Hindawi Publishing Corporation
Journal of Chemistry
Volume 2013, Article ID 748161, 7 pages
http://dx.doi.org/10.1155/2013/748161

Research Article

The Newest Member of the Family of Chloralose: Synthesis of β-Ribochloralose and Some Derivatives

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Received 8 February 2013; Revised 10 March 2013; Accepted 11 March 2013

Academic Editor: Huu Hao Ngo

Treatment of D-ribose with chloral in the presence of acid catalyst gives 1,2-*O*-(*S*)-trichloroethylidene-α-D-ribofuranose (**1**) (β-ribochloralose). Some derivatives of this product (**1**) were synthesized to be used as an intermediate in carbohydrate chemistry. Tricyclic orthoester structure (**3**, 77%) was obtained from the reaction of **1** with potassium *t*-butoxide. This novel orthoester is expected to be useful as a glycosyl donor in the formations of new ribofuranoside units. 3-*O*-Methyl-ribochloralose (**5**) was synthesized in 75% yield via the methylation of **1**. 5-*O*-Tosyl-ribochloralose (**6**, 61%) was prepared with monotosylation reaction of **1**. Treatment of **6** with NaN_3 in DMF gives a 5-azido-5-deoxy-ribochloralose (**7**) in 77% yield. The azidosugar (**7**) was reduced to 5-amino-5-deoxy-ribochloralose (**8**, 72%) with triphenylphosphine according to Staudinger's reduction procedure.

1. Introduction

Chloraloses are known as chloral derivatives of pentoses and hexoses. The first members of this class are α- and β-chloralose (or -glucochloralose) prepared via the reaction of anhydrous glucose and anhydrous chloral in the presence of sulfuric acid catalyst by Heffter [1] and the first time applied to therapeutics by Hanriot [2, 3]. In addition to glucochloraloses, preparations of other chloraloses (xylochloralose [3, 4], arabinochloralose [3, 5–7], galactochloralose [3, 8] and mannochloralose [3, 9]) have been also reported using the same synthetic method. All of chloraloses [3–9] synthesized so far contain 1,2-*O*-trichloroethylidene group in furanose form. Unlike most acetals, 1,2-*O*-trichloroethylidene acetals are very stable protecting group under acidic media because of inductive effects of trichloromethyl group and also stable in mild basic conditions. But, it is unstable against strong bases such as potassium *tert*-butoxide and is converted to most reactive ketene acetals [5, 9]. The only method for the removal of this protecting group has been reported as Raney-nickel procedure [10]. The most famous chloralose, (*R*)-1,2-*O*-trichloroethylidene-α-D-glucofuranose or α-chloralose, is a commercially available product and possesses anesthetic and hypnotic effects [2, 11]. It has been widely used as a rodenticide [12], bird repellent, and veterinary drug [11, 13, 14]. It was also used as an anaesthetic for human in the twentieth century [11]. Anesthetic properties of all stereoisomers for arabinochloralose were also investigated and β-D-arabinochloralose was found to be more reactive than others [15].

Chloraloses are also used as starting material for the synthesis of new compounds in carbohydrate chemistry due to potentially biological activity and stable protection in the 1,2-*O*-positions of theirs. Many derivatives of chloraloses have been reported such as amine [6], lactone [16], orthoesters [5, 7, 9], *O*-glycosides [7], dialdofuranose [9, 17], uronic acids [17], Wittig products [18], oxime [19], *spiro*-endoperoxide [20], thiosemicarbazone [21], and oxetane [22]. The most important ones of these derivatives, carbohydrate orthoesters, have been used very often as intermediate products in the synthesis of *O*-glycoside. Conventionally, 1,2-, 1,2,3- and 1,2,4-sugar orthoesters were usually prepared from glycosyl halides [23]. But Salman and coworkers reported the synthesis of 1,2,5- tricyclic carbohydrate orthoesters from intramolecular reaction of *galacto*- [5], *arabino*- [5], and *manno*-chloralose [9] with potassium *tert*-butoxide in *tert*-butanol as a new method. Rigid tricyclic orthoester rings are unstable against acids and cleavage was done easily [23]. Bamhaoud et al. used orthoester derivative of arabinochloralose for the synthesis of biologically important building

blocks and were described to nucleophilic opening of 1,2,5-orthoesters with alcohols, selenophenol, and ethanethiol in the presence of Lewis acid catalysts [7]. Additionally, 1,2,5-orthoesters of galactochloralose are used as versatile protecting groups during the total synthesis of biologically important sugar, D-digitalose [24].

In this work, we have synthesized and characterized 1,2-*O*-(*S*)-trichloroethylidene-α-D-ribofuranose (β-ribochloralose or ribochloralose) and its orthoester derivatives starting from D-ribose, a biologically important sugar (Scheme 1).

2. Results and Discussion

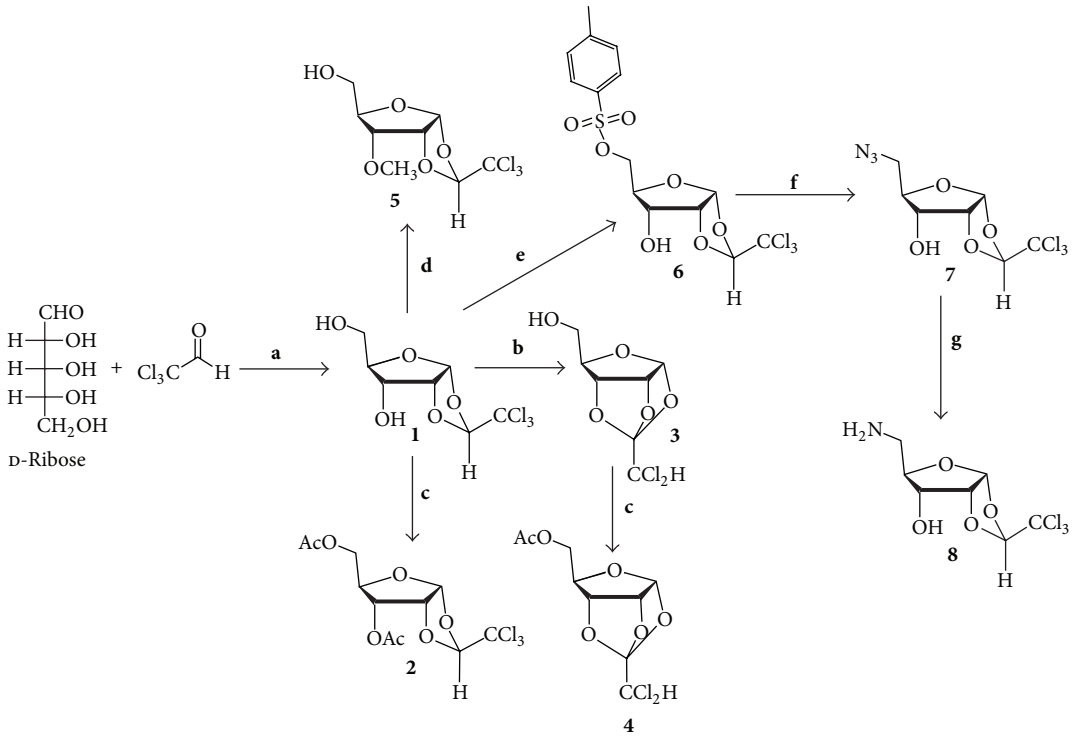
D-Ribose as a starting material was treated with catalytic amounts of sulfuric acid in chloral for 2 h under reflux to give 1,2-*O*-(*S*)-trichloroethylidene-α-D-ribofuranose (**1**) (β-ribochloralose) which was isolated via crystallization (Scheme 1). The low yield is attributed to the possibility of degradation of the sugar via the sulfuric acid catalyst. Pure single diastereomer (**1**) was obtained in 28% yield as a furanose form like all other chloralose molecules [3–9]. Although arabinochloralose [5], which is the diastereomer of **1,** was purified from water or methanol, **1** was not crystallized from water or methanol because of dissolving. If considering the anesthetic effects of α-chloralose arises from water-solubility [11], **1** most likely could also have similar effects. ^{1}H NMR and NOESY spectra (400 MHz) in C_5D_5N, in which all proton signals are of **1**, are well resolved including free hydroxyls. With respect to structural assignments, the characteristic coupling of *geminal* and *vicinal* protons was observed in the proton NMR spectrum of **1**: H-1 (doublet at 6.66 ppm), H-2 (triplet at 5.41), H-3 (dd at 4.83 ppm), H-4 (ddd at 4.73 ppm), H-5a (dd at 4.67 ppm), H-5b (dd at 4.45 ppm), two OH (bs at 7.09 ppm), and acetal proton (s at 6.36) signals were assigned. Coupling constant values (4.0 Hz) between the H-1/H-2 and H-2/H-3 proved *cis*-oriented *vicinal* protons. Similarly, $J_{3,4}$ (8.8 Hz) value showed *trans*-orientation of H-3 and H-4. *Geminal* protons of **1**, H-5a, and H-5b showed a strong coupling (12.4 Hz) to each other. These coupling constants of **1** were in agreement with the characteristic range of values observed for similar ribofuranose compound [25]. From a 2D NOESY experiment, cross-peaks between OH/H-3, OH/H-4, OH/H-5a, OH/H-5b, H-1/H-2, H-1/H-3, $HCCCl_3$/H-4, H-2/H-3, H-3/H-4, H-3/H-5a, H-3/H-5b, H-4/H-5b, and H-5a/H-5b of **1** could be observed, which proved the expected structure of **1** as a furanose (Figure 1, see Supplementary data available online at http://dx.doi.org/10.1155/2013/748161). As marked in Figure 1, evidence for the stereochemistry of the new stereogenic center (the acetal carbon configuration) was assigned on the basis of the NOESY spectrum which is showing the interaction between $HCCCl_3$ and H-4 proton clearly. C-1 (106.7 ppm), C-2 (83.3 ppm), C-3 (72.1 ppm), C-4 (83.7 ppm), C-5 (61.2 ppm), $\underline{C}HCCl_3$ (110.5 ppm), CCl_3 (101.1 ppm) signals of ribochloralose (**1**) were determined with ^{13}C and HMQC (Figure 2, see Supplementary data) NMR spectra. In addition to this information, the H-1/H-2, H-2/H-3, H-3/H-4, H-4/H-5a, H-4/H-5b, and H-5a/H-5b correlations were clearly collected from the COSY spectrum (Figure 3 and Figure 4, see Supplementary data). The long correlation of $HCCCl_3$ with H-4 was not observed. The HMBC spectrum (Figure 5, see Supplementary data) of compound **1** showed the correlations between H-acetal and C-1 and H-acetal and C-2. The correlation between H-1 and C-4 was also observed, expectedly.

These NMR experiments' results indicated that the trichloroethylidene group must occupy the positions C-1 and C-2 on a furanose structure and the proton of $HCCCl_3$ must be *endo*-position, and therefore the acetal carbon configuration must be *sinister (S)*. In the FTIR spectrum of diacetylated derivative (**2**), carbonyl peak was observed at 1742 cm^{-1}. ^{1}H and ^{13}C NMR spectra of **2** showed protons and carbons of two methyl groups of acetyl group moieties at 2.17 and 2.10 ppm and at 20.9 and 20.6 ppm, respectively.

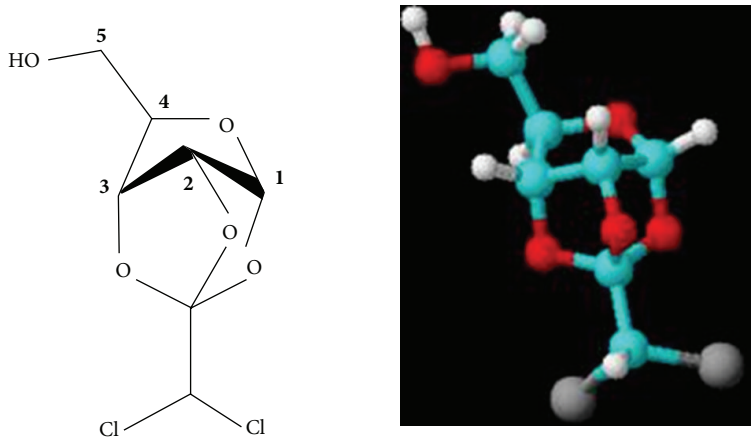
As shown in Scheme 1, the orthoester **3** was obtained via the reaction of **1** with potassium *tert*-butoxide in 77% yield and its molecular structure is a locked conformation (Scheme 2). Intramolecular orthoesterification reaction probably proceeds through ketene acetal mechanism as reported in the literature [5]. The tricyclic orthoester group of **3** can be used as a 1,2,3-*O*-protecting group for the manipulation of free 5-OH of D-ribose and has a high potential for synthesis of *O*-ribosides. In the ^{1}H NMR spectrum, a singlet at 6.02 ppm corresponds to $CC\underline{H}Cl_2$ and the coupling constant value between H-3 and H-4 of rigid tricyclic orthoester ring is approximately zero ($J_{3,4} \approx 0.0$ Hz). In addition, the proton signal of H-3 of **3** ascribable to intramolecular orthoesterification of **1** was shifted to the upper field as compared with those of **1**. In ^{1}H and ^{13}C NMR spectra of **4**, the signals at δ_H 2.10 and δ_C 20.9 corresponded to characteristic methyl signals of acetyl group, while signals of $CHCl_2$ were observed at δ_H 6.03 and δ_C 118.0. Furthermore, the characteristic IR absorption band of acetyl group at 1746 cm^{-1} was observed. Although NOESY correlations between H-1/H-2, H-2/H-3, H-3/H-5a, H-3/H5b, H-4/H-3, H-4/H-5a, and H-4/H-5b were observed, no NOE was represented for $HCCl_2$ in **4** (Figure 6, see Supplementary data). Moreover, in COSY spectrum of **4**, there were no long range correlations of H-3/H-4, H-3/H-5a, H-3/H-5b, and CCl_2H (Figure 7 and Figure 8, see Supplementary data). C-H correlations of **4** were observed in HMQC spectrum (Figure 9, see Supplementary data). All these spectroscopic data were proved in the structure of compound **4**.

In order to synthesize compound **5**, compound **1** was reacted with barium oxide as in Kuhn methylation method; hydroxyl group in position 5 was protected by trityl chloride in pyridine before methylation (Scheme 1). After deprotection of trityl group by acidic hydrolysis, compound **5** was gained and its structure was proved by ^{1}H and ^{13}C NMR techniques. A singlet relating to OH group at 2.07 ppm and a peak corresponds to a methyl at 58.6 ppm in ^{1}H and ^{13}C NMR spectra, respectively, indicated that methylation of position 3 and deprotection of position 5 occurred properly.

The regioselective tosylation of the 5-OH group of (**1**) was carried out in pyridine by reacting the diol (**1**) with tosyl chloride from 0°C to room temprature for 8 h in 61% yield,



Scheme 1: Reagent and conditions—(**a**) cat. H_2SO_4, reflux for 2 h, yield 28%; (**b**)1.2 equiv. potassium *tert*-butoxide in *tert*-butanol, at reflux for 3 h, yield 77%; (**c**)acetic anhydridein pyridine, for overnight in r.t., yield of **2**, 94% and yield of **4**, 88%; (**d**) (i) trityl chloride in pyridine, for overnight in r.t.; (ii) methyl iodide, $BaO/Ba(OH)_2.8H_2O$ in DMF for overnight in r.t., (iii) concd.HCl in $MeOH/H_2O$, at reflux for 3 h, yield 75%; (**e**) tosyl chloride in pyridine, r.t., yield 61%; (**f**) NaN_3 in DMF at 115°C for 2 h, yield 77%; (**g**) PPh_3 in methanol at reflux for 3 h, yield 72%.



Scheme 2: Locked conformation structure of 1,2,3-*O*-orthodichloroacetyl-α-D-ribofuranose (**3**).

giving rise to 5-*O*-tosyl-1,2-*O*-(*S*)-trichloroethylidene-α-D-ribofuranose (**6**) (Scheme 1). Compound **1** has two hydroxyl groups at the 3rd and 5th positions; hence, tosylation of **1** was yielded to two compounds. These two compounds were isolated via column chromatography. Benzene and methyl protons of tosyl group indicated doublets at 7.80 ppm (two protons), 7.36 ppm (two protons), and singlet at 2.45 ppm (three protons), respectively. ^{13}C NMR spectrum showed the benzene carbon atoms at 145.5, 132.7, 130.2, and 128.2 ppm and the methyl carbon atom at 21.9 ppm of tosyl group bonded to sugar molecule. Besides NMR data, the FTIR spectrum of monotosylate (**6**) showed characteristic absorptions at about 3154 cm^{-1} (OH), 1172 cm^{-1} (SO_2), and 1600 cm^{-1} (aromatic C=C).

The reaction of monotosylate with NaN_3 in DMF at about 115°C for 2 h was yielded 5-azido-5-deoxy-1,2-*O*-(*S*)-trichloroethylidene-α-D-ribofuranose (**7**) in 77% yield (Scheme 1). In the ^1H NMR spectrum of **7**, H-5 protons were

observed at 3.71 ppm (dd) and at 3.43 ppm (dd) instead of being at 4.35 (dd) and 4.20 (dd) ppm, and also in IR spectrum the disappearances of tosyl group and observing strong azide absorption peak at 2102 cm^{-1} confirm the substitution of tosyl group with azide.

Hydride reducers such as lithium aluminium hydride (LAH) were not suitable for the synthesis of amino-ribochloralose (**8**) from azido-ribochloralose (**7**), since elimination reaction could also take place in the trichloroethylidene ring. Thus, instead of LAH, triphenylphosphine in methanol was used in order to synthesize **8** from **7**. In ^{1}H NMR spectrum of **8**, a characteristic broad singlet at 8.40 ppm of amine protons proved that azide was converted to the amine group. Additionally, in the FTIR spectrum, the strong azide peak at 2102 cm^{-1} disappeared after reduction reaction with triphenylphosphine according to Staudinger's method (Scheme 1). The amine product (**8**, 72%) showed new peaks at 3248 cm^{-1} and 3118 cm^{-1} (-NH_2).

3. Experimental Section

3.1. General Methods. Melting points of the compounds were determined in open capillary tubes using a Gallenkamp Electrothermal melting point apparatus and are uncorrected. IR spectra were taken on a Perkin Elmer Spectrum 100 FTIR spectrometer. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and NOESY, HMQC, spectra were recorded on a Varian AS 400 NMR spectrometer and optical rotations were measured on a Rudolph Research Analytical Autopol II automatic polarimeter in a 0.5 dm cell at given temperature. Elemental analyses were performed on a LECO CHNS 932 analyser. TLC and column chromatography were performed on precoated aluminium silica gel plates G-60 F_{254} (Merck 5554) and 70-230 mesh silica gel (Merck 7734), respectively; the spots were visualized using ethanolic solution of H_2SO_4 (5%, v/v) followed by heating at 100°C. Solvents and reagents were bought from Merck, Sigma-Aldrich, and Alfa Aesar. All solvent removals were carried out under reduced pressure.

3.2. Preparation of Anhydrous Chloral (Trichloroacetaldehyde). The mixture of chloral hydrate (320 g) and concentrated H_2SO_4 (180 mL, d: 1.84 g/mL) was stirred and distilled with anhydrous $CaCl_2$ filled drying tube attached to receiver adapter of simple distillation apparatus. Distillation gave a pure anhydrous chloral (171 mL, 258.6 g, d: 1.51 g/mL, transparent liquid) with 91% yield.

*3.3. 1,2-O-(S)-Trichloroethylidene-α-D-ribofuranose (β-Ribochloralose) (**1**).* Dry D-ribose (40 g, 0.267 mol) was added to freshly dried anhydrous chloral (122 mL, 1.25 mol), and the mixture was stirred before concd. H_2SO_4 (1 mL) catalyst was added. The mixture was refluxed under stirring for 2 h. Excess chloral was evaporated under reduced pressure. Black-colored syrupy residue was dissolved in methanol (500 mL) and activated charcoal (2.0 g) was added. The mixture was refluxed for 30 min and filtered through a bed of silica gel topped celite. Subsequently, methanol was removed from yellow solution under reduced pressure. The residue was crystallized from boiling chloroform. The compound **1** was obtained as colorless crystals. Product **1** cannot be recrystallized from hot water or methanol due to dissolution unlike other chloraloses reported in literatures [5, 8, 9], yield: 21 g (28%); mp 122-123°C; $[\alpha]_D^{25}$ + 38.0 (*c* 1.0, CH_3OH); FTIR (cm^{-1} in KBr): 3497 and 3364 (2×OH), 2980, 2950, 2906 (C-H); ^{1}H NMR (400 MHz, C_5D_5N): δ 7.09 (bs, 2H, 2×OH), 6.66 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 6.36 (s, 1H, $HCCCl_3$), 5.41 (t, 1H, $J_{2,3}$ = 4.0 Hz, H-2), 4.83 (dd, 1H,$J_{3,4}$ = 8.8 Hz, H-3), 4.73 (ddd, 1H, $J_{4,5a}$ = 2.0 Hz, $J_{4,5b}$ = 4.4 Hz, H-4), 4.67 (dd, 1H, $J_{5a,5b}$ = 12.4 Hz, H-5a), 4.45 (dd, 1H, H-5b); ^{13}C NMR (100 MHz, C_5D_5N): δ 110.5 ($\underline{C}HCCl_3$), 106.7 (C-1), 101.1 (CCl_3), 83.7 (C-4), 83.3 (C-2), 72.1 (C-3), 61.2 (C-5); Anal. Calcd. for $C_7H_9Cl_3O_5$: C, 30.08; H, 3.25. Found: C, 29.86; H, 3.30.

*3.4. 3,5-Di-O-acetyl-1,2-O-(S)-trichloroethylidene-α-D-ribofuranose (**2**).* Acetic anhydride (1.35 mL, 0.0143 mol, d:1.08 g/mL, 4 eq.) was added to a solution of **1** (1.0 g, 0.0036 mol) in pyridine (15 mL). The mixture was slightly swirled and allowed to stand for overnight at room temperature in the dark. The completion of reaction was determined by TLC (Tol : MeOH, 8 : 2). The reaction mixture was poured into ice-water (100 mL) and stirred for 0.5 h. The mixture was extracted with CH_2Cl_2 (3 × 50 mL) and combined CH_2Cl_2 extracts were dried with Na_2SO_4, filtered, and evaporated to give **2** as a colorless solid, yield: 1.23 g (94%); purified via crystallization from boiling hexane, mp 66-67°C; $[\alpha]_D^{25}$ + 108.0 (*c* 1.0, CH_3OH); FTIR (cm^{-1} in KBr): 2995, 2971, 2942, 2921 (C-H), 1742 (Acetyl-C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.69 (s, 1H, $HCCCl_3$), 5.16 (dd, 1H, $J_{2,3}$ = 5.2 Hz, H-2), 4.72 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.39 (dd, 1H, $J_{5a,5b}$ = 12.4 Hz, $J_{4,5a}$ = 2.4 Hz, H-5a), 4.26 (ddd, 1H, $J_{4,5b}$ = 5.2 Hz, H-4), 4.16 (dd, 1H, H-5b), 2.17 and 2.10 (s, 6H, 2×CH_3-acetyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6 and 170.1 (2×Acetyl-C=O), 110.2 ($\underline{C}HCCl_3$), 106.8 (C-1), 99.3 (CCl_3), 79.3 (C-2), 76.8 (C-4), 72.0 (C-3), 62.2 (C-5), 20.9 and 20.6 (2×Acetyl-CH_3); Anal. Calcd. for $C_{11}H_{13}Cl_3O_7$: C, 36.34; H, 3.60. Found: C, 36.31; H, 3.58.

*3.5. 1,2,3-O-Orthodichloroacetyl-α-D-ribofuranose (**3**).* To a solution of **1** (3.0 g, 0.011 mol) in *t*-butanol (40 mL), potassium *t*-butoxide (1.44 g, 0.0129 mol) was added. The reaction mixture was stirred and heated under reflux for 3 h. The completion of reaction was determined by TLC (Tol : MeOH, 8 : 2). Solvent was removed under reduced pressure, the residue was dissolved in hot CH_2Cl_2 (150 mL) and then filtered. The filtrate was evaporated and solid residue was purified by column chromatography on silica gel with CH_2Cl_2-MeOH (100/1) to give **3** as a colorless syrup, yield: 2.05 g (77%); $[\alpha]_D^{25}$ + 24.0 (*c* 1.0, CH_3OH); FTIR (cm^{-1} on KBr disk): 3504 (OH), 3090 ($\underline{CH}Cl_2$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02 (s, 1H, $CCHCl_2$), 5.78 (d, 1H, $J_{1,2}$ = 2.4 Hz, H-1), 5.40 (t, 1H, $J_{2,3}$ = 2.4 Hz, H-2), 4.52 (d, 1H, $J_{3,4}$ = 0.0 Hz, H-3), 4.48 (t, 1H, $J_{4,5a}$ = 2.8 Hz, $J_{4,5b}$ = 2.8 Hz, H-4), 3.86 (ddd, 1H, $J_{5a,5b}$ = 12.2 Hz, $J_{5a,OH}$ = 4.8 Hz, H-5a), 3.76 (ddd, 1H, $J_{5b,OH}$ = 6.4 Hz, H-5b), 1.70 (dd, 1H, OH); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 117.8 ($\underline{C}CCl_2H$), 102.8 (C-1), 84.2, 80.1, 78.7, 64.6, 61.9 (C-2, C-3, C-4, C-5, CCl_2H); Anal. Calcd. for $C_7H_8Cl_2O_5$: C, 34.59; H, 3.32. Found: C, 34.02; H, 3.04.

*3.6. 5-O-Acetyl-1,2,3-O-orthodichloroacetyl-α-D-ribofuranose (**4**).* Acetic anhydride (0.39 mL, 0.0041 mol, d:1.08 g/mL, 2 eq.) was added to solution of (0.5 g, 0.0021 mol) **3** in pyridine (10 mL). The mixture was slightly swirled and allowed to stand for overnight at room temperature in the dark. The completion of reaction was determined by TLC (Tol : MeOH, 8 : 2). The reaction mixture was poured into ice-water (50 mL) and stirred for 0.5 h. The mixture was extracted with CH_2Cl_2 (3 × 25 mL). Combined organic phases were dried with Na_2SO_4, filtered, and evaporated to give **4** as a colorless solid. The product **4** was crystallized from boiling hexane as a colorless crystals, yield: 0.53 g (88%); mp 90-91°C; $[\alpha]_D^{25}$ + 40.0 (*c* 1.0, CH_3OH); FTIR (cm^{-1} in KBr): 2959 and 2893 (C-H), 1746 (Acetyl-C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 6.03 (s, 1H, $CCHCl_2$), 5.75 (d, 1H, $J_{1,2}$ = 2.4 Hz, H-1), 5.33 (t, 1H, $J_{2,3}$ = 2.4 Hz, H-2), 4.60 (t, 1H, $J_{4,5a}$ = 3.6 Hz, $J_{4,5b}$ = 3.6 Hz, H-4), 4.49 (dd, 1H, $J_{3,4}$ = 0.4 Hz, H-3), 4.25 (dd, 1H, $J_{5a,5b}$ = 12.4 Hz, H-5a), 4.17 (dd, 1H, H-5b), 2.10 (s, 1H, Acetyl-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3 (C=O), 118.0 ($\underline{C}CCl_2H$), 102.6 (C-1), 81.7 (C-4), 79.7 (C-2), 78.0 (C-3), 64.4 (CCl_2H), 63.2 (C-5), 20.9 (Acetyl-CH_3); Anal. Calcd. for $C_9H_{10}Cl_2O_6$: C, 37.92; H, 3.54. Found: C, 36.83; H, 3.17.

*3.7. 3-O-Methyl-1,2-O-(S)-trichloroethylidene-α-D-ribofuranose (3-O-Methyl-β-ribochloralose) (**5**).* Trityl chloride (7.5 g, 0.0268 mol, 1.5 eq.) was added to a solution of β-ribochloralose (5.0 g, 0.0179 mol) (**1**) in pyridine (30 mL). The reaction mixture was stirred at room temprature for 3 days, then poured into ice-water and allowed to warm up to room temperature; then the solution was decanted. Syrupy product was dissolved in toluene; then organic phase was washed, diluted HCl solution, and saturated sodium carbonate. The organic phase was dried under anhydrous Na_2SO_4 and evaporated. The residue was purified on silica gel by flash column chromatography eluted with CH_2Cl_2. The product (7.6 g) was not pure analytically, but this purity was enough to use it directly for the next step without extra purification.

BaO (5.0 g), $Ba(OH)_2 \cdot 8H_2O$ (0.2 g) and iodomethane (2.5 mL) were added to solution of crude product (7.6 g) in DMF (60 mL) at 0°C. After the addition, the mixture was stirred at room temprature for overnight. Solution was filtered, washed with CH_2Cl_2 (300 mL), and combined filtrates were evaporated. The residue was taken into CH_2Cl_2 and decolourized with sodium thiosulfate solution, washed with water, then dried under anhydrous sodium sulphate. The removal of the solvent gave syrupy product.

The syrupy product was mixed with methanol (60 mL), water (10 mL) and concd. HCl (2 mL). The solution was refluxed for 3 h. Hydrolysis process was monitored by TLC (toluene : methanol, 9 : 1). Most of the methanol was removed after neutralization with saturated sodium carbonate solution and the aqueous residue was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were dried over Na_2SO_4. Dried solution was evaporated and the syrupy product was purified on silica gel by flash column chromatography (Toluen : MeOH, 95 : 5). Titled compound was obtained as a syrup of 3.95 g, total yield from **1**: (75%). $[\alpha]_D^{22}$ + 90.0 (*c* 0.2, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 6.12 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.74 (s, 1H, $HCCCl_3$), 5.02 (t, 1H, $J_{2,3}$ = 4.0 Hz, H-2), 3.98-3.68 (m, 4H, H-3, H-4, H-5a and H-5b), 3.53 (s, 3H, CH_3) and 2.07 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.3 ($\underline{C}HCCl_3$), 106.9 (C-1), 99.7 (CCl_3), 80.3, 79.7, 79.1, 60.6 (C-2, C-3, C-4, C-5), 58.6 (OCH_3); Anal. Calcd. for $C_8H_{11}Cl_3O_5$: C, 32.73; H, 3.78. Found: C, 31.65; H, 3.38.

*3.8. 5-O-Tosyl-1,2-O-(S)-trichloroethylidene-α-D-ribofuranose (**6**).* A solution of tosyl chloride (1.03 g, 0.0054 mol, 1.2 eq.) in pyridine (10 mL) was added dropwise to a stirred solution of β-ribochloralose (**1**) (1.0 g, 0.0036 mol) in pyridine (20 mL) at 0°C for during 1 h and the mixture was allowed in room temprature for 8 h (monitored by toluene : MeOH, 9 : 1), then poured into ice-water (150 mL) and stirred for 1 h. The solution was extracted with CH_2Cl_2 (4 × 50 mL), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The syrupy residue was purified by column chromatography eluting with (Toluen : MeOH, from 99 : 1 to 95 : 5). Yield for the syrupy product: 0.95 g (61%); $[\alpha]_D^{24}$ + 12.0 (*c* 0.2, CH_3OH); FTIR (cm^{-1} on KBr disk): 3154 (OH), 3060 (Aromatic C-H), 3002, 2946, 2926, 2906 (Aliphatic C-H), 1600, 1448, 1422, 1392 (Aromatic C=C from tosyl group), 1356, 1172 (SO_2), 1098 (C-O-C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, 2H, J = 8.4 Hz, benzene), 7.36 (d, 2H, benzene), 6.05 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.69 (s, 1H, $HCCCl_3$), 5.02 (bt, 1H, $J_{2,3}$ = 4.0 Hz, H-2), 4.35 (dd, 1H, $J_{5a,5b}$ = 11.4 Hz, $J_{4,5a}$ = 2.4 Hz, H-5a), 4.20 (dd, 1H, $J_{4,5b}$ = 4.2 Hz, H-5b), 3.98 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{3,OH}$ = 9.6 Hz, H-3), 3.91 (ddd, 1H, H-4), 2.63 (d, 1H, OH), 2.45 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5 and 132.7 (*ipso*-benzene, 2×C), 130.2 and 128.2 (benzene, 4×C), 110.2 ($\underline{C}HCCl_3$), 106.6 (C-1), 99.4 (CCl_3), 81.0, 78.9, 71.5, 67.5, 58.6 (C-2, C-3, C-4, C-5), 21.9 (CH_3); Anal. Calcd. for $C_{14}H_{15}Cl_3O_7S$: C, 38.77; H, 3.49; S, 7.39. Found: C, 37.84; H, 3.51; S, 6.86.

*3.9. 5-Azido-5-deoxy-1,2-O-(S)-trichloroethylidene-α-D-ribofuranose (**7**).* NaN_3 (0.67 g, 0.01 mol) was added to a solution of compound **6** (0.90 g, 0.0021 mol) in dry DMF (15 mL). The mixture was heated and stirred at 115°C for 2 h. The reaction was monitored via TLC (Tol : MeOH, 9 : 1), and then the mixture was poured into ice-water (150 mL). Solid product was filtered and washed with cold water, dried in air. Colourless product is 0.49 g, yield 77%, mp 129–131°C; $[\alpha]_D^{24}$ + 92.0 (*c* 0.2, CH_3OH); FTIR (cm^{-1} in KBr): 3512 (OH), 3006, 2976, 2944, 2908 (Aliphatic C-H), 2102 (-N_3), 1120 (C-O-C); ^1H NMR (400 MHz, $CDCl_3$): δ 6.12 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.74 (s, 1H, $HCCCl_3$), 4.95 (bt, 1H, $J_{2,3}$ = 4.4 Hz, H-2), 4.02-3.93 (m, 1H, H-3), 3.89 (ddd, 1H, $J_{3,4}$ = 8.4 Hz, $J_{4,5a}$ = 2.4 Hz, $J_{4,5b}$ = 4.8 Hz, H-4), 3.71 (dd, 1H, $J_{5a,5b}$ = 13.6 Hz, H-5a), 3.43 (dd, 1H, H-5b), 2.49 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.3 ($\underline{C}HCCl_3$), 106.7 (C-1), 99.5 (CCl_3), 81.2, 80.3, 72.4 (C-2, C-3, C-4), 50.7 (C-5); Anal.

Calcd. for $C_7H_8Cl_3N_3O_4$: C, 27.61; H, 2.65; N, 13.80. Found: C, 26.29; H, 2.55; N, 12.51.

*3.10. 5-Amino-5-deoxy-1,2-O-(S)-trichloroethylidene-α-D-ribofuranose (**8**).* Triphenylphosphine (0.823 g, 0.0031 mol) was added to a solution of compound **7** (0.477 g, 0.0016 mol) in methanol (15 mL). The mixture was refluxed for 3 h and reaction was monitored by TLC (CH_2Cl_2 : MeOH, 9 : 1). The solvent was evaporated under reduced pressure. The residue was purified by column chromatography eluting with CH_2Cl_2 : MeOH (9 : 1). 0.32 g of yellowish solid product was obtained, yield: 72%, mp 200°C (dec.); $[\alpha]_D^{22}$ + 50.0 (*c* 0.2, CH_3OH); FTIR (cm^{-1} in KBr): 3430 (OH), 3248, 3118 (NH_2), 2936, 2918 (Aliphatic C-H), 1624 (N-H bending), 1158 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (bs, 2H, NH_2), 6.12 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.84 (s, 1H, $HCCCl_3$), 4.86 (bt, 1H, $J_{2,3}$ = 4.4 Hz, H-2), 4.01 (ddd, 1H, $J_{3,4}$ = 8.4 Hz, $J_{3,4}$ = 8.6 Hz, $J_{4,5a}$ = 2.8 Hz, $J_{4,5b}$ = 8.4 Hz, H-4), 3.87 (dd, 1H, H-3), 3.15 (dd, 1H, $J_{5a,5b}$ = 13.6 Hz, H-5a), 2.90 (dd, 1H, H-5b), 2.57 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.4 ($\underline{C}HCCl_3$), 106.7 (C-1), 100.2 (CCl_3), 94.3, 82.3, 77.4, 72.8 (C-2, C-3, C-4, C-5); Anal. Calcd. for $C_7H_8Cl_3NO_4$: C, 30.19; H, 3.62; N, 5.03. Found: C, 29.69; H, 3.32; N, 4.62.

4. Conclusions

It was demonstrated herein that 1,2-*O*-(*S*)-trichloroethylidene-α-D-ribofuranose (β-ribochloralose) (**1**) was synthesized with stereoselectivity. Stereochemical information of **1** was gathered from HMBC, HMQC, and NOESY experiments. 3,5-Diacetyl- (**2**), 1,2,3-tricyclic orthoester- (**3**) and 5-acetyl-1,2,3-tricyclic orthoester- (**4**), 3-*O*-methyl- (**5**), 5-*O*-tosyl- (**6**), 5-azido- (**7**), and 5-amino- (**8**), derivatives of ribochloralose (**1**), were obtained via known synthesis techniques in the literature. All new compounds were characterized by NMR and FTIR spectroscopic methods. These new compounds could be used as intermediates in synthetic carbohydrate chemistry.

Acknowledgment

The authors would like to thank Celal Bayar University for financial support.

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