

NUCLEOPHILIC ACYLATION IN CARBOHYDRATE CHEMISTRY :  
NOVEL METHODS FOR CHAIN BRANCHING AND EXTENSION.

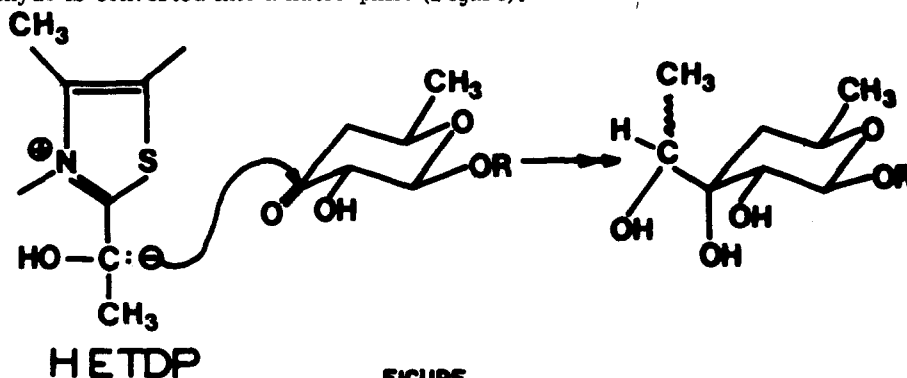
A.M. SEPULCHRE , A. GATEAU-OLESKER, G. LUKACS, G. VASS and S.D. GERO  
(Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif sur Yvette, France)  
and W. VOELTER

(Chemisches Institut der Universität, 74, Tübingen, Wilhelmstrasse 33, Germany)

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The widespread biological interest in the multitude of antibiotics containing branched and extended chain carbohydrate derivatives<sup>1-7</sup> has encouraged a great deal of synthetic work. Despite the considerable and successful activities in this field, we felt that an entirely new approach was necessary because none of the available methods<sup>9</sup> give a direct synthesis of a functionalized branched chain.

It has been shown<sup>1,4,8</sup> that the biosynthetic precursor for the hydroxyethyl branch of D-aldgarose—a component of aldgamycine E— is "active acetaldehyde"<sup>4,8</sup> hydroxyethylthiamine pyrophosphate (HETDP), in which the original electrophilic carbonyl function of acetaldehyde is converted into a nucleophile (Figure).



It occurred to us—inspired by the enzyme mediated reactions—that a generally applicable synthetic method for the preparation of any functionalized branched or extended chain carbohydrate derivatives would be available if one could generate similar carbanions derived from appropriately protected aldehydes. 1,3-Dithiane and related carbanion systems, in- \* genously used by Corey and Seebach<sup>10-13</sup> for "nucleophilic acylation" might fulfill this roll.

We report herein the stereospecific synthesis of carbohydrate derivatives containing a highly functionalized C<sub>2</sub> unit, by the reaction of carbanion 1 derived from 2-methyl-1,3-dithiane<sup>13</sup> with sugars possessing keto, aldehyde and lactone functions.

Reaction of methyl 3,4-O-isopropylidene- $\beta$ -D-erythro-pentopyranosid-2-ulose<sup>14</sup> 2  
\* Recently, the use of 2-lithio-1,3-dithiane has been explored<sup>18,30</sup>.

with equimolar quantities of 2-lithio-2-methyl-1,3-dithiane in dry tetrahydrofuran solution at  $-20^{\circ}$  for 18 hours afforded the highly crystalline, methyl 2-C-(1',3'-dithian-2'-methyl-2'-yl)-3,4-O-isopropylidene- $\beta$ -D-ribofuranoside 3, m.p.  $110-111^{\circ}$ ,  $[\alpha]_D -88^{\circ}$  (c 1.02 in  $\text{CHCl}_3$ ), in 71 % yield. Treatment of 3 with mercuric oxide boron trifluoride etherate in aqueous tetrahydrofuran gave crystalline methyl 2-C-acetyl-3,4-O-isopropylidene- $\beta$ -D-ribofuranoside 4, m.p.  $66-67^{\circ}$ ,  $[\alpha]_D -152^{\circ}$  (c 0.9 in  $\text{CHCl}_3$ ), in 87 % yield.

Similar treatment of 1,2 ; 5,6-di-O-isopropylidene- $\alpha$ -D-ribohexofuranose-3-ulose<sup>15</sup> 5 with 2-lithio-2-methyl-1,3-dithiane afforded the sirupy 3-C-(1',3'-dithian-2'-methyl-2'-yl)-1,2 ; 5,6-di-O-isopropylidene- $\alpha$ -D-allofuranose 6, (55 %),  $M^+ 392$ ,  $[\alpha]_D +9^{\circ}$  (c 1.3 in  $\text{CHCl}_3$ ). Compound 6, on treatment with Raney nickel catalyst in ethanol yielded 3-C-ethyl-1,2 ; 5,6-di-O-isopropylidene- $\alpha$ -D-allofuranose 7, m.p.  $87-88^{\circ}\text{C}$ ,  $[\alpha]_D +22^{\circ}$  (c 1.21 in  $\text{CHCl}_3$ ).

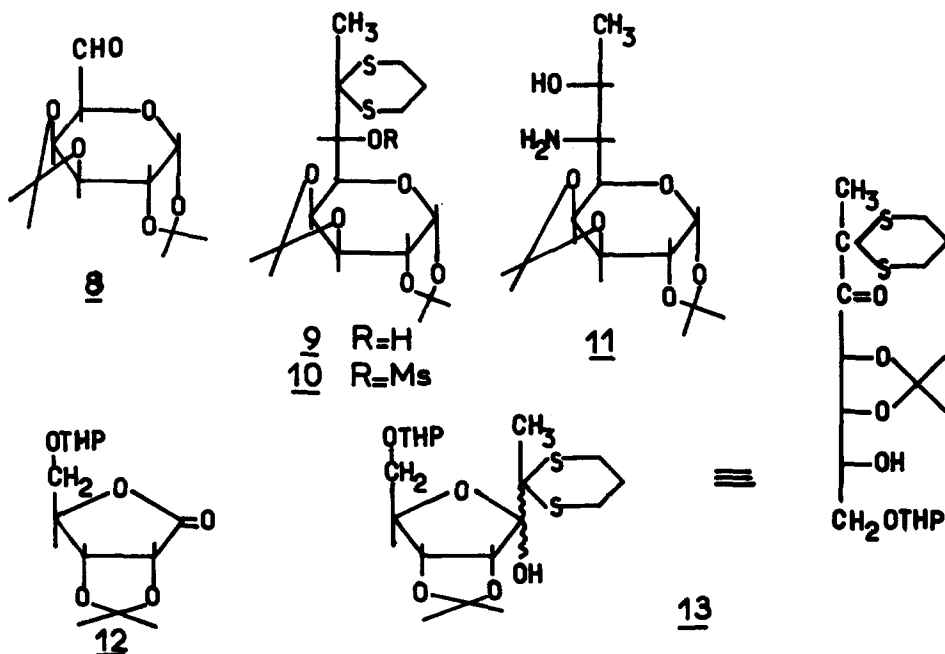
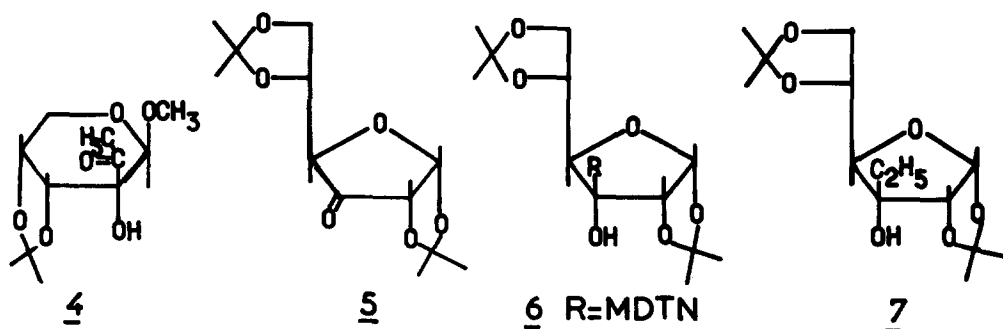
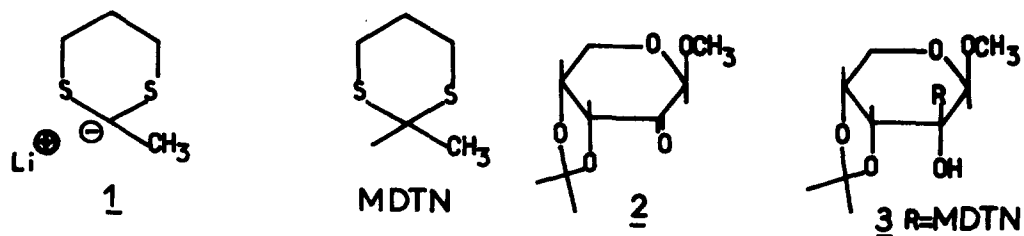
The D-ribo and D-allo configuration of 3 and 6 was deduced from comparative  $^{13}\text{C}$  N.M.R.<sup>16</sup> and circular dichroism studies<sup>17</sup> data with the recently reported<sup>18</sup> methyl 2-C-(1',3'-dithian-2'-yl)-3,4-O-isopropylidene- $\beta$ -D-ribofuranoside and 3-C-(1',3'-dithian-2'-yl)-1,2 ; 5,6-di-O-isopropylidene- $\alpha$ -D-allofuranose. Their absolute configurations at centres bearing the branched-chain were firmly established by chemical interconversions and degradations<sup>18</sup>.

The preparation of 8-deoxy-1,2 ; 3,4-di-O-isopropylidene-L-glycero- $\alpha$ -D-galacto-octos-7-ulose propylene dithioacetal 9 - a potential key intermediate for the synthesis of lincosamine 11 is a considerable interest<sup>2,9,19,20</sup>. Therefore it seemed attractive to attempt its construction by a one step synthesis from readily available 1,2 ; 3,4-di-O-isopropylidene- $\alpha$ -D-galacto-hexodialdo-1,5-pyranose<sup>21</sup> 8. Treatment of 8 with equimolar quantities of 2-lithio-2-methyl-1,3-dithiane in dry hexamethylphosphoric triamide (HMPT) solution at  $-20^{\circ}$  for 18 hours gave a crystalline product in 34 % yield,  $M^+ 392$ , m.p.  $111-112^{\circ}$ ,  $[\alpha]_D -53^{\circ}$  (c 1.17 in  $\text{CHCl}_3$ ), whose structure has been established as 8-deoxy-1,2 ; 3,4-di-O-isopropylidene-L-glycero- $\alpha$ -D-galacto-octos-7-ulose propylidene-dithioacetal 9. Sulphonylation of 9 with methansulphonyl chloride in pyridine at  $0^{\circ}$  yielded the methansulphonate 10 (75 %),  $M^+ 470$ , m.p.  $124-125^{\circ}$   $[\alpha]_D -67^{\circ}$  (c 1 in  $\text{CHCl}_3$ ).

The absolute configuration at the newly formed asymmetric centre (C-6 in 9) was established on the basis of circular dichroism studies. Compound 9 has a Cotton effect<sup>17</sup> which corresponds in sign and location with that of 6-C-(1',3'-dithian-2'-yl)-1,2 ; 3,4-di-O-isopropylidene-L-glycero- $\alpha$ -D-galacto-heptopyranose<sup>18</sup>. The L-glycero configuration of the latter was proved by chemical correlations<sup>18</sup>.

Extended chain carbohydrate derivatives at the terminal position are potential intermediates for the synthesis of naturally occurring C-nucleoside antibiotics<sup>2,3,9,22,27</sup>. A novel chain extension based on the nucleophilic addition of lactone 12 with 2-lithio-2-methyl-1,3-dithiane is now described.

2,3-O-isopropylidene-5-O-tetrahydropyranyl-D-ribonolactone<sup>25,26</sup> 12 reacted with 2-lithio-2-methyl-1,3-dithiane in tetrahydrofuran to give the sirupy C-(1',3'-



dithian-2'-methyl-2'-yl)-2,3-O-isopropylidene-5-O-tetrahydropyranyl-D-ribofuranose 13 in 55 % yield,  $M^+$  406,  $[\alpha]_D -17^\circ$  (c 1 in  $\text{CHCl}_3$ ). Its N.M.R. and mass spectral data were fully consistent with structure 13.

The present method and its logical extension deserves consideration as a generally applicable approach synthesizing branched and extended chain carbohydrate derivatives.

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