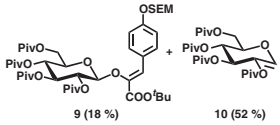
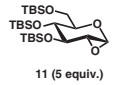
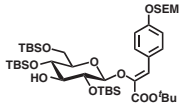
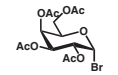
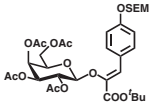
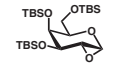
First, generation of enolate from properly protected aglycon (**3**) was examined. We examined several bases such as DBU, K_2CO_3, $(NH_4)_2CO_3$, and *t*-BuOK. Then, it was revealed that only *t*-BuOK efficiently generated an enolate. Coupling of **3** and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**4**) was carried out by using *t*-BuOK as a base to give **5** in 31% yield (Table 1). No α-isomer and no *C*-glycosylated product were obtained in this reaction. And no *E*-isomer was obtained in this reaction, because thermodynamically stable *Z*-enolate from **3** would predominatly exist under this condition. The low yield of coupling product **5** in this reaction was due to β-elimination to give **6** in 22% yield. And use of tosylate **7**,[9] which has a good leaving group on an anomeric position, as a glycosyl donor did not give any coupling product at all (Table 1). Thus, it is expected that without abstraction of 2′-H in **4** by the enolate, the yield of coupling product **5** would be improved. Using sterically hindered glycosyl donor **8**,[10] a bulky pivaloyl group would prevent the approach of the enolate to the 2′-H. However, coupling reaction using **8** gave the β-elimination product (**10**) predominantly and coupling product (**9**) was obtained in lower yield than in the case of **4** (Table 1). It was revealed that the competition between glycosidation and β-elimination caused serious difficulty using glucopyranosyl bromide as a glycosyl donor.

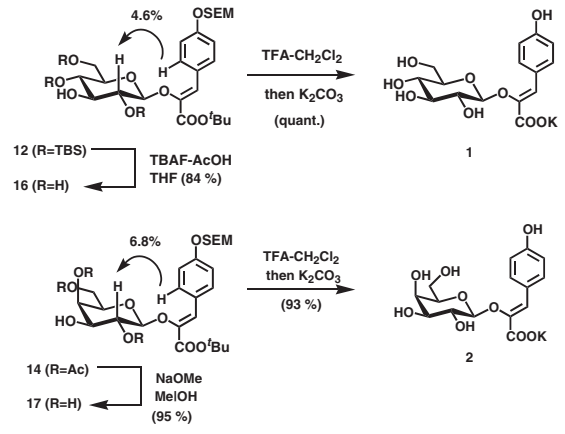
Then, we prepared an epoxide-type glycosyl donor, 3,4,6-tris-*O*-*tert*-butyldiemthylsilyl-1,2-anhydro-α-D-glucopyranose (**11**) according to the method by Danishefsky.[7] Glycosidation by nucleophilic attack of the enolate from **5** to epoxide **11** gave enol-glycoside. No *E*-isomer was obtained in this condition. The coupling product **12**, in which TBS group migrated to the 2′ position, was obtained in 43% yield (Table 1). The structure

of **12** was determined from the coupling between 3′-hydroxy H and 3′-H in the ^{1}H NMR spectrum. Stereochemistry of the olefin in **12** was determined to be *Z* from the NOE between aromatic 2-H and 2′-H of sugar moiety (Scheme 1). And following deprotection gave potassium isolespedezate (**1**)[3] in 35% yield in 3 steps from **11** (Table 1, Scheme 1).

Table 1. Reaction conditions of S_N2-type glycosidation



glycosyl donor / equiv.	Base/ equiv.	Temp/Time	product / yield
 4 (2 equiv.)	^{t}BuOK (2.5 equiv.)	0 °C/ 2 hrs	 5 (31%) + 6 (37 %)
 7 (2 equiv.)	^{t}BuOK (2.5 equiv.)	rt/ 24 hrs	–
 8 (2 equiv.)	^{t}BuOK (2.5 equiv.)	rt/ 5 hrs	 9 (18 %) + 10 (52 %)
 11 (5 equiv.)	^{t}BuOK (1.2 equiv.) 18-Crown-6 (1.2 eqiuv.)	rt/ 6 hrs	 12 (43 %)
 13 (4 equiv.)	^{t}BuOK (5 equiv.)	0 °C/ 1 hr	 14 (61%)
 15 (5 equiv.)	^{t}BuOK(1.2 equiv.) 18-Crown-6 (1.2 equiv.)	rt/ 24 hrs	–



Scheme 1. Synthesis of **1** and **2**.

Similarly, we examined the synthesis of potassium galactoisolespedezate (**2**) via direct formation of enol-glycoside. All synthetic probes such as fluorescence-labeled probe and photoaffinity probe that are designed on the structure of **1** have a common skeleton **2** to circumvent the hydrolysis by β-glucosidase in the plant body. Thus, efficient preparation of **2** is important for the development of probe compounds exploring bioorganic studies on nyctinasty. Coupling reaction with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**13**) and **5** using *t*-BuOK as a base gave coupling product **14** in 61% yield (Table 1). Stereochemistry of the olefin in **14** was determined to be *Z* from the NOE between aromatic 2-H and 2′-H of sugar moiety (Scheme 1). Fortunately, no β-elimination product was obtained in this case. This is because the abstraction of 2′-H by the enolate would be inhibited by steric hindrance due to the 4′-acetyl group in **13**. Inhibition of the abstraction of 2′-H in **13** would improve the yield of the coupling product compared with the case of glucosyl donor **4**. And following deprotection gave potassium galactoisolespedezate (**2**)[11] in 55% yield in 3 steps from **13** (Table 1 and Scheme 1).

On the other hand, coupling reaction with 3,4,6-tris-*O*-*tert*-butyldiemthylsilyl-1,2-anhydro-α-D-galactopyranose (**15**)[7] and **5** using *t*-BuOK as a base gave no coupling products (Table 1). It is assumed that steric hindrance between the TBS group on the 4′-position and enolate **5** might prevent the approach of **5** to the anomeric position of **15**.

In summary, we have confirmed an efficient biomimetic route to an important bioactive substance controlling nyctinasty, that is important for the development of synthetic probes for bioorganic study of nyctinasty.

This work was financially supported by the Ministry of Education, Culture, Sports, Science and Technology, Japan Grant-in-Aid for Scientific Research (No. 15681013).

References

1 M. Ueda and S. Yamamura, *Angew. Chem., Int. Ed.*, **39**, 1400 (2000).
2 T. Sugimoto, Y. Wada, S. Yamamura, and M. Ueda, *Tetrahedron*, **57**, 9817 (2001).
3 T. Sugimoto, T. Fujii, Y. Idutu, S. Yamamura, and M. Ueda, *Tetrahedron Lett.*, **45**, 335 (2004).
4 H. Shigemori, N. Sakai, E. Miyoshi, Y. Shizuri, and S. Yamamura, *Tetrahedron Lett.*, **30**, 3991 (1989).
5 M. Ueda, Y. Sawai, and S. Yamamura, *Tetrahedron*, **55**, 10925 (1999).
6 M. Bouktaib, A. Atmani, and C. Rolando, *Tetrahedron Lett.*, **43**, 6263 (2002); K. Tatuta and K. Toshima, *Chem. Rev.*, **93**, 1503 (1993).
7 R. L. Halcomb and S. J. Danishefsky, *J. Am. Chem. Soc.*, **111**, 6661 (1989).
8 S. Sato, S. Sumita, Y. Kanda, and Y. Sasaki, *Tetrahedron Lett.*, **33**, 7381 (1992).
9 A. Wisniewski, J. Madaj, E. Skorupowa, and J. Sokolowski, *J. Carbohydr. Chem.*, **13**, 873 (1994).
10 S. Velarde, J. Urbina, and M. R. Pena, *J. Org. Chem.*, **61**, 9541 (1996).
11 M. Ueda, Y. Sawai, and S. Yamamura, *Tetrahedron Lett.*, **40**, 3757 (1999).

Published on the web (Advance View) July 5, 2004; DOI 10.1246/cl.2004.976