Pergamon

Tetrahedron Letters, Vol. 38, No. 36, pp. 6411-6414, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01483-4

The New Observation of Intramolecular Acyl Transfer from Aglycon to Sugar of *C*-Glycoside. The Regioselective and Single Step Acylation of 2'-Hydroxyl Group of Free *C*-Glucopyranoside.

Man Ki Park*, Jeong Hill Park, Sool Yeon Cho, Young Geun Shin, Jae-Kyung Jung and Young-Ger Suh*

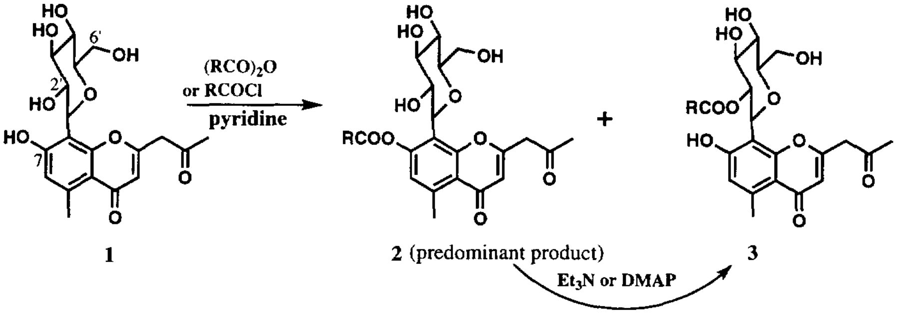
College of Pharmacy, Seoul National University, San 56-1, Shinrim-Dong,
Kwanak-Gu, Seoul 151-742, Korea

Abstract: A new intramolecular acyl transfer from aglycon to sugar moiety in *C*-glucopyranoside has been observed. This unusual acyl transfer reaction has been extended to the regioselective and direct acylations of 2'-hydroxyl group of free *C*-glucopyranoside and one step syntheses of four natural *C*-glycosylchromones from aloesin glucopyranoside have also been achieved by this method.

Over recent years *C*-glycosides have been the subject of considerable interest in carbohydrate chemistry including *C*-glycosylation as well as enzymatic and metabolic chemistry.[1] More recently, selective acylation of secondary hydroxyl groups of *C*-glycoside has emerged as a focus of carbohydrate chemistry due to its versatile synthetic utilities in a wide variety of the new *C*-glycosyl chromones[2] and flavonoids.[3] However, selective acylation of the secondary hydroxyl groups of free glycoside without prior protection of primary hydroxyl group has not yet been reported in spite of its significant synthetic utilities.[4]

We have been working on the selective acylations of 2'-hydroxyl group of the *C*-glucopyranoside for the efficient syntheses of the diverse 2'-*O*-acylated *C*-glucosylchromones which possess the potentially propound effects[5] on many cellular events such as proliferation, macromolecular synthesis, cell membrane transport and immune cell signal transfer. In this connection, we have developed an unique intramolecular acyl transfer from the phenolic hydroxyl group of aglycon to the 2'-hydroxyl group of sugar moiety in *C*-glucopyranoside. To the best of our knowledge, only few intramolecular acyl migrations in carbohydrate have been reported.[4c,6] Herewith we describe the first regioselective acylation of 2'-hydroxyl group of glucopyranoside with the various acyl groups in presence of free primary and secondary hydroxyl groups *via* intramolecular acyl transfer from aglycon to sugar moiety which can be importantly utilized in wide range of carbohydrate chemistry.

We have initially observed that reaction of the free aloesin **1** with acyl halide or acid anhydride for the preliminary protection of 6'-hydroxyl group prior to acylation of 2'-hydroxyl group affords 7-phenolic hydroxy acylated product **2** along with a small amount of the unexpected 2'-acyloxy product **3**[7] as shown in Scheme 1. However, the 7-acyloxy product **2** could be efficiently converted to the 2'-acyloxy product **3** by treatment with triethylamine or DMAP as a consequence of intramolecular acyl transfer. Thus, we have intensively investigated this unusual intramolecular acyl transfer in an attempt to develop a new direct and regioselective acylation of 2'-hydroxyl group of free glucopyranoside. After examination of various reaction conditions, 2'-hydroxyl group of the free aloesin **1** could be selectively acylated in a single step without prior protection of any other hydroxyl groups.



Scheme 1

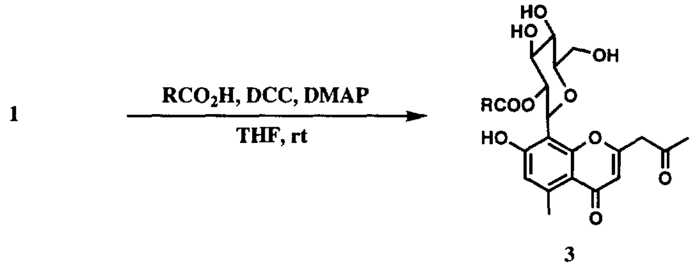
The free aloesin **1** was reacted with the corresponding carboxylic acids (1.5 eq.) in THF in the presence of DCC (2.0 eq.) and DMAP (0.5 eq.). The reaction mixture was stirred for 35 to 50 hours at room temperature and worked up by normal procedure. The acylation products were isolated by flash column chromatography on silica gel with a mixture of chloroform and methanol (8 : 1).

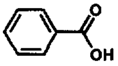
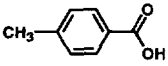
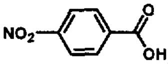
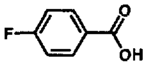
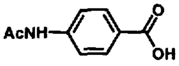
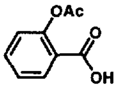
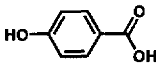
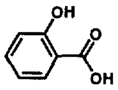
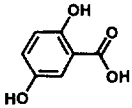
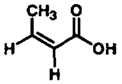
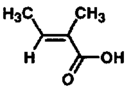
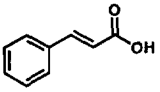
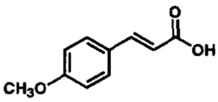
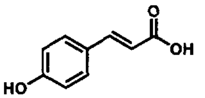
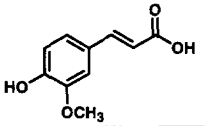
Table 1 illustrates the selective acylations of 2'-hydroxyl group of aloesin with various carboxylic acids. All reactions proceeded smoothly under the standard reaction conditions to provide the 2'-acylaloesins as only products in modest or good yields. The acyl transfer has been found to be successful with various carboxylic acids such as alkanoic, aromatic and conjugated acids regardless of their substitution patterns. It is noteworthy that acylations with benzoic (entry 8-10) and cinnamic acids (entry 15, 16) possessing free phenolic hydroxyl groups provide exclusively the 2'-*O*-acylated products. Especially, the single step syntheses of four natural *C*-glucopyranosides 2'-*O*-tigloylaloesin[2a] (entry 12), 2'-*O*-*p*-methoxycoumaroylaloesin[2b] (entry 14), aloeresin A (entry 15) and 2'-*O*-feruloylaloesin[2c] (entry 16) from aloesin have been achieved as preliminary attempts to investigate the potentiality of this method. The excellent regioselective acyl transfer is likely due to the favorable geometry between 2'-hydroxyl group of sugar and 7-phenolic hydroxyl group of aglycon and the labile acyl group of 7-phenolic hydroxyl seems to be an additional benefit for the facile acyl transfer.

In conclusion, an unusual regioselective acylation of 2'-hydroxyl group of free *C*-glucopyranoside has been observed as the first example of intramolecular acyl transfer form aglycon to sugar moiety of glycoside. This useful reaction has been also extended to the general synthetic route for the direct regioselctive acylation of the free *C*-glucopyranosides. Currently, the detailed studies on scope and applications of this procedure as well as expansion to other general and regioselective reaction of both *C* and *O*-glycosides are in progress and the successful results will be forthcoming.

Acknowledgement: This work was supported by the Ministry of Science and Technology (HAN-project) and Research Center for New Drug Development of Seoul National University, Korea.

Table 1. Regioselective acylation[a] of 2'-hydroxy group of the free aloesin glucopyranoside.



Entry	Acid(RCO$_2$H)	Time(h)	Yield[b,c](%)
1	CH$_3$COOH	18	91.7
2		48	80.2
3		48	82.5
4		48	71.1
5		48	66.4
6		48	64.9
7		48	57.2 (89.6)
8		36	48.0 (89.3)
9		48	55.6 (92.4)
10		48	16.7 (90.3)
11		40	75.2
12		40	70.8
13		36	74.7
14		36	72.6
15		36	66.8 (94.1)
16		36	59.1 (88.3)

a. All reactions were carried out by standard procedure.

b. Isolated yield. Numbers in parentheses indicate isolated yields based on recovered starting material.

c. Structures of all acylation products were fully characterized by spectroscopic methods (IR, ^{1}H and ^{13}C-NMR and Mass spectrometry.)

REFERENCES AND NOTES

1. Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545-8599.
2. a) Conner, J. M.; Gray, A. I.; Reynolds, T.; Waterman, P. G. *Phytochemistry* **1990**, *29*, 941-944.
   b) Mebe, P. P. *Phytochemistry* **1987**, *26*, 2646-2647.
   c) Gramatica, P.; Monti, D.; Speranza, G.; Manitto, P. *Tetrahedron Lett.* **1982**, *23*, 2423-2424. Makino, K.; Yagi, A.; Nishioka, I. *Chem. Pharm. Bull.* **1974**, *22*, 1565-1570. Speranza, G.; Martignoni, A.; Mantto, P. *J. Nat. Prod.* **1988**, *51*, 588-590.
   d) Conner, J. M.; Gray, A. I.; Reynolds, T.; Waterman, P. G. *Phytochemistry* **1989**, *28*, 3551-3553.
   e) Speranza, G.; Dada, G.; Lunazzi, L.; Gramatica, P.; Manitto, P. *Phytochemistry* **1986**, *25*, 2219-3333.
   f) Speranza, G.; Gramatica, P.; Dada, G.; Manitto, P. *Phytochemistry* **1985**, *24*, 1571-1573.
3. Franz, G.; Grun, G. *Planta Med.* **1983**, *47*, 131-140.
4. For selective acylations of the secondary hydroxy group of *O*-glycosides, see:
   a) Williams, J. M.; Richardson, A. C. *Tetrahedon* **1967**, *23*, 1369-1378.
   b) Pulido, R.; Gotor, V. *Carbohydr. Res.* **1994**, *252*, 55-68 and references cited therein.
   c) Haines, A. H.: Relative Reactivities of Hydroxyl Groups in Carbohydrates. In *Advances in Carbohydrate Chemistry and Biochemistry*; Tipson, R. S.; Horton D. Eds.; Academic Press: New York, 1976; vol 33, pp. 101-107.
   d)Slife, C. W.; Nashed, M. A.; Anderson, L. *Carbohydr. Res.* **1981**, *93*, 219-230.
5. Winters, W. D.: Proceedings of the International Congress of Phytotherapy *Phytotherapy Research* **1993**, *7* (Special Issue), S1-S72.
6. a) Tsuda, Y.; Yoshimoto, K. *Yuki Gosei Kagaku Kyokaishi* **1984**, *42*, 479-492.
   b) Wolfrom, M. L.; Szarek, W. A.: Esters. In *The Carbohydrates*; Pigman W; Horton, D. Eds.; Academic Press: New York, 1972; pp. 217-235.
7. It turned out that the 2'-acyloxy product **3** was formed by intramolecular acyl transfer instead of direct acylation of 2'-hydroxyl group.

(*Received in Japan* 29 *May* 1997; *revised* 15 *July* 1997; *accepted* 18 *July* 1997)