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SYNTHESES OF THE CHROMOMYCINONE SIDE CHAIN FROM CARBOHYDRATE PRECURSORS

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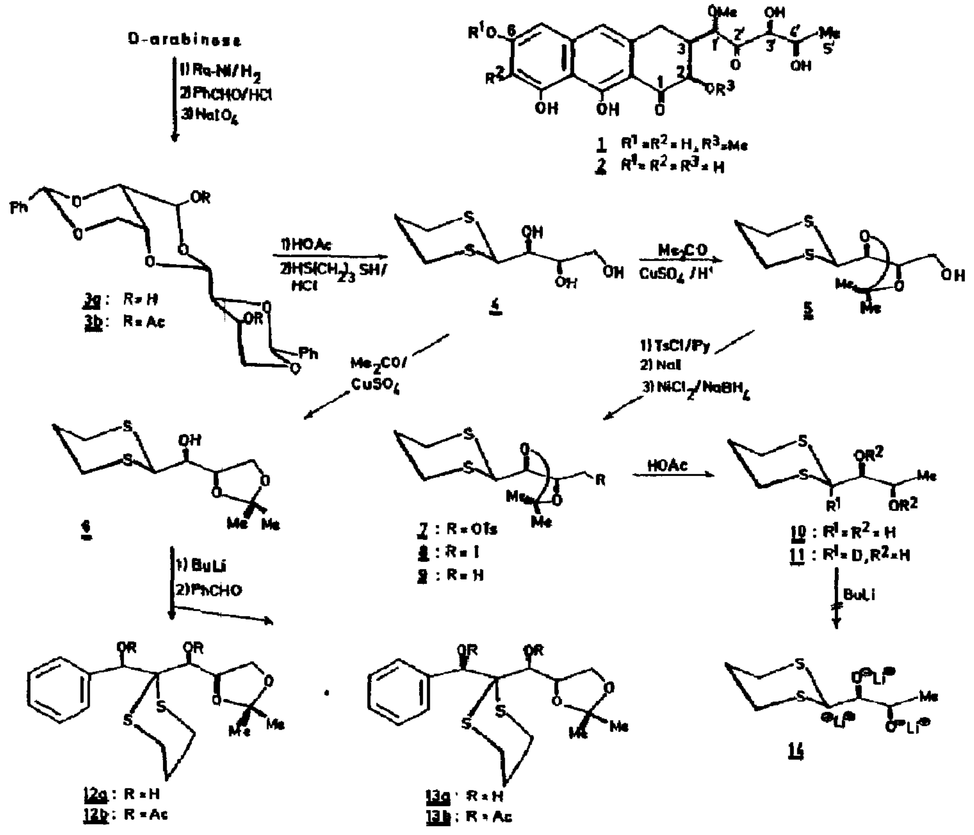
Summary: Appropriate dithiane derivatives of D-threo configuration were prepared starting with D-arabinose and D-galactose, respectively. Their dianions served for nucleophilic additions to model aldehydes, thus comprising syntheses of the complex side chain of chromomycinone. In contrast to former reports a trianion formation of a dithiane-blocked α,β-dihydroxy aldehyde could not be confirmed.

The oligodeoxyoligosaccharide cytostatics chromomycin A_3[1], olivomycin A[2], and mithramycin[3] exhibit marked antitumor activities[4] which exceed that of daunomycin typ agents quite considerably, although various toxic side effects have been reported in clinical application. Recently their constitutions were unequivocally elucidated and partially revised with respect to their saccharide linkages as well as their anomeric configurations[5,6]. The structure of the aglycone backbone of chromomycin A_3 and mithramycin was shown to be the tetrahydroanthracenone derivative chromomycinone (1)[7] with a complex substituted five carbon side chain at C-3 in trans position to the hydroxyl group at C-2[5,6]. Similarly, in olivomycin A the aglycone olivin (2) is present. Whereas considerable progress has been accomplished with regard to the syntheses of the oligodeoxyoligosaccharides[8a-c], there have been only a few communications on synthetic approaches to the aglycone moiety[9-11]. We wish to report here some studies concerning the synthesis of the oligofunctional side chain in chromomycinone starting from carbohydrate precursors.

Owing to the D-threo configuration of the hydroxyl groups at C-3′ and C-4′ in the side chain the first synthetic attempts were started with D-threose derivatives (scheme 1). The preparation of 2,4-O-benzylidene-D-threose[12] from D-arabinose was optimized. As evidenced by i.r., osmometric mass determination, and extensive n.m.r. studies this compound could be shown to adopt the dimeric cyclic acetal-hemiacetal constitution 3a which also applies to its diacetate 3b. The conversion of 3a to D-threose-trimethylenedithioacetal 4 (90 %, $[\alpha]_D^{20}=-2.3^\circ$)[13] was effected using 1,3-dimercaptopropane/fuming hydrochloric acid. With anhydrous copper sulfate and acetone predominantly the crystalline 3,4-O-isopropylidene derivative 6 (71 %, m.p. 65-66°C, $[\alpha]_D^{20}=-5.8^\circ$) was obtained which in the presence of dilute hydrochloric acid isomerizes almost completely to the more stabil 2,3-O-isopropylidene isomer 5. The latter was directly prepared from 4 under similar conditions as 6 but in the presence of catalytic amounts of concentrated sulfuric acid (81 %, $[\alpha]_D^{20}=36.5^\circ$). Treatment of 6 with n-butyl lithium (2.5 molar equiv., -65°C, N_2, THF)[14] gave the dianion which was used for a nucleophilic addition to benzaldehyde as a simple model for the aglycone moiety. Thus both the diastereomers 12a and 13a (m.p. 109°C, $[\alpha]_D^{20}=-6.7^\circ$ and $[\alpha]_D^{20}=-19.5^\circ$) were



- SCHEME 1 -

obtained and separated chromatographically either directly or more conveniently via their diacetates **12b** and **13b** ($[\alpha]_D^{20}$=-13.5° and $[\alpha]_D^{20}$=-11.1°). With respect to **1** and **2** **12a** and **12b** have the wrong, and **13a** and **13b** the correct stereochemistry, however, the determination of the absolute configuration awaits further experiments.

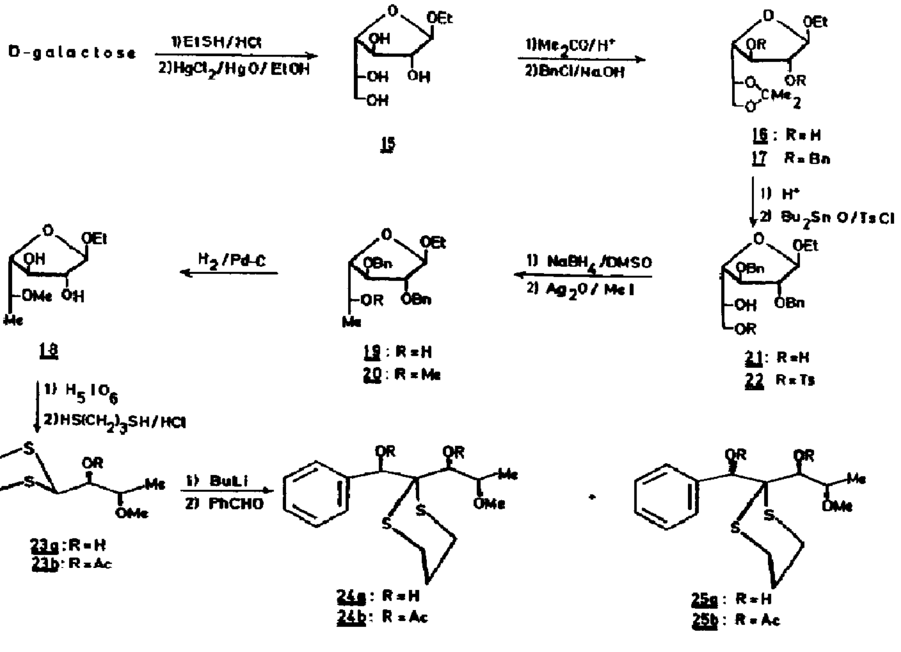
Following these results it was of interest to convert **5** to the 4-deoxy-D-threose-trimethylenedithioacetal (**10**)9). This could be easily accomplished by tosylation of **5** to **7** (97 %, $[\alpha]_D^{20}$=30.0°), its subsequent Finkelstein reaction to the iodide **8** (93 %, $[\alpha]_D^{20}$=21.2°), and a reduction employing the nickel boride procedure 15) to **10** (99 %, m.p. 67-67.5°, $[\alpha]_D^{20}$=-8.3°). The latter step was remarkably successful although 1,3-dithianes have been reported to be desulfurized under comparable conditions 16). The overall yield of **10** based on D-arabinose and this nine step procedure amounts to 8 %, and this competes favourably with a six step procedure starting from trans-crotonic acid (approx. 2 %)9,17).

According to former reports the trianion **14** was described to have been prepared with a 3 molar equiv. of n-butyl lithium from D,L-**10** [n.m.r. ($CDCl_3$): 1-H 3.9-4.4 m(1 H), 2-H 3.6 dd, 3-H ?, 4-CH_3 1.25 d, 2-,3-OH ?, dithiane-H 2.1 m(2 H) and 2.5-3.0 m(6 H); J(1,2)=8.0, J(2,3)=4.0, J(3,4)=8.0 Hz]9). Although its formation was checked by quenching with D_2O and inspection of the C-1 deuterated compound **11** the nucleophilic addition to simple aldehydes was said to be disappointing giving only low yields.

Using pure crystalline 10 [n.m.r.(270 MHz,CDCl$_3$):1-H 4.02 d,2-H 3.68 ddd,3-H 4.18 ddq,4-CH$_3$ 1.33 d,2-OH 2.87 d,3-OH 2.08 d,dithiane-H 1.94-2.14 m(2 H),2.66-2.79 m(2 H), and 2.89-3.00 m(2 H);J(1,2)=7.6,J(2,3)=2.8,J(2,2-OH)=3.6,J(3,4)=6.5,J(3,3-OH)=7.7 Hz] prepared by the above described procedure we were interested to repeat the reported experiments. Numerous attempts to prepare 14 using n-butyl lithium (3 - 6 molar equiv.,-65°C,N$_2$,THF) and subsequent quenching with D$_2$O did not show the formation of any C-1 deuterated derivative 11 as evidenced by careful integration around δ = 4.0.

With respect to these results we feel it necessary to call the reported formation[9] of a trianion 14 in question. We assume that the incorrect formulation relates to the poorly resolved and thus incorrectly assigned n.m.r. spectrum of 10, however, its remains uncertain why even low yields of addition products with aldehydes could have been observed at all. Other attempts to prepare a trianion species of D,L-glycerine-trimethylenedithioacetal did also not meet with success[18]. Thus the question of a trianion formation in dithiane-blocked α,β-dihydroxy aldehydes awaits further experiments.

According to these aspects a more appropriate dianion precursor was synthesized from D-galactose (scheme 2). After formation of D-galactose diethylmercaptal this was cyclized to give ethyl β-D-galactofuranoside (15)[19]. By isopropylidenation to 16, conventional benzylation to 17, and mild acid hydrolysis the dibenzyl derivative 21 ($[\alpha]_D^{20}$=-71.7°) was obtained in 64 % yield. Selective tosylation via an intermediate stannylidene derivative[20] gave 22 (81 %, $[\alpha]_D^{20}$=-45.5°) and reductive detosylation[21] the 6-deoxy compound 19 (82 %, $[\alpha]_D^{20}$=-76.6°). By subsequent methylation 20 (91 %, $[\alpha]_D^{20}$=-37.2°) could be prepared, and finally hydrogenation yielded 18 (91 %, $[\alpha]_D^{20}$=-68.7°). After glycol cleavage and direct treatment with 1,3-propanedithiol/hydrochloric acid 4-deoxy-3-O-methyl-D-threose-trimethylenedithioacetal (23a, 87 %, $[\alpha]_D^{20}$=-10.5°) was obtained and further characterized as



-SCHEME 2 -

its monoacetate 23b (89 %, $[\alpha]_D^{20}$=12.6°). With respect to D-galactose (eleven steps) the overall yield of the key compound 23a amounts to 13 %, based on 15 (nine steps) 37 % are achieved.

Again the generation of a dianion of 23a with n-butyl lithium and subsequent treatment with benzaldehyde as a model aldehyde gave both the diastereomeric compounds 24a and 25a ($[\alpha]_D^{20}$=-1.1° and $[\alpha]_D^{20}$=-32.0°) which could be separated as before and further characterized as their corresponding diacetates 24b and 25b ($[\alpha]_D^{20}$=10.8° and $[\alpha]_D^{20}$=-13.6°). Present studies in progress following these model reactions applied the dianion 23a to anthrachinone aldehydes and will be reported in due time.

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