

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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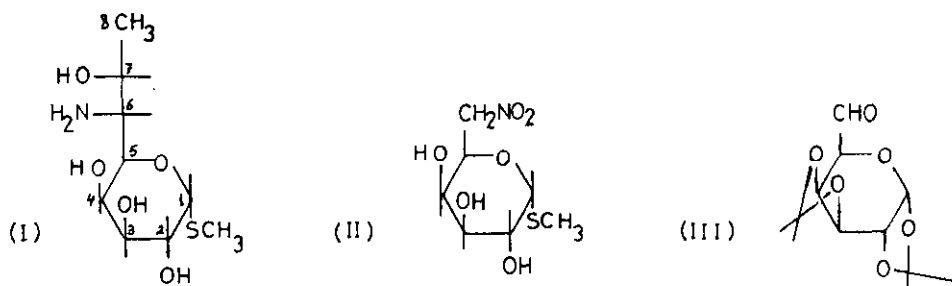
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Abstract— Synthesis of methyl 2,3,4,6-tetra-O-acetyl-1-thio-
 α -D-galactopyranoside and its β -anomer (3 and 4) from the
2,3,4,6-tetra-O-acetyl- α -D-galactopyranosyl bromide via the iso-
thiouronium salt in HMPT involved a considerable increase in 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 7-unsaturated bromo-sugar (9).

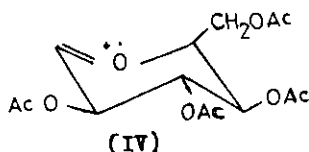
The total synthesis of methyl α -thiolincosaminide (I), the sugar moiety of lincomycin¹, was reported by Magerlein² starting with methylthio- α -D-galactopyranoside (obtained in very low yield in the acid-catalysed reaction of D-galactose with methanethiol) which is converted to the corresponding 6-deoxy-6-nitrothiosugar (II) followed by the chain-extension. Other methods of syntheses³⁻⁸ 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. Bannister⁹ indicated the conversion of the methylthio- β -D-galactopyranoside analogues of (I) into the corresponding α -anomer.

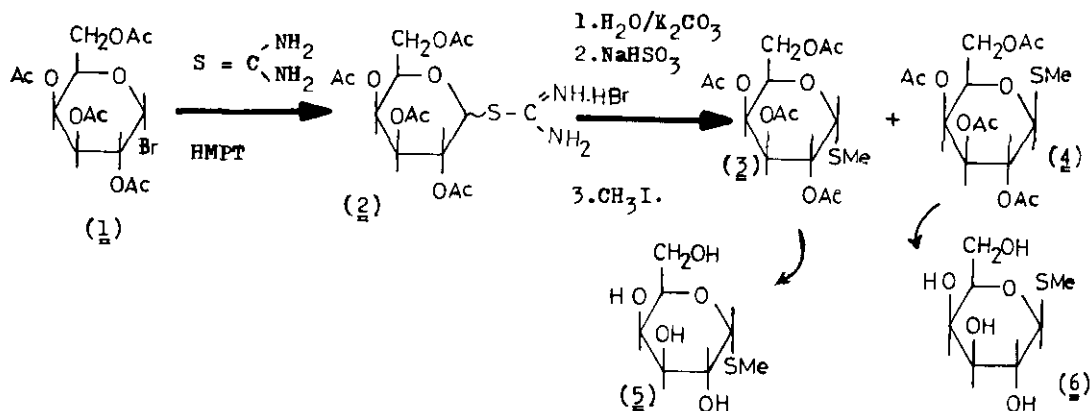
In previous paper¹⁰ we reported the chain extension of (III) through Wittig reaction using stabilised phosphoranes which would provide the same carbon skeleton of the sugar moiety of lincomycin modified at C-8. This paper describes the synthesis of the methylthio- α -D-galactopyranoside and their β -anomer and also the conver-

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

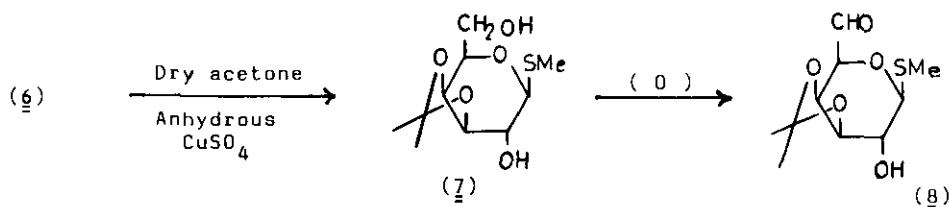


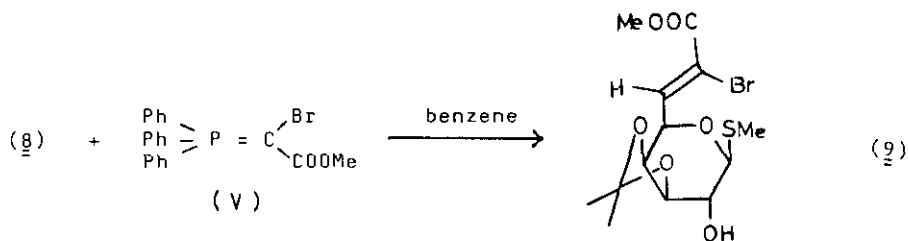
The application of the procedure of Cerny and Pacak¹¹ on 2,3,4,6-tetra-O-acetyl- α -D-galactopyranosyl bromide¹² (1) using dry hexamethylphosphoric triamide (HMPT) as solvent via the isothiuronium bromide (2) gave a mixture of two products (t.l.c), a major one (ethyl acetate - hexane 1:2) of R_f 0.34 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 finally the slower moving one in 41% yield. The latter was identified as the methylthio-B-D-galactopyranoside (4) by its mp 107-108°C and $[\alpha]_D^{+30}$ (in chloroform) which have been reported¹³. The ratio of 3 (\approx 12%) were determined by examining the integration area of H-C5 in the ¹H-nmr spectrum of the mixture. The two products (3 and 4) are consistent with the molecular formula C₁₅ H₂₂ O₉ S obtained by satisfactory elemental analysis, mass spectra and supported by ¹H-nmr¹⁴. 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 methanol¹³ 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 reaction¹⁷, stabilise a carbocation intermediate by solvation¹⁸, 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.





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-galactopyranose¹⁹. When the reaction was carried out without the addition of conc. sulphuric acid, (7) was isolated²⁰. The assignment of its structure was performed by the ¹H-nmr spectrum, which exhibits two signals at $\delta = 1.39$ and 1.53 (2s, 2X3H, acetonide H₃C X 2) and the mass spectrum which gives the characteristic fragmentation of the newly introduced isopropylidene group²¹. Oxidation of 7 with dipyridene-chromium (VI) oxide in CH₂Cl₂²² gave 8²³ 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 ¹H-nmr spectrum indicated the presence of the hydroxylic proton at $\delta = 3.05$ ppm, exchangeable with D₂O, but there was no aldehyde proton. Addition of the phosphorane (v) in benzene to the molar ratio of (8) gave the bromo-unsaturated methylthiosugar (9) characterised by a band at 1640 cm⁻¹ (-C=C-) in ir spectrum, the shielded proton at $\delta = 7.45$ ppm (d, 1H, HC-6) in ¹H-nmr and finally by the two isotopic peaks of equal intensity of bromine in its mass spectrum²⁴; The comparison of J_{5,6} and δ HC-6 values in ¹H-nmr with similar analogues¹⁰ indicated the Z-relative configuration.





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14. 3 : $^1\text{H-nmr}$ (CDCl_3) δ : 1.99, 2.05, 2.07 & 2.08 (4s, 4x3H, $-\text{OCOCH}_3$), 2.17 (s, 3H, $-\text{SCH}_3$), 4.15 (d, 2H, $-\text{CH}_2\text{OCO}$), 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 [$\text{M}^+ - \text{SMe}$] (33) and 169 [$\text{M}^+ - 209$] (100).
- 4 : $^1\text{H-nmr}$ (CDCl_3) δ : 1.98, 2.04, 2.08 & 2.17 (4s, 4x3H, $-\text{OCOCH}_3$), 2.21 (s, 3H, $-\text{SMe}$), 4.0 (m, 1H, HC-5), 4.15 (m, 2H, $-\text{CH}_2\text{OCO}$), 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 [$\text{M}^+ - \text{SMe}$] (100).

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- 6 : $^1\text{H-nmr}$ (D_2O) δ : 2.38 (s, 3H, -SMe), 3.7 - 4.6 (m, 7H, HC-1, 2, 3, 4, 5, and $\text{H}_2\text{C}-6$), ms, m/z (rel. int.) : 210 [M^+] (8), 163 [$\text{M}^+ - \text{SMe}$] (14).
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20. 7 : Colourless syrup, 87% yield, ir (KBr) cm^{-1} : 3460 (-OH), 1370 (isopropylidene). $^1\text{H-nmr}$ ($\text{CDCl}_3/\text{D}_2\text{O}$) δ : 1.39, 1.54 (2s, $2 \times 3\text{H}$, $\text{O} > \text{C} < \begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix}$), 2.21 (s, 3H, -SMe), 3.54 (dd, 1H, HC-2), 3.8 (m, 2H, $\text{H}_2\text{C}-6$), 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 [M^+] (7), 235 [$\text{M}^+ - \text{Me}$] (4), 203 [$\text{M}^+ - \text{SMe}$] (31).
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23. 8 : Brown syrup, $^1\text{H-nmr}$ (CDCl_3) δ : 1.37 and 1.35 (2s, $2 \times 3\text{H}$, $\text{O} > \text{C} < \begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix}$), 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 ($-\text{COOCH}_3$), 1640 ($-\text{C} = \text{C}-$), 1385 (isopropylidene), 652 ($=\text{C}-\text{Br}$). $^1\text{H-nmr}$ (CDCl_3) δ : 1.36 and 1.54 (2s, $2 \times 3\text{H}$, $\text{O} > \text{C} < \begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix}$), 2.23 (s, 3H, -SMe), 2.7 (m, 1H, -OH), 3.7 (dd, 1H, HC-3), 3.87 (s, 3H, $-\text{COOCH}_3$), 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 [$\text{M}^+ - \text{Me}$] (6), 337 and 335 [$\text{M}^+ - \text{SMe}$] (9).

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