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A Novel Reagent for the Synthesis of Branched-chain Functionalized Sugars. Dichloromethyllithium

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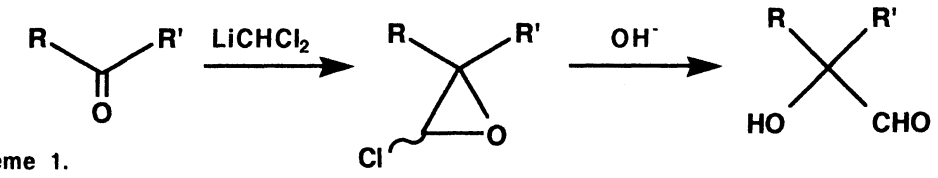
A few novel branched-chain functionalized sugars, which have important functions such as hydroxyl, hydro, chloro, or azido at quaternary carbon were prepared in good yield *via* the same intermediary spiro chloroepoxide derivative by use of dichloromethyllithium.

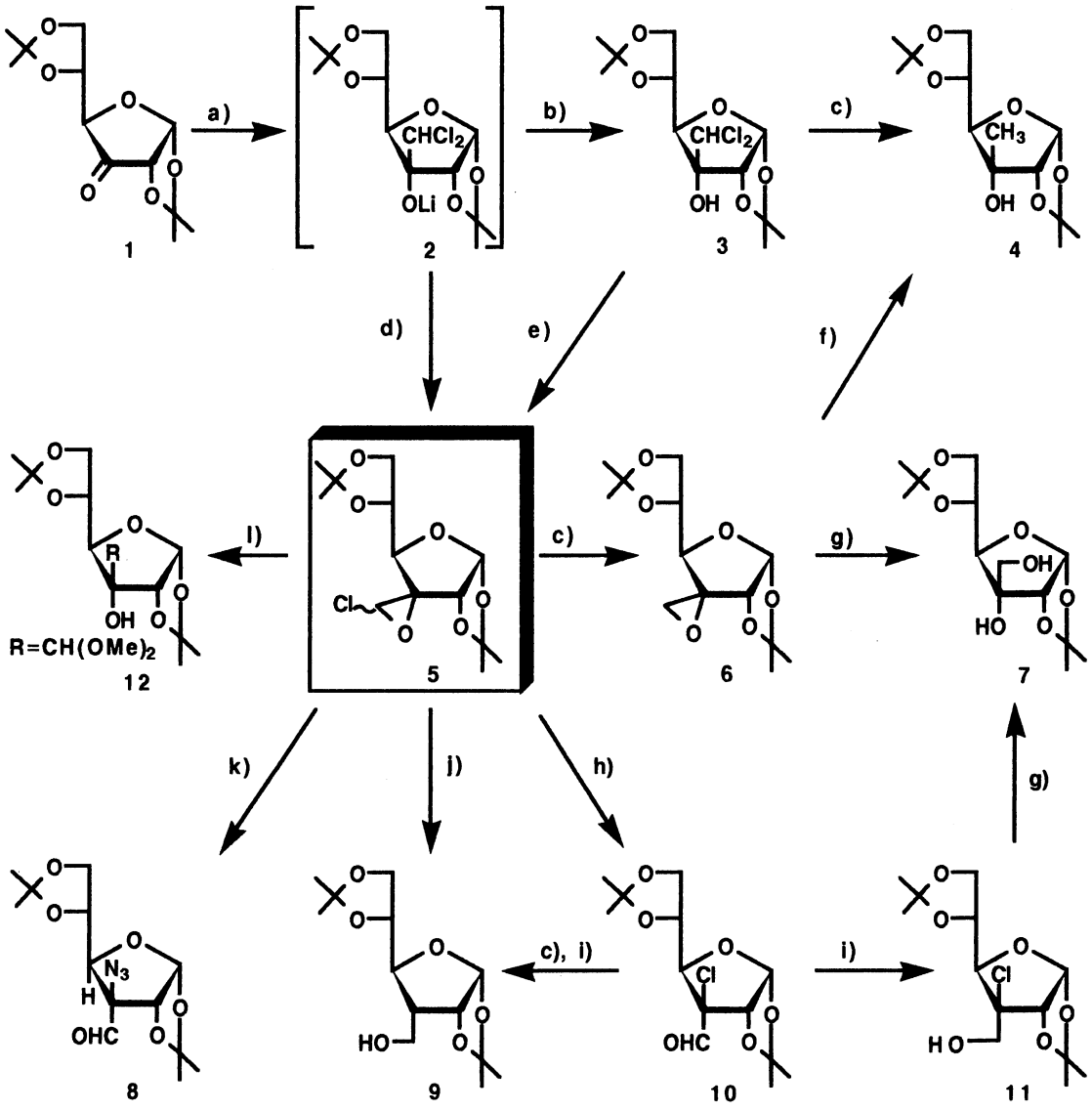
Numerous new branched-chain sugars as the glycosidic component of antibiotics during the past two decades have stimulated extensive researches on the chemistry and biochemistry of the sugars. Most of the branched-chain sugars found in nature have a polar substituent at the branching carbon-atom(Type A); tertiary alcohols are commonest, and in several instances, an amino or nitro group is attached to the tertiary carbon atom. In a few cases naturally occurring branched-chain sugars have no substituent at the branching carbon atom(Type B). In general, various branched-chain sugars have been synthesized by applying grignard reaction, reformatsky reaction, wittig reaction, organolithium, nitromethane, diazomethane, and cyanohydrin syntheses to a suitable glycosidulose.[1] In 1988, T.T. Thang et al.[2] reported an elegant approach to the synthesis of branched-chain sugars by the use of chloromethyl p-tolyl sulfone.

In this paper, we should like to report on a facile and effective simple reagent, dichloromethyllithium for the



Scheme 1.

synthesis of various functionalized branched-chain sugars, which are easily converted into almost any type of naturally occurring ones. In 1969, G. Köbrich et al.[3] reported that the above reagent gave an α-hydroxyaldehyde derivative from the carbonyl compound in good yield *via* the corresponding spiro chloroepoxy derivatives (Scheme 1).



a) LDA,CH_2Cl_2,THF,-78 °C b) H_2O c) n-Bu_3SnH,AIBN,Toluene d) 65 °C e) DBU,DMSO
f) $LiAlH_4$,Et_2O g) NaOH aq.,1.4-Dioxane h)NaOAc,15-crown-5,HMPA,70 °C i) $NaBH_4$,MeOH
j) $NaBH_4$,DMSO,80 °C k) NaN_3,15-crown-5,HMPA,70 °C l) NaOMe,HMPA,70 °C

Scheme 2.

In that report, the ring opening with hydroxy anion seems to occur with complete regiospecificity at the β-carbon with respect to the chloro group. But the stereochemical course of this reaction is not reported. We were inspired by Köbrich's work in constructing any type of naturally occurring functionalized branched-chain sugars, and tried to study the stereochemical course of this reaction. For the purpose of this study, we selected 1,2;5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose(**1**) as a fundamental starting model compound. (Scheme 2) The key intermediary branched-chain sugar(**3**) was synthesized by treatment of **1** with dichloromethyllithium. A treatment of **3** with nucleophilic reagents such as $NaBH_4$ and NaN_3 gave their corresponding useful branched-sugars (**8** and **9**) , but with NaOAc and NaOMe gave unexpected branched-sugars (**10** and **12**) in high yield respectively. The branched-sugars(**8**,**9**,**10**, and **12**) have useful functions such as azido, hydro, chloro, or hydroxy at quaternary carbon and are converted to branched-chain sugars of type A and B respectively. Among the above mentioned functional groups, azido group can be easily converted into amino or nitro group, and formyl group can be converted into hydroxymethyl, methyl, 1-hydroxyethyl, acetyl, 2-hydroxyacetyl, 1,2-dihydroxyethyl, higher alkyl, or carboxyl group, all of which groups are found in nature.

Reaction of 1,2;5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose **1** with dichloromethyllithium(2.0 equiv.) in oxolane at -78 °C gave 1,2;5,6-di-O-isopropylidene-3-C-dichloromethyl-α-D-allofuranose **3** *via* (**2**) in 88% yield. When the above reaction mixture of **2** was heated to 65 °C, spiro chloroepoxide(**5**) was obtained in 93% yield instead of tertiary alcohol **3**. The stereochemistry of all the products involved in this paper were determined mainly by the direct comparison with the known compounds. A successive treatment of **3** or **5** with tributyltin hydride in toluene at 110 °C gave known 1,2;5,6-di-O-isopropylidene-3-C-methyl-α-D-allofuranose (**4**)[4] and 3,3'-anhydro-3-C-hydroxymethyl-1,2;5,6-di-O-isopropylidene-α-D-allofuranose(**6**)[5,6a] respectively in quantitative yield. Reduction of **6** with lithiumalminum hydride in ether gave **4** in good yield. An alkali hydrolysis of **6** gave its corresponding hydroxymethyl derivative (**7**)[6b] in quantitative yield. A treatment of **3** or **5** with NaN_3(10 equiv.) and 15-crown-5 (catalytic amount) in hexamethylphosphoramide(HMPA) at 70 °C gave 3-C-azido-3-C-formyl-1,2;5,6-di-O-isopropylidene-α-D-glucofuranose(**8**) in 85% yield, whose structure was supported by nmr(NOE;10%,between formyl and H-4 proton). The deoxy compound (**9**) was derived by reduction of **3** or **5** with $NaBH_4$ in dimethylsulfoxide(DMSO) at 80 °C in 65% yield. **9** was acetylated to confirm its structure(Acetyl derivative of **9**: $J_{2,3}$=4.6, $J_{3,4}$=10.0 Hz). A similar treatment of **3** or **5** with NaOAc(10 equiv.) gave an unexpected migration product 3-C-chloro-3-C-formyl-1,2;5,6-di-O-isopropylidene-α-D-glucofuranose(**10**) instead of tertiary acetoxy derivative, in 83% yield. A radical reduction of **10** with tributyltin

hydride in toluene at 110 °C gave 3-deoxy-3-C-formyl-1,2;5,6-di-O-isopropylidene-α-D-allofuranose in the form of hydrate in 95% yield, which was reduced with $NaBH_4$ in methanol to give corresponding 3-deoxy-3-C-hydroxymethyl-1,2;5,6-di-O-isopropylidene-α-D-allofuranose **9** in 91% yield. A hydride reduction of **10** with $NaBH_4$ in MeOH-H_2O at room temperature gave 3-C-chloro-3-C-hydroxymethyl-1,2;5,6-di-O-isopropylidene-α-D-glucofuranose(**11**) in 96% yield, which was treated with 1N NaOH in 1,4-dioxane-H_2O(1: 1) in a reflux condition to give **7** *via* **6** in 70% yield. On the other hand, a treatment of **3** or **5** with NaOMe(10 equiv.) in HMPA at 70 °C gave 1,2;5,6-di-O-isopropylidene-3-C-dimethoxymethyl-α-D-allofuranose(**12**) in quantitative yield. In conclusion, ring opening of chloroepoxide with nucleophile such as -N_3, -H, or -Cl occur with a complete regiospecificity and S_N2 reaction at the β carbon in respect to the chloro group is shown. But in the case of methoxy anion, reaction occurred at α carbon. The difference in regiospecificity may be due to the reactivities of nucleophiles(hard and soft). Thus the method proposed herein may promise a wide application to the preparation of functionalized branched-chain sugars whose branching carbon is in the sterically hindered side.

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