# LINCOMYCIN ANALOGUES. II. CHAIN-EXTENSION OF METHYL-6-ALDEHYDO-3,4-O-ISOPROPYLIDENE-1-THIO- β-D-GALACTO-1,5-PYRANOSIDE

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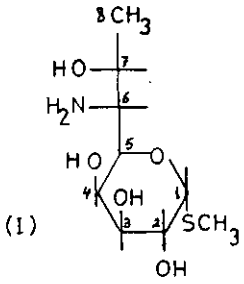
Abstract——— Synthesis of methyl 2,3,4,6-tetra-O-acetyl-1-thio-α-D-galactopyranoside and its β-anomer (3 and 4) from the 2,3,4,6-tetra-O-acetyl- α-D-galactopyranosyl bromide via the isothiouronium salt in HMPT involved a considerable increase in the proportion of the α-anomer. Deacetylation of (3 and 4) with sodium methoxide yielded 5 and 6 respectively. Conversion of (6) into the corresponding 3,4-isopropylidene derivative (7) followed by oxidation with Collin reagent gave the aldehydo-sugar (8) which when reacted with a stabilised phosphorane led in excellent yield to the Z-unsaturated bromo-sugar (9).

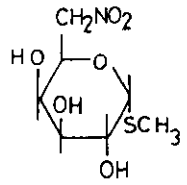
The total synthesis of methyl α-thiolincosaminide (I), the sugar moiety of lincomycin[1], was reported by Magerlein[2] starting with methylthio- α-D-galactopyranoside (obtained in very low yield in the acid-catalysed reaction of D-galactose with methanethiol) which is converted to the corresponding 6-deoxy-6-nitrothiosugar (II) followed by the chain-extension. Other methods of syntheses[3-8] involved the *chain extension of the aldehydo-sugar (III) and introduction of the methylthio-* group at C-1 at the final step through the acid catalysed reaction. Bannister[9] indicated the conversion of the methylthio- β-D-galactopyranoside analogues of(I) into the correspoding α-anomer.

In previous paper[10] we reported the chain extension of (III) through Wittig reaction using stabilised phosphoranes which would provide the same carbon skeleton of the sugar moiety of lincomycin modified at C-8. This paper describes the synthesis of the methylthio- α-D-galactopyranoside and their β-anomer and also the conver-

sion of the latter into the methylthio derivative of (III).



(I)



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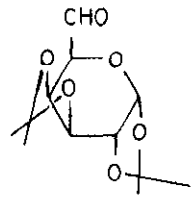
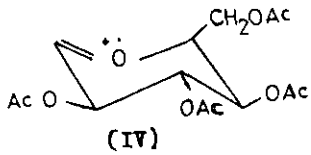
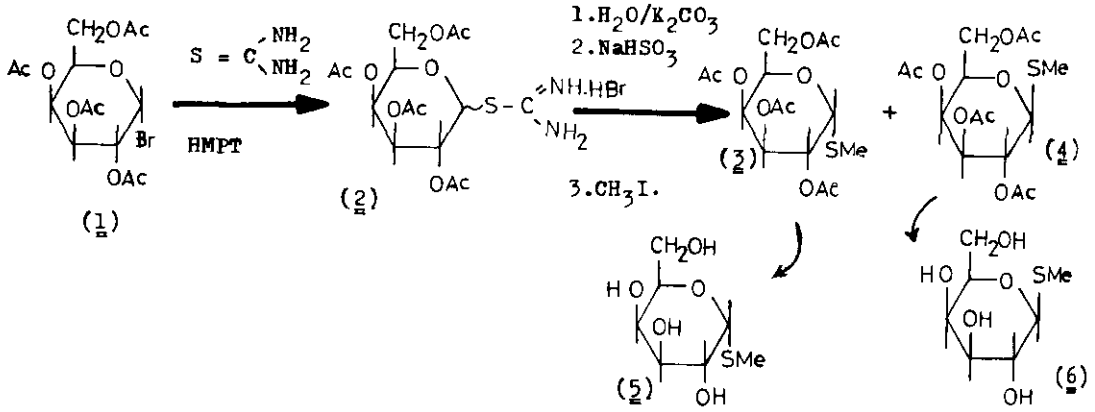


(III)

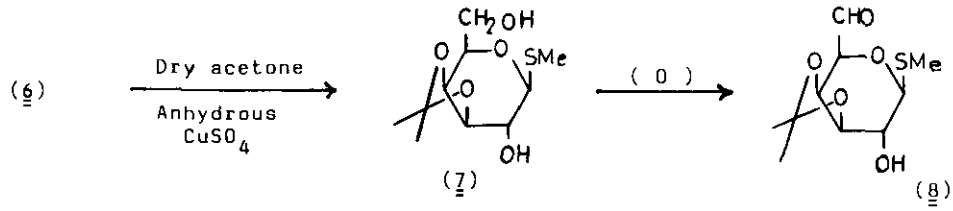
The application of the procedure of Cerny and Pacak[11] on 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosylbromide[12] (1) using dry hexamethylphosphoric triamide (HMPT) as solvent via the isothiouronium bromide (2) gave a mixture of two products (t.l.c), a major one (ethyl acetate - hexane 1:2) of $R_f$ 0.34 and a minor one of $R_f$ 0.38. The chromatographic separation of both products with a long column of "silica gel 60F 254 Merck" gave the faster moving component (3), mp 101-102°C, in 8% yield, followed by a mixture of both products in 30% yield and finelly the slower moving one in 41% yield. The latter was identified as the methylthio-β-D-galactopyranoside (4) by its mp 107-108°C and $[\alpha]_D$ +3° (in chloroform) which have been reported[13]. The ratio of 3 (≃ 12%) were determined by examining the integration area of H-C5 in the $^1$H-nmr spectrum of the mixture. The two products (3 and 4) are consistant with the molecular formula $C_{15}H_{22}O_9S$ obtained by satisfactory elemental analysis, mass spectra and supported by $^1$H-nmr[14]. The mass spectra of both products indicate the first elimination of the methylthio group giving (IV) like the tetra-acetylglycosides followed by the characteristic fragmentation of (IV)[15]. Hydrolysis of (3 or 4) with sodium methoxide in anhydrous methanol[13] gave the corresponding deacetylated derivatives (5 and 6)[16] identified as the α- and β-methylthiogalactopyranosides, respectively, through their mp and $[\alpha]_D$ which were consistent with reported data[2, 13]. Therefore, (3) was assigned as the methyl 2,3,4,6-tetra-O-acetyl- α-D-galactopyranoside. It is noteworthy that the use of HMPT (dipolar-aprotic solvent) would decrease the activation energy of the reaction[17], stabilise a carbocation intermediate by solvation[18], and render the thiourea (non charged nucleophile) more free to react as they are less solvated in the HMPT, thus promoting the formation of α-anomer.

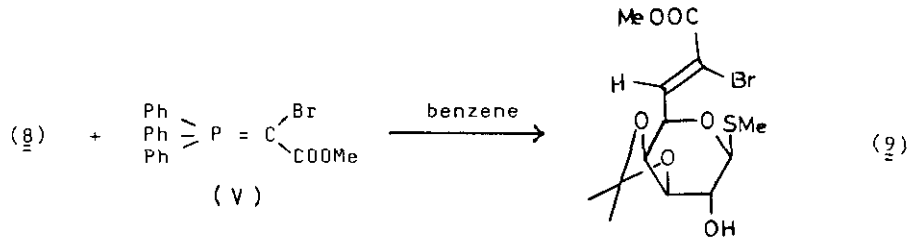


(IV)




Protection of (6) via the 3,4-isopropylidene formation using dry acetone, powdered anhydrous cupric sulfate and conc. sulfuric acid (sp. gr. 1.84) resulted in the elimination of the methylthio group and the formation of 1,2:3,4-di-O-isopropylidene - α -D-galactopyranose[19]. When the reaction was carried out without the addition of conc. sulphuric acid, (7) was isolated[20]. The assignment of its structure was performed by the $^1$H-nmr spectrum, which exhibits two signals at δ = 1.39 and 1.53 (2s, 2X3H, acetonide $H_3C$ X 2) and the mass spectrum which gives the characteristic fragmentation of the newly introduced isopropylidene group[21]. Oxidation of 7 with di-pyridene-chromium (VI) oxide in $CH_2Cl_2$[22] gave 8[23] as a syrup in 60% yield. Its ir spectrum showed a band at 3480 $cm^{-1}$ (-OH), at 1730 $cm^{-1}$ (-CHO) and at 1380 $cm^{-1}$ isopropylidene group). The $^1$H-nmr spectrum indicated the presence of the hydroxylic proton at δ = 3.05 ppm, exchangeable with $D_2O$, but there was no aldehyde proton. Addition of the phosphorane (9) in benzene to the molar ratio of (8) gave the bromo-unsaturated methylthiosugar (10) characterised by a band at 1640 $cm^{-1}$ (-C=C-) in ir spectrum, the shielded proton at δ = 7.45 ppm (d,1H,HC-6) in $^1$H-nmr and finally by the two isotopic peaks of equal intensity of bromine in its mass spectrum[24]; The comparison of $J_{5,6}$ and δ HC-6 values in $^1$H-nmr with similar analogues[10] indicated the Z-relative configuration.



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14. 3 : $^1$H-nmr ($CDCl_3$) δ : 1.99, 2.05, 2.07 & 2.08 (4s, 4x3H, $-OCOCH_3$), 2.17 (s, 3H, $-SCH_3$), 4.15 (d, 2H, $-CH_2OCO$), 4.57 (m, 1H, HC-5), 5.26 (m, 2H,HC-2 & HC-3), 5.47 (dd, 1H, HC-4), 5.62 (d, 1H, HC-1, $J_{1,2}$ = 3.1 Hz). ms, m/z (rel. int.) : 378 [$M^+$] (0.7), 331 [$M^+$ - SMe] (33) and 169 [$M^+$ - 209] (100).
4: $^1$H-nmr ($CDCl_3$) δ : 1.98, 2.04, 2.08 & 2.17 (4s, 4x3H, $-OCOCH_3$), 2.21 (s, 3H, -SMe), 4.0 (m, 1H, HC-5), 4.15 (m, 2H, $-CH_2OCO$), 4.42 (d, 1h HC-1), 5.1 (dd, 1H, HC-3), 5.29 (dd, 1H, HC-2), 5.48 (dd, 1H, HC-4). ms, m:z (rel. int.) : 331 [$M^+$ - SMe] (100).

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16. 5 : $^1$H-nmr ($D_2O$) δ : 2.3 (s, 3H, -SMe), 3.9 (m, 2H, $-CH_2OH$), 4.15 - 4.52 (m, 4H, HC-2, 3, 4, & 5), 5.6 (d, 1H, HC-1, $J_{1,2}$ = 5.6). ms, m/z (rel. int.) : 210 $\left[M^+\right]$ (47), 163 $\left[M^+ - SMe\right]$ (83).

6 : $^1$H-nmr ($D_2O$) δ : 2.38 (s, 3H, -SMe), 3.7 - 4.6 (m, 7H, HC-1, 2, 3, 4, 5, and $H_2C$-6), ms, m/z (rel. int.) : 210 $\left[M^+\right]$(8), 163 $\left[M^+ - SMe\right]$ (14).

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20. 7 : Colourless syrup, 87% yield, ir (KBr) $cm^{-1}$ : 3460 (-OH), 1370 (isopropylidene). $^1$H-nmr ($CDCL_3/D_2O$) δ : 1.39, 1.54 (2s, 2x3H, $\begin{matrix}O\\O\end{matrix}>C<\begin{matrix}CH_3\\CH_3\end{matrix}$), 2.21 (s, 3H, -SMe), 3.54 (dd, 1H, HC-2), 3.8 (m, 2H, $H_2C$-6), 4.0 - 4.36 (m, 3H, HC-3, 4, and 5), 4.4 (d, HC-1, $J_{1,2}$ = 10 Hz). ms, m/z (rel. int.) : 250 $\left[M^+\right]$(7), 235 $\left[M^+ - Me\right]$ (4), 203 $\left[M^+ - SMe\right]$ (31).

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23. 8 : Brown syrup, $^1$H-nmr ($CDCl_3$) δ : 1.37 and 1.35 (2s, 2x3H, $\begin{matrix}O\\O\end{matrix}>C<\begin{matrix}CH_3\\CH_3\end{matrix}$), 2.23 (s, 3H, -SMe), 3.09 (m, 1H, -OH), 3.5 - 4.3 (m, 5H, HC-1, 2, 3, 4, and 5).

24. 9 : Brown syrup, 76% yield, ir (KBr) $cm^{-1}$ : 3480 (-OH) 1730 ($-COOCH_3$), 1640 (-C = C-), 1385 (isopropylidene), 652 ( =C-Br ). $^1$H-nmr ($CDCl_3$) δ : 1.36 and 1.54 (2s, 2x3H, $\begin{matrix}O\\O\end{matrix}>C<\begin{matrix}CH_3\\CH_3\end{matrix}$), 2.23 (s, 3H, -SMe), 2.7 (m, 1H, -OH), 3.7 (dd, 1H, HC-3), 3.87 (s,3H, $-COOCH_3$), 4.17 (dd, 1H, HC-4), 4.30 - 4.45 (m, 2H, HC-1 and HC-2), 4.47 (dd, 1H, HC-5), 7.45 (D,1H, HC-6,). ms, m/z (rel. int.) : 369 and 367 $\left[M^+ - Me\right]$ (6), 337 and 335 $\left[M^+ - SMe\right]$ (9).

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