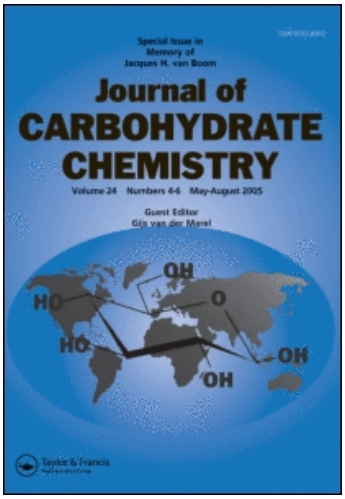


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# Synthesis and Structure of 2-Hydroxy-2-Methyl-1,3-Bis-(Methyl 3',4',6'-Tri-*O*-Acetyl-β-D-Glucopyranosid-2-yl)-Imidazolidine-4,5-Dione

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# Synthesis and Structure of 2-Hydroxy-2-Methyl-1, 3-Bis-(Methyl 3′,4′, 6′-Tri-*O*-Acetyl-β-D-Glucopyranosid-2-yl)-Imidazolidine-4,5-Dione

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The title compound was synthesized starting from methyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyranoside, oxalyl chloride, and methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside. The crystal and molecular structure of the obtained imidazolidine-4,5-dione have been determined by X-ray analysis as well as $^{1}H$ and $^{13}C$ NMR spectroscopy.

**Keywords** Oxamide, Imidazolidine-4,5-dione, X-ray diffraction analysis

## INTRODUCTION

Oxamides, especially *N*,*N*′-disubstituted oxamides, are important as ligands in organometallic complexes[1] and the preparation of polynuclear systems.[2] Looking for new oxamides in previous papers, we described the synthesis of an unsymmetrical oxamide. Acylation of methyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-α or β-D-glucopyranosides (**1α** or **1β**) with oxalyl chloride afforded *N*-acetyl *N*-(methyl 3,4,6-tri-*O*-acetyl-α or β-D-glucopyranosid-2-yl)

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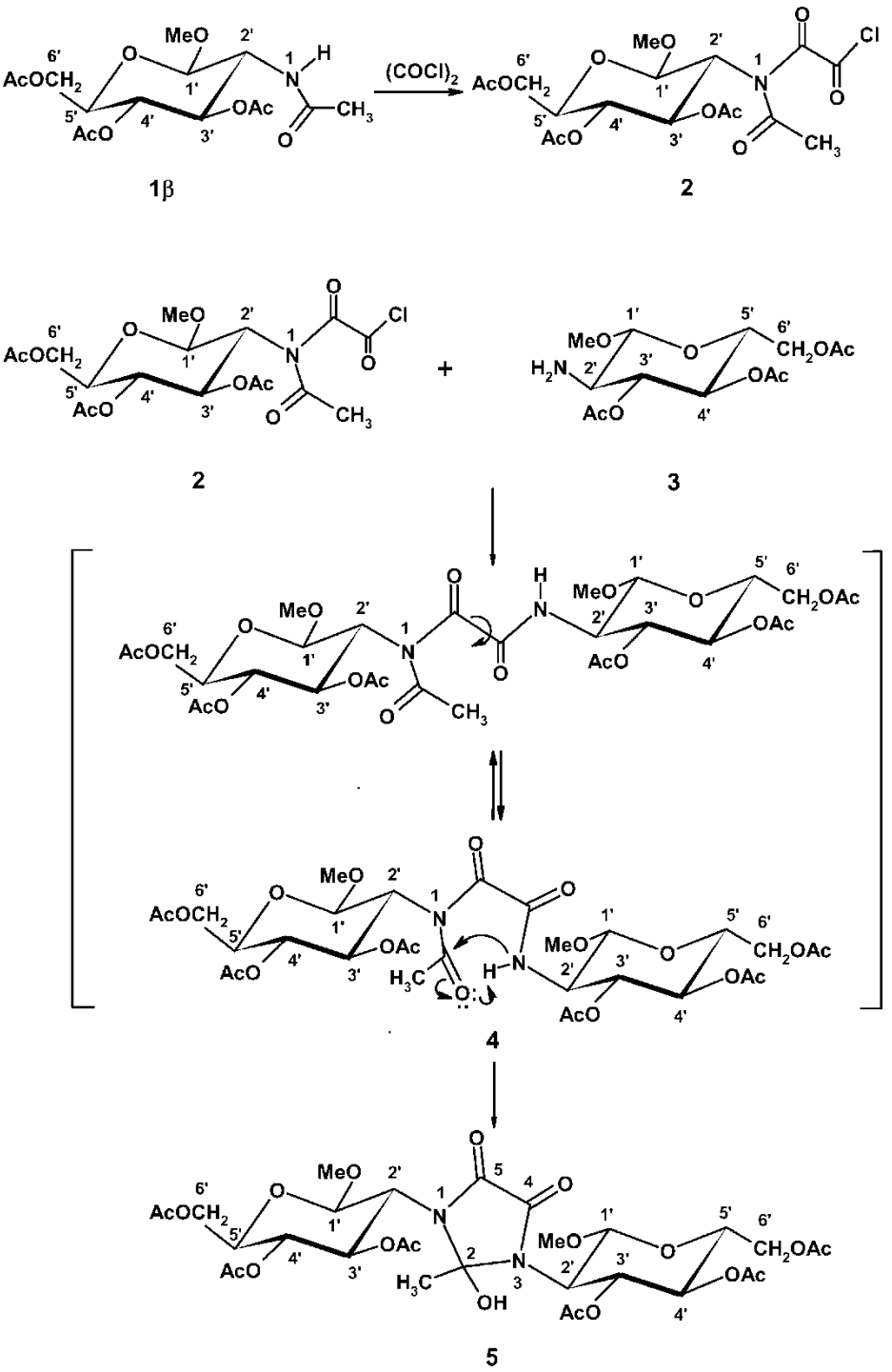
oxamic acid chloride **2**. The reaction of the oxamic acid chloride (**2**) with the corresponding amines gave unsymmetrical oxamides derivative of D-glucosamine and aliphatic or aromatic amines,[3] as well as amino acids or dipeptides.[4]

## RESULTS AND DISCUSSION

Our present aim was the synthesis of symmetrical oxamide [*N*,*N*′-bis-(methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside-2-yl)-oxamide] starting with **1β**,[5] oxalyl chloride, and methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside (**3**).[6] Unexpectedly, instead of symmetrical oxamide we obtained 2-hydroxy-2-methyl-1,3-bis-(methyl 3′4′6′-tri-*O*-acetyl-β-D-glucopyranosid-2-yl)-imidazolidine-4,5-dione (**5**) – new imidazolidine-4,5-dione in good yield. There is almost no information about the synthesis of 2-hydroxy-2-methyl-imidazolidine-4,5-diones. Only one paper described preparation of 2-hydroxy-2-methyl-1,3-diphenylimidazolidine-4,5-dione,[7] which was synthesized from *N*,*N*′-1, 2-ethanediylidene-bis-(benzenamine)-*N*,*N*′-dioxane[8] and acetic anhydride. Also, a mixture of 2-methoxy-2-methyl-imidazolidine-4,5-dione with 2-methyl-imidazole-4,5-dione was obtained from acetamidine hydrochloride and diethyl oxalate in methanol.[9]

As shown in Scheme 1, the formation of imidazolidine-4,5-dione **5** can be explained via intermediate **4**, obtained by acylation of **3** with oxamic acid chloride (**2**). Intermediate **4** was then converted into **5** by ring closure from the amide group at C-2′ and the acetyl group at N − 1. The $^{1}H$ and $^{13}C$ NMR spectra of the obtained compound **5** are in full agreement with the proposed structure. The β-configuration and $^{1}C_4$ conformation for compound **5** were confirmed by $^{1}H$ and $^{13}C$ NMR data. Carbon 2 of the imidazolidine ring of compound **5** is prostereogenic because mutual substitution of the *N*-linked sugar units would result in diastereoisomers.[10] In consequence, the two sugar units are located in chirotopic half spaces and are diastereotopic groups, which explains the two sets of proton/carbon signals in the $^{1}H/^{13}C$ NMR spectra. The assignment of signals for two glucopyranose rings of **5** was done by the analysis of $^{1}H$ spectrum and the two-dimensional $^{1}H-^{1}H$ and $^{1}H-^{13}C$ correlations (Figs. 1 and 2). The H-1′ signals were observed at 5.3 ppm and 5.18 ppm downfield in comparison with glucosyloxamides,[3] and this difference can be due to the influence of imidazolidine rings. A similar effect was observed of the C-3′ at 6.4 ppm and 5.80 ppm. The resonances of carbons, which are close to imidazolidine rings (C-2′ 58.12 ppm and 58.04 ppm), appeared upfield with respect to glucosyloxamides [e.g., 54.78 ppm at *N*-(methyl 3,4,6-tri-*O*-acetyl-2-β-D-glucopyranosid-2-yl), *N*′-methyl, *N*′-phenyloxamide].[3]

The X-ray analysis supports the proposed structure for compound **5.** Both β-D-glucopyranose rings exist in a $^{4}C_1$ conformation and all acetyl groups are




**Scheme 1**

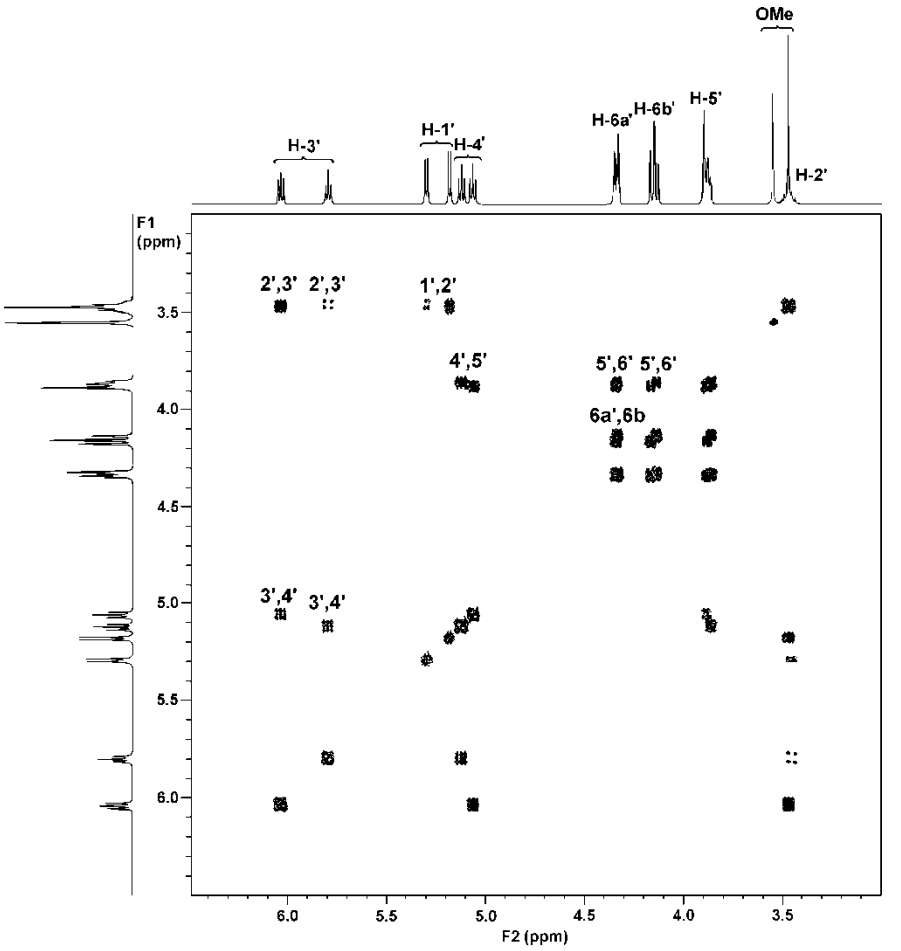



**Figure 1:** $^{1}$H-$^{1}$H COSY spectrum of 2-hydroxy-2-methyl-1,3-bis-(methyl 3′4′6′-tri-*O*-acetyl-2-deoxy-$\beta$-D-glucopyranosid-2-yl)-imidazolidine-4,5-dione (**5**).

almost planar. A comparison with open-chain oxamides[3,11–13] heterocyclic ring is almost planar (Fig. 3).

## EXPERIMENTAL

Optical rotations were measured on a Perkin-Elmer Model 241. The $^{1}$H and $^{13}$C NMR spectra were recorded in solutions with $CDCl_3$ (internal reference $Me_4Si$) with a Varian Unity Plus-500 spectrometer. TLC was performed on Silica Gel 60 ($F_{254}$ Merck), using dichloromethane-methanol (4 : 1) as eluent and detection by UV light or by charring with sulfuric acid. Column chromatography was conducted on Silica Gel 60 (Merck 230–400 mesh) with dichloromethane-methanol (4 : 1).

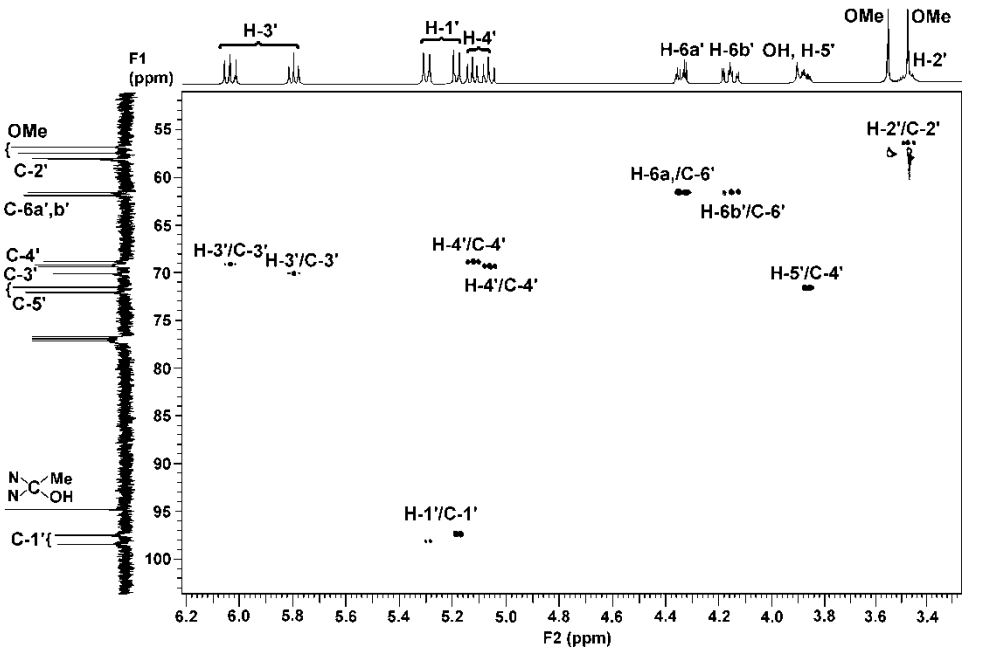



**Figure 2:** $^{1}H-^{13}C$ HETCOR spectrum of 2-hydroxy-2-methyl-1,3-bis-(methyl 3′4′6′-tri-*O*-acetyl-2-deoxy-$\beta$-D-glucopyranosid-2-yl)-imidazolidine-4,5-dione (**5**).



For X-ray structural analysis, compound **5** was crystallized slowly from ethanol. The X-ray measurement of **5** was performed at low temperature (at $100 \pm 2$ K) on a KUMA CCD k-axis diffractometer with graphite-monochromated Mo K$\alpha$ radiation (0.71073 Å). The crystal was positioned at 62.2 mm from the KM4CCD camera; 748 frames were measured at 0.8° intervals on a counting time of 35s. Data reduction and analysis were carried out with the Kuma Diffraction programs. The data were corrected for Lorentz and polarization effects, but no absorption correction was applied. The structures were solved by direct methods[14] and refined by using SHELXL.[15] The refinement was based on $F^2$ for all reflections except for those with very negative $F^2$. The weighted R factor, wR, and all goodness-of-fit S values are based on $F^2$. The nonhydrogen atoms were refined anisotropically, whereas the H-atoms, except for solvent molecules, were placed in the calculated positions. The atomic scattering factors were taken from the International Tables.[16] $C_{30}H_{42}N_2O_{19} \cdot H_2O$, colorless crystal, $0.05 \times 0.08 \times 0.1$ mm, formula weight $M = 752.7$. Although initially a solution was found in $P2_12_12_1$ space group with one molecule in the asymmetric unit of the unit cell, no further refinement was possible better than $R = 0.1531$ and $wR^2 = 0.3942$. Some of the refined atoms had unusually large anisotropic displacement parameters, while some of the bond lengths were obviously wrong; for example, the C7($sp^3$)–C71($sp^3$)

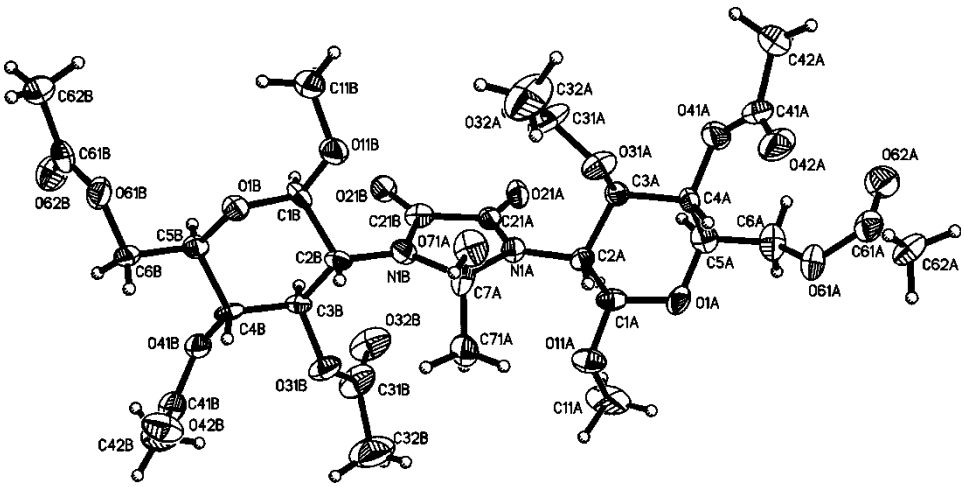



**Figure 3:** Molecular structure of 2-hydroxy-2-methyl-1,3-bis-(methyl 3′4′6′-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosid-2-yl)-imidazolidine-4,5-dione (**5**). Displacement ellipsoids are drawn at the 50% probability level.



and C7($sp^3$)–O71 bond length (see Fig. 3) were equal to 1.374 (24) Å and 1.368 (24)Å, respectively. Therefore, other possible space groups have been carefully analyzed and reasonable refinement was only possible in the monoclinic $P2_1$ space group: a = 9.061 Å (2), b = 35.267 (7) Å, c = 11.769 (2) Å, $\beta$ = 90.03 (3) deg., V = 3760.8 (13) $Å^3$, Z = 4, $D_x$ = 1.329 $Mg/m^3$, F(000) = 1592, absorption coefficient $\mu = 0.113\,mm^{-1}$. The collected data range was $3.32 < \Theta < 28.72$ deg. ($-12 \le h \le 12$, $-47 \le k \le 47$, $-15 \le l \le 14$), 33756 reflections collected, 14014 [R(int) = 0.1573] unique reflections, goodness-of-fit on $F^2 = 0.867$, final $R = 0.0861$, $wR^2 = 0.1758$ [for all 5201 $F_o > 4\ \sigma(F_o)$], R = 0.1802, $wR^2 = 0.2219$ (for all data), weight $= 1/[\sigma^2(F_o^2) + (0.0974P)^2 + 0.00P]$ where $P = (F_o^2 + 2\ F_c^2)/3$, extinction coefficient = 0.0062 (9), maximum and minimum difference electron densities were 0.487 and −0.364e. $Å^{-3}$. In the $P2_1$ space group there are two molecules of **5** and two molecules of $H_2O$ in the asymmetric unit of the unit cell. No correlation coefficients >0.5 were found between the refined parameters of these molecules. In the case of one molecule of **5** there is possibly a static disorder of the methyl groups (denoted as C32), and the largest residual maximum of the electron density map (0.467e. $Å^{-3}$) is 0.826 Å distant from one of the hydrogens of one of the methyl groups. The correct enantiomer was determined from the known chirality of starting material as well as from $^1H$ and $^{13}C$ NMR analysis. Figure 3 shows one molecule of **5** with displacement ellipsoids drawn at 50% probability level. Full crystallographic details, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre (CCDC 208584). These data may be obtained, on request, from The Directory, Cambridge

Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk. or www: http://www.ccdc.cam.ac.uk).

**2-Hydroxy-2-methyl-1,3-bis-(methyl 3′4′6′-tri-*O*-acetyl-β-D-glucopyranosid-2-yl)-imidazolidine-4,5-dione** (**5**). To a solution of **1β**[5] (0.98 g; 2.7 mmol) in dichloromethane (5 mL) was added a solution of threefold excess of oxalyl chloride (1.03 g; 8.16 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at 0°C for 10 min and at rt for 30 min. TLC then indicated the absence of **1**. Next, the reaction mixture was evaporated in vacuo and dissolved again in dichloromethane, and **2** was added. The mixture was stirred at rt for 2 hr. The resulting mixture was successively washed with hydrochloric acid (1M), water, and a saturated solution of sodium hydrogen carbonate, and then dried over magnesium sulfate. The organic layer was dried and concentrated. The residue was purified by chromatography with dichloromethane–methanol (4 : 1) as eluent. The solvent was evaporated in vacuo. Crystallization from ethanol gave **5** (0.99 g, yield 62.8 %). mp 217–220°C; $[\alpha]_D^{20} + 98.0$ (c 1.0, $CHCl_3$).

$^1$H NMR ($CDCl_3$): $\delta$ 6.04, 5.80 (2dd, 2H, $J_{2',3'} = 9.0$ Hz, $J_{3',4'} = 9.5$ Hz, 2H-3′), 5.30, 5.18 (2dd, 2H. $J_{1',2'} = 8.0$ Hz, 2H-1′), 5.19, 5.07 (2dd, 2H, $J_{4',5'} = 9.0$ Hz, 2H-4′), 4.36, 4.34 (2dd, 2H, $J_{5,6a} = 4.0$ Hz, $J_{6a,6b} = 12.0$ Hz, 2H-6a), 4.08 (2dd, 2H, $J_{5,6b} = 2.5$ Hz, 2H-6b), 3.91 (s, 1H, exchangeable, OH), 3.87 (2ddd, 2H, 2H-5), 3.55, 3.47 (2s, 6H, $2OCH_3$), 3.46 (m, 2H, 2H-2′), 2.10, 2.04, 2.03, 1.99, 1.96 (5s, 18H, 6OAc), 1.57 (s, 3H, C-2—$CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ 170.7, 170.8, 169.8, 169.6, 169.2 (6OAc), 156.9, 156.0 (2C═O), 98.39, 97.46 (2C-1′), 72.06, 71.52 (2C-5′), 70.14, 69.17 (2C-3′), 69.30, 68.77 (2C-4′), 61.86, 61.59 (2C-6′), 58.12, 58.04 (2C-2′), 57.41, 56.77 ($2OCH_3$′), 24.92 (C-2–$CH_3$). LSIMS (+) NBA $m/z$ 757.2 $[M + Na]^+$, Calc. for $C_{30}H_{42}O_{19}N_2 + Na$ 757.7 $[M + Na]^+$.



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