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Synthesis of Novel Calixsugars: Calix[4]arene–Monosaccharide Conjugates Based on Amide Bonds

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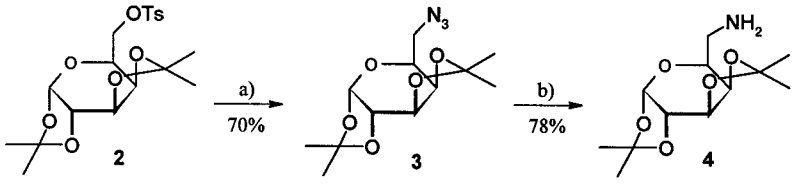
Abstract—Novel calix[4]arenes containing two sugar moieties in the molecule have been prepared. Both components are connected through the amidic bonds on the lower rim of a calixarene unit preorganised in the *cone* conformation. This design leads to new chiral receptors with potential recognition ability towards suitable guest molecules.

Calix[n]arenes, the well-known cyclic oligomers[1] of p-substituted phenols and formaldehyde, have been attracting much interest during the last decade. As a consequence of their simple one-pot preparation[2] and their unique structural properties, they are widely used as starting compounds and useful building blocks in the construction of more sophisticated molecular systems in supramolecular chemistry.[3] The easily tuneable shape of the molecule, together with the simple chemical derivatization of calix[4]-arene **1**, makes this molecule especially useful in the design and synthesis of wide range of receptors with recognition ability towards both neutral and charged molecules.[4]

Recently, great attention has been paid to the synthesis of novel molecular receptors with possible applications in the recognition of biologically active compounds (sugars, amino acids, peptides) under physiological conditions. It was shown that the introduction of the carbohydrate moiety into a calix[4]arene[5] or calix[4]resorcarene[6] skeleton can lead to water soluble derivatives: a fundamental prerequisite for such an application. The carbohydrate–calixarene conjugates thus represent a promising class of molecular receptors due to the chiral and polyhydroxylated nature of these compounds. Furthermore, the use of calix[4]arene as a molecular scaffold in the synthesis of these receptors enables total control of the shape of the whole molecule. In accordance with well-known calix[4]arene chemistry, four different basic conformations (*cone*, *partial cone*, *1,2- and 1,3-alternates*) can be used, each of them having its own specific shape and potentially unique complexation ability.

As a starting compound for the carbohydrate part of molecule we have chosen an easy accessible derivative of α-galactopyranose with protected hydroxy groups, i.e. 6-*O*-tosyl-1,2;3,4-di-*O*-isopropyliden-α-d-galactopyranose **2**.[7] This compound was converted into an appropriate azido derivative **3** in 70% yield by 2 days stirring with sodium azide in DMF at 120°C. Subsequent reduction of azido group using PPh_3 in THF[8] at room temperature gave the corresponding amino derivative **4** in 78% yield (Scheme 1).

The calixarene part of molecule is based on the diacid derivative **5** prepared by hydrolysis of corresponding diester. This compound is under common conditions fixed in the *cone* conformation, enabling the linkage of both saccharide units to the same side of the calixarene. The conversion of diacid **5** into its dichloride **6** was carried out



Scheme 1. (a) NaN_3, DMF–H_2O, NH_2CONH_2, 120°C, two days; (b) PPh_3, THF, rt.

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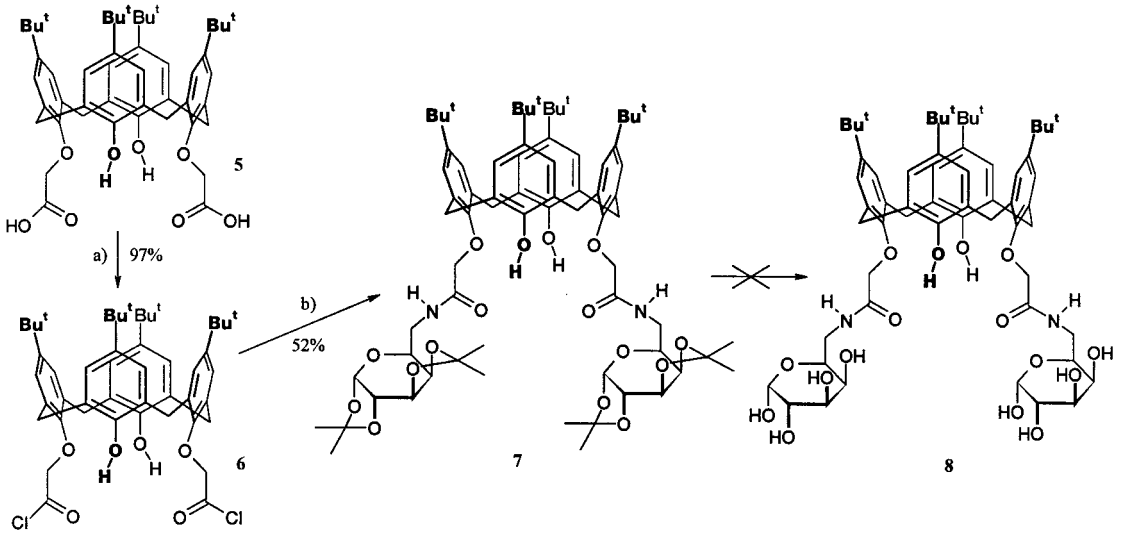


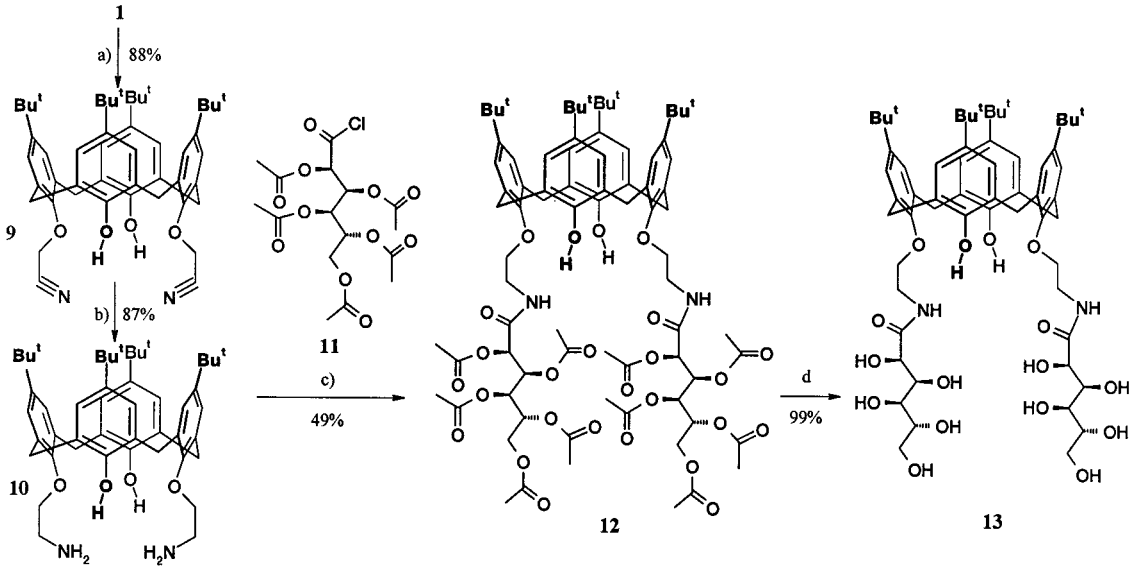
Scheme 2. (a) $(COCl)_2$, CCl_4, 3 h reflux; (b) **4**, Et_3N, THF, rt, 48 h.

using oxalyl chloride in high yield (97%). Subsequent treatment of dichloride with amino saccharide **4** yielded the required product **7**, isolated in 52% yield after column chromatography on silica gel (Scheme 2).

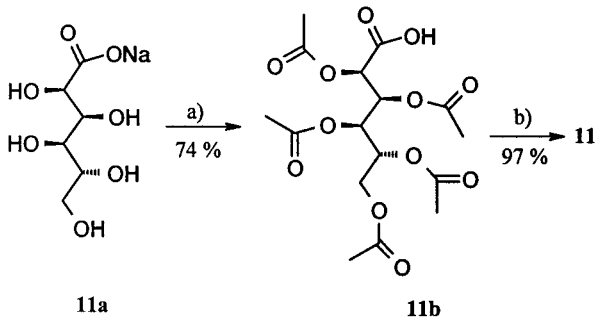
While the structures of derivatives **5** and **6** show the typical splitting pattern for a disubstituted calixarene, the ^1H NMR spectrum of **7** ($CDCl_3$) is more complex, reflecting the chirality imposed by sugar moieties. For example, the signals of the Ar–CH_2–Ar groups split into a set of four doublets ($J \cong 15$ Hz) thus proving a lower symmetry of the whole system. The same phenomenon is visible in the aromatic part of the spectrum where four doublets (with meta coupling, $J \cong 2.2$ Hz) can be found instead of two singlets for derivatives **5** and/or **6**. The FAB MS spectrum clearly showed a molecular peak at *m*/*z* 1247.

Unfortunately, the attempted elimination of protecting isopropylidene groups from derivative **7** failed. According to the conditions used, we only isolated starting compound: (a) Amberlit® IR-120, water–methanol, 60°C, 3 h; (b) sodium in abs. methanol, rt, 2 h; (c) $FeCl_3 \cdot 6H_2O$, CH_2Cl_2, rt, 15 min; (d) Dowex® 50WX8, methanol, rt, 20 h; or the reaction led to the destruction of molecule: (a) conc. CF_3COOH, rt, 4 h; (b) CF_3COOH:H_2O, 9:1, rt, 2 h; (c) $FeCl_3 \cdot 6H_2O$, abs. CH_2Cl_2, rt, 3 h; (d) Dowex® 50WX8, methanol, reflux, 2 h. As a consequence, the deprotected derivative **8** could not be prepared.[5a]

The synthetic failure described above led us to change of the synthetic strategy (Scheme 3). Calixarene **1** was distally alkylated[9] with chloroacetonitrile (acetone/K_2CO_4/reflux) to yield compound **9** in 88%, and subsequently reduced into aminoethyl derivative **10** (87%) using BH_3 in tetrahydrofuran.[10] This compound was acetylated by 2,3,4,5,6-pentaacetyl-d-gluconyl chloride **11**, prepared from sodium gluconate **11a** via acetylation[11] with acetyl anhydride and reaction of intermediate **11b** with oxalyl chloride according



Scheme 3. (a) $ClCH_2CN$, NaI, K_2CO_3, acetone, reflux, 7 h; (b) $BH_3 \cdot THF$, reflux, 7 h; (c) Et_3N, THF, rt, 12 h; (d) Na, abs. methanol, rt.



Scheme 4. (a) $Ac_2O+HCl/ZnCl_2$; (b) $(COCl)_2$, CCl_4.

to Scheme 4. Calix–sugar conjugate **12** with *O*-acetylated hydroxyl groups was obtained in 49% yield. In contrast to the above-mentioned unsuccessful transformation of **7** into **8**, the deprotection of **12** (sodium in dry methanol[12]) proceeds smoothly to yield calix–sugar derivative **13** in almost quantitative yield. The structure of compound was unambiguously proven by FAB MS which showed clearly visible signals at *m/z* 1092 and 1114 corresponding to $(M+2H^+)$ and $(M+Na^+)$, respectively. The ^1H NMR spectrum shows the splitting patterns typical for dialkylated calix[4]arenes in the cone conformation. Broad diffusion peaks of derivative **13** in non-polar solvents ($CDCl_3$) indicate the presence of slow chemical exchange phenomenon probably due to a self-aggregation process (intermolecular hydrogen bonds). The above-mentioned behaviour of **13** was studied by means of dynamic NMR spectra. In the temperature region studied (−90°C–+140°C, i.e. CD_2Cl_2 to $CDCl_2$–$CDCl_2$) the signals remain substantially broadened. The solution behaviour of compound **13** was also studied by standard dilution experiments at room temperature ($CDCl_3$, 25°C). The treatment of the data obtained assumed a dimer formation, assessed the dimerization constant 6300 M^{-1}.

Due to the surprisingly high solubility of compound **13** in chloroform we have performed complexation studies in $CDCl_3$ using commercially available sugar derivatives: 1-*O*-octyl-α-d-glucopyranoside (**14a**), 1-*O*-octyl-β-d-glucopyranoside (**14b**), and 1-*S*-octyl-β-d-thioglucopyranoside

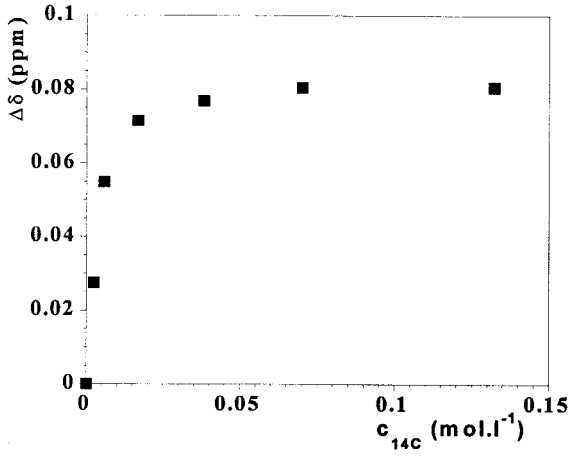


Figure 1. Typical titration curve of **13** (1.5 mmol·l^{-1}, $CDCl_3$, 298 K, 300 MHz) with **14c**.

(**14c**). The addition of glycosides to the solution of **13** induced chemical shift changes best observable in the aromatic (40 Hz) and amidic (150 Hz) regions of ^1H NMR spectrum[13] (the region containing the signals of sugar moiety could not be used due to its overlapping with signals of glycosides **14a**–**c**). The plot of induced chemical shifts versus glycoside concentration gave typical titration curves corresponding to the formation of a 1:1 complex (Fig. 1). The proposed stoichiometry of the complexation was confirmed by the measuring of Job plots. The appropriate complexation constants were calculated using a non-linear regression curve-fitting program and taking into account the concurrent dimerization process. Obviously, the self-association hampers the precise evaluation of appropriate binding constants, as we do not know exactly the character of interactions between associated species and sugar. Nevertheless, the values of stability constants should reflect the relative strength of the interactions. As expected, the complexation constants towards **14b** (K_C=1050 mol^{-1} dm^3) and **14c** (K_C=1000 mol^{-1} dm^3) are almost identical reflecting thus the high similarity of both structures (*O*- or *S*-β-glycosides). It seems that the configuration on C1 is not particularly important for the complexation as proved by the quite similar complexation constant for the α-anomeric structure **14a** (K_C=650 mol^{-1} dm^3).

As a conclusion, new calixarene–saccharide conjugates have been prepared using the reaction between the appropriate acyl chloride and an aminosaccharide derivative. The introduction of sugar moieties into the lower rim of calix[4]arene leads to novel receptors, the usefulness of which has been demonstrated by their interaction with various monosaccharide derivatives.

Experimental

Melting points were determined with a Boetius Block apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian Gemini 300 and a Bruker AMX3 400 spectrometer using tetramethylsilane as an internal standard. IR spectra were measured using a Nicolet 740 spectrometer. FAB MS were measured on ZAB-EQ VG Analytical spectrometer. Optical rotation values were obtained on Perkin–Elmer 241-Polarimetrie.

The following compounds were prepared according to known procedures: dicarboxymethyloxy derivative **5**,[9] 6-azido-6-deoxy-1,2;3,4-di-*O*-isopropylidene-α-d-galactopyranose **2**,[7] 6-amino-6-deoxy-1,2;3,4-di-*O*-isopropylidene-α-d-galactopyranose **3**,[7] bis(cyanomethyloxy) derivative **9**,[9] and bis(aminoethyloxy) derivative **10**.[10]

Synthesis of derivative 7

Diacid **5** (0.45 g, 0.59 mmol) was dissolved in 30 ml of carbon tetrachloride and oxalyl chloride (3 ml, 34 mmol) was added under N_2 atmosphere. The mixture was heated to reflux for 3 h and the unreacted oxalyl chloride and solvent were removed by distillation. The solid residue was diluted with 5 ml of CCl_4 and solvent was distilled off to remove traces of $(COCl)_2$. This procedure was

repeated three times and the solid residue was then dried under vacuum (1 Torr) at 80°C to give 0.46 g of dichloride **6** (97% yield).

The solution of the above prepared **6** in 20 ml of dry THF was added dropwise to the mixture of 6-amino-6-deoxy-1,2;3,4-di-*O*-isopropylidene-α-d-galactopyranose **3** (0.34 g, 1.3 mmol) and triethylamine (0.18 ml) in 20 ml of dry THF. The resulting mixture was stirred for 48 h at rt, then poured into 40 ml of water and extracted with chloroform (4×15 ml). The combined organic layers were dried over $MgSO_4$ and then evaporated to dryness to yield 0.70 g of crude product in the form of a brown oil. This oil was purified by column chromatography on silica gel using chloroform/ethyl acetate (5:1) mixture as an eluent to give 0.37 g of pure product **7** (52%, white solid), mp 168–171°C (ethanol). $[\alpha]_d^{20}=-32$ (c=0.5, $CHCl_3$); [Found: C, 66.96; H, 7.83; N, 2.15. $C_{72}H_{98}N_2O_{16}\cdot 2H_2O$ requires C, 67.36; H, 8.02; N, 2.18%]; ^{1}H NMR ($CDCl_3$) δ: 8.60 (d, 2H, J=3.8 Hz, –NH–), 7.21 (s, 2H, –OH), 7.03 (dd, 4H, J=2.2 Hz, J=9.9 Hz, Ar–H), 6.83 (dd, 4H, J=2.2 Hz, J=14.8 Hz, Ar–H), 5.32 (d, 2H, J=5.0 Hz), 4.67 (d, 2H, J=15.4 Hz, Ar–CH_2–Ar ax), 4.53 (dd, 2H, J=2.2 Hz, J=7.7 Hz), 4.38 (d, 2H, J=14.8 Hz, Ar–CH_2–Ar ax), 4.18 (m, 8H), 3.37 (d, 2H, J=13.9 Hz, Ar–CH_2–Ar eq), 3.28 (d, 2H, J=12.6 Hz, Ar–CH_2–Ar eq), 1.49 (s, 6H), 1.27 (s, 18H, Bu^t), 1.24 (s, 6H), 1.11 (s, 6H), 0.98 (s, 6H), 0.97 (s, 18H, Bu^t); IR ($CHCl_3$) ν_{max} (cm^{-1}): 1669 (C=O), 3346, 3490 (OH); MS FAB ($C_{72}H_{98}N_2O_{16}$) calcd. 1246.7, found 1247.2 (M^+).

2,3,4,5,6-Penta-*O*-acetyl-α-d-gluconic acid[10] (11b). Freshly fused $ZnCl_2$ (2.00 g, 14.7 mmol) was dissolved at room temperature in 25 ml of acetic anhydride and the resulting solution was cooled to −5°C. Sodium α-d-gluconate **11a** (6.4 g, 29 mmol) was then added and anhydrous hydrogen chloride was bubbled through the stirred reaction mixture while the temperature was maintained below 5°C. After 30 min the stream of hydrogen chloride was stopped, the cooling bath was removed and the milky coloured reaction mixture was stirred at room temperature overnight. The reaction mixture was cooled to 0°C, carefully quenched by the addition of ice (30 g) and stirred for 1 h at room temperature. The mixture was then diluted with 100 ml of water and extracted with $CHCl_3$ (4×20 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The residue (yellowish oil) was evaporated three times with 50 ml of toluene and dried in vacuum (1 Torr) at 80°C overnight to yield 8.8 g of product **11b** as a yellow oil. ^{1}H NMR was in agreement with a published spectrum[14] and compound was used in the next reaction without further identification.

2,3,4,5,6-Penta-*O*-acetyl-α-d-gluconyl chloride[15] (11). Oxalyl chloride (3 ml, 34 mmol) was added dropwise to a solution of the above-prepared compound **11b** (0.61 g, 1.5 mmol) in 30 ml of carbon tetrachloride and the resulting mixture was stirred at reflux for 3 h. The unreacted oxalyl chloride and solvent was removed by distillation. The oily residue was diluted with 5 ml of CCl_4 and the solvent was again distilled off to remove traces of $(COCl)_2$. This procedure was repeated three times and the oily residue was then dried under vacuum (1 Torr) at 80°C to yield 0.62 g of chloride **11** (97%). This compound was used for the next reaction without further purification.

Synthesis of derivative 12

The above prepared derivative **11** (0.62 g, 1.46 mmol) and bis(2-amino-ethyloxy) derivative **10** (0.50 g, 0.68 mmol) were dissolved in 20 ml of dry THF at room temperature under N_2 atmosphere. Then triethylamine (0.20 ml, 1.36 mmol) was injected via septum to this solution and resulting mixture was stirred for 12 h at room temperature. The reaction mixture was then poured into 40 ml of water and extracted with chloroform (4×15 ml). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness to yield 0.96 g of crude product as a purplish solid. Pure product was obtained by the recrystallization from dioxane/ethyl acetate (1:1) to give 0.50 g of **12** (49%, white crystals), mp 167–169°C. $[\alpha]_d^{20}=+31$ (c=0.5, $CHCl_3$); [Found: C, 62.02; H, 6.88; N, 1.81. $C_{80}H_{106}N_2O_{26}$ requires C, 62.07; H, 7.17; N, 1.81%]; ^{1}H NMR ($CDCl_3$) δ: 8.56 (s, 2H, –OH), 8.22 (m, 2H, –NH–), 7.06 (d, 2H, J=2.2 Hz, Ar–H), 7.02 (d, 2H, J=2.2 Hz, Ar–H), 6.99 (d, 2H, J=2.2 Hz, Ar–H), 6.96 (d, 2H, J=2.2 Hz, Ar–H), 5.67 (t, 2H, J=4.9 Hz), 5.41 (m, 4H), 5.05 (m, 2H), 4.28 (dd, 4H, J=13.2 Hz, J=28.0 Hz, Ar–CH_2–Ar ax), 4.26 (m, 4H, O–CH_2), 4.16 (dd, 2H, J=12.1 Hz, J=3.9 Hz), 4.05 (m, 4H, N–CH_2), 3.90 (dd, 2H, J=12.1 Hz, J=6.1 Hz), 3.38 (dd, 4H, J=20.3 Hz, J=12.6 Hz, Ar–CH_2–Ar eq), 2.06 (s, 6H, CH_3CO), 2.05 (s, 6H, CH_3CO), 2.04 (s, 6H, CH_3CO), 2.03 (s, 6H, CH_3CO), 1.90 (s, 6H, CH_3CO), 1.22 (s, 18H, Bu^t), 1.12 (s, 18H, Bu^t); IR ($CHCl_3$) ν_{max} (cm^{-1}): 1681, 1752 (C=O), 3310 (OH); MS FAB ($C_{80}H_{106}N_2O_{26}$) calcd 1510.7, found 1511.5 (MH^+).

Synthesis of derivative 13

Sodium metal (1.00 g) was dissolved in 30 ml of absolute methanol and to this solution was added derivative **12** (0.160 g, 0.106 mmol) in one portion. The course of the reaction was followed by TLC and after 10 min no starting compound was detected. Then activated Dowex® 50WX8 (approx. 5 ml) was added and reaction mixture was stirred overnight. The ion-exchange resin was removed by filtration and the filtrate was evaporated to dryness to yield 115 mg of product **13** (99%, white powder) with mp 176–180°C; [Found: C, 63.51; H, 7.99; N, 2.35. $C_{60}H_{86}N_2O_{16}\cdot 2H_2O$ requires C, 63.92; H, 8.05; N, 2.48%]; ^{1}H NMR ($CDCl_3$) δ: 8.19 (brs, 2H), 7.64 (brs, 2H), 6.97 (s, 4H, Ar–H), 6.79 (s, 4H, Ar–H), 4.42, 4.27, 4.19, 3.98, 3.80, 3.70, 3.23, 2.00 (all signals very broad), 1.20 (s, 18H, Bu^t), 0.96 (s, 18H, Bu^t); ^{13}C NMR ($CDCl_3$:CD_3OD, 4:1, v/v) δ: 29.38, 30.66, 31.17, 31.30, 33.54, 33.78, 38.93, 63.15, 70.20, 71.24, 72.34, 73.72, 74.63, 124.95, 125.57, 127.78, 132.63, 142.52, 147.93, 148.60, 149.16, 175.21; MS (FAB) ($C_{60}H_{86}N_2O_{16}$) calcd 1090.60, found 1092.1 (MH^+), 1114.1 ($M+Na^+$); IR ($CHCl_3$) ν_{max} (cm^{-1}): 1653 (C=O), 3401(OH).

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