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Synthesis of Nitrogen-Functionalized β-Cycloaltrins

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Abstract: We report the synthesis of functionalized β-cycloaltrins having azido groups at C-3, C-6, and both C-3 and C-6 by nucleophilic epoxy ring-opening of per-2,3-anhidro-β-cyclomannin derivatives. The value of these compounds as templates for further functionalization is exemplified by the conversion of heptakis(3,6-diazido-3,6-dideoxy)-β-cycloaltrin into the per-3,6-diamino, per-3,6-diacetamido, per-3,6-dichloroacetamido, and per[3,6-bis(*N*′-ethylureido)] derivatives in good yields.

Cyclodextrins (CDs) are macrocyclic oligosaccharides comprising six (α-CD), seven (β-CD), and eight (γ-CD) α-(1→4)-D-glucopyranosyl units, respectively, that are formed during the enzymatic degradation of starch. The hydrophobic cavities of these thorus-shaped structures are responsible of the main CD feature, that is the formation of inclusion complexes with a variety of geometrically and spatially compatible hydrophobic molecules in aqueous solution. This feature has found wide applications in analytical chemistry, pharmaceutical and biomedicinal sciences, industry, material sciences, etc.[1] The chemical modification of CDs also has received widespread interest in order to improve the molecular recognition properties of the parent CDs or to generate recognition features different from those of the CDs.[2] In this respect, the knowledge of the complex formation ability of nonglucose cyclooligosaccharides[3] is, however, little known. This is due in part to the lack of synthetic methodologies to produce a sufficient amount of such cyclooligosaccharides to perform the guest binding ability studies. Cyclomannins, the CD analogues composed of D-mannose,[4] as well as the *rhamno* isomer of α-CD (α-cyclorhamnin),[5] have been synthesized by a multistep procedure. However, cyclofructins can be obtained by enzymatic digestion of the polysaccharide inulin.[6] The report of the per-epoxidation of cyclodextrins[7] provided a route for the transformation of CDs into cycloaltrins, the nonglucose cyclooligosaccharides consisting of six, seven, or eight α(1→4)-linked altropyranoses.[8] Cycloaltrins are readily available from per(2,3-anhydro)cyclomannins by nucleophilic ring-opening reaction with water.[8e] For cyclic oligosaccharides of the α-cycloaltrin type of CD has shown the more profound changes in shape cavity and structural rigidity when compared with α-CD.[8a] X-ray crystallography revealed for α-cycloaltrin a macrocyclic structure with an alternating sequence of $^4C_1$ and $^1C_4$ pyranoid chair conformations.[8b] NMR and molecular dynamics simulations studies have shown that in solution the six altropyranoside units are in a complex dynamic equilibrium between the alternating $^4C_1/^1C_4$ form and the all skew-boat ($^OS_2$) form, providing a flexible cyclooligosaccharide framework with a variable hydrophobic pattern. Accordingly, α-cycloaltrin could be used as a host model for studying the induced-fit mode of interaction between hosts and guests.[8a]

The nucleophilic ring-opening of per(2,3-anhydro)-cyclomannins with other nucleophiles different from water could also provide a route for the synthesis of cycloaltrin derivatives[9] with additional interaction sites that could cooperate with the hydrophobic cavity and thus improve the guest binding ability of the macrocycle. We turned our attention to the synthesis of functionalized cycloaltrins as a part of a program involving the construction of site-specific drug delivery systems based on glyco-cyclodextrins with dual function as host for the complexation with guest molecules and lectin ligands.[10] In particular, we have explored the synthesis of perfunctionalized β-cycloaltrins having nitrogen-containing functions on one or both faces of the macrocyclic ring.

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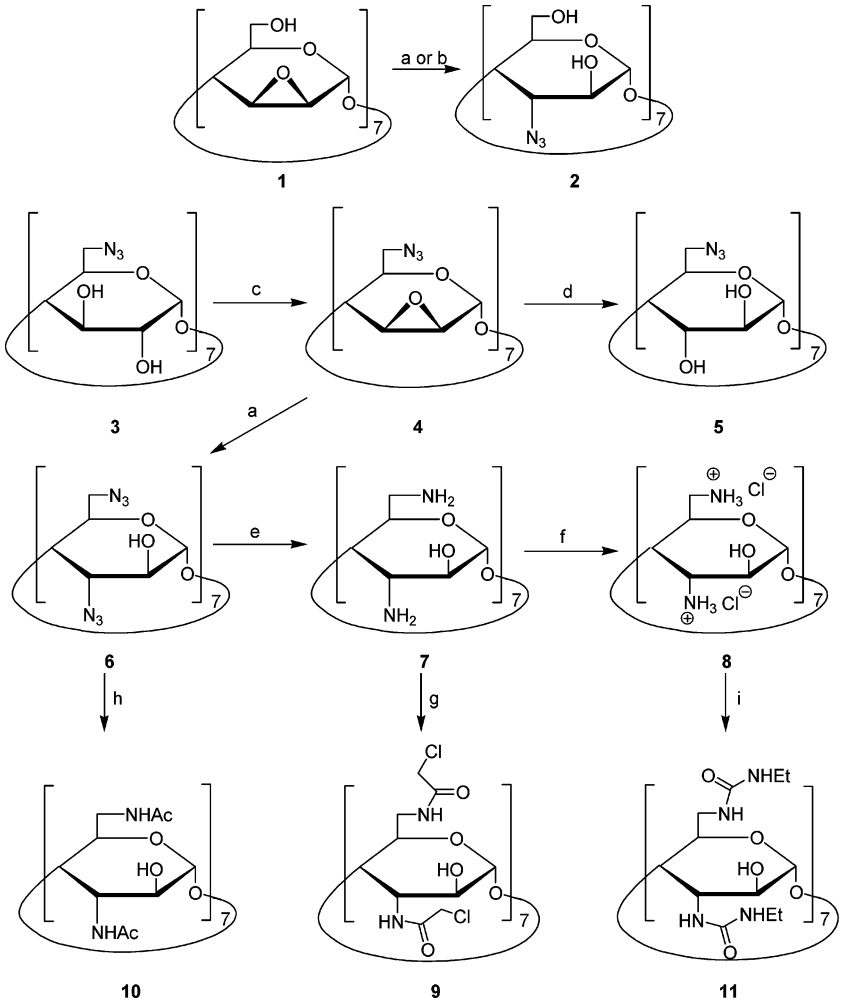
SCHEME 1[a]



[a] Reagents and conditions: (a) NaN_3, DMF/H_2O (9:1), 120 °C, 3 d, 36%; (b) NaN_3, DMF/NH_4Cl aq (9:1), 120 °C, 3 d, 76%; (c) NaH, DMF, rt, 5 h, then benzenosulfonyl chloride, rt, 1 h, 84%; (d) DMF/H_2O (1:2), 120 °C, 7 d, 55%; (e) PPh_3, DMF, rt, 1.5 h, then NH_3 aq, rt, 24 h, 91%; (f) HCl aq, 100%; (g) $(ClCH_2CO)_2O$, MeOH, rt, 24 h, 85%; (h) PPh_3, DMF, rt, 1 h, then NH_3 aq, rt, 24 h, followed by Ac_2O, MeOH, rt, 24 h, 52%; (i) $NaHCO_3$, EtNCO, H_2O/Me_2CO (2:1), rt, 24 h, 57%.

The first objective was to introduce the azide group at C-3 of β-cycloaltrin. Previous reports on the synthesis of cycloaltrins as well as per(3-deoxy)cyclomannins have shown that the epoxide cleavage with water, ammonia, and hydride occurs by nucleophilic attack at C-3 of the 2,3-anhydrocyclomannins to give the *trans*-diaxial ring opening,[7d,8e,9a,11] as had been shown also for oxiranes derived from monosaccharides.[12] Treatment of 2,3-anhydro-β-cyclomannin (**1**)[7b] with sodium azide in a mixture of DMF/H_2O at 120 °C for 3 days gave the corresponding per(3-azido-*altro*)cyclooligosaccharide **2** in 36% yield (Scheme 1). When a better proton source such as ammonium chloride was employed, compound **2** was isolated in 76% yield, but still it was necessary to heat the reaction mixture at the same elevated temperature for a long period of time.

For the synthesis of per(6-azido)cycloaltrin derivative **5**, we first obtained the per(6-azido-2,3-anhydro)cyclomannin **4** by treatment of per(6-azido)-β-CD[13] **3** with sodium hydride and benzenesulfonyl chloride. The 2,3-anydro derivative **4** was isolated in 84% yield. The NMR data for compound **4** were consistent with a *manno*-oxirane structure for the seven sugar units of the cyclooligosaccharide. For example, the ^1H NMR spectrum shows a singlet at 5.18 ppm for H-1, and two doublets at 3.35 and 3.16 ppm for H-3 and H-2, respectively, with a coupling constant of 3.6 Hz. These data are very similar to those reported for heptakis(2,3-anhydro)-β-cyclomannin[7b] **1**. Compound **4** was then heated at 120 °C in a mixture of DMF and water for 7 days to give in 55% yield the β-cycloaltrin derivative **5**, having the primary face per-substituted with azide. The reaction of **4** with sodium azide in DMF/H_2O at 120 °C afforded the per(3,6-diazido)-β-cycloaltrin **6** in 55% yield.

Azido-cycloaltrins **2**, **5**, and **6** were characterized by NMR spectroscopic techniques with COSY, HMQC, and HMBC experiments and high-resolution FAB mass spectrometry. Measurements of the NMR data were performed at 80 °C to avoid broadening of the signals. The

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NMR spectra show a single signal pattern for all saccharide residues in agreement with a C_7 symmetry for the macrocycles. The ^{1}H NMR signal for the anomeric protons of the three azido-cycloaltrins **2**, **5**, and **6** appeared at similar chemical shifts 4.80, 4.74, and 4.84 ppm, respectively. Similarly, the ^{13}C NMR spectra of **2**, **5**, and **6** display one anomeric carbon signal at 102.9−102.4 ppm. The presence of the azido group is revealed by the NMR carbon signals at 61.2 (C-3 for **2**), 51.2 (C-6 for **5**), 60.7 (C-3 for **6**), and 51.0 (C-6 for **6**) ppm which are upfield shifted up to 8.8−10.3 ppm when compared with the ^{13}C NMR chemical shifts of the β-cycloaltrin carbons.[8d]

As one of our objectives is to use de azido cycloaltrin derivatives as scaffolds for further functionalization with amino groups or derivatives, we carried out the reduction of the per(3,6-diazido)cycloaltrin **6** by employing triphenylphosphine, followed by treatment with aqueous ammonia solution. The water-soluble per(3,6-diamino) derivative **7** was isolated in 91% yield. Subsequent treatment of compound **7** with a HCl solution gave quantitatively the water-soluble HCl salt **8**. The HR-FAB mass spectra of **7** and **8** show M + H and M − 14HCl + H peaks, respectively. The NMR data also establish the presence of the amino function at C-3 and C-6. For example, in the ^{13}C NMR spectra of **7** and **8**, the resonance of C-3 and C-6 appears upfield shifted to 51.9 and 42.4 ppm for **7** and 50.9 and 38.7 ppm for **8** relative to the 3,6-diazido derivative **6**.

The amino cycloaltrin **7** is a key compound for the introduction of pendant hydrogen-bonding donor groups on both faces of the cycloaltrin. Thus, the reaction of the free amino **7** with chloroacetic anhydride gave the per-(3,6-di-*N*-chloroacetyl) derivative **9** in 85% yield. The tetradecaacetamide cycloaltrin **10** could be obtained in 52% yield by treatment of **6** with triphenylphosphine, then aqueous ammonia solution, followed by treatment of the crude product with acetic anhydride in methanol. Finally, the HCl salt **8** was treated first with aqueous $NaHCO_3$ and then with ethyl isocyanate to afford the per-[3,6-bis(*N*′-ethylureido)]cycloaltrin **11** in 57% yield after column chromatography.

In summary, we have described the synthesis of perfunctionalized β-cycloaltrins having azido groups at C-3, C-6, and both C-3 and C-6 by nucleophilic opening of the epoxy rings of per(2,3-anhidro)-β-cyclomannin derivatives. The value of these compounds as templates for further functionalization was exemplified by the conversion of heptakis(3,6-diazido-3,6-dideoxy)-β-cycloaltrin into the per(3,6-diamino), per(3,6-diacetamido), per-(3,6-dichloroacetamido), and per(3,6-diureido) derivatives in good yields.

Experimental Section

Heptakis(3-azido-3-deoxy)-β-cycloaltrin (2). A suspension of **1** (50 mg, 0.050 mmol) and NaN_3 (114 mg, 1.750 mmol) in a mixture of DMF (4.5 mL) and NH_4Cl aqueous solution (5% w/v, 0.5 mL) was stirred at 120 °C for 3 days. The solvent was removed by evaporation under vacuum and the crude product was purified by column chromatography (CH_3CN-H_2O 10:1) to give **2** (50 mg, 76%) as a solid: mp 166 °C dec; $[\alpha]_D$ +32 (*c* 0.125, MeOH); IR (KBr) 3432, 2931, 2116, 1043 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ 5.50 (br s, 7H, OH), 4.80 (d, 7H, $^3J_{1,2}$ = 4.1 Hz, H-1), 4.58 (br s, 7H, OH), 4.09−4.06 (m, 14H, H-4,5), 3.92 (dd, 7H, $^3J_{2,3}$ = 7.9 Hz, $^3J_{1,2}$ = 4.1 Hz, H-2), 3.80 (dd, 7H, $^3J_{2,3}$ = 7.9 Hz, $^3J_{3,4}$ = 3.1 Hz, H-3), 3.74 (m, 14H, H-6,6′); ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ 102.9 (C-1), 75.1 (C-4), 72.5 (C-5), 68.6 (C-2), 61.2 (C-3), 60.3 (C-6); HMRS (FAB) *m/z* calcd for $C_{42}H_{63}O_{28}N_{21}$ 1309.4151, found 1310.4200 (M + H)$^+$.

Heptakis(2,3-anhydro-6-azido-6-deoxy)-β-cyclomannin (4). To a solution of **3** (2 g, 1.5 mmol) in anhydrous DMF (150 mL) was added NaH (1.074 g, 44.780 mmol) in portions under an argon atmosphere. The solution was stirred at room temperature for 5 h. Benzenesulfonyl chloride (1.5 mL, 11.075 mmol) was added and the reaction mixture was stirred for 1 h more. The solution was poured into H_2O (500 mL) and filtered off. The residue was dried under vacuum to give **4** (1.497 g, 84%) as a solid: mp 130 °C dec; $[\alpha]_D$ +47 (*c* 0.5, $CHCl_3$); IR (KBr) 3496, 2925, 2107, 1292, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (s, 7H, H-1), 3.90 (d, 7H, *J* = 8.9 Hz, H-5), 3.77−3.73 (m, 14H, H-4,6), 3.51 (dd, 7H, $^2J_{6,6'}$ = 13.6 Hz, $^3J_{5,6'}$ = 7.4 Hz, H-6′), 3.35 (d, 7H, $^3J_{2,3}$ = 3.6 Hz, H-3), 3.16 (d, 7H, $^3J_{2,3}$ = 3.6 Hz, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.9 (C-1), 70.7 (C-5), 68.5 (C-4), 53.6 (C-3), 51.9 (C-6), 49.1 (C-2); HMRS (FAB) *m/z* calcd for $C_{42}H_{49}O_{21}N_{21}$ 1183.3412, found 1158.3580 (M + 3H$^+$ − N_2).

Heptakis(6-azido-6-deoxy)-β-cycloaltrin (5). A suspension of **4** (350 mg, 0.296 mmol) in a mixture of DMF (7 mL) and H_2O (14 mL) was stirred at 120 °C for 7 days. The solvent was removed by evaporation under vacuum. The product was precipitated by addition of Et_2O, filtered off, and suspended in water. The suspension was lyophilizated to give **5** (212 mg, 55%) as a solid: mp 133 °C dec; $[\alpha]_D$ −52 (*c* 0.125, H_2O); IR (KBr) 3397, 2927, 2105, 1060, 1025 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ 4.74 (d, 7H, $^3J_{1,2}$ = 3.2 Hz, H-1), 4.26 (dt, 7H, $^3J_{4,5}$ = 6.5 Hz, $^3J_{5,6}$ = 6.5 Hz, $^3J_{5,6'}$ = 3.5 Hz, H-5), 3.86 (dd, 7H, $^3J_{4,5}$ = 6.4 Hz, $^3J_{3,4}$ = 3.4 Hz, H-4), 3.79 (br t, 14H, H-2,3), 3.69−3.60 (m, 14H, H-6,6′); ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ 102.4 (C-1), 75.8 (C-4), 70.3 (C-5), 69.9 (C-2), 68.5 (C-3), 51.2 (C-6); MALDI-TOF-MS *m/z* calcd for $C_{42}H_{63}O_{28}N_{21}$ 1309.415, found 1332.365 (M + Na)$^+$.

Heptakis(3,6-diazido-3,6-dideoxy)-β-cycloaltrin (6). A suspension of **4** (736 mg, 0.62 mmol) and NaN_3 (1.410 g, 21.714 mmol) in a mixture of DMF (30 mL) and H_2O (3.4 mL) was stirred at 120 °C for 3 days. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and the organic phase was washed with H_2O (2 × 150 mL), dried (Na_2SO_4), filtered, and evaporated under vacuum. The crude product was purified by column chromatography (EtOAc−hexane 2:1) to give **6** (510 mg, 55%) as a solid: mp 70 °C; $[\alpha]_D$ +56 (*c* 0.5, MeOH); IR (KBr) 3421, 2926, 2017, 1094, 1031 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ 5.62 (d, 7H, *J* = 6.0 Hz, OH), 4.84 (d, 7H, $^3J_{1,2}$ = 3.6 Hz, H-1), 4.24 (dt, 7H, $^3J_{4,5}$ = 6.7 Hz, $^3J_{5,6'}$ = 6.7 Hz, $^3J_{5,6}$ = 3.1 Hz, H-5), 4.07 (dd, 7H, $^3J_{4,5}$ = 6.7 Hz, $^3J_{3,4}$ = 4.0 Hz, H-4), 3.98−3.92 (m, 7H, H-2), 3.85 (dd, 7H, $^3J_{2,3}$ = 7.4 Hz, $^3J_{3,4}$ = 3.8 Hz, H-3), 3.77 (dd, 7H, $^2J_{6,6'}$ = 13.3 Hz, $^3J_{5,6}$ = 3.2 Hz, H-6), 3.68 (dd, 7H, $^2J_{6,6'}$ = 13.3 Hz, $^3J_{5,6'}$ = 6.8 Hz, H-6′); ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ 102.8 (C-1), 76.0 (C-4), 70.5 (C-5), 68.6 (C-2), 60.7 (C-3), 51.0 (C-6); HMRS (FAB) *m/z* calcd for $C_{42}H_{56}O_{21}N_{42}$ 1484.4605, found 1457.4600 (M − N_2 + H)$^+$.

Heptakis(3,6-diamino-3,6-dideoxy)-β-cycloaltrin (7). A solution of **6** (76 mg, 0.051 mmol) and PPh_3 (421 mg, 1.607 mmol) in anhydrous DMF (10 mL) was stirred at room temperature for 1.5 h. Aqueous NH_3 (30% v/v, 2.5 mL) was added and the reaction mixture was stirred for 24 h. The solvent volume was reduced to 1 mL by evaporation under vacuum, and Et_2O was added until precipitation occurred. The solid was filtered off and washed with Et_2O. Then it was dissolved in water and the solution was lyophilized to yield **7** (52 mg, 91%) as a white solid: mp 165 °C dec; $[\alpha]_D$ +32 (*c* 0.5, MeOH); IR (KBr) 3432, 3372, 2924, 1061, 1023 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ 4.64 (d, 7H, $^3J_{1,2}$ = 4.6 Hz, H-1), 3.96 (dd, 7H, *J* = 10.1 Hz, *J* = 6.2 Hz, H-5), 3.84 (t, 7H, *J* = 4.6 Hz, H-4), 3.52 (dd, 7H, $^3J_{2,3}$ = 8.1 Hz, $^3J_{1,2}$ = 4.9 Hz, H-2), 3.00−2.75 (m, H-3,6,6′, OH, NH_2, NH_2′, H_2O); ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ 102.7 (C-1), 77.2 (C-4), 73.2 (C-5), 71.1 (C-2), 51.9 (C-3), 42.4 (C-6); HMRS (FAB) *m/z* calcd for $C_{42}H_{84}O_{21}N_{14}$ 1120.5935, found 1121.6000 (M + H)$^+$.

Heptakis(3,6-diamino-3,6-dideoxy)-β-cycloaltrin Chlorhydrate (8). A solution of **7** (96 mg, 0.086 mmol) in H_2O was

acidificated with HCl (5% v/v) to pH 2−3. The solvent was removed by evaporation under vacuum to give **8** (140 mg, 100%) as a yellow solid: mp 182 °C dec; $[\alpha]_D$ +25 (*c* 0.5, H_2O); IR (KBr) 3449, 2922, 1611, 1509, 1050, 1013 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 5.14 (d, 7H, $^3J_{1,2}$ = 6.0 Hz, H-1), 4.74 (m, H-5, HDO), 4.56 (t, 7H, *J* = 4.5 Hz, H-4), 4.23 (dd, 7H, $^3J_{2,3}$ = 9.6 Hz, $^3J_{1,2}$ = 6.0 Hz, H-2), 3.88 (dd, 7H, $^3J_{2,3}$ = 9.6 Hz, $^3J_{3,4}$ = 4.1 Hz, H-3), 3.54 (br d, 14H, *J* = 6.0 Hz, H-6,6′); ^{13}C NMR (75 MHz, D_2O) δ 102.0 (C-1), 75.5 (C-4), 70.9 (C-5), 66.3 (C-2), 50.9 (C-3), 38.7 (C-6). HMRS (FAB) *m/z* calcd for $C_{42}H_{98}O_{21}N_{14}Cl_{14}$ 1624.2670, found 1121.6000 $(M - 14HCl + H)^+$.

Heptakis(3,6-diamino-3,6-di-*N*-chloroacetyl-3,6-dideoxy)-*β*-cycloaltrin (9). A suspension of **7** (30 mg, 0.027 mmol) and $(ClCH_2CO)_2O$ (194 mg, 1.134 mmol) in dry MeOH (5 mL) was stirred in argon atmosphere at room temperature for 24 h. The solvent was evaporated under vacuum and the crude product was precipitated with Et_2O. The solid was filtered off and dried to give **9** (50 mg, 85%) as a brown solid: mp 202 °C dec; $[\alpha]_D$ −12 (*c* 0.25, H_2O); IR (KBr) 3431, 2927, 1616, 1399, 1044 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 5.03 (br d, 7H, $^3J_{1,2}$ = 6.0 Hz, H-1), 4.66−4.60 (m, 7H, H-5), 4.47 (t, 7H, *J* = 4.1 Hz, H-4), 4.11 (dd, 7H, $^3J_{2,3}$ = 9.7 Hz, $^3J_{1,2}$ = 6.2 Hz, H-2), 4.07 (br s, 28H, CH_2Cl), 3.76 (dd, 7H, $^3J_{2,3}$ = 9.9 Hz, $^3J_{3,4}$ = 3.7 Hz, H-3), 3.50−3.37 (m, 14H, H-6,6′); ^{13}C NMR (75 MHz, D_2O) δ 174.9 (CO), 102.2 (C-1), 75.7 (C-4), 71.1 (C-5), 66.4 (C-2), 51.0 (C-3), 43.9 (CH_2Cl), 38.4 (C-6).

Heptakis(3,6-diamino-3,6-di-*N*-acetyl-3,6-dideoxy)-*β*-cycloaltrin (10). A solution of **6** (75 mg, 0.067 mmol) and PPh_3 (556 mg, 2.121 mmol) in anhydrous DMF (2 mL) was stirred at room temperature for 1 h. Aqueous NH_3 (30% v/v, 1 mL) was added, and the reaction mixture was stirred for 24 h. The solvent was removed by evaporation under vacuum, and the crude was suspended in dry MeOH (4 mL). Ac_2O (3 mL, 37.738 mmol) was added and the suspension was stirred at room temperature for 24 h. After evaporation the crude product was precipitated with Et_2O and filtered off to give **10** (60 mg, 52%) as a pale yellow solid: mp 214 °C dec; $[\alpha]_D$ + 56 (*c* 0.5, MeOH); IR (KBr) 3404, 2927, 1646, 1554, 1106, 1068, 1035 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 80 °C) δ 7.76 (br s, 7H, NH-6), 7.32 (d, 7H, *J* = 8.0 Hz, NH-3), 4.65 (d, 7H, $^3J_{1,2}$ = 5.3 Hz, H-1), 4.09 (m, 14H, H-3,5), 3.87 (t, 7H, ^3J = 3.8 Hz, H-4), 3.69 (dd, 7H, ^3J = 9.4 Hz, ^3J = 5.2 Hz, H-2), 3.53−3.48 (m, 14H, H-6,6′), 2.00 (s, 21H, CH_3), 1.96 (s, 21H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ 169.5 (CO), 169.4 (CO), 104.3 (C-1), 77.7 (C-4), 72.4 (C-5), 68.5 (C-2), 50.1 (C-3), 39.0 (C-6), 22.5 (CH_3), 21.9 (CH_3); HMRS (FAB) *m/z* calcd for $C_{70}H_{112}O_{35}N_{28}$ 1708.7415, found 1709.7490 $(M + H)^+$.

Heptakis[3,6-bis(*N*′-ethylureido)-3,6-dideoxy]-*β*-cycloaltrin (11). To a solution of **8** (100 mg, 0.061 mmol) in H_2O (10 mL) was added a saturated solution of $NaHCO_3$ to pH 8. A solution of ethyl isocianate (133 mg, 1.879 mmol) in dry Me_2CO (5 mL) was then added dropwise. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed by lyophilization and the crude product was purified by column chromatography (CH_3CN-H_2O 5:1) to give **11** (74 mg, 57%) as a white solid: mp 228 °C dec; $[\alpha]_D$ +27 (*c* 0.25, H_2O); IR (KBr) 3383, 2974, 2930, 2887, 1639, 1565, 1098, 1024 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 80 °C) δ 6.28 (t, 7H, *J* = 5.3 Hz, N*H*CH_2-CH_3), 6.14 (t, 7H, *J* = 5.3 Hz, N*H*CH_2CH_3), 6.08 (t, 7H, *J* = 5.6 Hz, NH-6), 5.85 (d, 7H, *J* = 8.5 Hz, NH-3), 5.37 (d, 7H, *J* = 4.6 Hz, OH), 4.63 (d, 7H, $^3J_{1,2}$ = 4.6 Hz, H-1), 4.02−3.92 (m, 14H, H-3,5), 3.84 (t, 7H, ^3J = 5.0 Hz, H-4), 3.69 (br dd, 7H, $^3J_{2,3}$ = 8.7 Hz, $^3J_{1,2}$ = 4.4 Hz, H-2), 3.61 (m, 7H, H-6), 3.35 (m, 7H, H-6′), 3.20−3.11 (m, CH_2, CH_2′, H_2O), 1.14 (t, 21H, ^3J = 7.2 Hz, CH_3), 1.11 (t, 21H, ^3J = 7.1 Hz, CH_3′); ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ 158.3 (CO), 158.1 (CO), 104.2 (C-1), 77.5 (C-4), 72.0 (C-5), 68.9 (C-2), 50.7 (C-3), 40.1 (C-6), 33.9 (CH_2), 33.7 (CH_2′), 15.0 (CH_3), 14.9 (CH_3′); HMRS (FAB) *m/z* calcd for $C_{84}H_{154}O_{35}N_{28}$ 2115.1131, found 2116.1240 $(M + H)^+$.

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Supporting Information Available: General experimental methods and ^1H and ^{13}C NMR spectra for compounds **2** and **4**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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