A General Method for the Synthesis of Cyclodextrinyl Aldehydes and Carboxylic Acids

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The selective synthesis of the primary-side monoaldehyde of β-cyclodextrin, 6-deoxy-6-formyl-β-cyclodextrin, was accomplished by oxidation of the corresponding tosylate utilizing the Nace reaction (DMSO/collidine). This monoaldehyde was then used as the starting material in several reactions including reduction, addition of $NaHSO_3$, addition of the α-nucleophiles hydroxylamine and hydrazine, and reductive amination. Of particular interest is the conversion of the monoaldehyde to the primary side carboxylic acid, 6-deoxy-6-carboxy-β-cyclodextrin, via bromine oxidation. This general method sequence can be applied to any tosyl derivative of cyclodextrin as demonstrated in the synthesis of β-cyclodextrin-A,D-dialdehyde and β-cyclodextrin-A,D-diacid.

Introduction

Cyclodextrins have found wide utility in the synthesis of artificial enzymes due to their ability to bind compounds in aqueous solution.[1] In order to expand this area of chemistry, the synthesis of functionalized cyclodextrins on a preparative scale is necessary.[2] While the net reduction of cyclodextrin's primary side hydroxyl groups is known,[3] selective oxidation reactions are rare.[4] The synthesis of the heptacarboxylic acid derivative of β-cyclodextrin has been reported, although characterization was incomplete. The reported synthesis involved the oxidation of β-cyclodextrin with O_2/Pt or N_2O_4, as well as preparation from the heptaazido or the heptaformyl β-cyclodextrin.[5] Although the synthesis of the α-cyclodextrinyl monoaldehyde has been previously reported,[6] we have reported an experimentally simpler synthesis[7] involving the conversion of the β-cyclodextrin primary-side monotosylate directly to the β-cyclodextrin primary-side aldehyde using the Nace reaction.[8] We have now utilized this compound as a starting material for further conversions to novel derivatives. Of particular interest is the synthesis of the primary side carboxylic acid directly from the primary side aldehyde by oxidation with bromine. We have also demonstrated the generality of these procedures by their application to the synthesis of the primary side β-cyclodextrin-A,D-dialdehyde and β-cyclodextrin-A,D-dicarboxylic acid.

Results and Discussion

Synthesis of β-Cyclodextrinyl Monoaldehdye. The synthesis of the 6-deoxy-6-formyl-β-cyclodextrin, **2**, has been accomplished using a two-step procedure starting from β-cyclodextrin (Scheme 1). The first step of the synthesis involved the well-known reaction of β-cyclodextrin with *p*-toluenesulfonyl chloride in pyridine to form the primary-side monotosylate.[9] The purified tosylate[10] was then converted to the aldehyde via a DMSO oxidation.[11] This oxidation was performed by heating the tosylate in DMSO with collidine added as a non-nucleophilic base. Compound **2** has been characterized by ^1H NMR, ^{13}C NMR, mass spectrometry, and microanalysis.

The ^1H NMR of **2** provides some interesting information concerning the preference for the compound to exist in the aldehyde form or as a covalent hydrate.[12] In D_2O, **2** prefers to exist exclusively (by our detection limits) as covalent hydrate **3**, indicated by a broad singlet at 5.2 ppm that corresponds to the proton on the covalent hydrate carbon. However, in DMSO, **2** can exist in two forms depending upon the amount of water present in solution. With little or no water, the aldehydic proton can be observed at 9.7 ppm and the proton α to the aldehyde can now also be distinguished from the cyclodextrin mass as a doublet at 4.2 ppm. In contrast, with a small amount of water added to the solution, the aldehyde converts back to the covalent hydrate form. This can be seen in the appearance of a triplet at 5.2 ppm that corresponds, as before, to the proton on the carbon of the covalent hydrate. The splitting pattern can be explained by the coupling of this proton to the hydroxyl protons of the covalent hydrate that appear as a set of doublets centered at 5.5 ppm. As expected, deuterium exchange (D_2O) of the OH groups causes the triplet to convert back into a singlet. The presence of peaks due to the hydroxyl groups of the covalent hydrate has resolved any concern

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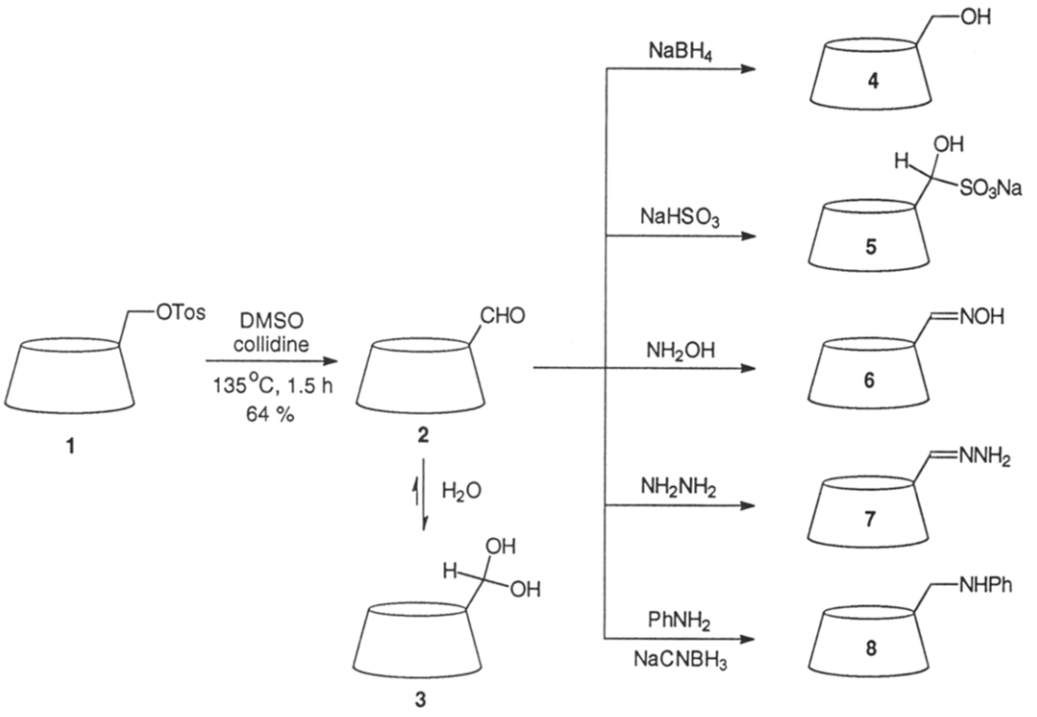
Scheme 1



	4	5	6	7	8
^1H, ^{13}C NMR	x	x	x	x	x
MS	x	x	x	x	x
EA			x		x

that the aldehyde might be capable of internal covalent hydrate formation with one of the various hydroxyl groups of the cyclodextrin as opposed to attack of solvent water on the aldehyde.

We have prepared several derivatives from **2** using classical organic procedures (Scheme 1). In this context, we have found the aldehyde functionality to be reactive toward reduction (**4**),[6] addition of $NaHSO_3$ (**5**),[13] addition of α-nucleophiles[14] (hydroxylamine (**6**) and hydrazine (**7**)), and reductive amination (**8**).[15]

Synthesis of β-Cyclodextrinyl Carboxylic Acid. Many conditions are available for the oxidation of aldehydes to carboxylic acids such as the following: chromic acid,[16] manganese derivatives,[17] Ag_2O,[18] basic I_2,[19] and peracetic acids.[20] We avoided metal-promoted oxidations; therefore, oxidations using basic I_2 and peracids were attempted. However, in basic solution **2** decomposed rapidly and the characteristic β-cyclodextrin doublet at 4.9 ppm in the ^1H NMR was lost after the reaction. After surveying several methods, we settled on bromine oxidation in aqueous solution (Scheme 2). The oxidation of reducing glucosides by Br_2 solution is well developed by various researchers.[21] According to Isabell *et al.*, glucopyranosides are oxidized to glucosidic acids by Br_2 in weak acidic buffer solution (barium phenolate, pH 6). This reaction is known to be highly sensitive to pH. We monitored the oxidation of **2** at pH's 6.0, 6.5, 7.0, 7.5, and 8.0. Reaction for 5 days at room temperature at pH 6 (0.1 M phosphate buffer) afforded the best compromise between reaction rate and yield. Under these conditions, β-cyclodextrin itself showed no observable reactivity as measured by TLC and NMR analysis of the reaction mixture. Oxidation of aldehyde **2** under these conditions yielded, after reversed phase chromatography, acid **9** in 24% isolated yield. Under longer reaction times and higher pH conditions, there was a change in the ^1H NMR of β-cyclodextrin that probably resulted from its oxidation. After 5 days at pH 6, there was still starting material detectable by NMR. This observation, along with likely product loss during the reversed phase chromatography, could be the rationale for the rather low-yielding oxidation step. The structure assignment is consistent with ^1H NMR, ^{13}C NMR, mass spectroscopy, and microanalytical data.

Synthesis of Bifunctional Oxidized Cyclodextrins. To demonstrate the generality of these oxidation conversions, we applied them to the synthesis of the cyclodextrin-A,D-dialdehyde and -diacid (Scheme 2). Preparation of the biphenyl-4,4′-disulfonyl "capped" β-cyclodextrin (**10**), established previously as the A,D-isomer,

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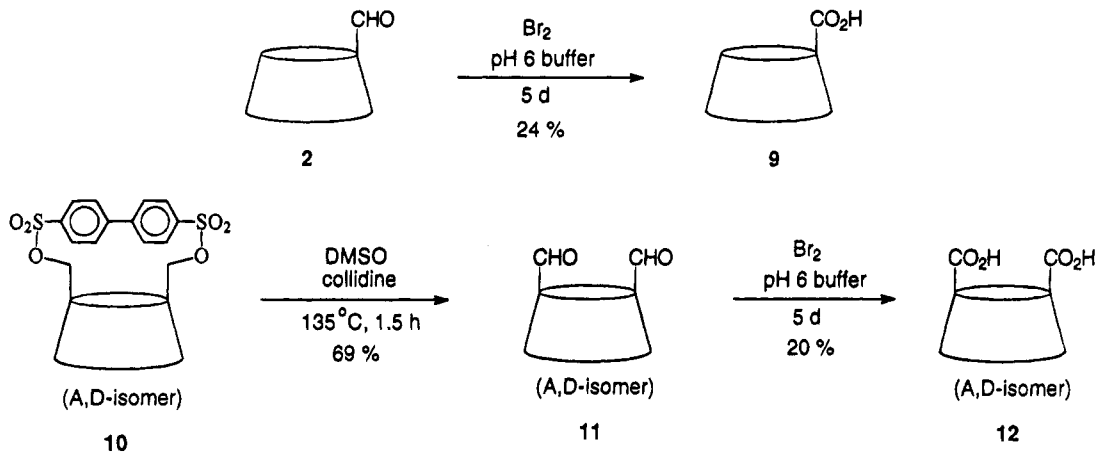
Scheme 2



was accomplished following the literature procedure.[22] We purified the A,D-isomer using reversed phase chromatography [30% aqueous MeOH (600 mL) followed by 60% aqueous MeOH (400 mL)]. Oxidation in hot DMSO/collidine afforded dialdehyde **11** in 69% yield. This material runs as a single spot on TLC different from that of **10**, but NMR in D_2O does not resolve the two aldehyde hydrate proton or carbon resonances. However, integration of the proton resonance is consistent with a two-proton signal, whereas that for monoaldehyde **2** gave a one-proton integration. Furthermore, the FAB mass spectrum gives the correct mass for the dialdehyde. Assignment as the A,D-isomer can only be inferred from the synthetic route.

Oxidation to the diacid was accomplished with aqueous bromine, affording compound **12** in 20% yield after reversed phase chromatographic purification. ^{13}C NMR in D_2O demonstrates a carbonyl resonance at 172.3 ppm, presumably comprised of two unresolved signals. FAB mass spectrometry gave the correct mass for the diacid, which is again presumed to be the A,D-isomer based on the structure of precursor **10**.

Conclusion

In summary, we report routes that provide for the preparative syntheses of cyclodextrinyl aldehydes and acids. In principle, these reactions may be applied to any of the numerous known sulfonated cyclodextrin compounds for the selective synthesis of the corresponding oxidized derivatives.

Experimental Section

General. Prepacked reversed phase column (LiChrosorb RP-18, 310 × 25 mm) was obtained from EM Separations, Gibbstown, NJ. Thin layer chromatography was performed on alumina-backed silica gel plates with solvent system A (*n*-butanol/ethanol/water, 5:4:3) or B (*n*-butanol/water/ethyl acetate/25% aqueous ammonia, 5:3:2:1). Cyclodextrin compounds were visualized by charring with MeOH/AcOH/H_2SO_4/*p*-anisaldehyde (200:20:10:1) spray.

6-Deoxy-6-formyl-β-cyclodextrin (2). β-Cyclodextrin monotosylate (**1**; 1.0 g, 0.78 mmol), recrystallized three times from water, was dissolved in DMSO (10 mL). Collidine (1 mL, 7.6 mmol) was added and the yellow solution heated at 135 °C for 1.5 h. The resulting dark brown solution was added dropwise to acetone (100 mL) and the precipitate collected under vacuum. The solid was dissolved in H_2O (10 mL) with warming and the solution added dropwise to ethanol (95%, 100 mL). The colorless precipitate was collected under vacuum to afford **2** (570 mg, 64%): R_f 0.32 (solvent system A); ^1H NMR (D_2O) δ 5.23 (s, 1), 4.90 (s, 7), 4.00–3.54 (m, 28), 3.54–3.30 (m, 14); ^1H NMR (DMSO-d_6) (note: this contains both the aldehyde and covalent hydrate form of the compound) δ 9.70 (s, 0.3), 5.97–5.55 (m, 12), 5.52 (d, 0.6), 5.48 (d, 0.6), 5.11 (t, 0.6), 4.99–4.90 (d, 1), 4.90–4.69 (br d, 6), 4.60–4.42 (m, 6), 4.18 (d, 1), 3.93–3.08 (m); ^{13}C NMR (DMSO-d_6) δ 198.3, 101.9, 87.5, 81.6, 73.0, 72.4, 72.0, 59.9; FAB mass spectrum *m/e* 1133 (M^+).

Anal. Calcd for $C_{42}H_{68}O_{35}\cdot 8H_2O$: C, 39.50; H, 6.63. Found: C, 39.40; H, 6.84.

β-Cyclodextrin (4). 6-Deoxy-6-formyl-β-cyclodextrin (**2**; 51 mg, 0.045 mmol) was dissolved in H_2O (10 mL). $NaBH_4$ (26 mg, 0.69 mmol) was added and the solution stirred at rt for 1 d. The pH of the solution was adjusted to ca. 4 with acetic acid. The solution was passed down a Dowex HCR-W2 resin (8.9 × 5.7 cm) with water elution. The appropriate fractions were pooled and lyophilized to afford a solid (37 mg, 72%). The sample was identical to an authentic sample of βCD as determined by TLC, ^1H NMR, ^{13}C NMR, and FAB mass spectrometry.

6-Sulfo-β-cyclodextrin Sodium Salt (5). 6-Deoxy-6-formyl-β-cyclodextrin (**2**; 150 mg, 0.132 mmol) was suspended in H_2O (15 mL). $NaHSO_3$ (19 mg, 0.18 mmol) was added, and the solution was stirred at rt for 3 d. The volume was reduced to ca. 2 mL by *in vacuo* solvent removal. The solution was added dropwise to 2-propanol (200 mL) and refrigerated overnight. A colorless solid was collected under vacuum (113 mg, 69%). The sample was purified by gel filtration chromatography (Sephadex G-25, 6.0 × 2.2 cm) eluting with water. Appropriate fractions were pooled and lyophilized to yield a colorless solid (92% recovery) containing approximately 70% **5** as evidenced by microanalysis: R_f 0.29 (solvent system A); ^1H NMR (D_2O) δ 4.89 (s, 7), 4.13 (d, 1), 3.97–3.53 (m, 28), 3.53–3.22 (m, 14); ^{13}C NMR (D_2O) δ 105.3, 104.8, 104.7, 104.3, 84.9, 84.0, 83.9, 83.6, 83.3, 75.9, 75.7, 75.0, 74.9, 74.7, 74.5, 73.2, 63.2, 62.7; FAB mass spectrum *m/e* 1238 ($M^+ + 1$).

Anal. Calcd for $C_{42}H_{69}NaSO_{38}\cdot 8H_2O$: C, 36.52; H, 6.20; Na, 1.66; S, 2.32. Found: C, 36.25; H, 6.04; Na, 1.46; S, 1.69.

6-Deoxy-6-oxo-β-cyclodextrin Oxime (6). 6-Deoxy-6-formyl-β-cyclodextrin (107 mg, 0.0944 mmol) was dissolved in a 50% aqueous solution of H_2NOH (10 mL) and stirred at rt for 4 h. The solution was added dropwise to ethanol (95%, 200 mL) and refrigerated for 5 h. The colorless precipitate was collected under vacuum to yield **6** (46 mg, 43%). The compound was compared to an authentic sample of the oxime as previously prepared in our laboratory:[23] R_f 0.37 (solvent system A); ^1H NMR (DMSO-d_6) δ 7.23 (d, 0.8), 6.67 (d, 0.2), 5.97–5.57 (m, 14), 5.54 (br s, 1), 5.02–4.73 (m, 7), 4.62–4.42

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(m, 6), 4.10 (t, 1), 3.97–3.13 (m); ^{13}C NMR (D_2O) δ 146.6, 102.1, 101.8, 83.9, 81.4, 73.2, 72.9, 72.6, 72.2, 71.9, 69.3, 68.9, 59.9, 59.6, 58.9; FAB mass spectrum m/e 1149 ($M^+ + 1$).

Anal. Calcd for $C_{42}H_{69}NO_{35}\cdot 8H_2O$: C, 39.04; H, 6.63; N, 1.08. Found: C, 38.92; H, 6.68; N, 0.96.

6-Deoxy-β-cyclodextrin Hydrazone (7). 6-Deoxy-6-formyl-β-cyclodextrin (**2**; 100 mg, 0.0883 mmol) was dissolved in H_2O (10 mL). Hydrazine hydrate (3 mL, 0.1 mol) was added and the solution stirred at rt overnight. The solution was added dropwise to 2-propanol (200 mL) and refrigerated for 1 h. The precipitate was collected under vacuum, dissolved in H_2O (1.5 mL), and added dropwise to 2-propanol (60 mL). The solution was refrigerated for 1 h and the colorless solid collected under vacuum (60 mg, 60%): R_f 0.33 (solvent system A); ^{1}H NMR (D_2O) δ 7.06 (d, 1), 4.89 (d, 7), 4.11 (t, 1), 3.95–3.59 (m, 27), 3.59–3.27 (m, 14); ^{13}C NMR (DMSO-d_6) δ 137.6, 102.1, 81.7, 81.4, 73.2, 72.9, 72.6, 72.2, 71.9, 60.0, 59.6; FAB mass spectrum m/e 1148 ($M^+ + 1$).

Anal. Calcd for $C_{42}H_{70}N_2O_{34}\cdot 7H_2O$: C, 39.62; H, 6.65; N, 2.20. Found: C, 39.49; H, 6.72; N, 1.65.

6-Deoxy-6-(*N*-phenylamino)-β-cyclodextrin (8). 6-Deoxy-6-formyl-β-cyclodextrin (**2**; 203 mg, 0.179 mmol) was placed in H_2O (20 mL), and aniline (0.20 mL, 2.2 mmol) was added. The pH of the solution was adjusted to 6.0 with dilute HCl. $NaCNBH_3$ (1.0 M in THF, 0.50 mL, 0.5 mmol) was added and the solution stirred at rt for 6 d. The solution was added dropwise to acetone (250 mL). After refrigeration for 1 h, the colorless precipitate was collected under vacuum and rinsed with acetone (3 × 50 mL) to yield a colorless solid (191 mg, 88%). Purification can be accomplished utilizing reversed phase column chromatography, eluting with an increasing gradient of MeOH to H_2O from 0 to 30% with a 34% recovery: R_f 0.35 (solvent system A); ^{1}H NMR (DMSO-d_6) δ 7.00 (t, 2), 6.59 (d, 2), 6.49 (t, 1), 6.05–5.50 (m, 14), 5.21 (br t, 1), 4.97–4.75 (m, 7), 4.72–4.30 (br m, 6), 3.90–3.05 (m); ^{13}C NMR (DMSO-d_6) δ 148.7, 128.8, 112.8, 112.4, 101.9, 81.2, 72.6, 72.3, 69.7, 59.9; FAB mass spectrum m/e 1211 ($M^+ + 1$).

Anal. Calcd for $C_{48}H_{75}NO_{34}\cdot 8H_2O$: C, 42.57; H, 6.77; N, 1.03. Found: C, 42.66; H, 6.72; N, 1.02.

6-Deoxy-6-carboxy-β-cyclodextrin (9). To a solution of 6-deoxy-6-formyl-β-cyclodextrin (**2**; 300 mg, 0.26 mmol) in 0.1 M phosphate buffer solution (pH 6, 4 mL) was added bromine (1 mL, 18 mmol). The reaction was stirred at rt in the dark for 5 d. Excess bromine was extracted using ether, and the aqueous solution was added dropwise to acetone (200 mL). The precipitate was collected under vacuum and purified by reversed phase column chromatography, eluting with water (300 mL) followed by 10% aqueous methanol (200 mL). The appropriate fractions were concentrated to 5 mL under vacuum and lyophilized to give the desired product as a fluffy colorless solid (72 mg, 24%): R_f 0.64 (solvent system B); ^{1}H NMR (D_2O) δ 4.95 (d, 1), 4.90 (d, 6), 4.12 (d, 1), 3.87–3.55 (m, 25), 3.55–3.37 (m, 14); ^{13}C NMR (D_2O) δ 175.0, 104.2, 104.0, 84.5, 83.5, 83.0, 75.6, 75.5, 75.4, 74.8, 74.6, 74.5, 74.3, 74.1, 62.8, 62.2; FAB mass spectrum m/e 1149 (M^+).

Anal. Calcd for $C_{42}H_{68}O_{36}\cdot 8H_2O$: C, 39.01; H, 6.55. Found: C, 38.89; H, 6.42.

A,D-Diformyl-β-cyclodextrin (11). Biphenyl-4,4′-disulfonyl-A,D-capped β-cyclodextrin[22] (**10**; 500 mg, 0.354 mmol) was dissolved in dimethyl sulfoxide (5 mL). Collidine (0.5 mL, 3.8 mmol) was added, and the solution was heated at 135 °C for 1.5 h. The dark yellow solution was cooled slightly and added dropwise to acetone (150 mL). The precipitate was collected under vacuum and dissolved in water with heating. The solution was added dropwise to ethanol (200 mL) to give the desired product (275 mg, 69%): R_f 0.7 (solvent system B); ^{1}H NMR (D_2O) δ 5.19 (s, 2), 4.93 (d, 2), 4.82 (d, 5), 3.85–3.57 (m, 24), 3.52–3.28 (m, 14); ^{13}C NMR (D_2O) δ 101.8, 87.1, 82.1, 81.0, 72.7, 72.0, 71.7, 71.2, 60.1; FAB mass spectrum m/e 1131 (M^+).

Anal. Calcd for $C_{42}H_{66}O_{35}\cdot 6H_2O$: C, 40.71; H, 6.35. Found: C, 40.73; H, 6.36.

A,D-Dicarboxy-β-cyclodextrin (12). To a solution of A,D-diformyl-β-cyclodextrin (**11**; 200 mg, 0.18 mmol) in 0.1 M phosphate buffer (pH 6, 3 mL), was added bromine (1 mL, 18 mmol). The reaction was stirred at rt in the dark for 5 d. Excess bromine was extracted using ether, and the aqueous solution was added dropwise to acetone (150 mL). The precipitate was collected under vacuum and purified by reversed phase column chromatography, eluting with water (300 mL) followed by 5% aqueous methanol (150 mL). The appropriate fractions were concentrated to 5 mL under vacuum and lyophilized to give the desired product as a fluffy colorless solid (42 mg, 20%): R_f 0.60 (solvent system B); ^{1}H NMR (D_2O) δ 4.95 (t, 2), 4.90 (t, 5), 4.11 (dd, 2), 3.87–3.52 (m, 22), 3.52–3.35 (m, 14); ^{13}C NMR (D_2O) δ 172.3, 101.7, 101.2, 101.1, 81.5, 81.2, 80.9, 80.4, 73.1, 73.0, 72.9, 72.7, 72.0, 71.7, 71.5, 71.4, 60.2, 59.6; FAB mass spectrum m/e 1163 (M^+).

Anal. Calcd for $C_{42}H_{66}O_{37}\cdot 8H_2O$: C, 38.59; H, 6.32. Found: C, 38.55; H, 6.24.

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