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Total Synthesis of Undeculofuranosiduronic Acid Derivatives Related to Herbicidins.

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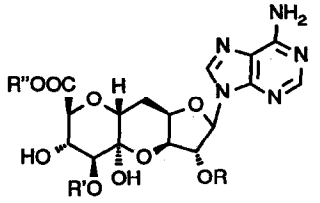
Key words: *long-chain, branched carbohydrates, methyl 6,10-anhydro-5-deoxy-β-DL-lyxo-LD-talo-7-undeculofuranuronate, C-glycosides.*

Abstract: *The reaction of methyl 5-deoxy-2,3-O-isopropylidene-β-DL-ribo-hexodialdo-1,4-furanoside with the enolate of 5-deoxy-2-O-mesyl-3-O-methoxymethyl-β-DL-arabino-hexo-furanurono-6,1-lactone gave a branched dodecose derivative which was converted into 6,10-anhydro-5-deoxy-DL-lyxo-LD-talo-7-undeculofuranuronic acid derivatives.*

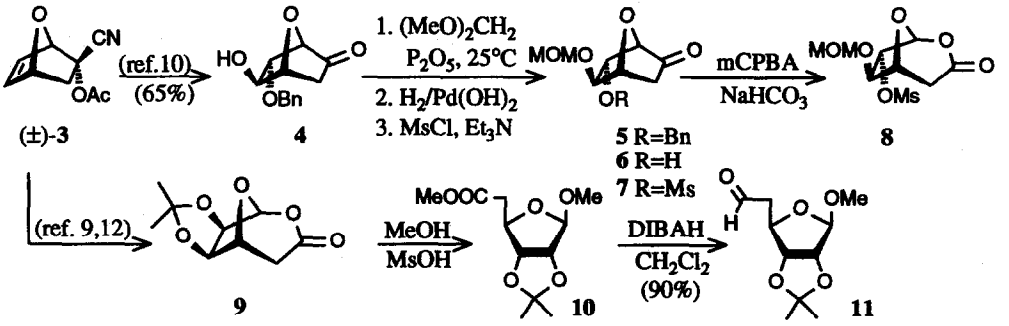
The search for new antibiotics by fermentation technologies has produced unusual nucleosides such as hikizimycin,[1] tunicamycin,[2] herbicidins[3] (**1**) and aureonuclemycin[4] (**2**) that incoporate undecose moieties within their structure. The herbicidins exhibit herbicidal and antialgal activity. Herbicidin A (**1a**) and B (**1b**), as well as **2**, are efficient inhibitors of *Xanthomonas oryzae*, a bacterium which causes rice infection.[1,4]



1a : Herbicidin A (R=Me, R'=(E)-CO(CH$_2$OH)C=CHMe, R''=Me)
1b : Herbicidin B (R=R''=Me, R'=H)
1c : Herbicidin E (R=R''=Me, R'=COCHMe$_2$)
1d : Herbicidin F (R=R''=Me, R'=(E)-CO(Me)C=CHMe)
1e : Herbicidin G (R=H, R'=(E)-CO(Me)C=CHMe, R''=H)
2 : Aureonuclemycin (R=R'=R''=H)

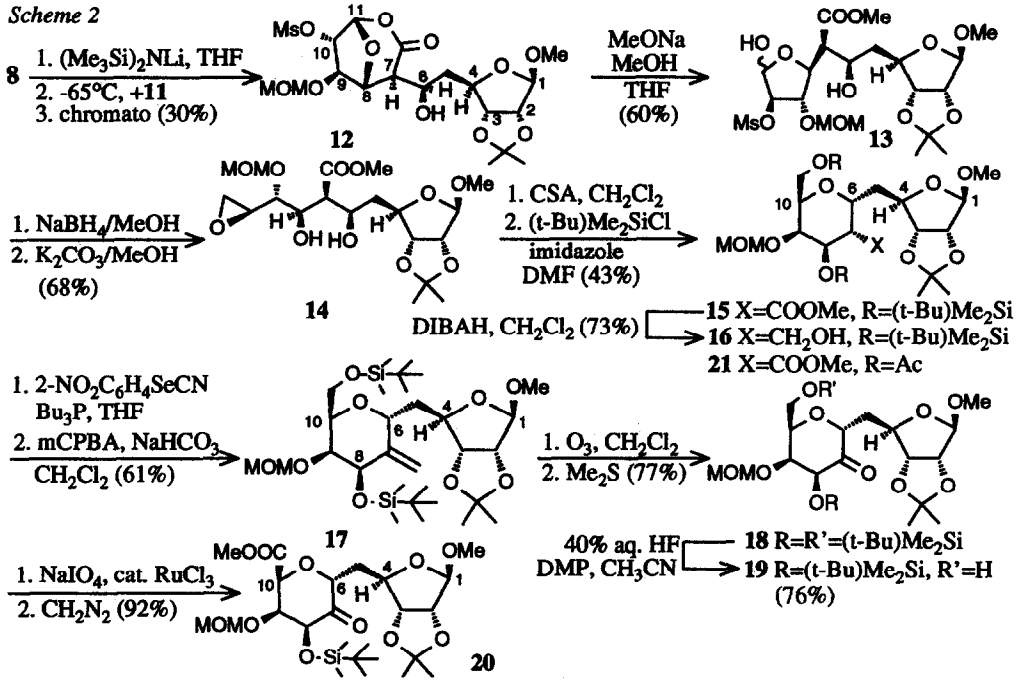
Their carbohydrate moiety is constituted of 6,10-anhydro-5-deoxy-β-D-*arabino*-L-*ido*-7-undeculo-(3,7-pyranose)-furanosiduronic acid a rare long-chain carbohydrate[5] that can be viewed as a α-C-(1→5)-pyranoside of 5-deoxy-D-*xylo*-furanose. We report here our preliminary studies on the total synthesis of related systems making use of the "naked sugar" technology[6] which has been shown to be a quite versatile approach to the synthesis of octoses and analogues,[7] and of C-glycosides.[8] Our method involves the aldol condensation of urono-6,1-lactone **8** (which bears three differently protected hydroxy groups) with methyl 5-deoxy-2,3-O-isopropylidene-β-*ribo*-hexodialdo-1,4-furanoside (**11**).

Scheme 1



The *Diels-Alder* adduct of furan with 1-cyanovinyl acetate (±)-3[9] was converted to **4** (4 steps, 65%) following the method of *Le Drian*,[10] the alcohol moiety being protected as **5**. The exchange of the *endo* benzylic ether group for a mesylate following standard procedures gave **7** (45%, overall), the *Baeyer-Villiger* oxidation of which provided lactone **8** (95%) (Scheme 1). Aldehyde **11** (90%) was derived from the known methyl uronate **10**[9,12] by reduction with diisobutylaluminium hydride (DIBAH) in CH_2Cl_2 at -78°C. Deprotonation of uronolactone **8** with $(Me_3Si)_2NLi$ (-65°C, THF) followed by the addition of aldehyde **11** (THF, -65°C, 10 min) led to a mixture from which the major product **12**[13] could be isolated in 30% yield by flash chromatography on silica gel together with unreacted **11**. The relative configuration of the alcohol moiety was established by a NOESY spectrum of derivative **21** (see below); the *exo* mode of addition of the aldehyde **11** was expected for steric reasons and was confirmed by the absence of vicinal coupling constant between the proton α to the lactone moiety (H-C(7)) and the adjacent bridgehead proton (H-C(8)).

Scheme 2



Methanolysis of **12** could be achieved without epimerization at C(6) or loss of water by treatment with MeONa in anh. THF (-30 to -5°C, quenching with aqueous NH_4Cl and CH_2Cl_2 at -5°C). This afforded furanose **13** (60%) which was reduced with $NaBH_4$ (anh. MeOH, 0°C, 10 min) into the corresponding branched dodecofuranoside. Without purification, the latter was treated with anh. K_2CO_3/MeOH (40°C, 1 h) yielding epoxide **14**[14] (68%). Acidic rearrangement[15] of **14** (camphorsulfonic acid, 1 equiv., CH_2Cl_2, 0°C, 1 h), followed by silylation of the resulting diol with (t-Bu)Me_2SiCl and imidazole (DMF, 70°C, 18 h) afforded **15** (43%). Attempts to carry out an oxidative decarboxylation of **15** via the formation of the corresponding methyl ketone failed. Reduction of **15** with DIBAH (CH_2Cl_2, 0°C, 30 min) gave the corresponding alcohol **16** (73%), the displacement of which with orthonitrobenzeneselenyl cyanide and tri-n-butylphosphine,[16] followed by treatment with metachloroperbenzoic acid and $NaHCO_3$ in CH_2Cl_2 led to the methylidene sugar **17**[17] (61%). Ozonolysis (3% O_3 in O_2, CH_2Cl_2, -78°C), followed by treatment with

Me_2S (-78 to +20°C, 1 h) gave the protected methyl 6,10-anhydro-5-deoxy-β-DL-*lyxo*-LD-*talo*-7-undeculofuranoside **18**. Selective deprotection of the primary alcohol with 40% aq. HF (3% in CH_3CN containing 15% $(MeO)_2CMe_2$, 0°C, 40 min) furnished **19**[19] (76%), the oxidation[18] of which with $NaIO_4$ (4 equiv.) and aq. $RuCl_3$ (0.2 equiv.) in $CH_3CN/CCl_4/H_2O$ 2:2:3 (20°C, 40 min) gave the corresponding uronic acid which was characterized as its methyl ester **20**[19] (92%) obtained by treatment with CH_2N_2 (Et_2O). Treatment of **20** with CF_3COOH/MeOH (20°C, 24 h) cleaved all the protective groups, except the methyl ester.

The structures of the new compound **12-20** were given by their modes of formation and reaction and were confirmed by their spectral data and the elemental analyses of the solids. When the product of acid-induced rearrangement of **14** was acetylated with Ac_2O/pyridine (20°C, 1 h), the diacetate **21** was obtained, the structure of which was established by a NOESY spectrum. This allowed determination of the relative configuration of centers C(6) and C(7) in **12-16**. The NOESY spectrum of **20** did not show NOE between H-C(6) and H-C(10) although NOE's were observed between H-C(8) and H-C(10) (*axial* protons). If the centre C(6) had the opposite configuration H-C(6) would also occupy an *axial* position and thus show a NOE with H-C(8) and H-C(10).

Work is underway in our laboratory to apply the technology disclosed here for the total synthesis of 6,10-anhydro-5-deoxy-undecose derivatives to further systems starting with stereomers of uronolactone **8** and aldehyde **11**, including optically pure "naked sugars".[6]

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11. Data of **8**: m.p.: 96-99°C; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 5.99 (dd, ^3J=4, ^4J=1 Hz, H-C(1)); 5.10 (ddd, ^3J=4, 2, ^4J=1, H-C(7)); 4.79, 4.72 (2d, ^2J=7, O-CH_2-O); 4.63 (dt, ^3J=6.5, ^4J=1, H-C(5)); 4.16 (d, ^3J=2, H-C(6)); 3.42 (s, MeO); 3.17 (s, Ms); 3.13 (dd, ^2J=18.5, ^3J=6.5, H_{exo}-C(4)); 2.65 (d, ^2J=18.5, H_{endo}-C(4)).

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13. Data of **12**: m.p. 154-155°C; IR ($CHCl_3$) ν: 3480, 3000, 2940, 1760, 1370, 1180 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 5.98 (dd, ^3J=4, J<1 Hz, H-C(11)); 5.10 (ddd, ^3J=4, 2, 4, ^4J<1Hz, H-C(10)); 4.95 (s, H-C(8)); 4.80, 4.73 (2d, ^3J=7, H-C(2), H-C(3)); 4.78 (br.s, H-C(1)); 4.65, 4.61 (2d, ^2J=6, -OCH_2O-); 4.48 (*m*, H-C(4), H-C(6)); 4.14 (d, ^3J=2, H-C(9)); 3.43 (s, COOMe); 3.37, 3.18 (2s, 2 MeO); 2.81 (d, ^3J=5, H-C(7)); 1.93, 1.68 (m, H_2C(5)); 1.48, 1.33 (2s, 2 Me).

14. Data for **14**: colourless oil; IR ($CHCl_3$) ν: 3500, 2980, 2940, 2830, 1710, 1435, 1370, 1155 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 4.95 (s, H-C(1)); 4.67, 4.61 (2d, ^3J=7, H-C(2), H-C(3)); 4.60 (s, OCH_2O); 4.47 (dd, ^3J=10.5, 4, H-C(4)); 4.26-4.22 (m, H-C(6)); 4.08 (ddd, ^3J=7, 5.5, 5.0, H-C(8)); 3.75 (s, COOMe); 3.59 (d, ^3J=7, HO-C(8)); 3.55 (dd, ^3J=5.5, 5.4, H-C(9)); 3.36, 3.35 (2s, 2 MeO); 3.14 (ddd, ^3J=5.4, 4, 2.5, H-C(10)); 3.06 (d, ^3J=7, HO-C(6)); 2.84 (dd, ^3J=5, 4.9, H-C(7)); 2.80 (dd, ^2J=5, ^3J=4, H-C(11)); 2.73 (dd, ^2J=5, ^3J=2.5, H'-C(11)); 1.85 (ddd, ^2J=14, ^3J=10.5, 2.5, H-C(5)); 1.62 (ddd, ^2J=14, ^3J=10, 4, H'-C(5)); 1.47, 1.30 (2s, 2 Me); MS (CI, NH_3): m/z = 437 ($M+H^+$, 1), 185 (100).

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17. Data of **17**: colourless oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 5.18 (dd, ^2J=1.5, ^4J=1.4), 5.04 (dd, ^2J=1.5, ^4J=1.4, H_2C=C(7)); 4.97 (s, H-C(1)); 4.95, 4.68 (2d, ^2J=6.5, OCH_2O); 4.69 (dd, ^3J=10.5, 3.5, H-C(4)); 4.62 (d, ^3J=6, H-C(2)); 4.59 (d, ^3J=6, H-C(3)); 4.40 (dt, ^3J=2.5, ^4J=1.4, 1 H_2C=C(8)-H, H-C(8)); 4.39 (dd, ^3J=11, 4.5, H-C(6)); 3.89 (d, ^3J=2.5, H-C(9)); 3.80-3.73 (m, H-C(10), H_2C(11)); 3.38, 3.37 (2s, 2 MeO); 2.12 (ddd, ^2J=14, ^3J=10.5, 4.5, H-C(5)); 1.63 (ddd, ^2J=14, ^3J=11, 3.5, H'-C(5)); 1.47, 1.31 (2s, Me_2C); 0.93, 0.90 (2s, 2 t-Bu); 0.08, 0.07, 0.065, 0.06 (4s, 2 Me_2Si).

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19. Data of **19**: m.p. 92-92.5°C; data of **20**: colourless oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 4.99 (s, H-C(1)); 4.87, 4.56 (2d, ^2J=6.5, O-CH_2-O); 4.84 (d, ^3J=5.5, H-C(10)); 4.74 (d, ^3J=2, H-C(8)); 4.68 (br.d, ^3J=6.5, H-C(3)); 4.67 (dd, ^3J=10, 2.5, H-C(6)); 4.63 (d, ^3J=6.5, H-C(2)); 4.60 (dd, ^3J=5.5, 2, H-C(9)); 4.48 (dd, ^3J=9.5, 5.5, H-C(4)); 3.81 (s, COOMe); 3.34, 3.29 (2s, 2 MeO); 2.30 (ddd, ^2J=14, ^3J=9.5, 2.5, H-C(5)); 1.70 (ddd, ^2J=14, ^3J=10, 5.5, H'-C(5)); 1.48, 1.31 (2s, 2 Me); 0.92 (s, t-Bu); 0.17, 0.06 (2s, Me_2Si); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C: 208.0 (s, C(7)); 169.1 (s, C(11)); 112.1 (s), 109.6 (d, C(1)); 97.5 (t, OCH_2O), 85.5, 84.2, 83.7, 77.9, 76.4, 76.2, 75.6 (7d, C(2), C(3), C(4), C(6), C(8), C(9), C(10)); 56.3, 54.9, 52.0 (3q, 3 MeO); 35.8 (t, C(5)); 26.6, 25.7, 25.65, 25.6, 25.0 (5q); 18.1 (s), -4.6, -5.8 (2q).

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