Unusual Dimethyl Ketal from Cycloadduct of 4,6-*O*-Benzylidene-D-allal and Dichloroketene

Keun Ho Chun, Taemoon Yoon, Jeoung E Nam Shin, Choonsil Jo,† Yun Ju Jo,† Hoseop Yun,‡ and Jonghoon Oh†,*

Department of Chemistry, Soongsil University, Seoul 156-743, Korea
*†Department of Chemistry, Chonnam National University, Gwangju 500-757, Korea. *E-mail: jnoh@chonnam.ac.kr*
‡Department of Chemistry, Ajou University, Suwon 442-749, Korea
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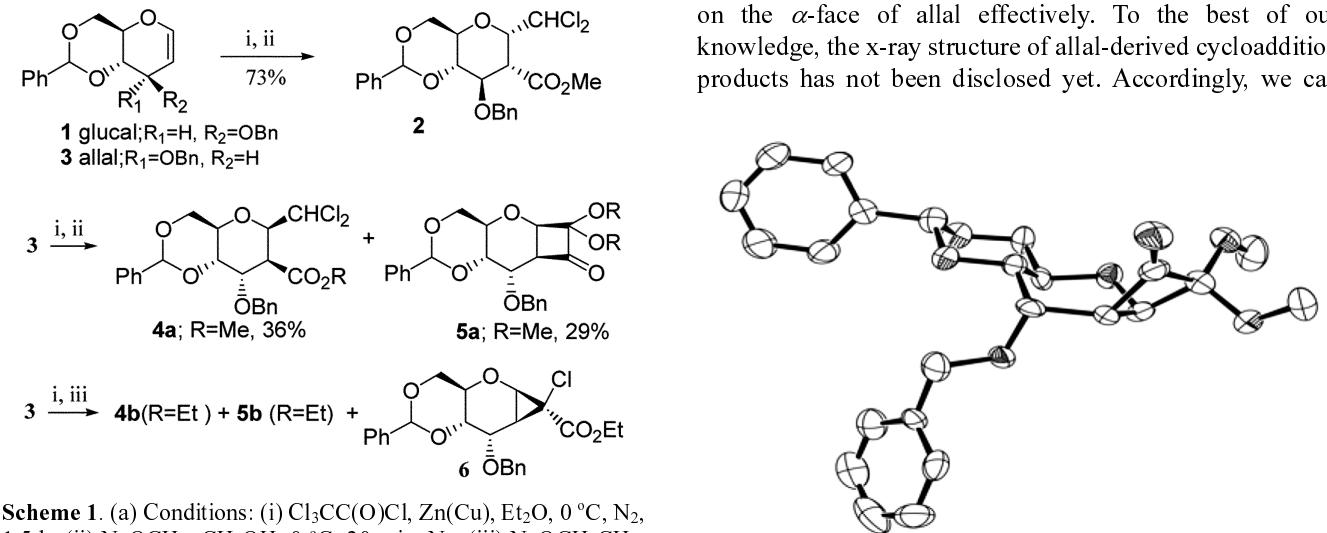
Glycal derivatives are useful building blocks in organic synthesis as well as in carbohydrate chemistry.[1] Cycloadditions of dichloroketene to tri-*O*-benzyl or tri-*O*-acetyl-D-glucal and D-galactal were reported to produce α-oriented cyclobutanone ring, and the resulting bicyclic cyclobutanones were converted into lactone compounds by oxidation.[2-6] Although they showed high stereo and regioselectivity with moderate yield, this methodology has not been widely applied for synthetic purpose. For the last few years, we have studied the cycloaddition of ketene to glucal, galactal, and allal derivatives and their application for the synthesis of *C*-glycoside derivatives[4,5] and modified nucleosides.[6] Even though, in case of allal,[7] β-oriented cyclobutane ring formation is reported,[8] no direct evidence supporting the face selectivity of dichloroketene cycloaddition to allal derivatives has been reported yet. Thus herein we report the X-ray structure of an unusual ketal from allal-derivative as the evidence that the facial selectivity of cycloaddition to glycal is controlled by the stereochemistry of C-3 constituent and discuss the mechanism for the formation of the unsual dimethyl ketal.

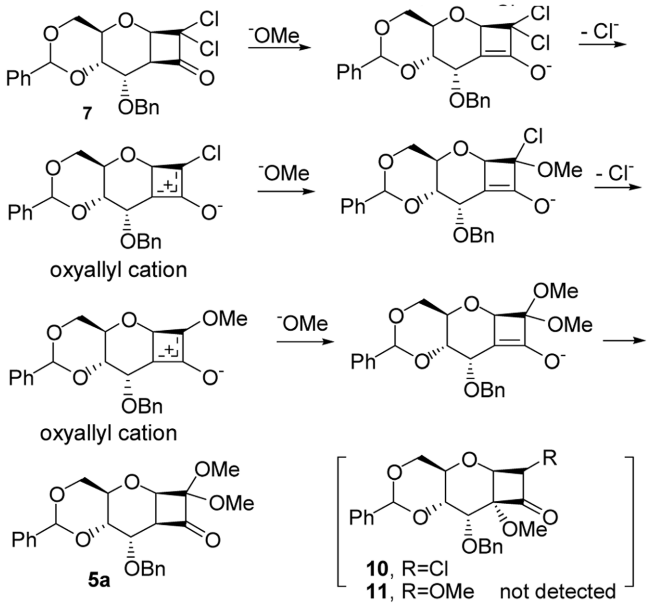
To substantiate the evidence for facial selectivity, glucal and allal derivatives (**1** and **3**, respectively) were subject to dichloroketene cycloaddition reaction and treated with sodium methoxide in methanol. As expected, 3-*O*-benzyl-4,6-*O*-benzilidene-D-glucal (**1**) was converted to C-1 and C-2 dialkylated *C*-glycoside,[5] 3-*O*-benzyl-4,6-*O*-benzylidene-1-dichloromethyl-2-methoxycarbonyl-1,2-dideoxy-α-D-glucopyranoside (**2**) in 73% yield. To our surprise, 3-*O*-benzyl-4,6-*O*-benzylidene-D-allal[7] (**3**) provided two products,[9] *O*-benzyl-4,6-*O*-benzylidene-1-dichloromethyl-2-methoxycarbonyl-1,2-dideoxy-β-D-altropyranoside (**4a**) and dimethyl ketal (**5a**), in 36% and 29% isolated yield from allal (**3**), respectively (Scheme 1). The stereochemistry of C2 of **2** was determined by coupling constant between H2 and H3 (9.3 Hz, 1,2-diaxial orientation) and the previous results from glucal and galactal.[3,6] Although *C*-glycoside from allal-derivative has not been reported in the literature, methoxy carbonyl group on C2 of **4a** was determined to orient axially based on coupling constant between H2 and H3 (3 Hz, 1,2-diequatorial). This assignment of stereochemistry of C2 was confirmed by X-ray structure[10] of **5a**.

In solid state the ketal (**5a**) has chair conformation of benzylidene unit, twisted chair conformation of six membered sugar ring, and axial orientation of C3 benzyloxy substituent. Besides, more importantly, cyclobutanone is located on β-face of sugar ring, showed in Figure 1. This stereochemistry is attributed to the steric hindrance of bulky group on C3, which prevented dichloroketene from reacting on the α-face of allal effectively. To the best of our knowledge, the x-ray structure of allal-derived cycloaddition products has not been disclosed yet. Accordingly, we can

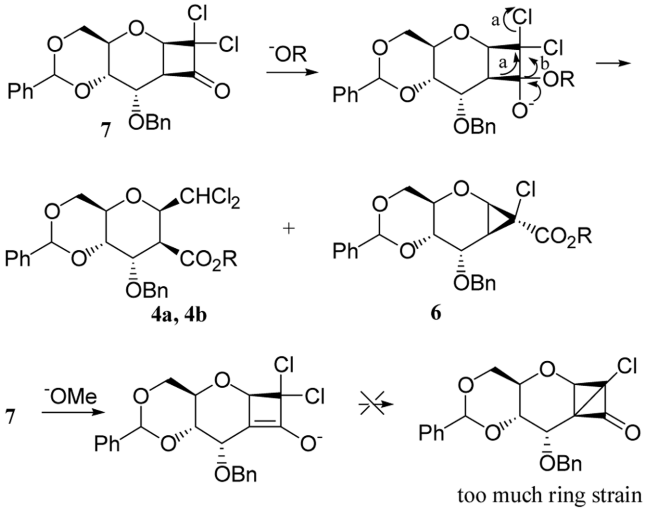


Scheme 1. (a) Conditions: (i) $Cl_3CC(O)Cl$, Zn(Cu), Et_2O, 0 °C, N_2, 1.5 h; (ii) $NaOCH_3$, CH_3OH, 0 °C, 20 min, N_2; (iii) $NaOCH_2CH_3$, CH_3CH_2OH, 0 °C, 20 min, N_2.

Figure 1. x-ray structure of ketal **5a**.



Scheme 2. Proposed Oxyallyl Mechanism for the formation of ketal **5a** and **5b**.



Scheme 3. Proposed Mechanism for the formation of **2**, **4a**, **4b**, and **6**. Favorskii rearangement reaction *vs* benzilic acid rearrangement.

now prove unequivocally that the facial selectivity of cycloaddition reaction of glycal and dichloroketene is directed by the stereochemistry of C3 alkoxy group. Furthermore, the formation of ketal compound **5a** clearly shows that configuration of cyclobutanone group of intermediate **7** is subtly involved on its reactivity toward methoxide nucleophile. α,α-Dichlorocyclobutanone derivatives have been known to give disubstitution products under basic condition (NaOMe/MeOH).[11,12] Usually, methoxide anion attacks the α-carbon to carbonyl group that does not have chlorine atoms. Interestingly, dimethyl ketal **5a** and its ethyl analogue **5b** are not typical substitution products, because two methoxide groups are inserted to α-carbon that has had two chlorines. The mechanism for the unusual substitution product is proposed as in Scheme 2. A key intermediate for the mechanism is believed to be oxyallyl cation (**8**).[13] The absence of products (**10** or **11**) can usually be an evidence to exclude the existence of oxyallyl cation. However, in our case, the formation of compound **11** is expected less favorable than ketal **5a** because of steric reason. Therefore, the possibility of existence of oxyallyl cation cannot be taken away in our reactions.

In contrast to methoxide reaction, chlorocyclopropanated sugar (**6**) was isolated from ethoxide reaction. The structure of **6** was determined by ^{1}H and ^{13}C NMR spectra.[14] It is believed that ethyl ester **4b** and chlorocyclopropanated sugar **6** could have common intermediate as shown in Scheme 3. Favorskii type reaction pathway would be impossible because chlorocyclopropanone has high ring strain. Alternatively, benzilic acid rearrangement would be more probable reaction path through common intermediate for **2**, **4a**, **4b**, and **6**.

In conclusion, the reaction of methoxide with a cycloadduct of allal derivative and dichloroketene provided an unusual dimethyl ketal, and its x-ray structure was elucidated for explaining the stereochemistry and stereoselectivity of cycloaddition to dichloroketene. Additionally, we expect its result would be the direct evidence that the stereochemistry of C3 substituent of glycals controls the facial selectivity of dichloroketene cycloaddition. For explaining the formation of unusual products, the reaction mechanism via oxyallyl intermediate for unusual substitution and benzilic acid rearrangement for cyclobutanone ring opening and cyclopropanated sugar were suggested.

Experimental Section

Experimental procedure for 4 and 5. To a stirred mixture of Zn(Cu) (660 mg, 0.01 mol) and 3-*O*-benzyl-4,6-*O*-benzylidene-D-allal (**3**) (198 mg, 0.61 mmol) in ether (6 mL) was added trichloroacetyl chloride 325 mg (1.79 mmol) in ether (2 mL) slowly under nitrogen atmosphere at 0 °C and the resulting mixture was stirred further 1.5 h. Hexane was added, the supernatant was decanted and washed with a cold aqueous solution of sodium bicarbonate and a cold brine and then dried over magnesium sulfate. After evaporation of the solvents under reduced pressure the residue was dissolved in methanol (3 mL) and sodium methoxide (4 mL of 0.28 N solution in methanol) was added at 0 °C and then the resulting mixture was stirred for 20 min under nitrogen atmosphere. The mixture was concentrated under reduced pressure and purified by fresh column chromatography (hexane : ethyl acetate; 10 : 1) to give **4a** (101 mg) and **5a** (76 mg), in 36% and 29% yield, respectively; spectral data for methyl ester **4a**; IR 1737 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.22 (m, 10H), 6.18 (d, J = 9 Hz, 1H, -C<u>H</u>Cl_2), 5.53 (s, 1H), 4.9 (d, J = 12 Hz, 1H), 4.70 (d, J = 12 Hz, 1H), 4.41-4.35 (m, 2H, H-3, H-6), 4.32-4.29 (dd, J = 9Hz, 3 Hz, 1H, H-1), 4.20 (m, 1H, H-5), 3.75 (m, 2H, H-4, H-6), 3.74 (s, 3H, -OCH_3), 3.44 (t, J = 3 Hz, 1H, H-2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.35, 137.91, 137.29, 129.12,

128.40, 128.27, 127.80, 127.68, 126.17, 102.22, 78.83, 78.22, 73.68, 73.34, 71.47, 68.98, 67.73, 52.34, 47.91 for ketal **5a**; IR 1793 cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$) δ7.48-7.24 (m, 10H), 5.52 (s, 1H), 4.89-4.86 (d, J = 11.7 Hz, 1H), 4.64-4.61 (d, J = 11.7 Hz, 1H), 4.48 (d, J = 6 Hz, 1H), 4.35 (dd, J = 6 Hz, 11 Hz, 1H), 4.28 (s, 1H), 4.05 (m, 1H), 3.74-3.59 (m, 3H), 3.41 (s, 3H), 3.33 (s, 3H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.69, 138.25, 137.47, 129.06, 128.35, 128.26, 127.76, 127.70, 126.12, 111.53, 101.85, 78.60, 73.62, 70.28, 69.31, 69.03, 62.41, 59.51, 52.48, 51.68.

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