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SYNTHESIS OF METHYL 2,6-DIDEOXY-4-THIO-α-D-*RIBO*-HEXO-PYRANOSIDE, A NEW THIO SUGAR FOUND IN CALICHEMICINS

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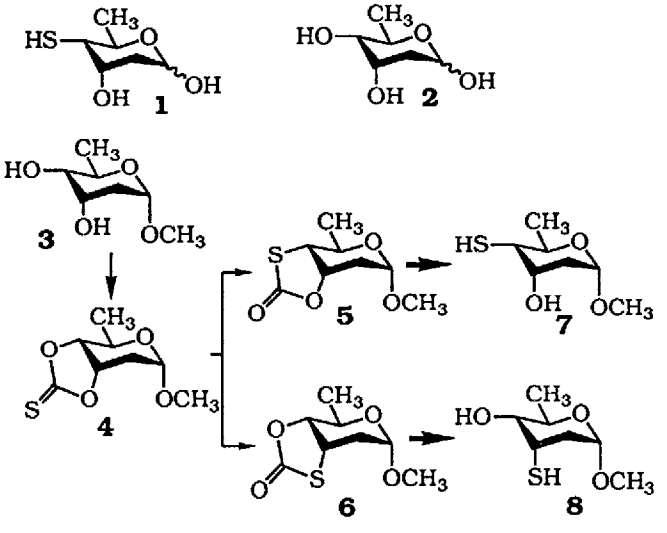
Abstract - The radically induced rearrangement of the 3,4-O-thionocarbonate **4** leads to the two regioisomeric thiol-carbonates **5** and **6**, respectively. Alkaline hydrolysis affords the title compound **7** and its regioisomer **8**.

The calichemicins are a new class of antitumor antibiotics isolated from *Micromonospora echinospora* ssp. calichensis.[1] The discovery and structure elucidation of calichemicin γ_1 was achieved by Lee at al.[1] during their search for new fermentation - derived antitumor antibiotics. Their extraordinary potency against murine tumors generates great interest in syntheses of partial structures of these new natural products. Our synthetic interest is concentrated on that part of the molecule containing 2,6-dideoxy-4-thio-D-*ribo*-hexopyranose **1**, a new sulfur substituted deoxy sugar, connected to a highly substituted aromatic carboxylic acid.[2] **1** is the 4-thio-analogue of 2,6-dideoxy-D-*ribo*-hexopyranose **2** (D-digitoxose), which is easily prepared by the method of Horton et al..[3] Starting from methyl 2,6-dideoxy-α-D-*ribo*-hexopyranoside **3** the 3,4-O-thionocarbonate **4** is prepared by esterification with thiocarbonyldiimidazole (1.2 eq) in dry toluene at 60°C in a yield of 81%.[4] The thionocarbonate **4** is treated with tributyltin hydride (0.5 eq) and azodiisobutyronitrile (1.2 eq) in boiling benzene using a modified procedure of Tsuda et al..[5] The reaction leads to both rearranged regioisomeric thiol carbonates **5** and **6** in 31% and 41% yield, respectively.[6] The deoxygenated methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside is isolated as a byproduct in 9% yield.[6] The desired thio sugar **1** is obtained as its methyl glycoside **7** by alkaline cleavage of the thiol carbonate **5** in 75% yield.[7] The regioisomeric thio sugar **8** can be obtained in an analogous manner.[8]



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References

1. M.D. Lee, T.S. Dunne, M.M. Siegel, C.C. Chang, G.O. Morton, D.B. Borders, *J. Am. Chem. Soc.*, **1987**, *109*, 3464; M.D. Lee, T.S. Dunne, C.C. Chang, G.A. Ellestad, M.M. Siegel, G.O. Morton, W.J. McGahren, D.B. Borders, *J. Am. Chem. Soc.*, **1987**, *109*, 3466.
2. This carboxylic acid was first prepared by K.C. Nicolaou, T. Ebata, N.A. Stylianides, R.D. Groneberg, P.J. Carrol, *Angew. Chem.*, **1988**, *100*, 1138; Int. Ed. Engl., **1988**, *27*, 1097. For a synthesis on preparative scale see K. van Laak and H.-D. Scharf, *Tetrahedron*, in press.
3. D. Horton, T-M. Cheung, W. Weckerle, Methods in Carbohydrate Chem. VIII, 195; Academic Press, New York 1980.
4. Compound **4**: m.p. 100°C, $[\alpha]_D^{20} = +159.6°$ (c = 1.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, 3H, CH_3-6), 2.24 (ddd, 1H, H-2e), 2.34 (dt, 1H, H-2a), 3.36 (s, 3H, OCH_3), 3.95 (dq, 1H, H-5), 4.51 (dd, 1H, H-4), 4.77 (dd, 1H, H-1), 5.01 (dt, 1H, H-3) $J_{1,2a} = 5$, $J_{1,2e} = 4$, $J_{2a,2e} = 15.4$, $J_{2a,3} = 6$, $J_{2e,3} = 5.5$, $J_{3,4} = 7.1$, $J_{4,5} = 9.1$, $J_{5,6} = 6.4$ Hz. - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.53 (C-6), 30.01 (C-2), 55.35 (OCH_3), 62.14 (C-5), 77,65, 81.08 (C-3, -4), 96.01 (C-1), 191.30 (C=S).
5. Y. Tsuda, K. Kanemitsu, K. Kakimoto, T. Kikuchi, *Chem. Pharm. Bull.*, *35*, 2148 (1987).
6. The products of this reaction were separated by column chromatography on silica gel (toluene/ethyl acetate, 5/1). Compound **5**: syrup, $[\alpha]_D^{20} = +107.3°$ (c = 1.23, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, 3H, CH_3-6), 2.07 (dt, 1H, H-2a), 2.41 (ddd, 1H, H-2e), 3.35 (dd, 1H, H-4), 3.36 (s, 3H, OCH_3), 3.97 (dq, 1H, H-5), 4.77 (td, 1H, H-3), 4.82 (dd, 1H, H-1), $J_{1,2a} = 4.5$, $J_{1,2e} = 1.5$, $J_{2a,2e} = 15.4$, $J_{2a,3} = 4.7$, $J_{2e,3} = 2.5$, $J_{3,4} = 4.7$, $J_{4,5} = 10.4$, $J_{5,6} = 6.4$ Hz. - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.92 (C-6), 30.84 (C-2), 51.09 (C-4), 55.33 (OCH_3), 64.48, 77.17 (C-3, -5), 96.56 (C-1), 171.23 (C=O). - Compound **6**: m.p. 53°C, $[\alpha]_D^{20} = +114.6°$ (c = 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, 3H, CH_3-6), 2.04 (ddd, 1H, H-2a), 2.29 (dt, 1H, H-2e), 3.38 (s, 3H, OCH_3), 4.02 (ddd, 1H, H-3), 4.05 (dq, 1H, H-5), 4.36 (dd, 1H, H-4), 4.75 (t, 1H, H-1), $J_{1,2a} = 5.7$, $J_{1,2e} = 5.6$, $J_{2a,2e} = 14.5$, $J_{2a,3} = 10$, $J_{2e,3} = 5$, $J_{3,4} = 7$, $J_{4,5} = 8$, $J_{5,6} = 6.4$ Hz. - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.03 (C-6), 32.21 (C-2), 42.22 (C-3), 55.21 (OCH_3), 63.75, 82.04 (C-4, -5), 97.60 (C-1), 172.21 (C=O). - Methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside: syrup, ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, 3H, CH_3-6), 1.6-1.9 (m, 4H, H-2, -3), 3.25 (m, 1H, H-4), 3.35 (s, 3H, OCH_3),, 3.57 (dq, 1H, H-5), 4.62 (d, 1H, H-1), $J_{4,5} = 9$, $J_{5,6} = 6.4$ Hz. - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.94 (C-6), 27.60, 29.58 (C-2, -3), 54.39 (OCH_3), 69.35, 71.97 (C-4, -5), 97.33 (C-1).
7. Compound **7**: syrup, $[\alpha]_D^{20} = +156.9°$ (c = 0.64, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, 3H, CH_3-6), 1.95 (dt, 1H, H-2a), 2.08 (d, 1H, SH), 2.17 (ddd, 1H, H-2e), 2.54 (td, 1H, H-4) 3.38 (s, 3H, OCH_3), 3.56 (d, 1H, OH) 3.83 (dq, 1H, H-5), 3.89 (dq, 1H, H-3), 4.84 (dd, 1H, H-1), $J_{1,2a} = 3.4$, $J_{1,2e} = 1.3$ $J_{2a,2e} = 14.4$, $J_{2a,3} = 3.3$, $J_{2e,3} = 3.0$, $J_{3,4} = 2.7$, $J_{4,5} = 10.4$, $J_{5,6} = 6.2$, $J_{SH,4} = 10.2$, $J_{OH,3} = 9.9$ Hz. - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.48 (C-6), 36.50 (C-2), 47.47 (C-4), 55.19 (OCH_3), 66.09, 68.41 (C-3, -5), 98.87 (C-1).
8. Compound **8**: syrup, $[\alpha]_D^{20} = +144.7°$ (c = 1.50, $CHCl_3$); ^1H NMR (300 MHz, D_5-pyridine): δ = 1.47 (d, 3H, CH_3-6), 2.25 (m, 2H, H-2a, -2e), 2.72 (d, 1H, SH), 3.30 (s, 3H, OCH_3), 3.52 (m, 1H, H-3) 3.68 (dd, 1H, H-4), 4.28 (dq, 1H, H-5), 4.72 (dd, 1H, H-1), 5.7 (bs, 1H, OH), $J_{1,2} = 3.3$, $J_{2,3} = 4.6$, $J_{3,4} = 4.4$, $J_{4,5} = 8.5$, $J_{5,6} = 6.4$, $J_{SH,3} = 8.4$ Hz. - ^{13}C NMR (75 MHz, D_5-pyridine): δ = 18.17 (C-6), 36.73 (C-2), 39.51 (C-3), 54.66 (OCH_3), 65.61, 72.54 (C-4, -5), 98.39 (C-1).

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