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

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Abstract—Synthesis of methyl 2,3,4,6-tetra-0-acetyl-1-thio-\alpha-D-galactopyranoside and its \beta-anomer (\(\mathfrak{z}\) and \(\mathfrak{t}\)) from the 2,3,4,6-tetra-0-acetyl-\alpha-D-galactopyranosyl bromide via the isotiocarbenium salt in HMPT involved a considerable increase in the proportion of the \alpha-anomer. Deacetylation of (\(\mathfrak{z}\) and \(\mathfrak{t}\)) with sodium methoxide yielded \(\mathfrak{z}\) and \(\mathfrak{t}\) respectively. Conversion of (\(\mathfrak{z}\)) into the corresponding 3,4-isopropylidene derivative (8) followed by oxidation with Collin reagent gave the aldehydo-sugar (9) which when reacted with a stabilised phosphorane led in excellent yield to the \(\overline{\beta}\)-unsaturated bromo-sugar (9).

The total synthesis of methyl \(\alpha\)-thiolincomycin (I), the sugar moiety of lincomycin, was reported by Magerlein starting with methylthio-\(\alpha\)-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 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 indicated the conversion of the methylthio-\(\beta\)-D-galactopyranoside analogues of(I) into the corresponding \(\alpha\)-anomer.

In previous paper 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-\(\alpha\)-D-galactopyranoside and their \(\beta\)-anomer and also the conver-
sion of the latter into the methylthio derivative of (III).

The application of the procedure of Cerny and Pačak\textsuperscript{11} on 2,3,4,6-tetra-O-acetyl-\(\alpha\)-D-galactopyranosylbromide\textsuperscript{12} (I) using dry hexamethylphosphoramic triamide (HMPT) as solvent via the isothiouronium bromide (Z) 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 (I), mp 101-102°C, in 8% yield, followed by a mixture of both products in 50% yield and finally the slower moving one in 41% yield. The latter was identified as the methylthio-\(\beta\)-D-galactopyranoside (Y) by its mp 107-108°C and [\(\alpha\)]\textsubscript{D} +3° (in chloroform) which have been reported\textsuperscript{13}. The ratio of I (\(\approx\) 12%) were determined by examining the integration area of H-C5 in the \(^1\text{H}-\text{nmr}\) spectrum of the mixture. The two products (I and Y) are consistent with the molecular formula C\textsubscript{15} H\textsubscript{22} O\textsubscript{9} S obtained by satisfactory elemental analysis, mass spectra and supported by \(^1\text{H}-\text{nmr}\)\textsuperscript{14}. The mass spectra of both products indicate the first elimination of the methylthio group giving (IV) like the tetra-acetylglucosides followed by the characteristic fragmentation of (IV)\textsuperscript{15}. Hydrolysis of (I or Y) with sodium methoxide in anhydrous methanol\textsuperscript{13} gave the corresponding deacetylated derivatives (Z and Z)\textsuperscript{16} identified as the \(\alpha\)- and \(\beta\)-methylthiogalactopyranosides, respectively, through their mp and [\(\alpha\)]\textsubscript{D} which were consistent with reported data\textsuperscript{2, 13}. Therefore, (I) was assigned as the methyl 2,3,4,6-tetra-O-acetyl-\(\alpha\)-D-galactopyranoside. It is noteworthy that the use of HMPT (dipolar-aprotic solvent) would decrease the activation energy of the reaction\textsuperscript{17}, stabilise a carbocation intermediate by solvation\textsuperscript{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 \(\alpha\)-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-\(\alpha\)-D-galactopyranose.\(^9\) 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 \(\delta = 1.39\) and 1.53 \((2m, 2\times 3H,\,\text{acetone} \, H_{\text{CH}} \times 2)\) and the mass spectrum which gives the characteristic fragmentation of the newly introduced isopropylidene group.\(^21\) Oxidation of (7) with dipyridine-chromium (VI) oxide in CH\(_2\)Cl\(_2\) gave (8) 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 hydroxyl proton at \(\delta = 3.05\) ppm, exchangeable with D\(_2\)O, but there was no aldehyde proton. Addition of the phosphorane (9) in benzene to the molar ratio of (8) gave the bromo-unsaturated methylthiosugar (9) characterised by a band at 1640 cm\(^{-1}\) (C=C-\(\cdot\)) in ir spectrum, the shielded proton at \(\delta = 7.45\) 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 \(\delta\) HC-6 values in \(^1\)H-nmr with similar analogues\(^10\) indicated the \(\beta\)-relative configuration.

\[\text{CH}_2\text{OH} \quad \overset{\text{O}}{\overset{\text{Sm}}{\overset{\text{OH}}{\text{O}}}} \quad \overset{\text{O}}{\overset{\text{Sm}}{\overset{\text{OH}}{\text{H}}}} \]
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REFERENCES AND NOTES

14. 3: \(^{1}H\)-nmr (CDCl\(_{3}\)) δ: 1.99, 2.05, 2.07 & 2.09 (4s, 4x3H, -OCOCH\(_{3}\)), 2.17 (s, 3H, -SCH\(_{3}\)), 4.15 (d, 2H, -CH\(_{2}\)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). 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\(_{2}\)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). m/z (rel. int.) : 331 [M\(^{+}\) - SMe] (100).
HETEROCYCLES, Vol. 24, No. 5, 1986


16. δ: 1H-nmr (D₂O) δ: 2.3 (s, 3H, -SMe), 3.9 (m, 2H, -CH₂OH), 4.15 - 4.52 (m, 4H, 
HC-2, 3, 4, & 5), 5.6 (d, 1H, HC-1, J₁₂ = 5.6). ms, m/z (rel. int.): 210 [M + H]⁺ (47), 163 [M⁺ - SMe]⁻ (83).

δ: 1H-nmr (D₂O) δ: 2.38 (s, 3H, -SMe), 3.7 - 4.6 (m, 7H, HC-1, 2, 3, 4, 5, and 
H₂-C-6), ms, m/z (rel. int.): 210 [M + H]⁺ (8), 163 [M⁺ - SMe]⁻ (14).


20. δ: Colourless syrup, 87% yield, ir (KBr) cm⁻¹: 3460 (-OH), 1370 (isopropylidyne). 1H-nmr (CDCl₃/D₂O) δ: 1.39, 1.54 (2s, 2x3H, O₃C-CCH₃), 2.21 (s, 3H, -SMe),
3.54 (dd, 1H, HC-2, 3.8 (m, 2H, H₂C-6), 4.0 - 4.36 (m, 3H, HC-3, 4, and 5), 4.4 (d, 1H, J₁, J₂ = 10 Hz). ms, m/z (rel. int.): 250 [M⁺]⁻ (7), 235 [M⁺ - Me]⁻ (4),
203 [M⁺ - SMe]⁻ (31).


23. δ: Brown syrup, 1H-nmr (CDCl₃) δ: 1.37 and 1.35 (2s, 2x3H, O₃C-CCH₃), 2.23 (s, 
3H, -SMe), 3.09 (m, 1H, -OH), 3.5 - 4.3 (m, 5H, HC-1, 2, 3, 4, and 5).

24. δ: Brown syrup, 76% yield, ir (KBr) cm⁻¹: 3480 (-OH), 1730 (-COOCH₃), 1640 
(-C = C-), 1385 (isopropylidene), 692 ( =C-Br ). 1H-nmr (CDCl₃) δ: 1.36 and 
1.54 (2s, 2x3H, O₃C-CCH₃), 2.23 (s, 3H, -SMe), 2.7 (m, 1H, -OH), 3.7 (dd, 1H, 
HC-3), 3.87 (s, 3H, -COOCH₃), 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 [M⁺ - Me]⁻ (6), 337 and 335 [M⁺ - SMe]⁻ (9).

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