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$Sc(OTf)_3$-CATALYZED *C*-GLYCOSYLATION OF β-DIKETONES. A FACILE ACCESS TO USEFUL PRECURSORS OF HETEROAROMATIC *C*-GLYCOSIDES

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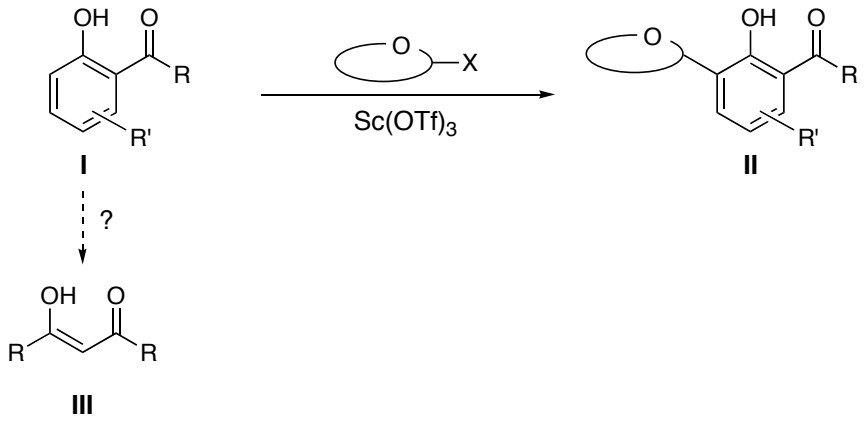
Abstract – Scandium tris(triflate) efficiently catalyzes *C*-glycosylation of β-diketones with glycosyl acetate. Elaboration of the β-diketo moiety in the resulting *C*-glycosides to heterocycles provides a flexible route to the *C*-nucleoside analogs.

INTRODUCTION

C-Nucleosides constitute a class of compounds containing a heterocycle connected to a sugar through a C–C bond, which is hydrolytically and enzymatically stable in contrast to the glycoside bond of the usual *N*-nucleosides. Due to significant antiviral and antitumor activities exhibited by some of the members, considerable synthetic efforts have been devoted to these natural products and their analogs.[1] A general synthetic strategy involves the initial installation to a sugar with a simple unit that serves as the progenitor of the desired heterocycle. β-Diketo moiety as the C(1) substituent is among the useful progenitors, from which various heterocycles could be derived. However, despite many different methods for *C*-glycosylation of malonate esters and β-keto esters,[2] only a few methods are available for the reaction of β-diketone derivatives.[3]

We previously discovered some prominent features of $Sc(OTf)_3$ as the promoter for *C*-glycosylation of phenol derivatives.[4,5] Of note, it catalyzes even the reaction of phenols (**I**) possessing a carbonyl functionality at the *ortho* position, which had been ranked as poor glycosyl acceptor. By analogy to the structure of such phenols (Scheme 1), we were interested in the possibility of *C*-glycosylation of β-diketone derivatives under $Sc(OTf)_3$ catalysis.

This paper is dedicated to the memory of Professor Kenji Koga.



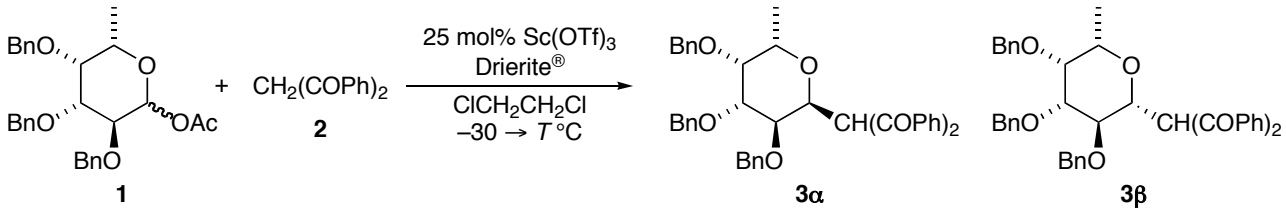
Scheme 1.

In this communication, we describe a facile procedure for the *C*-glycosylation of β-diketones by utilizing $Sc(OTf)_3$ as catalyst. Utility of the resulting *C*-glycosides as the precursor to *C*-nucleoside derivatives is also illustrated with several examples.

RESULTS AND DISCUSSION

As the first set of experiments, we examined the reactions of 1,3-diphenylpropane-1,3-dione (**2**) (3 mol) and acetate (**1**) (1 mol) with 25 mol% of $Sc(OTf)_3$ (Table 1). Compounds (**1**) and (**2**) were mixed with the catalyst and Drierite® in dichloroethane at –30 °C, and the mixture was allowed to warm up.[6]

Table 1. Reactions of fucosyl acetate (**1**) and 1,3-diphenylpropane-1,3-dione (**2**).



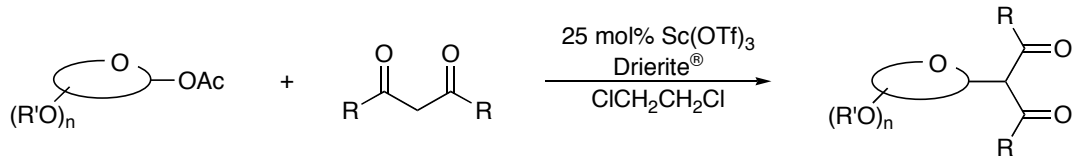
Run	*T* (°C)	Time (h)[a]	Yield (%)	α/β
1	–25[b]	5	84	10/1
2	+5[c]	11	89	2/1
3	+15[d]	31	72	1/5

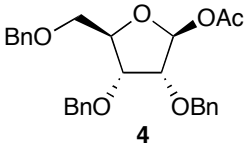
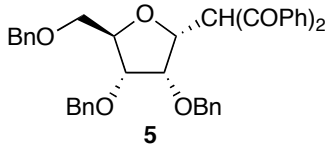
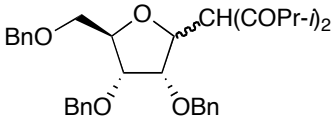
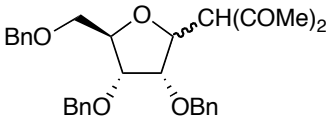
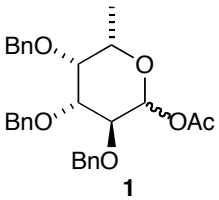
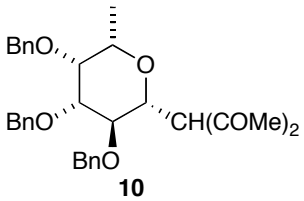
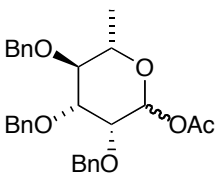
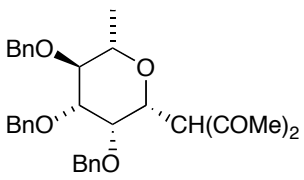
a) Reaction time at *T* °C. b) The reaction was warmed to –25 °C for 5 min. c) The reaction was warmed to +5 °C for 1.5 h. d) The reaction was warmed to +15 °C for 0.5 h.

TLC-analysis showed consumption of **1** at –25 °C (5 h), and quenching gave the desired *C*-glycoside (**3**) in 84% yield in the α/β-ratio 10/1. The isomers could be separated by silica-gel chromatography, and the anomeric stereochemistries were assigned by ^{1}H NMR spectra; the $J_{H1,H2}$ is 0 Hz for **3α**, and 9.4 Hz for **3β**, and n.O.e. was observed between H1 (5.18 ppm) and H6 (1.24 ppm) in **3α**. NMR spectrum also showed that the β-diketo moiety entirely exists as the keto form for each isomer, which indicates that steric congestion around the *C*-glycoside bond hinders the molecule to adopt the planar enol form.[7]

α-Glycoside (**3α**), preferentially formed at lower temperature, underwent gradual isomerization to the β-isomer, as the reaction temperature was raised (runs 2 and 3). The α/β-ratio was reversed, reaching to 1/5 at 15 °C, which implied the existence of equilibration between the isomers. Indeed, the isolated β-isomer (**3β**) underwent partial isomerization, upon treatment with diketone (**2**) (2 equiv.) and $Sc(OTf)_3$ (25 mol%) [dichloroethane, Drierite®, 15 °C, 18 h], giving 1:5-mixture of **3α** and **3β**.

Table 2. *C*-Glycosylations of β-diketones.[6]



Run	Glycosyl acetate	β-diketone [Conditions]	Product	Yield (%), α/β
1	 **4**	$PhCOCH_2COPh$ (**2**) (3 equiv.) [–30 °C→10 °C for 5 h][c]	 **5**	92%, α only
2	**4**	*i*-$PrCOCH_2COPr$-*i* (**6**) (3 equiv.) [–30 °C→25 °C for 6.5 h, and 23 h at 25 °C][d]	 **7**	80%, α/β = 1.1/1
3[a]	**4**	$MeCOCH_2COMe$ (**8**) (2 equiv.) [–30 °C→20 °C for 4 h, and 11 h at 20 °C][e]	 **9**	91%, α/β = 1.2/1
4[a]	 **1**	$MeCOCH_2COMe$ (**8**) (2 equiv.) [–30 °C→–5 °C for 1 h]	 **10**	98%, α/β = 1/18
5[b]	 **11**	$MeCOCH_2COMe$ (**8**) (2 equiv.) [–30 °C→–5 °C for 1 h]	 **12**	73%, α/β = 1/15

a) 15 mol% of $Sc(OTf)_3$. b) Molecular sieves 3A was used in place of Drierite®. Use fo Drierite® gave lower yield. c) The α/β-ratio altered to 2/1 by warming the raction to 60 °C followed by stirring for 2 h. d) Quenching the reaction at early stage [–30 °C→10 °C, 1 h, 22% conversion of **4**] gave **7α** as a single isomer. e) Quenching the reaction at early stage [–30 °C→–5 °C, 1 h, 27% conversion of **4**] gave a 28/1-mixture of the isomers.

Table 2 shows that the present *C*-glycosidation method is applicable to various combinations of glycosyl acetate and β-diketone.[6,8] Though the final α/β-ratio depends on their structures, a general trend for isomerization decreases with the bulkiness of the substituents on the carbonyl carbons in the β-diketo moiety (R).

The ribose-derived glycosyl acetate (**4**) cleanly reacted with diketone (**2**) to give, by quenching the reaction at 10 °C, α-*C*-glycoside (**5α**) as a single isomer in 92% yield (run 1). β-Glycoside was not observed even after prolonged reaction time at 10 °C, while heating of the reaction at 60 °C caused isomerization of **5α** to give, after 2 h, 2:1-mixture of the α- and β-glycosides. In contrast, the reactions of ribosyl acetate (**4**) with 2,6-dimethylheptane-3,5-dione (**6**) and acetylacetone (**8**) led to isomerization of the initially formed α-glycoside bond at/below room temperature (runs 2 and 3). The α/β-ratio reached almost unity during the glycosyl donor (**4**) was thoroughly consumed, though the α-glycosides predominated at early stages — for the reaction of diketone (**6**), only the α-glycoside was obtained at the 22% conversion of **4** (10 °C), while for diketone (**8**), the α/β-ratio was 28 /1 at the 27% conversion of **4** (–5 °C).

Also in the reaction of acetylacetone (**8**) with fucosyl acetate (**1**) or rhamnosyl acetate (**11**), the glycoside formation and its isomerization concurrently proceeded (runs 4 and 5). β-Glycosides predominated when the quenching was just done when the glycosyl donors were thoroughly consumed.

The α/β isomerization probably takes place by ring opening–reclosure at the C(1)–oxygen bond *via* the acyclic intermediate (**A**) and/or heterolytic disconnection–recombination of the glycoside bond *via* the ion pair (**B**) (Figure 1).[9] Considering the planarity of the β-diketo moiety in **A** and **B**, sever steric interference would be exerted between the sugar moiety and the substituent R in the transition states leading to such intermediates. This could account for the observed tendency of the isomerization.

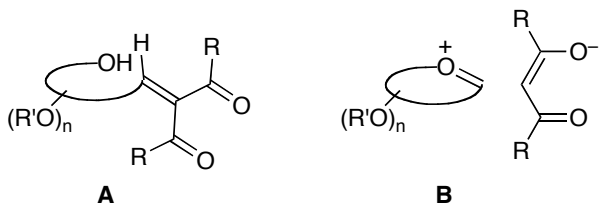


Figure 1. Isomerization of the anomeric stereochemistry.

It is worthwhile to note the X-Ray structure and behavior of β-*C*-glycoside (**10β**) obtained by the reaction of **8** with **1** (run 4 in Table 2). In this case, the resulting β-glycoside (**10β**) existed in both keto and enol forms (keto/enol = 1.2/1), which was different from the *C*-glycosides of other runs in Table 1 and Table 2.[7] Although *C*-glycosides (**10α**) and (**10β**) could not be separated by silica gel chromatography, recrystallization of the mixture gave a pure sample of **10β** in keto form (**10β-keto**).[10] This compound,

at least in the crystal lattice, adopts the conformation in which the π-faces of the carbonyl groups are not coplanar [the angle between dipoles defined by both carbonyl groups is 141.0°], unfavorable to the isomerization.[11] Furthermore, NMR spectral analyses exhibited that the energy barrier of tautomerization is high. When a solution of **10β-keto** in $CDCl_3$ (NMR tube) was allowed to stand at room temperature, the keto/enol-ratio reached only 13/1 in two days and 2.0/1 in two weeks.

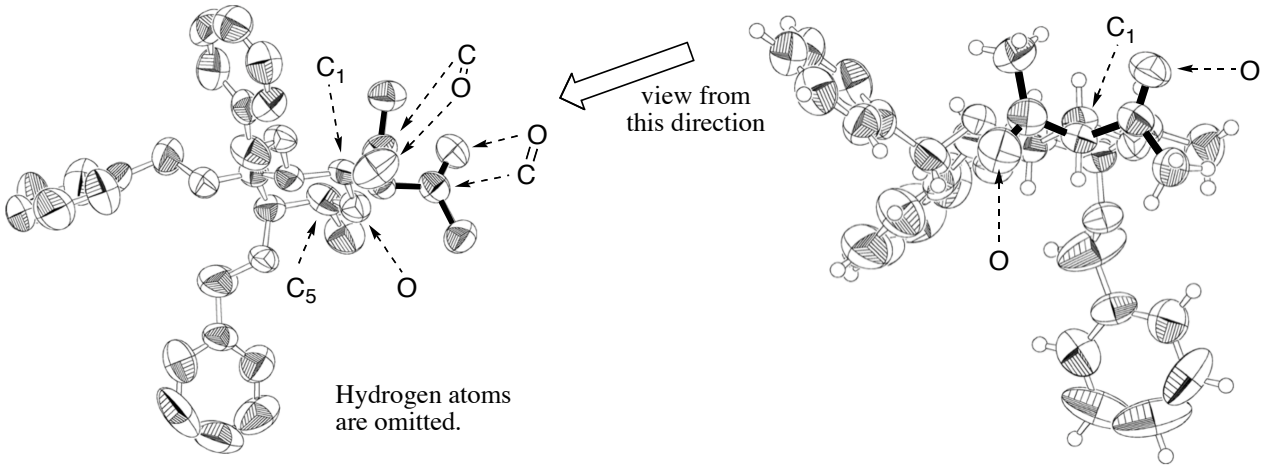
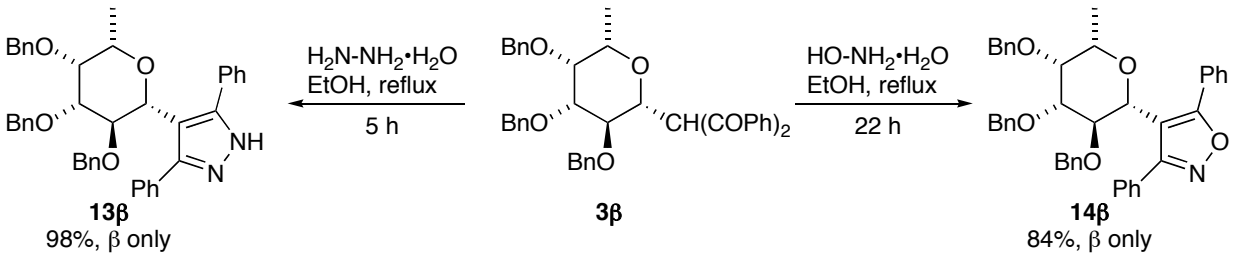


Figure 2. *ORETP* drawing of **10β-keto** (β-diketone framework is drawn by bold lines).

The *C*-glycosides were exploited to standard reactions for heterocyclic construction from β-diketone in order to examine their utility in the synthesis of *C*-nucleoside analogs.

Scheme 2 shows conversions of *C*-fucosylated diketone (**3β**) to the pyrazole and isoxazole derivatives. Diketone (**3β**) was treated with hydrazine monohydrate or *N*-hydroxylamine hydrochloride in refluxing ethanol to give the desired heterocyclic *C*-glycosides (**13β**) and (**14β**) in high yields. Both reactions proceeded stereospecifically, and none of the α-isomers were detected.



Scheme 2. Reaction of *C*-fucosylated diketone (**3β**) with hydrazine or hydroxylamine.

Examples of the heterocycles derived from *C*-glycosyl β-diketones are shown in Figure 3. Pyrazole and isoxazole formations were carried out by the similar methods as above, and pyrazolo[1,5-*a*]pyrimidine system was constructed by condensation with 3-amino-5-phenylpyrazole in acetic acid and ethanol.[12]

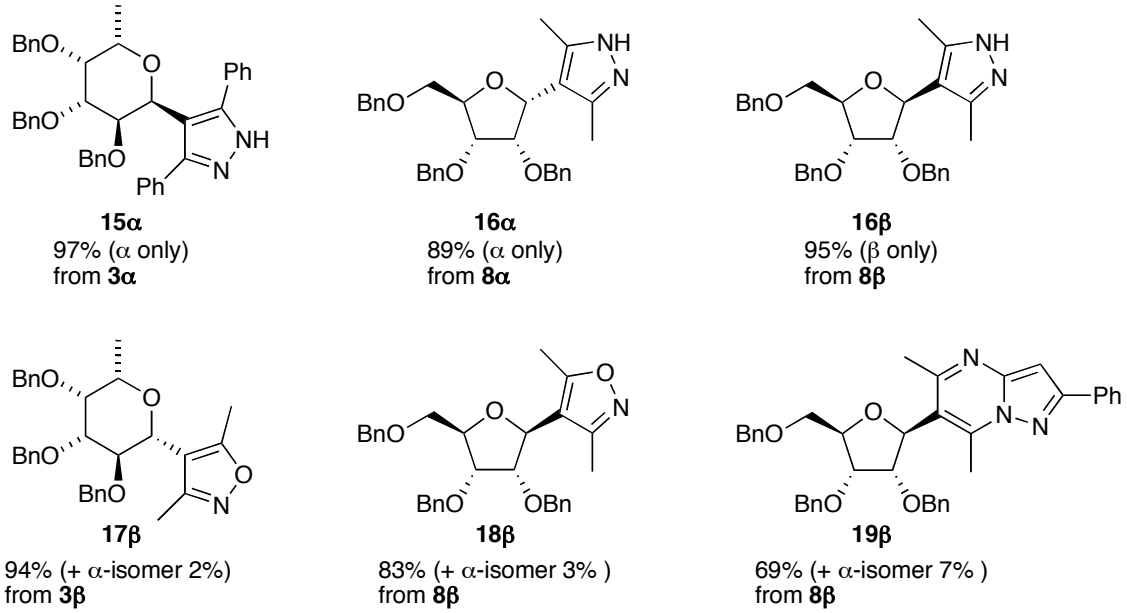


Figure 3. Selected examples of heterocyclic construction form *C*-glycosyl β-diketones.

Pyrazoles (**15α**, **16α**, and **16β**) were obtained as single isomers as expected, while small quantities of the undesired isomers concomitantly formed in the synthesis of isoxazoles (**17β**, **18β**) and pyrazolopyrimidine (**19β**). Since these heteroaromatic *C*-glycosides, once formed, were configurationally stable under the reaction conditions, formation of the undesired isomers could be attributed to the isomerization of the starting material during the reactions. Although the anomeric stereochemistry is not always retained perfectly in the formation of the heterocyclic aglycon, these results demonstrate that the *C*-glycosyl β-diketones, obtained by the present *C*-glycosylation method, could serve as the useful precursors to a variety of *C*-nucleoside analogs.

In summary, $Sc(OTf)_3$ catalyzed *C*-glycosylation of β-diketones in high yields, and the β-diketone moiety in the *C*-glycosides could be easily converted to heterocyclces by conventional methods. Because of its facility and efficiency, the present method will find utilities in the synthesis of *C*-nucleoside analogs of biological interest.

ACKNOWLEGEMENTS

We thank Dr M. Bando, Otsuka Pharmaceutical Co., for X-Ray analysis.

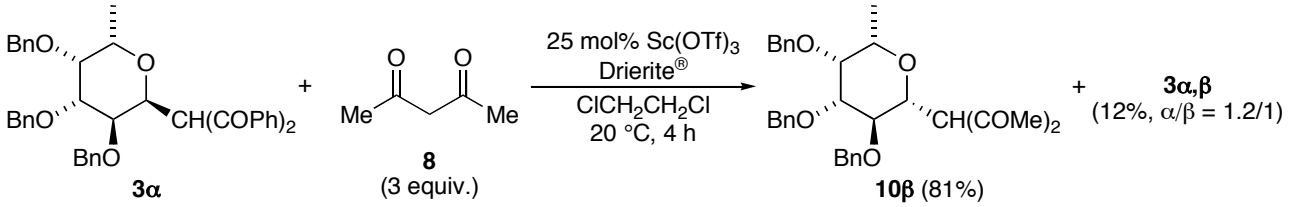
REFERENCES AND NOTES

1. (a) C. Simons, 'Nucleoside Mimics Their Chemistry and Biological Properties,' Gordon and Breach Science Publishers, Australia, Canada, 2001. H. D. M. Postema, '*C*-Glycoside Synthesis,' CRC Press, London, 1995. (b) Q. Wu and C. Simons, *Synthesis*, 2004, 1533. U. Hacksell and G. D.

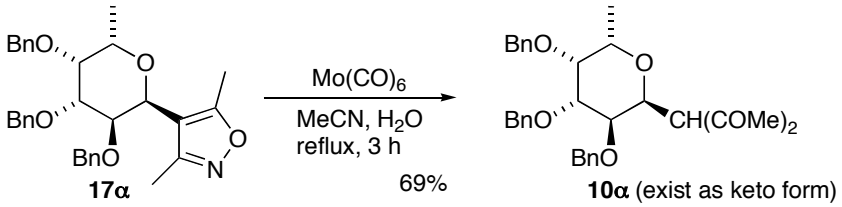
Daves, Jr, *Prog. Med. Chem.*, 1985, **22**, 1.

2. Examples of *C*-glycosylation of malonate esters and β-keto esters, (a) the reactions with glycosyl halide or its equivalent: H. Ohrui and J. J. Fox, *Tetrahedron Lett.*, 1973, 1951. S. Hanessian and A. G. Pernet, *Can. J. Chem.*, 1974, **52**, 1266. J. Gervay and M. J. Hadd, *J. Org. Chem.*, 1997, **62**, 6961. P. Allevi, M. Anastasia, P. Ciuffreda, A. Fiecchi, and A. Scala, *J. Chem. Soc., Chem. Commun.*, 1987, 101. A. O. Stewart and R. M. Williams, *J. Am. Chem. Soc.*, 1985, **107**, 4289. P. Allevi, M. Anastasia, P. Ciuffreda, A. Fiecchi, and A. Scala, *J. Chem. Soc., Chem. Commun.*, 1988, 57. (b) Knoevenagel-type condensation with a lactol: M. Yamaguchi, A. Horiguchi, C. Ikeura, and T. Minani, *J. Chem. Soc., Chem. Commun.*, 1992, 434. (c) Lewis acid or palladium mediated reactions of glycal derivatives: S. Yougai and T. Miwa, *J. Chem. Soc., Chem. Commun.*, 1983, 68. M. Brakta, P. Lhoste, and D. Sinou, *J. Org. Chem.*, 1989, **54**, 1890.
3. Among the methods cited in references 2, those in (c) are also valid to β-diketones. It is noteworthy that the reaction of a seemingly most simple substrate combination, *i.e.* glycosyl halide (or its equivalent) and β-diketone (or its anion equivalent), has been not reported so far. For *O*-glycosylation of β-diketones, see: D. Carriere, S. J. Meunier, F. D. Tropper, S. Cao, and R. Roy, *J. Mol. Catal. A*, 2000, **154**, 9.
4. A. Ben, T. Yamauchi, T. Matsumoto, and K. Suzuki, *Synlett*, 2004, 225.
5. For reviews on $Sc(OTf)_3$ in organic synthesis, see: S. Kobayashi, *Eur. J. Org. Chem.,* 1999, 15. S. Kobayashi, '*Lewis Acids in Organic Synthesis*,' Vol. 2, ed. by H. Yamamoto, Wiley-VCH, Weinheim, 2000, p. 883.
6. Typical experimental procedure for the *C*-glycosylation of β-diketones is described for the synthesis of **9α** and **9β** (run 3 in Table 2): To a stirred mixture of powdered Drierite® (1.6 g), $Sc(OTf)_3$ (109 mg, 0.221 mmol), acetylacetone (**8**) (312 mg, 3.12 mmol) in 1,2-dichloroethane (20 mL) was added ribosyl acetate (**4**) (688 mg, 1.49 mmol) in 1,2-dichloroethane (10 mL) at –30 °C. After gradual warming to 20 °C during 4 h, the stirring was continued for 11 h. The mixture was poured into sat. aq. $NaHCO_3$ solution, and filtrated through a Celite pad. The products were extracted with EtOAc, and the combined organic extracts were washed with brine, and dried over Na_2SO_4. Removal of the solvents in vacuo and purification by silica gel column chromatography (hexane/EtOAc = 3/1) afforded α-*C*-glycoside (**9α**) (365 mg, 49%) as a colorless oil {$[\alpha]^{32}_D$ +176° (*c* 1.37, $CHCl_3$)} and β-*C*-glycoside (**9β**) (314 mg, 42%) as colorless needles [mp 90–91 °C (hexane–ethyl acetate)].
7. The *C*-glycosides in Table 1 and Table 2, except for **10β**, exist as the keto form.
8. The reaction did not proceed with β-diketone derivatives possessing a substituent at the α position.
9. Treatment of *C*-glycoside (**3α**) with acetylacetone and $Sc(OTf)_3$ afforded **10β**. This shows that, in the course of the *C*-glycosidation, the ion pair (**B**) could be generated from the initially formed

C-glycoside and involved in the α/β isomerization. However, the pathway through the acyclic intermediate (**A**) cannot be excluded.



10. A pure sample of **10α** was obtained from isoxazol (**17α**) as shown below, and its structure was unambiguously determined. Isoxazol (**17α**) was obtained as the minor isomer in the synthesis of isoxazol (**17β**) and easily separable from **17β** (see Figure 3).



11. For the conformation of β-diketone derivatives possessing a bulky substituent at the α position, see: J. Emsley and N. J. Freeman, *J. Mol. Structure*, 1987, **161**, 181. M. Moreno-Manas, J. F. Piniella, A. Alvarez-Larena, N. Galvez, M. E. Lloris, J. Marquet, A. C. Siani, and G. Germain, *Tetrahedron*, 1992, **48**, 3611.
12. D. R. Compton, S. Sheng, K. E. Carlson, N. A. Rebacz, I. Y. Lee, B. S. Katzenellenbogen, and J. A. Katzenellenbogen, *J. Med. Chem.*, 2004, **47**, 5872.