Synthesis and Charactarization of 2'-Oxopropylene Derivatives of Chloraloses

[1]*Kadir Ay*, [1]*Emriye Ay*, [1]*Nilgün Yenil and* [2]*Levent Yüceer*

[1]Department of Chemistry, Faculty of Art and Sciences, Celal Bayar University, 45030, Manisa, Turkey
[2]Department of Chemistry, Faculty of Science, Ege University, 35100, Bornova, İzmir, Turkey

Abstract: 2'-Oxopropylene chloralose derivatives were prepared from 5,6-*O*-isopropylidene-3-ulose derivatives of chloraloses. 3-Uloses were synthesized via conventional oxidation method with pyridinium chlorochromate (PCC)/molecular sieve 4 °A (MS 4 °A). The Wittig products were obtained from the diacetal protected furanos-3-ulose of chloralose using (acetylmethylene)triphenylphosphorane. The products were characterized by FTIR, elemental analysis, ^{1}H and ^{13}C NMR.

Key words: Branched-chain sugars · Wittig reaction · Ketosugar · Chloralose

INTRODUCTION

The Wittig olefination is a well-investigated reaction in the carbohydrate field and frequently used in carbohydrate chemistry for synthesis of branched-chain sugar derivatives. Wittig products were obtained via the reaction of stabilized or unstabilized phosphoranes reacted with in the anomeric center or other carbon atoms of sugar molecules. The reaction in anomeric center has been extensively applied in *C*-glycoside synthesis [1]. Wittig products were also obtained by reactions of other carbon atoms on sugar skeleton [2,3]. For instance, the reactions of 2,3-*O*-isopropylidene-D-ribofuranose with Ph$_3$P=C(Me)CO$_2$Me, Ph$_3$P=C(Me)CN and Ph$_3$P=CHCOMe gave olefinic products [4]. Sugar derivative-Wittig products are important compounds with physiological activites, such as antitumor [5], antibiotics and nucleotides [6]. Wittig reaction and its variants (e.g. Wadworth-Emmons, Wittig-Horner and others) used for chain extension on sugar compounds in carbohydrate chemistry were reviewed [7].

Ketosugars that can be introduced to aldose derivatives with the oxidation of free secondary hydroxyl groups by using of different oxidation reagent such as dimethylsulphoxide, chromium salts, ruthenium and iodine etc. Ferrier and Collins [8] are more interesting compounds for the Wittig olefination reactions in carbohydrate chemistry. It is known that chromium reagent has been widely used for the synthesis of ketosugars [9]. While the oxidation of carbohydrate derivatives and other alcohols with pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC), moleculer sieves can be used as a catalyst [10]. The most efficient method is that the usage of PCC and PDC reagents for the oxidation of secondary hydroxyl group are prefered to get the furanose type 3-ketosugars which can be reacted with the stabilized phosphoranes. In this way, the typical Wittig products can be easily obtained as a mixture of *E*- and *Z*-isomers of the unsaturated sugar ketones such as the reaction of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*- and *xylo*-hexofuranos-3-uloses with the stable phophorous ylides [3].

It is very common that acetals and ketals are used as the protecting groups for diols. As for comparing these protecting groups, trichloroethylidene acetal rings are highly stable under acidic and mildly basic conditions and they are more useful protecting groups for further modifications of sugars however there are not enough studies found on them in the literature. The removing of these trichloroethylidene acetals from the molecule is only possible when the hydrogenation reaction, followed by acidic hydrolysis, occurs with using of Raney nickel as a catalyst [11]. Trichloroethylidene acetals are also potentially biologically active compounds; such as α-chloralose (1,2-*O*-*R*-trichloroethylidene-α-D-glucofuranose) is a hypnotic drug and has been used as a surgical anaesthetic in laboratory animals. It is also widely used in neuroscience and veterinary medicine as an anesthetic and sedative. In addition, it is well known that arabinochloralose is used for development of new antituberculosis drugs in pharmaceutical research [12]. It is proved that the Wittig products of sugar dialdofuranose derivatives protected with 1,2-*O*-trichloroethylidene acetal group are synthesized as *trans*

Corresponding Author: Dr. Kadir Ay, Department of Chemistry, Faculty of Sciences and Arts, Celal Bayar University, Campus of Muradiye, 45030, Manisa, Turkey

isomers while using of appropriate phosphoranes [13]. These unsaturated sugar derivatives are additionally important as they can be used for the synthesis of many important substances such as spiro-endoperoxides that we have been obtained and reported of their antimicrobial activities in our previous works [14,15]. We have also been published the synthesis of 3,6-anhydro furano sugar derivatives from the related intermediate Wittig products, not explained and characterized as their structural analysis before, via the Wittig-cyclization procedure [16]. These 2'-oxopropylene derivatives can be obtained from the reaction of 3-ketosugar chloraloses with (acetylmethylene)triphenylphosphorane. In this work, we would like to present these new compounds as their synthesis, purifications and characterization of molecular structures by spectroscopic methods.

MATERIALS AND METHODS

General Methods: ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Varian AS 400 NMR spectrometer. IR spectra were recorded on Perkin Elmer Spectrum 100 FTIR Spectrometer. Optical rotation measurements were carried out on a Schimidt-Haensch Polartronic E polarimeter. Elemental analyses were carried out on a LECO CHNS-932 elemental analyzer. Melting points were determined on a Gallenkamp Electrothermal apparatus and were uncorrected. TLC and column chromatography were performed on precoated aluminium plates (Merck 5554) and silica gel G-60 (Merck 7734), respectively. All solvent removals were carried out under reduced pressure.

5,6-*O*-isopropylidene-1,2-*O*-(*S*)-trichloroethylidene-α-D-*ribo*-hexofuranos-3-ulose Hydrate (1): A solution of 5,6-*O*-isopropylidene-1,2-*O*-(*S*)-trichloroethylidene-α-D-glucofuranose [13] (10.5 g, 0.03 mol) in dichloromethane (200 mL) was mixed with powdered MS 4 °A (26 g) and PCC (39.2 g, 0.18 mol) and the mixture was stirred at room temperature for 24 h. TLC (toluene-methanol, 9:1) showed a singal product. Diethylether (800 mL) was added in this reaction mixture. The etheral phase was separeted and applied on a silica gel column (180 g). And the column was eluted with diethylether. Fractions containing the pure product were combined and extracted with aqueous saturated sodium hydrogen carbonate (3x250 mL) and then dried with anhydrous sodium sulphate. Organic solvent was filtered and evaporated under pressure to give a white solid. This crude product was crystallizated with diethylether-hexane to get the pure compund. The

yield was 85% (9.36 g), mp 124-125°C, $[\alpha]_D^{23}$ + 30.0 (*c* 0.1, CH$_2$Cl$_2$). IR: double OH; 3453 and 3400 cm^{-1}. Anal. Calcd for C$_{11}$H$_{15}$Cl$_3$O$_7$: C, 36.14; H, 4.14. Found: C, 36.35; H, 4.07.

5,6-*O*-isopropylidene-1,2-*O*-(*R*)-trichloroethylidene-α-D-*ribo*-hexofuranos-3-ulose (2): 5,6-*O*-Isopropylidene-1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose [17] (10.5 g, 0.03 mol) was oxidized as described in synthesis of compound 1. After purification, the white crystals were obtained and the yield was 73% (7.63 g), mp 114-116°C, + 64.0 (*c* 0.11, CH$_2$Cl$_2$), IR: C=O 1772 cm^{-1}. Anal. Calcd for C$_{11}$H$_{13}$Cl$_3$O$_6$: C, 38.01; H, 3.77. Found: C, 37.99; H, 3.82.

5,6-*O*-isopropylidene-1,2-*O*-(*S*)-trichloroethylidene-α-D-*xylo*-hexofuranos-3-ulose (3): 5,6-*O*-Isopropylidene-1,2-*O*-(*S*)-trichloroethylidene-α-D-galactofuranose [18] (10.5 g, 0.03 mol) was oxidized as described in synthesis of compound 1. After purification, the white crystals were obtained and the yield was 91% (7.25 g), mp 134-136°C, $[\alpha]_D^{22}$ -14.6 (*c* 0.11, CH$_2$Cl$_2$), IR: 1772 cm^{-1}. Anal. Calcd for C$_{11}$H$_{13}$Cl$_3$O$_6$: C, 38.01; H, 3.77. Found: C, 37.89; H, 3.66.

(*E*) and (*Z*) 3-Deoxy-5, 6-*O*-isopropylidene-3-*C*-(2'-oxopropylene)-1, 2-*O*-(*S*)-trichloroethylidene-α-D-*ribo*-hexofuranoses (1a and 1b): A solution of compound 1 (1.44 g, 0.004 mol) in CHCl$_3$ (40 mL) was mixed with (acetylmethylene)triphenylphosphorane (3.81 g, 0.012 mol). The mixture was stirred at room temperature for 120 h. The solvent was removed completely and the residue was extracted with diethylether and filtered off. After removing of solvent, the syrupy product was obtained as a mixture of stereoisomers which were separated on a silica gel column with gradient elution of diethylether-hexane (from 5:100 to 20:80). The compound 1b (*Z* isomer) was obtained from the column as a first elution. The combined fractions belonging to 1b were evaporated to give a solid residue which was crystallized from boiling hexane and the yield was 11% (0.17 g), mp 107-108°C, $[\alpha]_D^{22}$ +193.7 (*c* 0.095, CH$_2$Cl$_2$), IR: C=O 1697 cm^{-1}; C=C 1648 cm^{-1}. Anal. Calcd for C$_{14}$H$_{17}$Cl$_3$O$_6$: C, 43.38; H, 4.42. Found: C, 43.36; H, 4.24. Further fractions gave the compound 1a (*E* isomer) obtained as a colourless syrupy product which was crystallized from ethyl acetate-hexane. The yield was 61% (0.95 g), mp 75-77°C, $[\alpha]_D^{22}$ +110.9 (*c* 0.11, CH$_2$Cl$_2$), IR: C=O 1707 cm^{-1} ; C=C 1653 cm^{-1}. Anal. Calcd for C$_{14}$H$_{17}$Cl$_3$O$_6$: C, 43.38; H, 4.42. Found: C, 43.04; H, 4.42. Owing to the obtaining of 1a and 1b as a mixture of unsapareted stereoisomers (0.14 g, 9%) as well the total yield of Wittig reaction was 81%.

3-Deoxy-5, 6-*O*-isopropylidene-3-*C*-(2'-oxopropyl)-1, 2-*O*-(*R*)-trichloroethylidene-α-D-*erythro*-hex-3-enofuranose (2a): A solution of compound 2 (1.44 g, 0.004 mol) in CHCl₃ (35 mL) was mixed with (acetylmethylene) triphenylphosphorane (3.81 g, 0.012 mol). The mixture was stirred at room temperature for 72 h. The solvent was removed completelyl and the residue was extracted with diethylether and filtered off. The filtrate was concentrated and applied to a silica gel column with gradient elution of ether-hexane (from 5:100 to 30:70). Examined fractions containing the pure compound with TLC (ether-hexane, 2:1) were combined and evaporated to give a pale yellow syrupy product. The yield was 62% (0.96g), $[\alpha]_D^{23}$, + 126.7 (c 0.15, CH₂Cl₂), IR: C=O 1707 cm⁻¹; C=C 1653 cm⁻¹. Anal. Calcd for C₁₄H₁₇Cl₃O₆: C, 43.38; H, 4.42. Found: C, 43.59; H, 4.59.

(*Z*) 3-Deoxy-5,6-*O*-isopropylidene-3-*C*-(2'-oxopropylene)-1, 2-*O*-(*S*)-trichloroethylidene-α-D-*xylo*-hexofuranose (3b): A solution of compound 3 (10.3 g, 0.03 mol) in THF (200 mL) was mixed with (acetylmethylene) triphenylphosphorane (14.2 g, 0.045 mol). The mixture was refluxed for 18 h with continuous stirring. TLC (toluene-MeOH, 9:1) indicated a single product with an appreciable amount of unreacted starting compound. The dark coloured mixture was evaporated and the residue was extracted with boiling hexane (3x150 mL). After removing of hexane, the dark brown syrupy residue was obtained. It was then applied to a silica gel column with gradient elution of hexane-ethyl acetate (from 100:5 to 90:10) to give a colourless syrupy product which was crystallized from hexane. The yield was 33% (3.85 g), mp 113-114°C, $[\alpha]_D^{22}$ -89.5 (c 0.11, CH₂Cl₂), IR: C=O 1723 cm⁻¹; C=C 1646 cm⁻¹. Anal. Calcd for C₁₄H₁₇Cl₃O₆: C, 43.38; H, 4.42. Found: C, 43.08; H, 4.33.

RESULTS AND DISCUSSION

Furanos-3-uloses (1-3) were obtained by the oxidation of appropriate diacetals using a conventional PCC/MS 4 °A method [10] which can be reacted with acetylmethylenetriphenylphosphorane affording the Wittig products as a mixture of *E* and *Z* isomers in good yields. The compound 1 was isolated as its hydrate form, but the compound 2 and 3 were obtained as their crystalline keto form (Scheme 1). The IR spectra of these furanose-3 ulose derivatives exhibited that the OH absorpsition was observed at 3453 and 3400 cm⁻¹ for
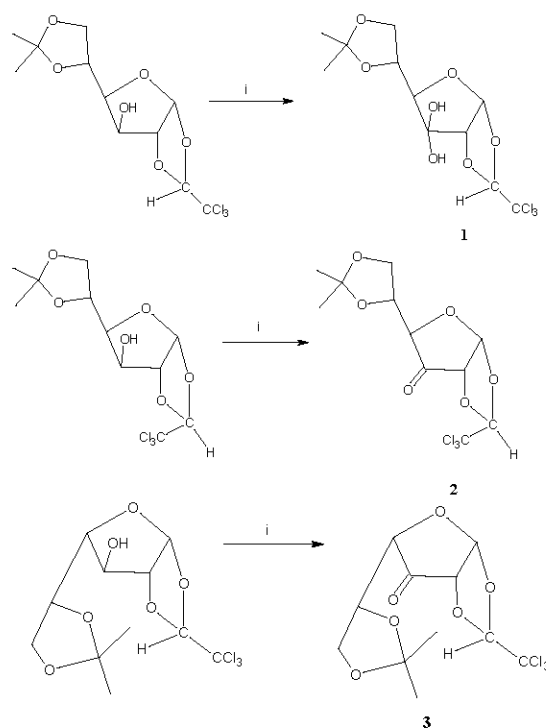
Reagents and conditions: i: PCC/MS 4°A in CH₂Cl₂ for 24 h at room temp.

Scheme 1: The oxdation of chloralose derivatives

compound 1 and the C=O group absorption was observed at 1772 cm⁻¹ for compound 2 and 3. Furthermore, ¹H NMR spectra of these compounds proved that the signals of geminal OH groups at 4.02 ppm and 3.65 ppm as broad singlets were observed for compound 1. However, ¹H NMR spectra of compound 2 and 3 in keto sugar formation indicated that the long range couplings (~1 Hz) were observed between H-2 and H-4 protons. It is so clear that this coupling was not exist in the ¹H NMR spectra of the compound 1 (Table 1).
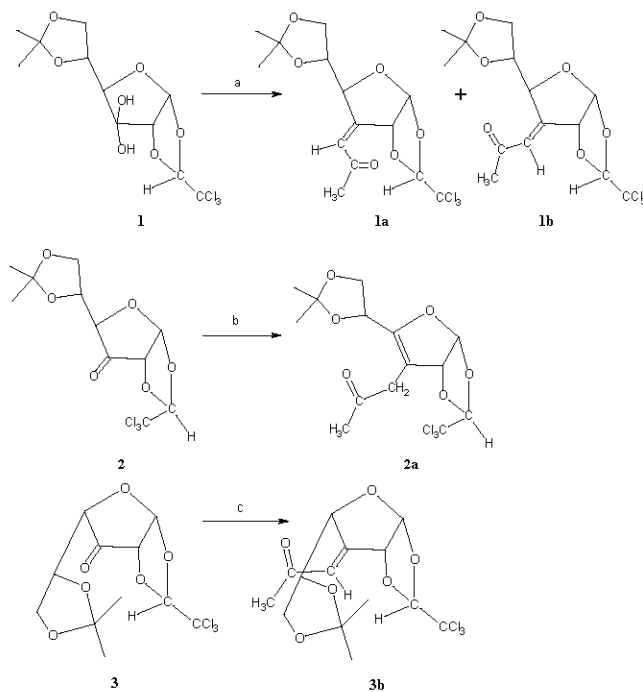
All furanos-3-ulose derivatives were reacted with acetylmethylene-triphenylphosphorane under two different reaction conditions in order to get the expected olefinic Wittig products (1a, 1b and 3a) except 5,6-*O*-isopropylidene-1,2-*O*-*R*-trichloroethylidene hexofuranos-3-ulose (2). The reaction of this compound with acetylmethylenetriphenylphosphorane not only in tetrahydofuran, under reflux but also in chloroform, at room temperature did not afford the expected Wittig product but instead gave only one epimerization product as a compound 2a (Scheme 2). This result may also be related with the *endo*-trichloromethyl group, twisted conformation of the furanose ring, in compound 2. As

Table 1: ^{1}H NMR chemical shifts (δ ppm) and $J_{H,H}$ values (Hz) in CDCl$_3$, for the ketosugars

Comp.	H-1	H-2	H-4	H-5	H-6a	H-6b	HCCl$_3$	CH$_3$	OH
1	6.15 d,	4.63 d,	3.85 d,	4.42 ddd,	4.15 dd,	4.09 dd,			
	$J = 3.9$ Hz	$J = 3.9$ Hz	$J = 6.5$ Hz	$J = 6.5, 6.5, 5.5$ Hz	$J = 9.0, 6.5$ Hz	$J = 9.0, 5.5$ Hz	5.73 s	1.39-1.38 s	4.02 br s, 3.65 br s
2	6.37 d,	4.61 dd,	4.48 dd,	4.37 ddd,	4.06 dd,	4.02 dd,			
	$J = 4.7$ Hz	$J = 4.7, \sim 1.0$ Hz	$J = 2.7, \sim 1.0$ Hz	$J = 7.2, 7.2, 2.7$ Hz	$J = 8.5, 7.2$ Hz	$J = 8.5, 7.2$ Hz	5.56 s	1.34-1.38 s	-
3	6.38 d,	4.76 dd,	4.17 dd,	4.42 ddd,	4.10 dd,	4.01 dd,			
	$J = 4.7$ Hz	$J = 4.7, \sim 1.0$ Hz	$J = 2.7, \sim 1.0$ Hz	$J = 8.2, 2.7, 6.6$ Hz	$J = 8.2, 6.6$ Hz	$J = 8.2, 8.2$ Hz	5.76 s	1.50-1.38 s	-

Table 2: ^{1}H NMR chemical shifts (δ ppm) and $J_{H,H}$ values (Hz) in CDCl$_3$, for the Wittig products

Comp.	H-1	H-2	H-4	H-5	H-6a	H-6b	Ac	H-1'	HCCCl$_3$	CH$_3$
1a	6.10 d,	5.98 ddd,	4.60 ddd,	4.11 ddd,,	4.04 dd,	4.03 dd	2.35 s	6.72 dd,	5.61 s	1.45-1.38 s
	$J = 3.9$ Hz	$J = 3.9, \sim 1.5$,	$J = 7.5, \sim 1.5$,	$J = 7.5, 7.5$	$J = 7.5$,	$J = 7.5$,		$J = \sim 1.5$,		
		~ 1.5 Hz	~ 1.5 Hz	3.0 Hz	7.5 Hz	3.0 Hz		~ 1.5 Hz		
1b	6.14 d,	5.41 ddd,	5.71 ddd,	4.35 ddd	3.99 dd,	3.51 dd,	2.34 s	6.68 dd,	5.48 s	1.33-1.31 s
	$J = 4.3$ Hz	$J = 4.3, \sim 2.0$,	$J = 2.7, \sim 2.0$,	$J = 7.8, 6.2$,	$J = 9.0$,	$J = 9.0$,		$J = \sim 2.0$,		
		~ 2.0 Hz	~ 2.0 Hz	2.7 Hz	6.2 Hz	7.8 Hz		~ 2.0 Hz		
3b	6.18 d,	5.29 ddd,	5.27 ddd,	4.62 ddd,	4.14 dd,	3.97 dd,	2.32 s	6.64 dd,	5.87 s	1.52-1.35 s
	$J = 4.3$ Hz	$J = 4.3, \sim 1.0$,	$J = 1.0, \sim 1.0$,	$J = 8.0, 1.0$,	$J = 8.0$,	$J = 8.0$,		$J = \sim 1.0$,		
		~ 1.0 Hz	~ 1.0 Hz	7.0 Hz	7.0 Hz	8.0 Hz		~ 1.0 Hz		

Reagents and conditions: a: Ph$_3$P=CHCOMe in CHCl$_3$ for 120 h at room temp.;
b: Ph$_3$P=CHCOMe in CHCl$_3$ for 72 h at room temp.; c: Ph$_3$P=CHCOMe in THF for 18h at reflux.

Scheme 2: The Wittig reactions of 3-uloses of chloralose derivatives

comparing with α-chloralose (1,2-*O*-*S*-trichloroethylidene-α-D-glucofuranose) derivatives, H-4 proton signal of α-chloralose (1,2-*O*-*R*-trichloroethylidene-α-D-glucofuranose) derivatives appears at lower fields than expected in their ^{1}H NMR spectra owing to the approaching of the *endo*-trichloromethyl group to the H-4 hydrogen [11,13,19]. This reasonable thinking is that allylic prototropy may take place just after the formation of the usual Wittig product for consisting of 2a from compound 2. This rearrangement was occurred via

Table 3: ^{1}H NMR chemical shifts (δ ppm) and $J_{H,H}$ values (Hz) in CDCl$_3$, for the allylic prototropic rearrangement Wittig product

Comp.	H-1	H-2	H-5	H-6a	H-6b	H-1'a	H-1'b	HCCl$_3$	Ac	CH$_3$
2a	6.16 d,	5.60 dd,	4.65 m	4.17 dd,	3.98 dd,	3.56 d,	3.38 d,	5.45 s	2.21 s	1.47-1.39 s
	J=4.8 Hz	J=4.8, ~0.5 Hz		J=8.4, 7.0 Hz	J=8.4, 7.0 Hz	J=18.0 Hz	J=18.0 Hz			

Table 4: ^{13}C NMR chemical shifts (δ ppm) for Wittig products

Comp.	C=O	C=C	C-1, CHCCCl$_3$, C(CH$_3$)$_2$	CCl$_3$	C-2, C-4, C-5, C-6	CH$_3$(Ac)	CH$_3$(isopropylidene)
1a	197.4	150.0, 125.5	110.6, 109.2, 105.8	99.3	80.3, 80.1, 76.7, 67.6	31.8	27.0-25.6
1b	197.3	151.8, 125.0	109.3, 107.7, 103.8	98.2	83.3, 81.4, 79.0, 65.7	31.9	26.2-25.7
2a	205.1	154.8, 110.8	106.8, 104.3, 104.1	98.4	88.1, 38.2 (C-1'), 70.7, 67.8	29.9	26.0-25.7
3b	197.8	152.5, 125.6	110.4, 110.3, 105.8	99.7	84.7, 81.2, 75.9, 66.5	31.9	25.9-25.8

double-bond shift into furanose ring from outside the ring bonding branched-chain. Table 3 shows the chemical shift values of compound 2a. Similar allylic prototropic rearrangement could be obtained from the analogous Wittig products by heating them in a basic solvent such as pyridine or even in dimethyl sulfoxide [3]. Data from the ^{1}H NMR spectra of 2a is very similar with the data of its previously known 1,2:5,6-di-O-isopropylidene analogous, including the long range coupling ($J_{2,5}$ < 1 Hz) [3]. The absence of any signals for H-3 and H-4 and the presence of an AB quartet for CH$_2$ group at C-1' at 3.56 ppm and 3.38 ppm are evidence for the structure 2a (Table 3). ^{13}C NMR data is also consistent with the proposed structure, exhibiting two double bond carbons (Table 4).

Between the reaction of isolated hydrate form of compound 1 and acetylmethylenetriphenylphosphorane gave two Wittig products (1a; *E* and 1b; *Z*), separated by column chromatograpy, as expected. According to the Wittig reaction mechanism, *E* isomer can be formed if the stable phospharane is add *syn*. Otherwise, the *anti* addition can be ensured the formation of *Z* isomer. ^{1}H and ^{13}C NMR spectra of the *E* and *Z* isomers of the Wittig products are very alike. The only appreciable difference was the chemical shift values of H-2 and H-4 proton signals. Thus, in the *E* isomers, carbonyl group is nearer to H-2 and H-2 signal resonates at a lower field due to the anisotropic effect. Similarly, in the *Z* isomers, carbonyl group is nearer to H-4 and this proton is dishielded to lower field by the anisotropic effect. It is crucial that the ^{13}C NMR datas of the isomers are also consistent with these discussions explained clearly the determination of the stereochemistry. Table 2 and 3 show that H-4 signals appear at 4.64 ppm and 5.66 ppm and H-2 signals appear at 5.60 ppm and 5.10 ppm respectively in the ^{1}H NMR

spectra of compound 1a (*E* isomer) and compound 1b (*Z* isomer).

The yield of the Wittig product 3b, obtained from the reaction of compound 3 with acetylmethylenetriphenylphosphorane and isolated either only *Z* isomer, was quite low. Therefore, it was not possible to compare the NMR data of the stereoisomers. In spite of this case we cautiously assume that the stereochemistry of this Wittig product 3b could be *Z* isomer since the chemical shift of H-2 signal at 5.29 ppm is an expected value and H-4 signal at 5.27 is at low field in the spectrum of 3b while comparing with the other galactochloralose derivatives.

CONCLUSION

2'-Oxopropylene containing 3-*C*-branced chloraloses were synthesized. C=C-linked were prepared by Wittig olefination reactions of hexofuranos-3-uloses from chloraloses. The structure of these new products were characterized by using the spectroscopic methods. Wittig products of α-chloralose were isolated expected *E*- (1a) and *Z*- (1b) but only one *Z*-isomer of product 3b was obtained from galactochloralose. The single product 2a was obtained from α-chloralose because of the allylic prototropic rearrangement.

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