Reactions of 2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl Acetate with Enol Silyl Ethers Catalyzed by Tin(IV) Chloride. Regiochemical Features[1)]

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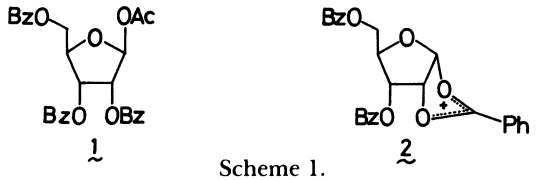
In condensation reactions of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl acetate with various kinds of enol silyl ethers in the presence of tin(IV) chloride, the acetate behaves as an ambident electrophile to give two types of products arising from nucleophilic attack of the enol ether on C-1 carbon of the ribose derivative and on carbonyl carbon of 2-benzoyloxyl group, depending remarkably on the enol silyl ethers.

Much attention has recently been attracted on *C*-glycosyl nucleosides because of their important antibiotic properties and potent anticancer and antiviral activities.[2)] It is quite important and valuable to prepare them and their structural analogues easily, from the viewpoint to research for higher bioactive compounds. Some of synthetic studies have already been described on formycin,[3)] showdomycin,[4)] pyrazomycin,[5)] and their analogues.[6)] Although they had few synthetic relation to each other, most of these syntheses have a common strategy which involves an introduction of a cyano, aryl, or other nucleophilic moieties to C-1 position of 1-halo- or 1-acetoxy-β-D-ribofuranose derivatives to construct appropriate heterocycles. From this viewpoint, a key reaction is to make the new carbon-carbon bond between C-1 carbon of ribose and various nucleophilic reagents. It has been well documented that 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl acetate (**1**), an easily accessible material, generates an electrophilic species, 1,2-*O*-benzylidene oxonium ion (**2**), by the aid of either appropriate bases or acids through neighboring participation of C-2 benzoyloxyl group. The resulting electrophile **2** has two reaction sites for nucleophiles; C-1 carbon and carbonyl carbon of 2-benzoyloxyl group. Under basic conditions C–C bond formation between **2** and nucleophiles takes place at C-1 and/or 2-benzoyloxyl carbonyl,[6c,7)] whereas reactions with olefins including 1-trimethylsiloxycyclohexene have been reported to proceed selectively on C-1 position in the presence of Lewis acid.[8)]

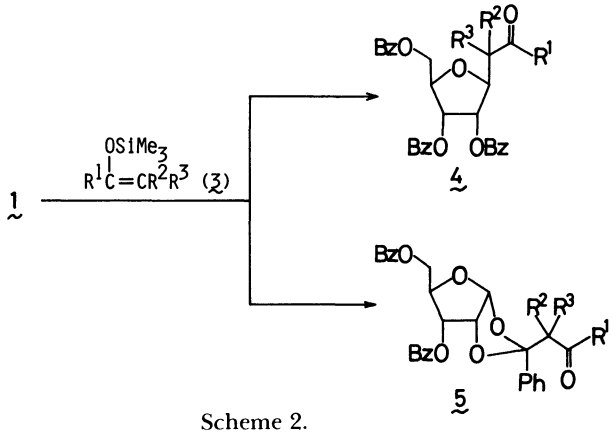
Based on such feature, we previously examined the use of a enol silyl ether for such purpose and reported synthesis of showdomycin which includes the C–C bond formation between **1** and 1,2-bis(trimethylsiloxy)-cyclobutene as a key step.[4a)] However, it has not been systematically studied what kind of enol silyl ethers react to form desired carbon-carbon linkages. In this paper we describe regiochemical features of the reaction between 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl acetate (**1**) and various kinds of enol silyl ethers, which disclose the scope and limitations to use enol silyl ethers for synthesis of *C*-nucleosides and their analogues.



Scheme 1.

Enol silyl ethers **3a—g** have been chosen as typical nucleophiles and their reactions with **1** have been studied under the influence of 1 equiv of tin(IV) chloride in dichloromethane at room temperature. On contrary to our expectation, the condensation reaction at C-1 position of **1** is not a general phenomenum even on using enol silyl ethers; some of them (**3e—g**) give the desired C-1 condensation products **4e—g**, whereas others (**3a—d**) are found to yield the products **5a—d** selectively arising from their nucleophilic attack on carbonyl carbon of 2-benzoyloxyl group[9)] under same reaction conditions.

As shown in the table, regiochemical results of the reaction are definitely determined by the kind of enol silyl ethers used and no regio-isomer could be detected in every case. According to these results, enol silyl

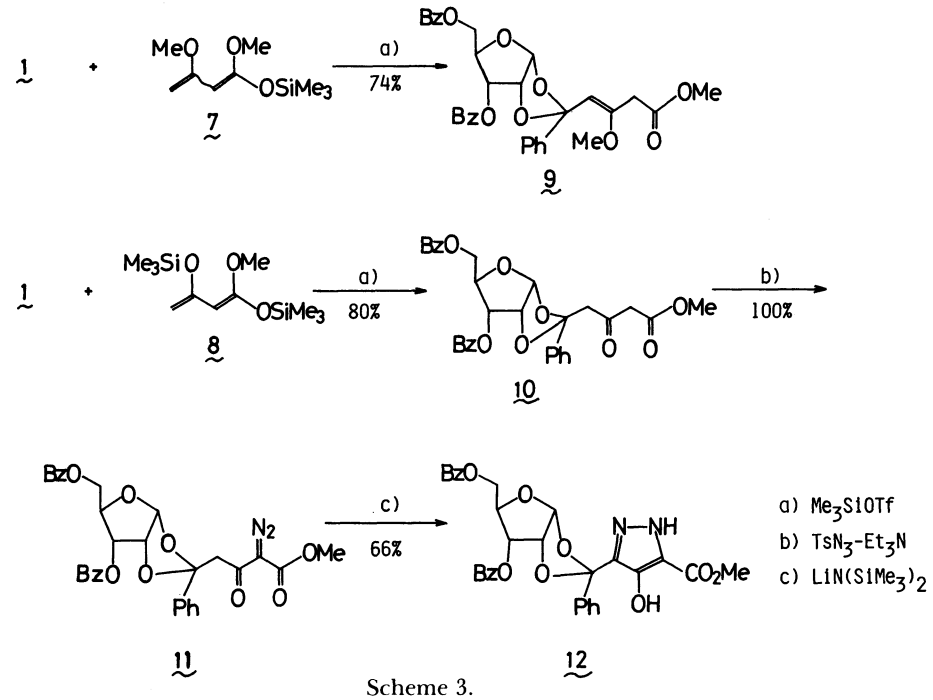


Scheme 2.

TABLE 1. REACTIONS OF 2,3,5-TRI-*O*-BENZOYL-D-RIBOFURANOSYL ACETATE **1** WITH ENOL SILYL ETHERS (**3**)

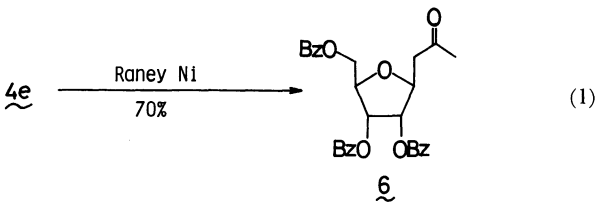
	Enol silyl ethers (**3**)			Reaction period/h	Yield/%[a)]	
	R^1	R^2	R^3		**4**	**5**
a	C_2H_5	H	CH_3	1.5	—	88
b	$(CH_3)_3C$	H	H	16	—	55
c[b)]	C_2H_5O	H	H	1	—	32
d	C_2H_5O	H	C_6H_5S	2	—	82
e	CH_3	H	C_6H_5S	1	83	—
f	$(CH_3)_3C$	H	C_6H_5S	2	45	—
g[c)]	$-(CH_2)_2-$		Me_3SiO	2	95	—
h[d)]	$-(CH_2)_4-$		H	1	95	—

a) Isolated yield. b) *t*-Butyldimethylsilyl ether was used. c) Taken from Ref 4a. d) Taken from Ref 8.



Scheme 3.

ethers seem to be classified into the following two categories. Those of usual acyclic ketones (**3a** and **3b**) and of esters (**3c** and **3d**) generally react on carbonyl carbon of 2-benzoyloxyl group to give the products of type **5**. On the other hand, in the case of enol ethers of ketones having α-hetero substituents (**3e**, **3f**, and **3g**), the reaction takes place selectively on C-1 site of **1** to afford the desired products **4e—g**. Thus, a site-determining influence of α-hetero substituent has now become very important from synthetic viewpoints of *C*-nucleosides. Enol silyl ethers of ketones bearing α-phenylthio group are quite useful for the introduction of 2-oxoalkyl group on C-1 position of **1** because the phenylthio group is easily removable by reduction. For example, α-phenylthio ketone (**4e**) gave the desulfurization product **6** in 70% yield on treatment with Raney nickel in boiling ethanol.



(1)

These regiochemical features have aroused a question whether there are any differences in actual nucleophilic species between these two types of enol silyl ethers. As reported already, tin(IV) chloride readily reacts with usual enol silyl ethers to afford the corresponding α-trichlorostannyl ketones,[10] which might act as real nucleophilic species in this case. In order to clarify such possibility, tin(IV) chloride was treated with **3a** in deuterochloroform at room temperature, and an immediate formation of the corresponding α-trichlorostannyl ketone was confirmed by ^1H NMR analysis of the reaction mixture. Further, treatment of the resulting solution with **1** led to the formation of **5a**.

In the cases of enol silyl ethers (**3e—g**), on the other hand, α-subsituents seem to prevent silyl/stannyl exchange, and the silyl ethers remain unchanged on exposure to tin(IV) chloride.

On the basis of these results, we wish to suggest the following points on the different behaviors observed here. On treatment with **1** in the presence of tin(IV) chloride, enol silyl ethers of usual acyclic ketones and of esters, *e.g.* **3a—d**, undergo silyl/stannyl exchange with tin(IV) chloride initially to yield α-stannyl ketones. Then, the resulting α-stannyl ketones act as nucleophiles to **1** to afford the corresponding **5a—d**. On the other hand, **3e—g** react as olefinic[8] or aromatic nucleophiles[11] in a usual Friedel-Crafts like manner to yield the desired C-1 condensation products **4e—g**.

However, other uncertain site-determining factors might also be involved in this type of reaction, considering an anomolous behavior of 1-trimethylsiloxycyclohexene which affords the condensation product of type **4**[8] irrespective of its facile silyl/stannyl exchange reaction with tin(IV) chloride.

Finally, in order to explore a simple synthetic route to pyrazomycin, we also examined the introduction of an acetoacetic ester moiety on C-1 position by using dienal ethers **7** or **8**. In the presence of trimethylsilyl triflate,[12,13] however, they react on C-2 benzoyloxyl group exclusively to yield **9** or **10**, although construction of requisite pyrazole ring can be efficiently performed through its diazo compound as shown in Scheme 3.

Experimental

General Procedures. IR spectra were taken on a Hitachi 260-10 spectrometer; absorptions are given in reciprocal centimeters. ^1H NMR spectra were recorded on a Hitachi R-24B (60 MHz) or a Varian EM-390 (90 MHz) spectrometer; chemical shifts (δ) are expressed in parts per million down-

field from internal tetramethylilane.

Column chromatography was performed on Wakogel C-200 or Florisil (mesh 100—200). All the reactions were carried out in an glass sealed tube with magnetic stirring bar under dry nitrogen.

Materials. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl in a recycling still immediately before use. Chlorotrimethylsilane, triethylamine, and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride. Acetonitrile and dichloromethane were distilled successively from phosphorus pentaoxide and potassium carbonate under nitrogen. 3-Trimetylsiloxy-2-pentene (**3a**), 3,3-dimethyl-2-trimethylsiloxy-1-butene (**3b**), 1-phenylthio-2-trimethylsiloxy-1-propene (**3e**), and 3,3-dimethyl-1-phenylthio-2-trimethylsiloxy-1-butene (**3f**) were prepared by the method of House.[14] 1-Ethoxy-1-(*t*-butyldimethylsiloxy)ethylene (**3c**)[15] and 1,3-bis(trimethylsiloxy)-1-methoxy-1,3-butadiene **8**[16] were prepared according to the reported procedure. 1-Ethoxy 2-phenylthio-1-trimethylsiloxyethylene (**3d**) and 1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene (**7**) were prepared by using THF instead of DME as a solvent in the method of House.[14]

Condensation of 2,3,5-Tri-O-benzoyl-D-ribofuranosyl Acetate (1) with Enol Silyl Ethers (3). 3-Trimethylsiloxy-2-pentene (3a): A mixture of the acetate **1** (75.1 mg, 0.15 mmol) and tin(IV) chloride (0.18 mmol) in dichloromethane (2 ml) was stirred for 5 min at room temperature, and the enol silyl ether **3a** (0.18 mmol) was added to the resulting solution. After stirring for 1.5 h, aq K_2CO_3 solution was added to the reaction mixture and was extracted with ether repeatedly. Organic layer was washed with satd. aq NaCl, dried over anhyd. Na_2SO_4, and concentrated to give an oil, which was separated by silica-gel column chromatography to give **5a** (95.3 mg, 88%) as an oil. Calcd for $C_{31}H_{30}O_8$: C, 70.18; H, 5.70%. Found: C, 69.72; H, 5.70%. **5a** could be separated into diastereomers **5a**$_1$ and **5a**$_2$ by column chromatography **5a**$_1$: IR (neat) 1730, 1715 cm^{-1}; NMR (60 MHz) (CCl_4) δ=0.87 (t, J=7 Hz, 3H), 0.99 (d, J=7 Hz, 3H), 2.21 (q, J=7 Hz, 2H), 2.93 (q, J=7 Hz, 1H), 3.40 (m, 1H), 4.17 (m, 2H), 4.76 (dd, J=9 and 5 Hz, 1H), 5.10 (dd, J=5 and 4 Hz, 1H), 5.90 (d, J=4 Hz, 1H), 7.30 (m, 11H), 7.84 (m, 4H). **5a**$_2$: IR(neat) 1730, 1715 cm^{-1}; NMR (60 MHz) (CCl_4) δ=0.94 (d, J=7 Hz, 3H), 0.97 (t, J=7 Hz, 3H), 2.36 (q, J=7 Hz, 2H), 2.90 (q, J=7 Hz, 1H), 3.45 (m, 1H), 4.18 (m, 2H), 4.70 (m, 2H), 6.05 (d, J=4 Hz, 1H), 7.30 (m, 11H), 7.78 (m, 4H).

In a similar manner, 3,3-dimethyl-2-trimethylsiloxy-1-butene (**3b**), 1-ethoxy-1-(*t*-butyldimethylsiloxy)ethylene (**3c**), and 1-ethoxy-2-phenylthio-1-trimethylsiloxyethylene (**3d**) gave the corresponding condensation products **5b—d**, and 1-phenylthio-2-trimethylsiloxy-1-propen (**3e**) and 3,3-dimethyl-1-phenylthio-2-trimethylsiloxy-1-butene (**3f**) gave **4e** and **4f**, respectively. **5b**: An amorphous oil; IR (Nujol) 1730, 1720 cm^{-1}; NMR(60 MHz) (CCl_4) δ=1.06 (s-like, 9H), 2.86 (s-like, 2H), 6.05 (d, J=4 Hz, 1H), 7.32 (m, 11H), 7.85 (m, 4H); Calcd for $C_{32}H_{32}O_8$: C, 70.58; H, 5.92%. Found: C, 70.74; H, 6.17%. **5c**: An amorphous oil: IR (Nujol) 1720 cm^{-1}; NMR (60 MHz) (CCl_4) δ=1.24 (t, J=7 Hz, 3H), 2.74 (s-like, 2H), 3.56 (m, 1H), 4.04 (q, J=7 Hz, 2H), 4.22 (m, 2H), 4.78 (dd, J=9 and 5 Hz, 1H), 5.20 (dd, J=5 and 4 Hz, 1H), 6.10 (d, J=4 Hz, 1H), 7.30 (m, 11H), 7.85 (m, 4H). **5d**: An amorphous oil: IR (Nujol) 1730, 1720 cm^{-1}; NMR (60 MHz) (CCl_4) δ=1.03 (t, J=7 Hz, 3×1/2H), 1.07 (t, J=7 Hz, 3×1/2H), 3.90 (q, J=7 Hz, 2×1/2H), 3.96 (q, J=7 Hz, 2×1/2H), 4.23 (m, 2H), 4.67 (s, 1×1/2H), 4.78 (s, 1×1/2H), 5.00 (m, 2H), 6.10 (d, J=4 Hz, 1×1/2H), 6.19 (d, J=4 Hz, 1×1/2H), 7.25 (m, 16H), 7.80 (m, 4H); Calcd for $C_{36}H_{32}O_9S$: C, 67.49; H, 5.03; S, 5.00%. Found: C, 67.40; H, 5.05; S, 4.91%. **4e**: An amorphous oil: IR (Nujol) 1730, 1715 cm^{-1}; NMR (60 MHz) (CCl_4) δ=2.17 (s, 3×5/9H), 2.27 (s, 3×4/9H), 3.75 (d, J=8 Hz, 1×4/9H), 3.92 (d, J=4 Hz, 1×5/9H), 4.50 (m, 4H), 5.68 (m, 2H), 7.25 (m, 14H), 7.85 (m, 6H); Calcd for $C_{35}H_{30}O_8S$: C, 68.84; H, 4.95; S, 5.25%. Found: C, 68.89; H, 5.15; S, 5.51%. **4f**: An amorphous oil: IR (Nujol) 1730, 1720 cm^{-1}; NMR (60 MHz) (CCl_4) δ=1.10 (m, 9H), 3.55 (m, 1H), 4.50 (m, 4H), 5.65 (m, 2H). 7.30; (m, 14H), 7.85 (m, 6H); Calcd for $C_{38}H_{36}O_8S$: C, 69.92; H, 5.56; S, 4.91%. Found: C, 70.03; H, 5.16; S, 5.15%.

Desulfuriztion of 4e. Raney nickel (W-2; 1.5 g) was added to a solution of **4e** (105.5 mg, 0.17 mmol) in ethanol (10 ml) and it was heated to reflux for 1 h. Filtration of the reaction mixture through Celite followed by removal of the solvent gave an oil, which was purified by column chromatography on silica gel to afford the desulfurization product **6** (61.6 mg, 70%). IR (Nujol) 1720 cm^{-1}; NMR (60 MHz) (CCl_4) δ=2.10 (s, 3H), 2.79 (d, J=7 Hz, 2H), 4.50 (m, 4H), 5.52 (m, 2H), 7.37 (m, 9H), 7.93 (m, 6H).

The Reaction of 1 with 1,3-Bis(trimethylsiloxy)-1-methoxy-1,3-butadiene (8). The acetate **1** (320.1 mg, 0.63 mmol) was dissoled in dichloromethane (2 ml) and trimethylsilyl triflate (0.80 mmol) was added to this solution at room temperature. After stirring for 5 min, the enol silyl ether **8** (1.0 mmol) was added. The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with satd. aq K_2CO_3 and was extracted several times with ether. The combined organic extracts were washed with satd. aq NaCl and dried over anhyd. Na_2SO_4. Removal of the solvent followed by column chromatography on silica-gel afforded **10** (282.1 mg, 80%) as an oil. IR (neat) 1730 cm^{-1}; NMR(90 MHz) ($CDCl_3$) δ=3.06 (s-like, 2H), 3.41 (s-like, 2H), 3.61 (m, 1H), 3.64 (s, 3H), 4.22 (dd, J=12 and 5 Hz, 1H), 4.45 (dd, J=12 and 4 Hz, 1H), 4.92 (dd, J=9 and 5 Hz, 1H), 5.26 (dd, J=5 and 4.5 Hz, 1H), 6.18 (d, J=4.5 Hz, 1H), 7.38 (m, 11H), 7.93 (m, 4H); Calcd for $C_{31}H_{28}O_{10}$: C, 66.42; H, 5.03%. Found: C, 66.31; H, 5.32%.

In a similar manner, 1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene (**7**)[17] gave the corresponding **9** as an oil in 74% yield. IR (neat) 1730 cm^{-1}; NMR (60 MHz) (CCl_4) δ=3.32 (s-like, 2H), 3.36 (s, 3H), 3.52 (s, 3H), 3.70 (m, 1H), 4.24 (m, 2H), 4.70 (dd, J=9 and 5 Hz, 1H), 4.86 (s, 1H), 5.02 (dd, J=7 and 6 Hz, 1H), 5.93 (d, J=4 Hz, 1H), 7.27 (m, 11H), 7.83 (m, 4H); Calcd for $C_{32}H_{30}O_{10}$: C, 66.89; H, 5.26%. Found: C, 66.95; H, 5.50%.

Diazo Compound 11 from Diketone 10. To a solution of diketone **10** (923.9 mg, 1.65 mmol) in acetonitrile (5 ml) was added triethylamine (0.3 ml, 2.14 mmol) and *p*-toluenesulfonyl azide (345.2 mg, 1.75 mmol) at room temperature. The mixture was stirred for 1.5 h at that temperature, and the solvent was removed under reduced pressure. The residue was dissolved in ether, washed successively with dil. aq NaOH and satd. aq NaCl, and dried over anhyd. Na_2SO_4. Removal of the solvent followed by column chromatography on Florisil afforded the diazo compound **11** (966.8 mg, 100%). IR (neat) 2150, 1730 cm^{-1}; NMR (90 MHz) ($CDCl_3$) δ=3.45 (s-like, 2H), 3.74 (s, 3H), 3.67 (m, 1H), 4.18 (dd, J=12 and 5 Hz, 1H), 4.42 (dd, J=12 and 4 Hz, 1H), 4.88 (dd, J=9 and 5 Hz, 1H), 5.22 (dd, J=5 and 5 Hz, 1H), 6.15 (d, J=5 Hz, 1H), 7.45 (m, 11H), 7.95 (m, 4H); Calcd for $C_{31}H_{26}O_{10}N_2$: C, 63.48; H, 4.47; N, 4.78%. Found: C, 63.78; H, 4.66; N, 4.66%.

Cyclizatio of Diazo Compound 11. Lithium hexamethyldisilazanide (1.6 ml of 0.58 M THF solution, 0.92 mmol) was added to the diazo compound **11** (253 mg, 0.43 mmol) in a mixture of THF (0.5 ml) and HMPA (0.25 ml) at −78 °C. Then it was warmed up to −20 °C and stirred for 1 h at that temperature. The reaction mixture was poured into buffered solution and extracted several times with ether. The organic layer was washed with satd. aq NaCl and dried over anhyd. Na_2SO_4. Removal of the solvent followed by column chromatography on Florisil afforded the pyrazole **12** (188.5 mg,

66%). IR (neat) 1730 cm^{-1}; NMR (90 MHz) ($CDCl_3$) δ= 3.83 (s, 3H), 4.14 (quint, J=4.5 Hz, 1H), 4.32 (dd, J=12 and 5 Hz, 1H), 4.56 (dd, J=12 and 4 Hz, 1H), 5.02 (dd, J=9 and 5 Hz, 1H), 5.27 (dd, J=5 and 5 Hz, 1H), 6.29 (d, J=5 Hz, 1H), 6.75 (br s, 1H), 7.43 (m, 11H), 7.95 (m, 4H); Calcd for $C_{31}H_{26}O_{10}N_2$: C, 63.48; H, 4.47; N, 4.78%. Found: C, 63.19; H, 4.60; N, 4.68%.

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