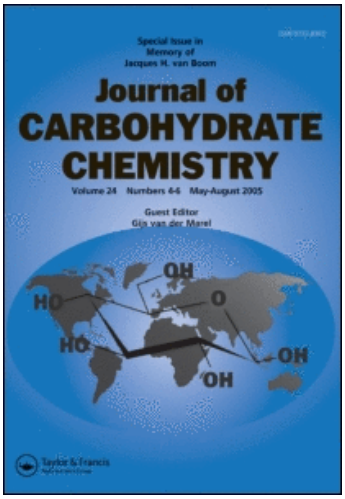

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SILVER ION MEDIATED DESULFURIZATION-CONDENSATION OF GLUCOSYL ISOTHIOCYANATE WITH HYDROXY ACIDS

Yasuo Gama,* Isao Shibuya and Masao Shimizu

National Institute of Materials and Chemical Research, 1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan

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ABSTRACT

Desulfurization-condensation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate with α-hydroxy acids and salicylic acid in the presence of silver trifluoroacetate and triethylamine gave glucosylamino heterocycles in good yields, while the reaction with β-hydroxy acids afforded *N*-glucosyl olefinic amides with the evolution of carbon dioxide.

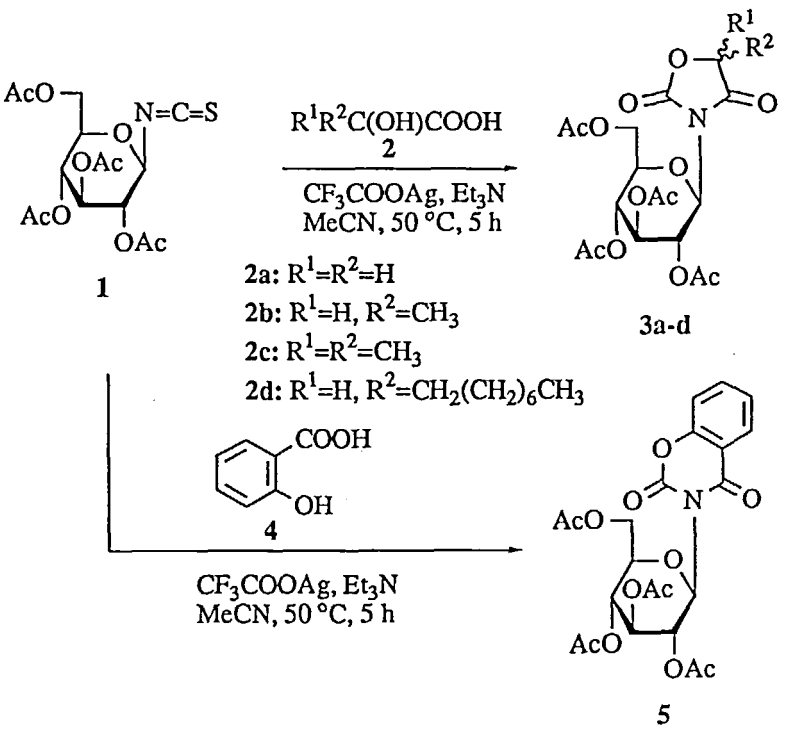
INTRODUCTION

Recently, we reported that the silver ion mediated desulfurization-condensation of thiocarbonyl compounds with active methylenes, amines and diols under mild conditions gives olefins, imines, acetals, and orthocarbonic acid esters.[1-4] We also demonstrated that the reaction of glycosyl isothiocyanates with *N*-substituted amino acids in the presence of silver ion affords glycosylamino heterocycles as a nucleoside analog in good yields.[5] Glycosyl isothiocyanates have been widely used as valuable precursors in the synthesis of glycosyl thiourea derivatives,[6,7] glycosylamino heterocycles,[8] *N*-glycopeptides,[9,10] or nucleoside analogs.[11-13] However, there still remains a strong demand to develop simple and efficient methods for the synthesis of glycosylamino heterocycles as nucleoside

analogs. In this paper, we wish to report on a new and efficient synthesis of glucosylamino heterocycles by desulfurization-condensation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**1**) with various α-hydroxy acids (**2a-d**) and salicylic acid (**4**) in the presence of silver ion under basic conditions. We also describe the reaction of **1** with β-hydroxy acids (**6a-b**) to give *N*-glucosyl olefinic amides (**7a-b**) with the evolution of carbon dioxide.

RESULTS AND DISCUSSION

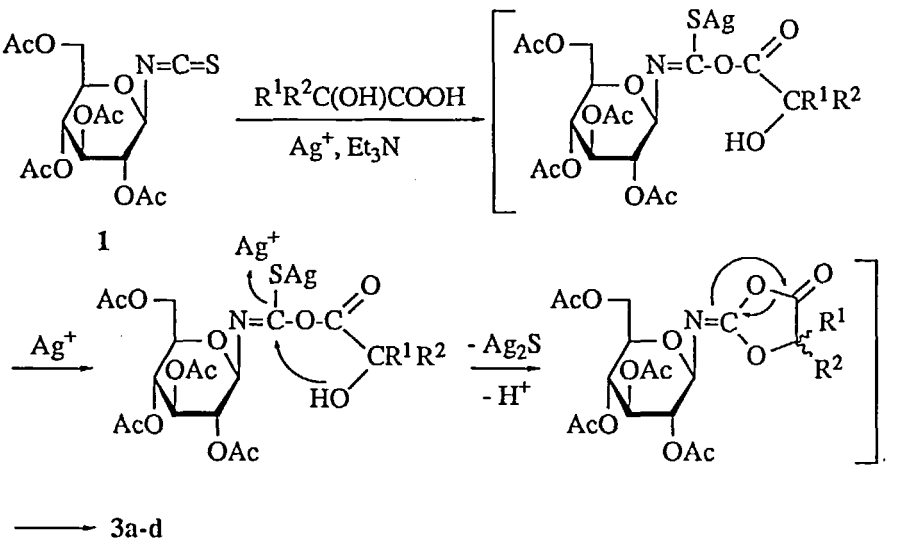
We first tried the condensation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**1**) and 1.3 equivalents of glycolic acid (**2a**) using 2.5 equivalents of silver trifluoroacetate in dry acetonitrile in the presence of 3.6 equivalents of triethylamine for 5 h at 50 °C and found a product (**3a**) was obtained in 73% yield (Scheme 1). The structures of compound **3a-d** were determined by elementary analyses, IR, ^{1}H and ^{13}C spectroscopic data. The product **3a** shows ν_{max} at 1820 and 1740 cm^{-1}, characteristic of oxazolidine-2,4-dione derivatives.[14] The ^{1}H NMR spectrum of **3a** shows a newly formed anomeric



Scheme 1

proton (H-1') as a doublet at δ 5.64 and the β-configuration was confirmed by the value of the coupling constant ($J_{1',2'}$ = 9.3 Hz). In the ^{13}C NMR spectrum of compound **3a**, the signals of two carbonyl carbons in the heterocycle shown at δ 153.64 and 170.07, respectively, were in agreement with simple 2,4-oxazolidinedione derivatives.[14] From other α-hydroxy acids such as L-lactic acid (**2b**), 2-hydroxyisobutyric acid (**2c**), or DL-2-hydroxydecanoic acid (**2d**), novel *N*-glucosyl 2,4-oxazolidinedione derivatives (**3b-d**) were obtained in good yields under the same conditions. Compound **3d** was obtained as an inseparable mixture of diastereomers since the starting hydroxylic acid **2d** was a racemate. In the ^1H NMR spectrum, **3d** is shown as a pair of diastereomers (ca. 3 : 2). The methine proton in the heterocycle for the major diastereomer is at δ 4.74 (dd, J = 4.8, 7.8 Hz) and that of the minor diastereomer at δ 4.76 (dd, J = 3.9, 7.4 Hz). The reaction of **1** with salicylic acid (**4**) under the same conditions gave *N*-glucosyl 1,3-benzoxazin-2,4-dione derivative (**5**) in 68% yield. Compound **5** was identified by comparison of the melting point and optical rotation with reported ones.[15]

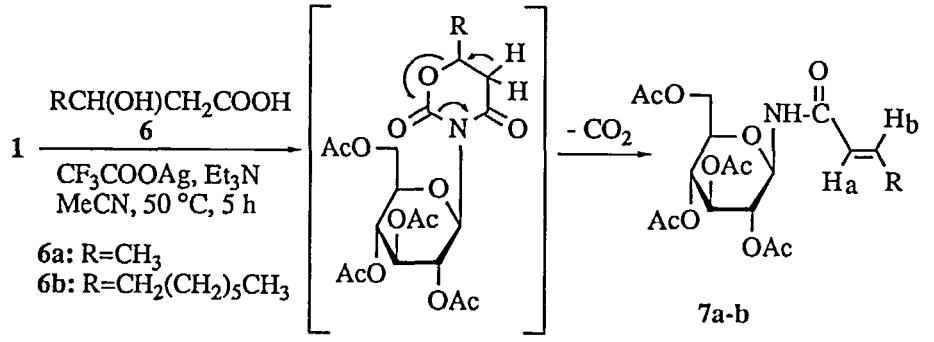
This desufurization including rearrangement can be considered to proceed as follows (Scheme 2). The reaction is initiated when the silver ion attacks the sulfur atom of isothiocyanate. Continuous attack by the nucleophilic carboxylate of the hydroxy acid results in formation of an *O*-acylimino product. In the presence of another equivalent



Scheme 2

of silver ion, the oxygen atom of the hydroxy group attacks the carbon atom of the *O*-acylimino product to give a cyclic intermediate with liberation of Ag_2S. In the final step, the cyclic *O*-acylisoimido rearranges into the 2,4-oxazolidinedione or 1,3-benzoxazin-2,4-dione derivatives.[16] On the other hand, **1** with β-hydroxy acids such as DL-3-hydroxybutyric acid (**6a**) or DL-3-hydroxydecanoic acid (**6b**) reacted under the same conditions to give *trans*-olefinic amides (**7a-b**) in good yields. A plausible mechanism affording to **7a-b** from **1** is shown in Scheme 3. The IR spectrum of **7a** shows characteristic absorptions at 1694 (Amide I), 1539 (Amide II), and 3362 cm^{-1} (NH). In the ^1H NMR spectrum, the olefinic protons of **7a** are shown at δ 5.77 (dd, $J_{Ha,Me}$ = 1.5 and $J_{Ha,Hb}$ = 15.1 Hz, Ha) and 6.89 (dq, $J_{Hb,Me}$ = 6.9 and $J_{Ha,Hb}$ = 15.1 Hz, Hb), characteristic of *trans*-olefinic derivatives. In the ^{13}C spectrum of **7a**, the olefinic carbons are observed at δ 124.46 and 142.86, and the carbonyl carbon of the amide is shown at δ 166.08. It is assumed that **1** first reacts with **6a-b** to afford six-membered heterocycles as an intermediate in the same manner as α-hydroxy acids, and then the evolution of carbon dioxide occurs to give *N*-glucosyl *trans*-olefinic amides. But the reason affording only *trans*-isomer is not clear.

In conclusion, we have described the silver ion mediated desulfurization-condensation of glucosyl isothiocyanate with various α-hydroxy acids affording glucosylamino heterocyles in good yields, while the reaction with β-hydroxy acids gives *N*-glucosyl olefinic amides also in good yields.



Scheme 3

EXPERIMENTAL

General. Melting points were determined on a Mettler FP 90 apparatus and are uncorrected. IR spectra were recorded on a JASCO FT-IR 5300 instrument using KBr disks. NMR spectra were obtained with a Varian Gemini 300 BB spectrometer for solutions in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard. Optical rotations were measured at 24 °C with a JASCO DIP-370 digital polarimeter. TLC was conducted on plates coated with silica gel 60 F_{254} (Merck), and products were detected by UV light and/or by charring with H_2SO_4. Column chromatography was carried out in columns of silica gel (Wakogel C-200).

General procedure for the preparation of 3a-d, 5, and 7a-b: To a solution of glucosyl isothiocyanate (**1**, 1 mmol), hydroxy acid (1.3 mmol), and triethylamine (3.6 mmol) in dry acetonitrile (10 mL) was added silver trifluoroacetate (2.5 mmol). The reaction mixture was stirred for 5 h at 50 °C. After evaporation of the solvent under reduced pressure, ethyl acetate and brine were added to the residue, and silver salts were removed by filtration. The organic layer was separated and washed with water and brine. The washed solution was dried ($MgSO_4$) and concentrated, and the residue was purified by chromatography on silica gel. The yield, mp, $[\alpha]_D$, and the characterization data are shown below.

3-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2,4-oxazolidinedione (3a). 73%; mp 178-179 °C ($^iPr_2O$-EtOH); $[\alpha]_D$ -7.7° (*c* 1.0, DMSO); IR 1820, 1754, 1740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.97, 2.01, 2.02 (3s, 12H, OAc), 4.12 (m, 2H, H-6'), 4.24 (m, 1H, H-5'), 4.89 (s, 2H, Het. CH_2), 5.49 (t, 1H, J = 9.3 Hz, H-2'), 5.00 (t, 1H, J = 9.9 Hz, H-4'), 5.59 (d, 1H, J = 9.3 Hz, H-1'), 5.71 (t, 1H, J= 9.3 Hz, H-3'); ^{13}C NMR (DMSO-d_6) δ 20.28, 20.34 (2C), 20.48, 61.53 (C-6'), 67.19, 67.43 (Het. CH_2), 67.84, 72.59, 73.13, 79.09 (C-1'), 153.64 (Het. C=O), 169.34 (2C), 169.62, 170.07 (2C, Het. C=O and OAc).

Anal. Calcd for $C_{17}H_{21}NO_{12}$: C, 47.34; H, 4.91; N, 3.25. Found: C, 47.22; H, 5.00; N, 3.21.

5-Methyl-3-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,4-oxazolidinedione (3b). 65%; mp 189-190 °C ($^iPr_2O$-EtOH); $[\alpha]_D$ -1.8° (*c* 1.1, $CHCl_3$); IR

1830, 1757, 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (d, 3H, J = 6.9 Hz, CH_3), 2.01, 2.04, 2.06, 2.09 (4s, 12H, OAc), 3.85 (m, 1H, H-5'), 4.22 (m, 2H, H-6'), 4.86 (q, 1H, J = 6.9 Hz, Het. CH), 5.19 (d, 1H, J = 9.6 Hz, H-1'), 5.20 (t, 1H, J = 9.6 Hz, H-4'), 5.31 (t, 1H, J = 9.3 Hz, H-2'), 5.81 (t, 1H, J = 9.3 Hz, H-3'); ^{13}C NMR ($CDCl_3$) δ 16.34 (CH_3), 20.47, 20.59, 20.61, 20.71, 61.67 (C-6'), 67.73, 67.98, 73.00, 74.84, 75.76 (Het. CH), 79.46 (C-1'), 152.78 (Het. C=O), 169.63, 169.92, 170.33, 170.93, 172.21 (Het. C=O).

Anal. Calcd for $C_{18}H_{23}NO_{12}$: C, 48.54; H, 5.21; N, 3.14. Found: C, 48.45; H, 5.11; N, 3.23.

5,5-Dimethyl-3-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,4-oxazolidinedione (3c). 78%; mp 117-118 °C ($^iPr_2O$-EtOAc); $[\alpha]_D$ +8.4° (*c* 1.7, $CHCl_3$); IR 1825, 1757, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.00, 2.03, 2.05 , 2.09 (4s, 12H, OAc), 3.84 (m, 1H, H-5'), 4.22 (m, 2H, H-6'), 5.20 (t, 1H, J = 9.6 Hz, H-4'), 5.22 (d, 1H, J = 9.6 Hz, H-1'), 5.31 (t, 1H, J = 9.6 Hz, H-2'), 5.82 (t, 1H, J = 9.6 Hz, H-3'); ^{13}C NMR ($CDCl_3$) δ 20.41, 20.60, 20.61, 20.76, 23.30 (CH_3), 23.49 (CH_3), 61.69 (C-1'), 67.78, 67.91, 73.08, 74.84, 79.67 (C-1'), 83.49 (Het. C), 153.11 (Het. C=O), 169.23, 169.70, 170.34, 170.93, 174.58 (Het. C=O).

Anal. Calcd for $C_{19}H_{25}NO_{12}$: C, 49.67; H, 5.49; N, 3.05. Found: C, 49.45; H, 5.34; N, 3.12.

5-Octyl-3-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,4-oxazolidinedione (3d). 72% (a mixture of diastereomers, ca. 3 : 2); mp 88-91 °C ($^iPr_2O$); $[\alpha]_D$ -1.6° (*c* 1.3, $CHCl_3$); IR 1828, 1754, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) for major diastereomer δ 0.88 (t, 3H, J = 6.9 Hz, CH_3), 1.99, 2.03, 2.05, 2.09 (4s, 12H, OAc), 1.27-1.44 (m, 14H), 3.82 (m, 1H, H-5'), 4.20 (m, 2H, H-6'), 4.74 (dd, 1H, J = 4.8, 7.8 Hz, Het. CH), 5.20 (d, 1H, J = 9.3 Hz, H-1'), 5.20 (t, 1H, J = 9.6 Hz, H-4'), 5.30 (t, 1H, J = 9.3 Hz, H-2'), 5.86 (t, 1H, J = 9.3 Hz, H-3'); ^{13}C NMR ($CDCl_3$) for major diastereomer δ 14.1 (CH_3), 20.49, 20.59 (2C), 20.73, 22.67, 22.91, 28.12, 29.10, 29.16, 31.80, 32.23, 61.67 (C-6'), 67.76, 73.19, 73.30, 74.83, 79.40 (Het. CH), 79.63 (C-1'), 153.30 (Het. C=O), 169.56, 169.61, 170.37, 170.88, 171.79 (Het. C=O). ^1H NMR ($CDCl_3$) for minor diastereomer δ 0.88 (t, 3H, J = 6.9 Hz, CH_3), 1.27-1.47 (m, 14H), 1.99, 2.03, 2.05, 2.09 (4s, 12H, OAc), 3.82 (m, 1H, H-5'), 4.20 (m, 2H, H-6'),

4.76 (dd, 1H, J = 3.9, 7.4 Hz, Het. CH), 5.20 (d, 1H, J = 9.3 Hz, H-1'), 5.21 (t, 1H, J = 9.6 Hz, H-4'), 5.29 (t, 1H, J = 9.3 Hz, H-2'), 5.87 (t, 1H, J = 9.3 Hz, H-3'). The ^{13}C NMR spectrum of the minor diastereomer was completely overlapped by that of the major diastereomer.

Anal. Calcd for $C_{25}H_{37}NO_{12}$: C, 55.24; H, 6.86; N, 2.58. Found: C, 55.45; H, 6.66; N, 2.61.

3-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)benzo[*e*][1,3]oxazine-2,4-dione (5). 68%; mp 153-154 °C (MeOH) (lit.,[15] 154-156 °C); $[\alpha]_D$ -26.3° (*c* 1.0, $CHCl_3$) [lit.,[15] $[\alpha]_D$ -26.8° (*c* 5.0, $CHCl_3$)]; IR 1770, 1755, 1715, 1599 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04, 2.07, 2.09 (3s, 12H, OAc), 3.90 (m, 1H, H-5'), 4.23 (m, 2H, H-6'), 5.30 (t, 1H, J = 9.6 Hz, H-4'), 5.40 (t, 1H, J = 9.3 Hz, H-2'), 6.10 (t, 1H, J = 9.1 Hz, H-3'), 6.20 (d, 1H, J = 9.1 Hz, H-1'), 7.28-8.80 (m, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 20.31, 20.44 (2C), 20.58, 61.52 (C-6'), 67.59, 68.25, 73.15, 74.52, 79.14 (C-1'), 112.90, 116.55, 125.50, 128.47, 136.78, 144.61, 152.73 (Het. C=O), 160.47 (Het. C=O), 169.23, 169.64, 169.95, 170.53.

Anal. Calcd for $C_{22}H_{23}NO_{12}$: C, 53.55; H, 4.70; N, 2.84. Found: C, 53.58; H, 4.45; N, 3.01.

***trans*-But-2-enoic acid *N*-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)amide (7a).** 61%; mp 138-139 °C (hexane-EtOAc); $[\alpha]_D$ -2.0° (*c* 1.0, $CHCl_3$); IR 3362, 1754, 1694, 1539 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (dd, 3H, J = 1.5, 6.9 Hz, CH_3), 2.03, 2.04, 2.08 (3s, 12H, OAc), 3.86 (m, 1H, H-5'), 4.08 (dd, 1H, J = 1.8 , 12.6 Hz, H-6'a), 4.32 (dd, 1H, J = 4.3, 12.6 Hz, H-6'b), 4.96 (t, 1H, J = 9.6 Hz, H-4'), 5.08 (t, 1H, J = 9.6 Hz, H-2'), 5.33 (t, 1H, J = 9.6 Hz, H-3'), 5.34 (t, 1H, J = 9.3 Hz, H-1'), 5.77 (dd, 1H, J = 1.5, 15.1 Hz, olefinic H), 6.34 (d, 1H, J = 9.3 Hz, NH), 6.89 (dq, 1H, J = 6.9, 15.1 Hz, olefinic H); ^{13}C NMR ($CDCl_3$) δ 17.94 (CH_3), 20.62 (2C), 20.71, 20.77, 61.82 (C-6'), 68.34, 70.80, 72.90, 73.67, 78.49 (C-1'), 124.46 (C=C), 142.86 (C=C), 166.08 (C=O), 169.91, 170.19, 170.95, 171.42.

Anal. Calcd for $C_{18}H_{25}NO_{10}$: C, 52.05; H, 6.07; N, 3.37. Found: C, 52.06; H, 6.05; N, 3.30.

***trans*-Dec-2-enoic acid *N*-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)amide (7b).** 57%; mp 61-62 °C (hexane-EtOAc); $[\alpha]_D$ -5.0° (*c* 1.4, $CHCl_3$); IR 3326, 1750, 1676, 1647, 1541 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.2 Hz), 1.27-

1.43 (m, 10H), 2.03 (s, 3H), 2.04 (s, 6H), 2.08 (s, 3H), 2.19 (m, 2H, allylic H), 3.87 (m, 1H, H-5'), 4.13 (dd, 1H, J = 2.1, 12.6 Hz, H-6'a), 4.33 (dd, 1H, J = 4.3, 12.6 Hz, H-6'b), 4.96 (t, 1H, J = 9.6 Hz, H-4'), 5.08 (t, 1H, J = 9.6 Hz, H-2'), 5.33 (t, 1H, J = 9.6 Hz, H-3'), 5.34 (t, 1H, J = 9.3 Hz, H-1'), 5.73 (dd, 1H, J = 1.5, 15.3 Hz, olefinic H), 6.32 (d, 1H, J = 9.3 Hz, NH), 6.88 (dq, 1H, J = 6.9, 15.3 Hz, olefinic H); ^{13}C NMR ($CDCl_3$) δ 14.11 (CH_3), 20.63, 20.72 (2C), 20.78, 22.67, 28.12, 29.10, 29.16, 31.80, 32.23, 61.80 (C-6'), 68.32, 70.79, 72.90, 73.67, 78.52 (C-1'), 122.84 (C=C), 148.00 (C=C), 166.26 (C=O), 169.93, 170.20, 170.97, 171.47.

Anal. Calcd for $C_{24}H_{37}NO_{10}$: C, 57.70; H, 7.47; N, 2.80. Found: C, 57.75; H, 7.39; N, 2.84.

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