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Design, Synthesis, and Delivery Properties of Novel Guanidine-Containing Molecular Transporters Built on Dimeric Inositol Scaffolds

Kaustabh K. Maiti, Ock-Youm Jeon, Woo Sirl Lee, and Sung-Kee Chung*[a]

Abstract: We have developed a novel class of synthetic molecular transporters that contain eight residues of guanidine with an inositol dimer as the scaffold. The dimers were prepared by connecting two units of *myo*- or *scyllo*-inositol via a carbonate or amide linkage, and the multiple units of the guanidine functionality were constructed on the inositol scaffold by means of peracylation with ω-aminocarboxylate derivatives of varying length. Bioassays based on confocal laser scanning microscopy and fluorescence-activated cell sorter analyses indicated that these transporters display a varying degree of membrane translocating ability, and the intracellular localization and mouse-tissue distribution studies strongly suggested that these transporters undergo substantially different mechanistic processes from those of peptide transporters reported to date. It was also shown that doxorubicin, an anticancer antibiotic, can be efficiently delivered into mouse brain by aid of this type of transporter.

Keywords: drug delivery · guanidine · inositol · membrane translocation · molecular devices

Introduction

Therapeutic efficiency of a drug or a drug candidate depends on its ability to overcome biological barriers and reach the desired tissue and intracellular target sites. It is generally understood that cellular membrane barriers allow only those molecules with an appropriate range of molecular size, polarity, and charge to pass through them. As a result, many drug candidates with promising in vitro activities fail to be developed into clinically useful agents. Thus, developing molecular transporters that enable or enhance cellular uptake of a drug candidate or molecular probe is a highly desirable and challenging goal in the field of drug research and development. A number of peptides are known to translocate across cell membranes. They are variously known as cell-penetrating peptides (CPPs), protein transduction domains (PDTs), and membrane translocating sequences (MTSs), and they are capable of delivering exogenous molecules into cells as covalent conjugates. The cell-membrane penetrating property was initially observed in viral proteins, for example, HIV-1 Tat protein (Tat-86), Antennapedia (Antp) protein of *Drosophila*, and herpes simplex virus type 1 (HSV-1) VP 22. Furthermore, their membrane penetrating ability has been found to be associated with relatively short peptide fragments, for example, 9 basic amino acid residues for the Tat protein (residues 49–57; Tat peptide, RKKRRQRRR), 16 amino acid residues for the Antp protein (residues 43–58; penetratin, RQIKIWFQNRRMKWKK) that have a potentially amphipathic and basic helical structure, and 12 hydrophobic amino acid residues for the Kaposi sarcoma fibroblast growth factor (KFGF) MTS (AAVLLPVLLAAP).[1–4] Although the underlying mechanisms of the cellular uptake of these peptides could be multiple and have not been clearly defined, there have been many attempts to utilize these peptides as delivery vectors in order to improve the pharmacology of poorly bioavailable drugs including small molecules,[5] proteins,[6–10] nucleotides, and genes.[11–13] More recently, there have been several reports on the development of synthetic molecular transporters mimicking natural and unnatural peptides and their structural analogues, especially in the area of polycationic peptide mimetics, such as peptoids, oligocarbamates, β,β-peptides, peptide nucleic acids, guanidinoglycosides, and heterocyclic guanidinium salts.[14–23]

The CPPs commonly show good in vitro efficiency as molecular transporters but their structural motifs and physicochemical properties are too diverse to reveal a common translocation mechanism. It is quite possible that different

[a] Dr. K. K. Maiti, O.-Y. Jeon, W. S. Lee, Prof. Dr. S.-K. Chung
Department of Chemistry, Division of Molecular and Life Sciences
Pohang University of Science & Technology, Pohang 790-784 (Korea)
Fax: (+82) 54-279-2103
E-mail: skchung@postech.ac.kr

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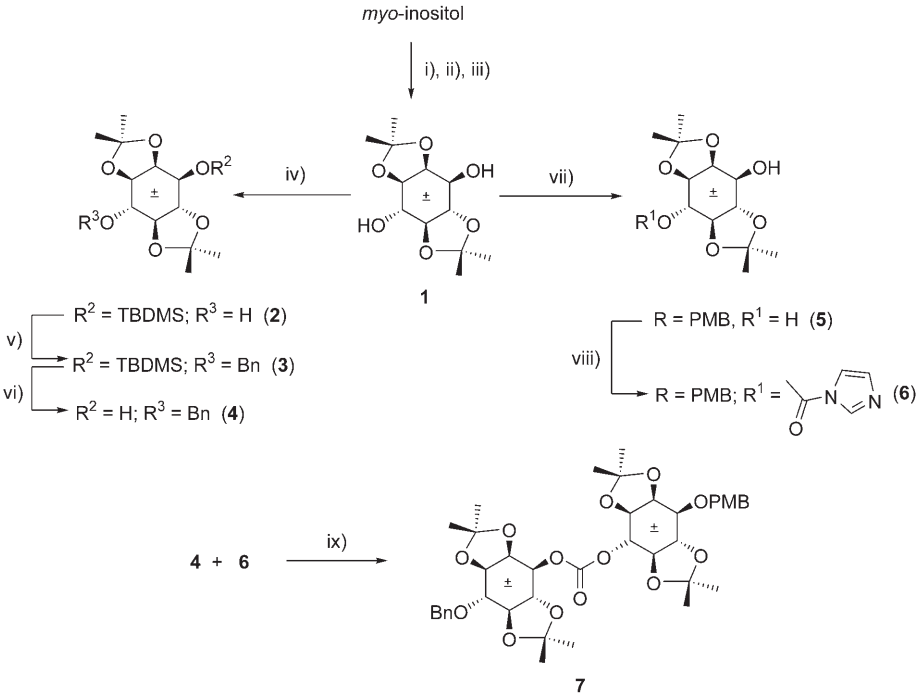
CPPs may use different mechanistic processes for translocation and even the same peptide may use alternative pathways depending on the conditions of administration, concentration, and the nature of the cargo.[10,24] A number of studies have shown that in the basic CPPs the guanidine head group is important, because arginine oligomers enter into cells more rapidly than the corresponding oligomers of lysine, histidine, or ornithine, and various arginine oligomers show membrane permeability similar to that of the Tat peptide. It has been found that the optimum number of guanidine residues is about eight or nine, and the linking chain length also plays a substantial role in the case of peptoid transporters.[14–18]

We envisaged that modifications of the structure and physicochemical properties of even the known molecular transporters could generate novel transporters that have different in vivo and in vitro spectra, as well as different translocation efficiencies. Additionally, the in vivo efficacy, the susceptibility to various endogenous peptidases, the synthetic cost, and the observed neurotoxicity liability of the known arginine-rich peptides are often considered as potential problems for development. Keeping all these technically and practically important issues in mind, we have developed a novel class of cell-penetrating transporters as potential delivery vectors. In the molecular design of novel transporters, we decided to utilize carbohydrate and inositol structures as the backbone scaffold, because they have the highest functionality density among organic compounds with hydroxyl groups in diverse stereochemical variations, and they are highly water soluble and largely free of any noticeable toxicity. Previously, several groups have attempted to design various peptidomimetics on carbohydrate scaffolds in order to take advantage of the structural characteristics.[25] Herein, we describe the synthesis and properties of the initial version of such molecular transporters. The architecture of these synthetic molecular transporters is based on dimeric inositol scaffolds and eight units of guanidine functionality, which are attached to the scaffold as ω-aminocarboxylate derivatives of varying chain length. Moreover, two additional functional groups are reserved on the scaffold as handles on which a cargo (drug or diagnostic device) and/or a fluorescent probe (or targeting ligand) may be conjugated.

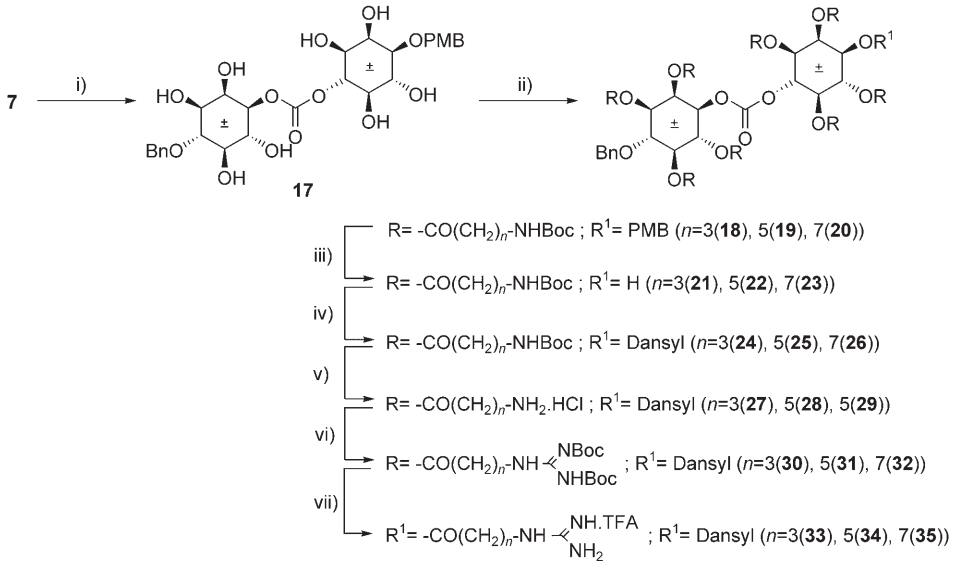
Results and Discussion

We employed two inositol stereoisomers (*myo*- and *scyllo*-) as the initial backbone starting material. *myo*-Inositol is the most abundant inositol in nature and is readily available, but substitution at any position other than the C-2 and C-5 generates a diastereomeric mixture. On the other hand, *scyllo*-inositol is less readily available but has a higher degree of symmetry with all hydroxyl groups in the equatorial orientation. Thus, we decided to use both inositols. To prepare suitably protected dimeric inositol scaffolds, we synthesized the requisite *myo*- and *scyllo*-inositol derivatives as follows. *myo*-Inositol was converted to 2,3:5,6-di-*O*-isopropylidine-*myo*-inositol (**1**),[26] and the 1-OH and 4-OH groups were regioselectively protected as *tert*-butyldimethylsilyl (TBDMS) and benzyl (Bn) ethers, respectively, to give **2**[27] and **3**. Removal of the TBDMS group in **3** yielded **4**.[28] Similarly, **1** was converted to the *p*-methoxybenzyl (PMB)-protected **5**,[29] which was then treated with CaH_2 and carbonyldiimidazole to give **6**. Compounds **4** and **6** were coupled to give a diastereomeric mixture of **7** (87% yield) in the presence of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) in toluene (Scheme 1). Next, *myo*-inositol was transformed to *scyllo* compound **8** by inversion of the C-2 stereochemistry by means of the Mitsunobu reaction.[30] Formation of bisacetonide groups followed by regioselective handling of the two hydroxyl groups gave the suitable intermediates **12** and **15**. Treatment of **12** with carbonyldiimidazole and CaH_2 provided **13**, which was coupled with **15** in the presence of NaH in THF (instead of DBU in toluene as was used in Scheme 1)

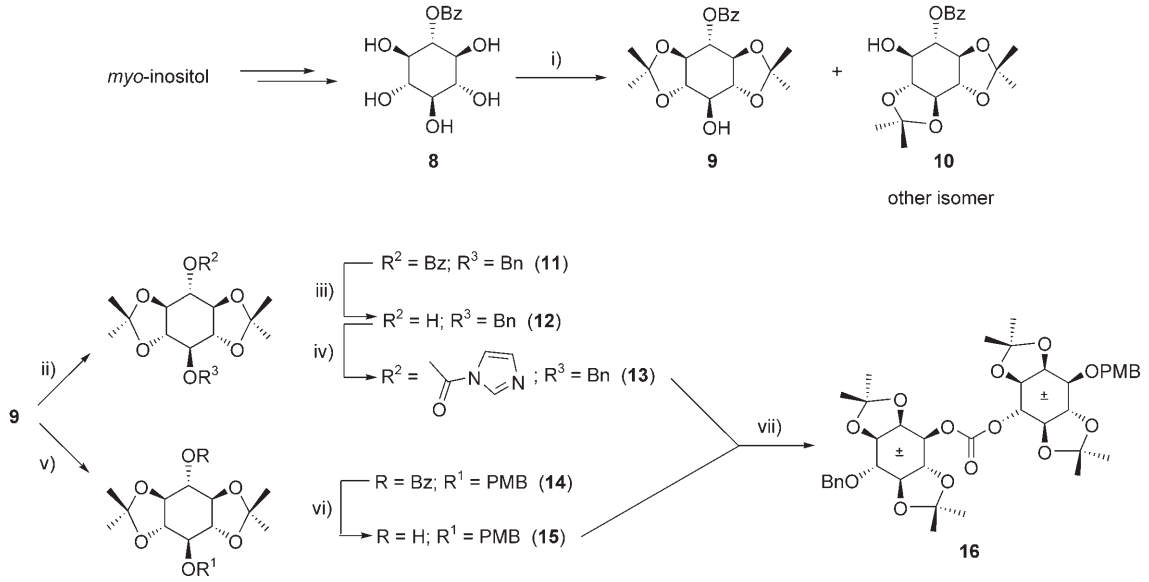


Scheme 1. i) 2,2-Dimethoxypropane, *p*-TSA, DMF; ii) BzCl, pyridine; iii) NaOMe, MeOH, overall yield 62%; iv) TBDMSCl, imidazole, DMF, 70%; v) BnBr, Ag_2O, TBAI, 97%; vi) TBAF, THF, quant.; vii) PMBCl, NaH, DMF, 76%; viii) CaH_2, carbonyldiimidazole, toluene, 94%; ix) DBU, toluene, 87%.

to give **16** in a 62% yield (Scheme 2). Now the two synthetic scaffolds **7** and **16**, which are built with two units of inositol linked through a carbonate bridge, were ready for further structural elaborations such as octaguanidinylation and conjugations involving a fluorescent probe and drug cargo. The acid-catalyzed removal of the acetonide protecting groups in **7** with *p*-toluenesulfonic acid (*p*-TSA) in CH_2Cl_2 and MeOH gave **17** in an 83% yield, which was then exhaustibly acylated with ω-*N*-Boc-aminocarboxylic acids of varying chain lengths in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 4-dimethylaminopyridine (DMAP) in DMF to provide **18**–**20** in 60–85% yields after purifying by means of column chromatography on silica gel. The PMB protecting group of **18**–**20** was removed by using ammonium cerium(IV) nitrate (CAN) in acetonitrile and toluene, and dansylated to give **24**–**26**. After removal of the Boc group from the aminocarboxylate residues, perguanidinylation reactions were carried out on **27**–**29** by using *N*,*N*′-di-Boc-*N*″-trifluoromethanesulfonylguanidine[31] and triethylamine (TEA) in DMF to afford the octaguanidine products **30**–**32** in 55–65% yields after purification by means of column chromatography. Finally, the *N*-Boc groups from the guanidine moiety were cleaved by using trifluoroacetic acid (TFA) and dichloromethane to afford, after rigorous purification, the TFA salts **33**, **34**, and **35** as potential molecular transporters (Scheme 3). The target compounds were thoroughly characterized by using NMR spectroscopy and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectral analyses. The same synthetic protocols carried out on dimer **16** gave the octaguanidinylated *scyllo*-inositol dimeric transporter **72** (see Supporting Information, Scheme 1). In this case, only



Scheme 3. i) *p*-TSA, CH_2Cl_2/MeOH 1:9, 83%; ii) EDC, DMAP, *N*-Boc-protected 4-aminobutyric acid ($n=3$), aminocaproic acid ($n=5$), ω-aminocaprylic acid ($n=7$), DMF, 60–85%; iii) CAN, CH_3CN/toluene 3:1, 55–78%; iv) dansyl-Cl, CH_3CN, DMAP, 55–85%; v) HCl_g in EtOAc, quant.; vi) *N*,*N*′-di-Boc-*N*″-trifluoromethanesulfonylguanidine, TEA, DMF, 55–65%; vii) TFA/CH_2Cl_2 1:1, 85–90%.

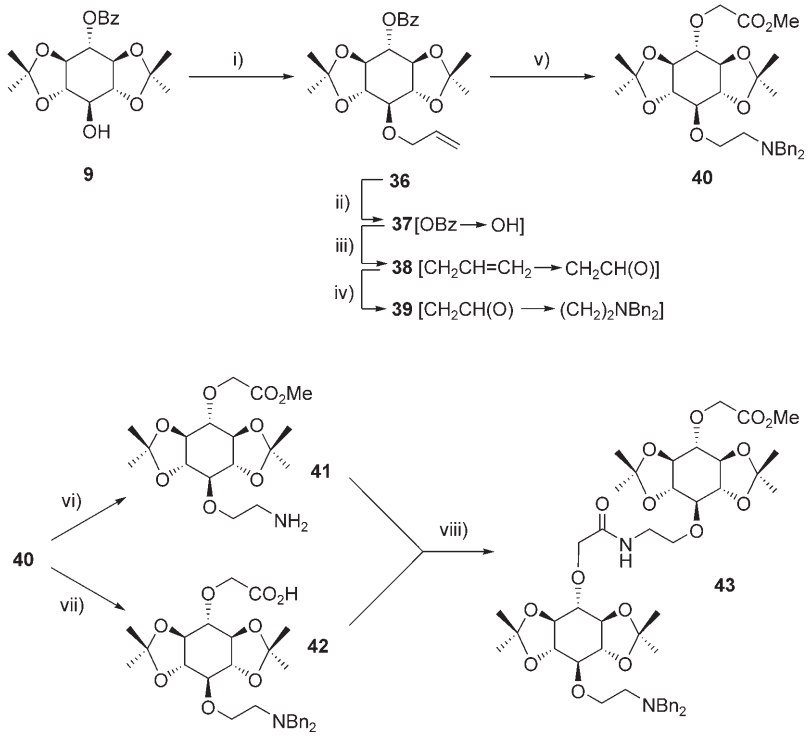


Scheme 2. i) 2-Methoxypropene, *p*-TSA, DMF, **9** (30%), **10** (51%); ii) BnBr, Ag_2O, TBAI, CH_2Cl_2, 80%; iii) NaOMe, MeOH, 97%; iv) CaH_2, carbonyldiimidazole, toluene, 88%; v) PMBCl, NaH, DMF, 74%; vi) NaOMe, MeOH, 97%; vii) NaH, THF, 62%.

one transporter molecule with an *N*-Boc-aminocaproic acid linker chain ($n=5$) was prepared for comparison with the *myo* dimer (**34**) in bioassays.

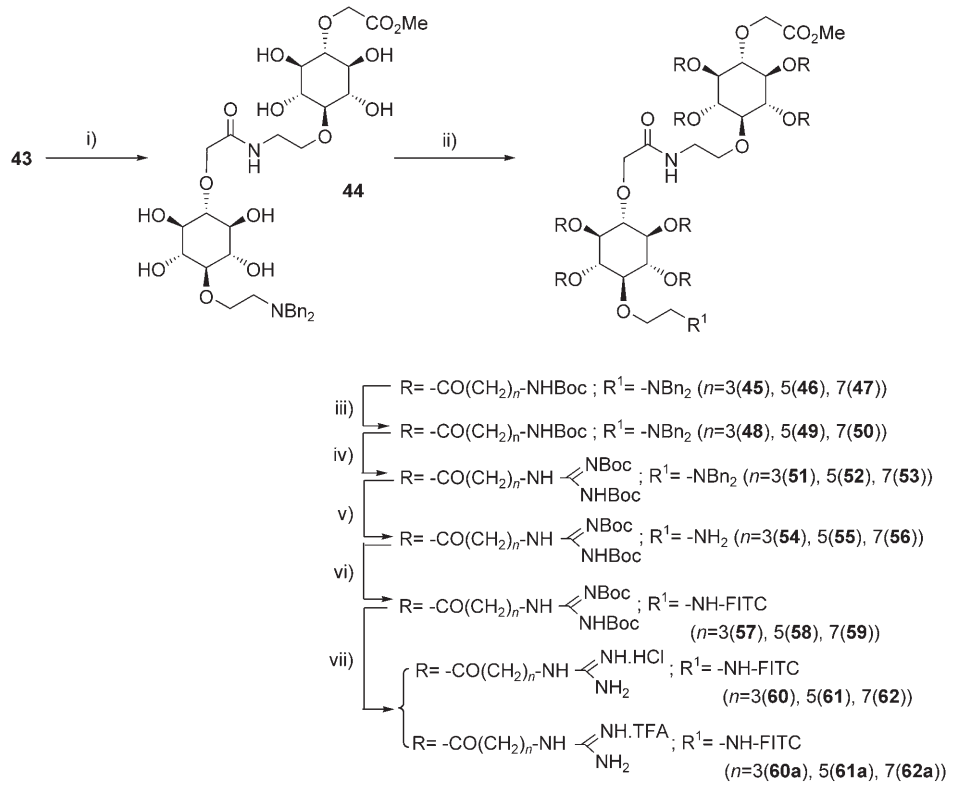
Considering the possible hydrolytic instability and rigidity associated with the carbonate functionality used in linking two units of the inositol skeleton, we next investigated the amide linkage for the formation of a dimeric *scyllo*-inositol scaffold. Thus, compound **9** was treated with allyl bromide in the presence of Ag_2O and tetrabutylammonium iodide (TBAI) to give **36** in a 94% yield. Hydrolysis of the benzoate of **36**, ozonolysis at −78°C in CH_2Cl_2/MeOH (6:1) buffered with sodium bicarbonate (1.5 equiv) followed by a reductive workup, and reductive amination with dibenzylamine and $NaBH(OAc)_3$ at 0°C gave **39** in a reasonable overall yield. The hydroxyl group of **39** was coupled with methyl bromoacetate to give **40** in a 94% yield. Debenzylation of **40** under hydrogenation conditions with 10% Pd/C afforded the free amine compound **41**, whereas hydrolysis of the methyl ester group in **40** gave carboxylate **42** in a 92% yield. Coupling between **41** and **42** was performed by using EDC and DMAP in DMF to give the amide-linked dimeric *scyllo*-inositol **43** in a 65% yield after purification by means of column chromatography (Scheme 4). Similar structural elaborations were carried out on **43** as described for **16** to prepare the octaguanidinylated transporter molecules **51–53**, namely, 1) exhaustive acylation reactions with three different ω-*N*-Boc-aminocarboxylate derivatives after the acid-catalyzed hydrolysis of the acetonide protecting groups, and 2) guanidinylation of the free amino groups. In all steps reasonably good yields were obtained after the usual purification procedures. Then, a fluorescent tag was attached by reacting fluorescein-5-isothiocyanate (FITC-I) with the free amino groups of **54–56** to afford the fluorescein-labeled compounds **57–59** in 45–65% yields after purification by using flash column chromatography. Although the dansyl group as a fluorophore is easier to handle synthetically, fluorescein has a higher quantum efficiency and is better suited for confocal laser scanning microscopy (CLSM) detection. The final octaguanidinylated transporters **60–62** were obtained as TFA and HCl salts by deprotection of the guanidine with TFA and ethyl acetate saturated with HCl, respectively. The deprotection yields are generally higher for TFA salt formation, but the HCl salts have better aqueous solubility (Scheme 5).

In the last phase of the synthetic work we investigated an experimental protocol for the transporter–doxorubicin conjugation. Doxorubicin (Adriamycin) is a potent anticancer drug, which is used clinically and is fluorescent. Compound **62** was chosen for the conjugation among the various synthetic transporters, because of its presumed higher hydrolytic stability and flexibility relative to the carbonate-linked transporters, and also because of its excellent membrane translocating ability. Compound **56** and carbobenzoxy (Cbz)-protected L-serine were first coupled under the EDC coupling conditions, and the hydroxyl group of the serine moiety of **63** was further coupled with the primary amino group in the sugar residue of doxorubicin through a carbamate bond to give **64**.[32] In the last step, all Boc groups in the guanidine moieties of **64** were removed by using gaseous HCl to yield the covalent conjugate **65** as an HCl salt (Scheme 6). The target product in the salt form was purified by means of reverse-phase medium-pressure liquid chromatography (MPLC) on a C-8 column (H_2O/CH_3CN, 1:1–1:2 containing 0.1% TFA), and its purity was evaluated by analytical high-pressure liquid chromatography (HPLC) analysis. The key intermediates and target compounds were also satisfactorily characterized by using NMR spectroscopy and MALDI-TOF mass spectral analyses.

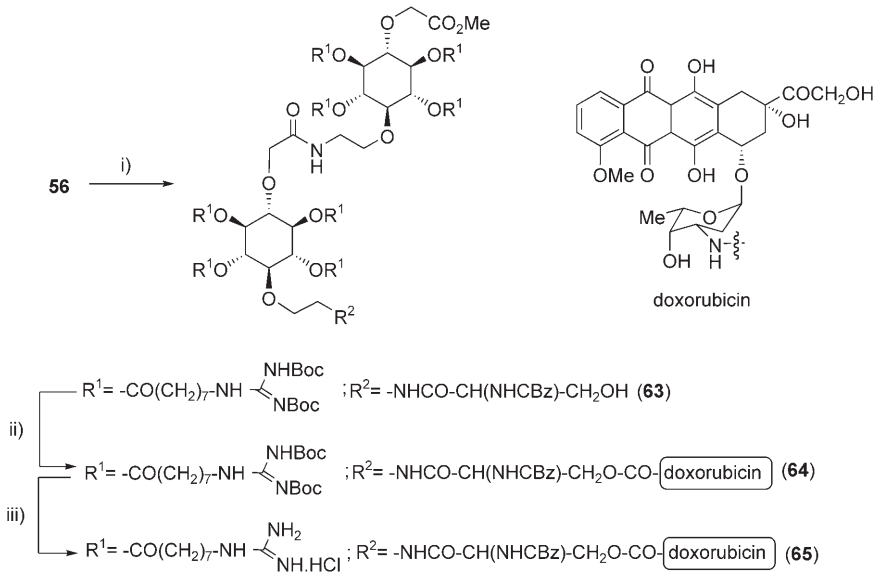


Scheme 4. i) Allyl bromide, Ag_2O, TBAI, CH_2Cl_2, 94%; ii) NaOMe, MeOH, 92%; iii) $NaHCO_3$, CH_2Cl_2/MeOH 6:1, O_3, −78°C, PPh_3, 86%; iv) Bn_2NH, $NaBH(OAc)_3$, DCE, 76%; v) $BrCH_2CO_2Me$, Ag_2O, TBAI, CH_2Cl_2, 94%; vi) 10% Pd/C, H_2 (1 atm), CH_2Cl_2/MeOH 1:9, quant.; vii) NaOH, MeOH, then AcOH, 92%; viii) **41**, **42**, EDC, HOBT, TEA, DMF, 65%.

Preliminary membrane translocating properties of the synthetic transporters (**33–35**, **72**, **60–62**) were examined by means of confocal laser scan-



Scheme 5. i) *p*-TSA, CH_2Cl_2/MeOH (9:1), quant.; ii) EDC, DMAP, *N*-Boc-protected 4-aminobutyric acid ($n=3$), aminocaproic acid ($n=5$), ω-aminocaprylic acid ($n=7$), DMF, 65–80%; iii) HCl_g in EtOAc, quant.; iv) *N*,*N*′-di-Boc-*N*″-trifluoromethanesulfonylguanidine, Et_3N, dioxane/H_2O 5:1, 55–75%; v) 10% Pd/C, H_2 (1 atm), MeOH/CH_2Cl_2 9:1, 80–90%; vi) FITC-I, Et_3N, THF, absolute EtOH, 52–65%; vii) HCl_g in EtOAc, 76–80% or TFA/CH_2Cl_2 1:1, 86–94%.



Scheme 6. i) **56**, *N*-Cbz-L-serine, EDC, HOBT, DMF, 72%; ii) *p*-NC, pyridine, CH_2Cl_2, RT, 3 h, then TEA, doxorubicin–HCl, DMF, 77%; iii) HCl_g in EtOAc, 76%.

ning microscopy (CLSM) with three cell lines: simian kidney COS-7, mouse macrophage RAW264.7, and HeLa cells (Figure 1). After 3–5 min exposure to the cultured cells, the cellular uptake of the transporters was visually compared with arginine nonamer (dansyl- and Fl-R9). The transporters based on the *myo*-inositol dimer linked with carbonate (**33**–**35**) displayed qualitatively similar cellular uptake properties to dansyl-R9 in the COS cell assays, although the transporters with longer chain lengths, **34** and **35**, showed somewhat better translocation than **33** (Figure 1A). The transporters built on the *myo*- and *scyllo*-inositol scaffolds (**34** and **72**) showed qualitatively similar translocation ability in RAW264.7 cells (Figure 1B). With HeLa cells the transporters based on the *scyllo*-inositol dimer linked with amide (**60**–**62**) again showed good translocation, and the longer chains seem to contribute to a better uptake, that is, **62** > **61** > **60** (Figure 1C). The internalization efficiency of **60**–**62** was more precisely compared with that of fluorescein-labeled octaarginine (Fl-R8) through fluorescence-activated cell sorter (FACS) analysis. The analysis showed that with HeLa cells at 37 °C for 1 h, **61** and **62** (10 μM) internalized 1.8 and 2.5 times as much as Fl-R8, respectively, whereas the amount of internalized **60** was about half of that for Fl-R8. A kinetic study carried out on the most efficient transporter (**62**) in comparison with Fl-R8 revealed that the total cellular uptake of **62** was more than three times higher than that of Fl-R8. These results suggest that transporters with this particular structural framework are helped by an increased chain length due to either the increased hydrophobicity or the higher flexibility for the interaction with the cell membrane.[14] The intracellular localization pattern studies on **62** with HeLa cells in the presence of tetramethylrhodamine-labeled transferrin, tetramethylrhodamine-labeled Tat peptide,

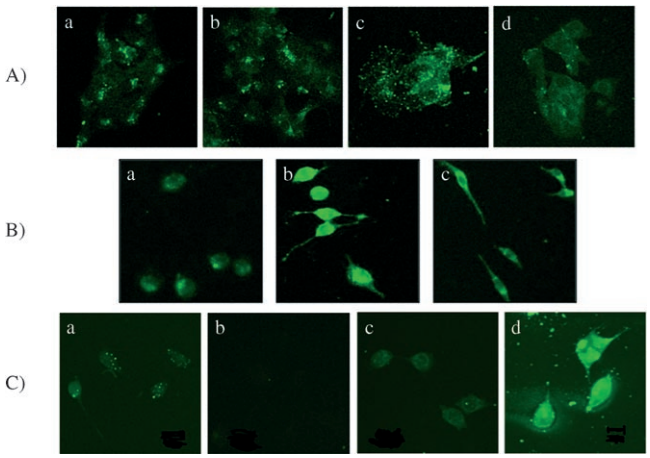


Figure 1. Fluorescence microscope images: A) a) dansyl-R9 (10 μM), b) **33** (10 μM), c) **34** (10 μM), and d) **35** (10 μM) in COS 7 cells incubated for 3 min at RT; B) a) dansyl-R9 (10 μM), b) **34** (10 μM), and c) **72** (10 μM) in RAW 264.7 cells incubated for 3 min at RT; C) a) Fl-R9 (10 μM), b) **60** (10 μM), c) **61** (10 μM), and d) **62** (10 μM) in HeLa cells incubated for 15 min at 37 °C.

MitoTracker, and LysoTracker at 37 and 4 °C showed few similarities and co-localization, thus strongly suggesting that **62** may use different mechanisms of internalization and cellular localization from the arginine-rich transporters reported to date.[33]

Compound **62** also showed a unique in vivo distribution pattern compared with the Tat-related peptides, which were previously reported to show an even distribution in liver, kidney, lung, heart muscle, and spleen tissues.[23,34] When injected intraperitoneally (ip) into eight-week-old mice, significantly lower extents of internalization of **62** were observed in the liver, kidney, and spleen, whereas the heart, lung, and brain tissues showed much higher distributions of **62**. At present the reasons for the uneven distribution have not been determined. In the repeated tissue distribution experiment of **62** with mice, the brain cortex region showed strong fluorescence 20 min after the ip injection, which suggests that the transporter clearly crossed the blood–brain barrier (BBB) rapidly and efficiently. Development of vectors to help cross the BBB is one of the major challenges in drug delivery, and the above observations should be highly relevant to developing organ-selective delivery technologies. Doxorubicin hydrochloride (Adriamycin) is extensively used clinically for the treatment of a variety of neoplastic diseases including leukemia, and breast, ovarian, and solid cancers, but not brain cancer because it does not overcome the BBB.[35] Doxorubicin has good UV/Vis absorption bands and is also highly fluorescent. Cellular uptake studies of conjugate **65** with HeLa cells at both 10 and 30 μM concentrations showed a much-enhanced translocation of the conjugate into the cytoplasm, effectively killing cells at 10 μM, a concentration at which neither doxorubicin nor carrier **62** caused significant cell damage. At present it is not clear whether the efficient cell killing is due to cleaved doxorubicin or the conjugate, nor whether it is due to more efficient delivery of doxorubicin or a higher toxicity of the conjugate. The in vivo experiments with mice convincingly showed that conjugate **65** was also extensively distributed in the cortex region of the mouse brain 20 min after ip injection, whereas very little doxorubicin translocated into the brain cortex during the same time frame. These results suggest that the uptake of doxorubicin through the BBB is indeed very inefficient, and that conjugation to the transporter significantly increases the uptake by the brain as well as the intercellular permeation of doxorubicin in the brain tissue.[33]

Conclusion

We have successfully designed and synthesized novel transporter molecules based on dimeric inositol scaffolds and we have demonstrated that these transporters possess some interesting cellular uptake characteristics together with unique spectra of in vitro and in vivo distributions. More specifically, the amide-linked dimeric inositol transporters **61** and **62** have been found to be superior to arg-8-mer (R8) and arg-9-mer (R9) in terms of the uptake efficiency and amount. The novel transporters also display interesting intracellular and tissue distribution patterns that are different from those of Tat-related or arginine-rich peptides, thus suggesting that the exciting possibility of designing highly sophisticated, organellar- and tissue-selective transporters may be feasible by varying structural parameters, such as the backbone scaffold and linker, and the associated physicochemical parameters, such as charge density and hydrophobicity. In addition, the novel synthetic transporters may have practical value as drug-delivery vehicles in terms of better absorption, distribution, metabolism, and excretion (ADME) characteristics and stability toward endogenous enzymes. Studies on the next version of molecular transporters with different and improved delivery characteristics are currently underway.

Experimental Section

General methods: All nonhydrolytic reactions were carried out in oven-dried glassware under an inert atmosphere of dry argon or nitrogen. All commercial chemicals were used as received except for solvents, which were purified and dried by means of standard methods prior to use. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates (0.25 mm thickness), analytical reverse-phase TLC on Merck RP-8 F254s plates; visualization was carried out be using UV light ($\lambda = 254$ and 365 nm) or by spraying the plates with a 5% solution of phosphomolybdic acid or ninhydrine solution followed by charring with a heat gun. Column chromatography was performed on Merck 60 silica gel (70–230 or 230–400 mesh), and MPLC was performed on Fluka 100 C_8 reversed-phase silica gel. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on Bruker DPX 300 (^{1}H NMR at 300 MHz; ^{13}C NMR at 75 MHz) and Bruker DRX 500 (^{1}H NMR at 500 MHz; ^{13}C NMR at 125 MHz) spectrometers. Tetramethylsilane was used as the reference for ^{1}H NMR spectra. The abbreviations "app." and "dist." signify an apparent peak or set of peaks and a distorted peak, respectively. Analytical HPLC was performed by using an Agilent 1100-HPLC Chemstation with a BU-300 analytical column (30 nm pore size and 10 μm spherical, 4.6 mm i.d. × 25 cm).

Low-resolution mass spectra were determined on a Micromass PLATFORM II (EI and FAB) instrument. High-resolution mass spectra were determined on a JMS-700 instrument, and MALDI-TOF mass spectra on a Voyager-DE STR system at the Korea Basic Science Support Center. The standard extraction work-up procedure consisted of pouring the reaction mixture into a large amount of water, extracting with the organic solvent indicated, washing the combined extracts successively with water and with brine, drying the extract over anhydrous Na_2SO_4 or $MgSO_4$, and evaporating the solvent.

(+)-2,3:5,6-Di-*O*-isopropylidene-*myo*-inositol (1) was prepared according to a literature procedure.[26]

(+)-1-*tert*-Butyldimethylsilyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol (2) was prepared from **1** according to a literature procedure.[27]

(+)-4-*O*-Benzyl-2,3:5,6-di-*O*-isopropylidene-1-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (3): Silver(I) oxide (10.7 g, 46 mmol), benzylbromide (5.47 mL, 46 mmol), and TBAI (0.55 g, 1.5 mmol) were added to a solution of **2** (5.7 g, 15 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at RT for 2 h, and filtered through Celite. The filtrate was washed with CH_2Cl_2, and concentrated under vacuum. The crude product was purified by using column chromatography on silica gel to afford **3** as a colorless solid (4.91 g, 97%). R_f=0.3 (EtOAc/*n*Hex 1:10); m.p. 89°C; ^{1}H NMR ($CDCl_3$): δ=0.12 (s, 6H; $SiMe_2$), 0.90 (s, 9H; CMe_3), 1.31, 1.35, 1.40, 1.41 (4s, 3H each; $2CMe_2$), 3.31 (t, J=9.7 Hz, 1H; H-3), 4.07 (t, J=5.6 Hz, 1H; H-1), 4.27 (t, J=5.6 Hz, 1H; H-6), 4.80 (s, 2H; PhCH_2), 7.21–7.40 ppm (m, 5H; Ph); ^{13}C NMR ($CDCl_3$): δ=18.9, 26.1, 26.3, 27.3, 27.4, 27.5, 28.4, 71.0, 72.3, 77.0, 79.1, 79.3, 80.3, 80.4, 110.0, 112.1, 128.4, 128.7, 127.8, 138.8 ppm; MS (FAB): m/z: 465.36 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{25}H_{41}O_6Si$: 465.2694; found: 465.2672 $[M+H]^+$.

(+)-4-*O*-Benzyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol (4): Tetrabutylammonium fluoride (TBAF) (1.0 M solution in THF, 29.7 mL) was added to a solution of **3** (4.6 g, 9.9 mmol) in THF (35 mL), and the solution was stirred at RT for 7 h. The resulting mixture was concentrated, diluted with EtOAc and washed with water and with brine. The organic extract was dried and concentrated to give the crude product, which was recrystallized from *n*-hexane to obtain **4** as a colorless solid (3.7 g, quant.). R_f= 0.21 (EtOAc/*n*Hex 1:5); m.p. 131°C (lit. 132–134°C);[28] ^{1}H NMR ($CDCl_3$): δ=1.33, 1.36, 1.43, 1.46 (4s, 3H each; $2CMe_2$), 2.40 (d, J= 8.4 Hz, 1H; OH), 3.39 (t, J=9.6 Hz, 1H; H-5), 3.65 (dd, J=6.4, 10.4 Hz, 1H; H-4), 3.78 (t, J=9.8 Hz, 1H; H-1), 3.94–4.02 (m, 1H; H-3), 4.18 (t, J=5.6 Hz, 1H; H-2), 4.24 (t, J=4.9 Hz, 1H; H-6), 4.80 (s, 2H; PhCH_2), 7.22–7.40 ppm (m, 5H; Ph).

(+)-1-*O*-*p*-Methoxybenzyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol (5): *p*-Methoxybenzylchloride (3.2 mL, 24 mmol) was added to a solution of **1** (5.59 g, 20 mmol) and NaH (0.96 g, 40 mmol) in DMF (90 mL) at 0°C, and the mixture was stirred at RT. After 10 h, the reaction mixture was quenched with EtOAc and water at 0°C. The standard extraction work-up procedure using CH_2Cl_2 gave the crude product, which was subjected to chromatography on silica gel to afford **5** as a colorless solid (6.2 g, 76%). R_f=0.13 (EtOAc/*n*Hex 1:2); m.p. 153–154°C (lit. 158–160°C);[29] ^{1}H NMR ($CDCl_3$): δ=1.32, 1.44, 1.46, 1.52 (4s, 3H each; $2CMe_2$), 2.27 (d, J=2.5 Hz, 1H; OH), 3.24 (d, J=9.7 Hz, 1H; H-5), 3.75 (dd, J=4.3, 10.1 Hz, 1H; H-1), 3.79 (s, 3H; OCH_3), 3.83–3.92 (m, 2H; H-3, H-6), 4.79 (d, J=12.6 Hz, 1H; $PhCH_aCH_b$), 4.91 (d, J=12.5 Hz, 1H; $PhCH_aCH_b$), 6.86 (d, J=8.6 Hz, 2H; Ph), 7.32 ppm (d, J=8.6 Hz, 2H; Ph).

(+)-4-*O*-(1′-Imidazolylcarbonyloxy)-2,3:5,6-di-*O*-isopropylidene-1-*O*-*p*-methoxybenzyl-*myo*-inositol (6): CaH_2 (0.59 g, 13.3 mmol) was added in portions to a solution of **5** (2.2 g, 5.8 mmol) and carbonyldiimidazole (2.35 g, 15.4 mmol) in toluene (40 mL), and the mixture was stirred for 11 h at RT. The mixture was filtered and the filtrate was evaporated to give the crude product, which was purified by using column chromatography on silica gel to obtain **6** as a colorless solid (2.6 g, 94.2%). R_f=0.42 (EtOAc/*n*Hex 2:1); m.p. 144–145°C; ^{1}H NMR ($CDCl_3$): δ=1.35, 1.44, 1.46, 1.63 (4s, 3H each; $2CMe_2$), 3.49 (dd, J=9.3, 11.4 Hz, 1H), 3.80 (s, 3H; OCH_3), 4.15–4.19 (m, 2H), 4.32 (t, J=4.4 Hz, 1H), 4.74 (d, J= 12.2 Hz, 1H; $PhCH_aCH_b$), 4.86 (d, J=12.2 Hz, 1H; $PhCH_aCH_b$), 5.35 (dd, J=6.9, 11.4 Hz, 1H; H-6), 6.89 (d, J=8.7 Hz, 2H; Ph), 7.05 (dd, J= 0.6, 1.5 Hz, 1H; imidazole-H_4), 7.35 (d, J=8.7 Hz, 2H; Ph), 7.41–7.42 (m, 1H; imidazole-H_5), 8.12 ppm (s, 1H; imidazole-H_2); ^{13}C NMR ($CDCl_3$): δ=26.2, 27.1, 27.3, 28.1, 55.6, 72.0, 73.4, 76.2, 77.3, 78.9, 79.3, 111.3, 113.5, 114.2, 117.6, 129.8, 130.5, 131.0, 137.5, 148.2, 159.9 ppm; MS (FAB): m/z: 475.13 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{24}H_{31}N_2O_3$: 475.2102; found: 475.2080 $[M+H]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-[(1-*O*-*p*-methoxybenzyl-2′,3′:5′,6′-di-*O*-isopropylidene-*myo*-inositol)carbonyloxy]-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol (7): DBU (0.05 mL, 0.34 mmol) was added to a solution of **6** (1.62 g, 3.4 mmol) and **4** (1.8 g, 5 mmol) in toluene (21 mL), and the mixture was stirred at RT for 18 h. The standard extraction work-up procedure followed by recrystallization from *n*-hexane/EtOAc (5:1) gave **7** as a colorless solid (2.23 g, 86.7%). R_f=0.44 (EtOAc/*n*Hex 1:2, eluted twice); m.p. 225–226°C; ^{1}H NMR ($CDCl_3$): δ=1.10–1.72 (m, 24H; $4CMe_2$), 3.35 (t, J=9.3 Hz, 2H), 3.49 (t, J=9.3 Hz, 2H), 3.72–3.77 (m, 2H), 3.81 (s, 3H), 4.00–4.39 (m, 4H), 4.69 (t, J=3.2 Hz, 2H), 4.82 (br s, 4H), 4.95–5.06 (m, 1H), 5.09–5.17 (m, 1H), 6.89 (d, J=8.7 Hz, 2H), 7.24–7.42 ppm (m, 7H); ^{13}C NMR ($CDCl_3$): δ=26.1, 26.3, 26.4, 27.28, 27.32, 28.1, 71.9, 72.5, 73.5, 73.7, 73.9, 74.7, 74.8, 74.9, 75.1, 75.2, 76.6, 77.16, 77.21, 79.0, 79.1, 79.3, 79.7, 80.1, 81.5, 110.6, 110.9, 113.0, 113.1, 114.2, 128.0, 128.4, 128.6, 130.1, 130.4, 138.4, 154.0, 159.9 ppm; IR (KBr): $\tilde{\nu}$=1748 cm^{-1}; MS (FAB): m/z: 779.32 $[M+Na]^+$; HRMS (FAB): m/z calcd for $C_{40}H_{53}O_{14}$: 757.3457; found: 757.3443 $[M+H]^+$; m/z calcd for $C_{40}H_{52}O_{14}Na$: 779.3357; found: 779.3241 $[M+Na]^+$.

1-*O*-Benzoyl-2,3:5,6-di-*O*-isopropylidene-*scyllo*-inositol (9) and 1-*O*-benzoyl-2,3:4,5-di-*O*-isopropylidene-*scyllo*-inositol (10): 2-Methoxypropene (20 mL, 211.2 mmol) was added over 30 min to a solution of **8** (6 g, 21.11 mmol)[30] and *p*-TSA (400 mg, 2.1 mmol) in dry DMF (100 mL) at RT. After 24 h, the reaction mixture was quenched with aqueous $NaHCO_3$. The standard extraction work-up procedure using EtOAc gave the crude product, from which two regioisomeric products, **9** (2.1 g, 30%) and **10** (4.3 g, 51%), were isolated as colorless solids by using column chromatography on silica gel. Compound **9**: R_f=0.26 (EtOAc/*n*Hex 1:2); m.p. 284–286°C;[30] ^{1}H NMR ($CDCl_3$): δ=1.44, 1.48 (2s, 6H each; $2CMe_2$), 2.46 (d, J=2.8 Hz, 1H; OH), 3.76 (app. t, J=9.4 Hz, 2H; H-3, H-5), 3.88 (app. t, J=9.4 Hz, 2H; H-2, H-6), 4.13 (dt, J=2.8, 8.8 Hz, 1H; H-4), 5.70 (t, J=9.3 Hz, 1H; H-1), 7.27–8.1 ppm (m, 5H; Ph). Compound **10**: R_f=0.34 (EtOAc/*n*Hex 1:2); m.p. 206–207°C;[29] ^{1}H NMR ($CDCl_3$): δ=1.47, 1.49 (2s, 6H each; $2CMe_2$), 2.88 (d, J=4.1 Hz, 1H; OH), 3.67–3.90 (m, 4H; H-2, H-3, H-4, H-5), 4.13 (m, 1H; H-6), 5.43 (dd, J=7.9, 10.5 Hz, 1H; H-1), 7.45–8.11 ppm (m, 5H; Ph).

1-*O*-Benzoyl-4-*O*-benzyl-2,3:5,6-di-*O*-isopropylidene-*scyllo*-inositol (11): BnBr (0.19 mL, 1.64 mmol) was added to a solution of **9** (200 mg, 0.549 mmol), Ag_2O (381 mg, 1.64 mmol), and TBAI (40 g, 0.109 mol) in dry CH_2Cl_2 at RT. After 2 h, the reaction mixture was filtered through Celite and washed with CH_2Cl_2. The filtrate was washed with aqueous $NaHCO_3$ and with brine, and the organic layer was separated, dried, and concentrated to give the crude product, which was purified by using column chromatography on silica gel to give **11** as a colorless, foamy solid (200 mg, 80%). R_f=0.49 (EtOAc/*n*Hex 1:9); ^{1}H NMR ($CDCl_3$): δ= 1.44, 1.46 (2s, 6H each; $2CMe_2$), 3.81–3.90 (m, 5H; H-2, H-3, H-4, H-5, H-6), 4.86 (s, 2H), 5.58 (app. t, J=9.3 Hz, 1H; H-1), 7.25–7.56 (m, 7H), 8.06 ppm (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=27.0 (4C; $2CMe_2$); 70.1, 72.4, 74.5 (2C), 78.7, (2C), 80.6 (2C) (inositol ring carbon atoms); 113.7 (2C), 127.3, 128.0, 128.4, (2C), 128.8 (2C), 130.1 (2C), 130.4 (2C), 133.6, 138.2, 165.9 ppm (*C*OPh); MS (FAB): m/z: 455.18 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{26}H_{31}O_7$: 455.2118; found: 455.2073 $[M+1]^+$.

1-*O*-Benzyl-2,3:5,6-di-*O*-isopropylidene-*scyllo*-inositol (12): NaOMe (0.04 mL, 0.17 mmol, 25% w/v) was added to a solution of **11** (200 mg, 0.44 mmol) in MeOH (15 mL), and the solution was placed at reflux for 3 h. After cooling, the reaction mixture was filtered through silica gel. The filtrate was concentrated and the crude product was washed with 5% EtOAc in *n*-hexane to remove the byproduct, methyl benzoate. The washed product was dried under vacuum to afford **12** as a colorless solid (150 mg, 97%). R_f=0.33 (EtOAc/*n*Hex 1:1); m.p. 215–216°C; ^{1}H NMR ($CDCl_3$): δ=1.46 (s, 12H; $2CMe_2$), 2.41 (d, J=2.7 Hz, 1H; OH), 3.63 (t, J=9.1 Hz, 2H; H-2,6 or H-3,5), 3.71 (t, J=9.0 Hz, 2H; H-2,6 or H-3,5), 3.87 (t, J=8.9 Hz, 1H; H-4), 4.10 (app. t, J=9.1 Hz, 1H; H-1), 4.83 (s,

2H; PhCH_2-), 7.26–7.39 ppm (m, 5H; $PhCH_2$-); ^{13}C NMR ($CDCl_3$): δ = 26.7 (4C; 2CMe_2), 69.4, 72.4, 75.2, 77.0 (2C), 80.6 (2C), 80.7 (2C), 113.5, 126.9, 128.0 (2C), 128.7 (2C), 138.5 ppm; MS (FAB): *m/z*: 351.47 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{27}NO_6$: 351.1844; found: 351.1812 $[M+H]^+$.

4-*O*-(1′-Imidazolylcarbonyloxy)-2,3:5,6-di-*O*-isopropylidene-1-*O*-benzyl-*scyllo*-inositol (13): Carbonyldiimidazole (81 mg, 0.49 mmol) was added to a solution of **12** (70 mg, 0.19 mmol) and CaH_2 (21 mg, 0.49 mmol) in dry toluene (6 mL) at RT. After 18 h, the reaction mixture was filtered and washed with EtOAc (20 mL). The filtrate was concentrated under vacuum, and the crude product was purified by using column chromatography on silica gel to provide **13** as an off-white solid (78 mg, 88%). R_f = 0.37 (EtOAc/*n*Hex 1:1); m.p. 214–216 °C; ^{1}H NMR ($CDCl_3$): δ = 1.45, 1.47 (2s, 6H each; 2CMe_2), 3.80–3.87 (m, 5H), 4.85 (s, 2H; PhCH_2-), 5.45 (app. t, *J* = 9.1 Hz, 1H; H-1), 7.07 (s, 1H), 7.29–7.42 (m, 6H), 8.16 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 27.0 (2C; 2CMe_2); 72.5, 73.8, 74.7, 77.0, 78.1 (2C), 80.7 (2C) (inositol ring carbon atoms); 114.1, 117.7, 128.0, 128.2 (2C), 128.7 (2C), 131.1, 137.6, 138.3, 148.0 ppm; MS (FAB): *m/z*: 445.20 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{23}H_{29}N_2O_7$: 445.2021; found: 445.1976 $[M+H]^+$.

1-*O*-Benzoyl-4-*O*-*p*-methoxybenzyl-2,3:5,6-di-*O*-isopropylidene-*scyllo*-inositol (14): PMBCl (0.12 mL, 0.93 mmol) was slowly added to a solution of **9** (300 mg, 0.85 mmol) and NaH (57.8 mg, 1.44 mmol) in dry DMF (10 mL) at 0 °C. A catalytic amount of TBAI was added to the reaction mixture, and it was allowed to slowly warm up to RT. After 4 h with stirring, the reaction mixture was subjected to the standard extraction work-up procedure using EtOAc to give the crude product, which was purified by using column chromatography on silica gel to afford **14** as a colorless solid (296 mg, 74%). R_f = 0.43 (EtOAc/*n*Hex 1:1); m.p. 218–220 °C; ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 12H; 2CMe_2), 3.66–3.85 (m, 8H), 4.78 (d, *J* = 10.2 Hz, 2H), 5.56–5.69 (m, 1H), 6.88 (dd, *J* = 8.4, 6.0 Hz, 2H), 7.31–7.56 (m, 5H), 8.08 ppm (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 27.1, 27.2 (4C; 2CMe_2), 56.7, 70.1, 72.0, 72.1, 74.5, 74.7, 80.69, 80.74, 113.1, 113.6, 114.1, 128.7, 130.0, 130.5, 133.6, 159.6, 165.7 ppm; MS (FAB): *m/z* calcd for $C_{27}H_{33}O_8$: 485.2197; found: 485.1520 $[M+H]^+$; *m/z* calcd for $C_{27}H_{32}O_8Na$: 507.2097; found: 507.2013 $[M+Na]^+$.

1-*O*-*p*-Methoxybenzyl-2,3:5,6-di-*O*-isopropylidene-*scyllo*-inositol (15): NaOMe (0.04 mL, 0.17 mmol, 25% w/v) was added to a solution of **14** (200 mg, 0.44 mmol) in MeOH (15 mL), and the solution was placed at reflux for 3 h. After cooling to RT, the reaction mixture was filtered through silica gel. The filtrate was concentrated and the residue was washed with 5% EtOAc in *n*-hexane to remove the byproduct, methyl benzoate. The product was dried under vacuum to afford **15** as a colorless solid (150 mg, 97%). R_f = 0.33 (EtOAc/*n*Hex 1:1); m.p. 198–200 °C; ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 12H; 2CMe_2), 2.41 (brs, 1H; OH), 3.59–3.63 (m, 5H), 3.65 (s, 3H; OCH_3), 3.80 (app. t, *J* = 9.1 Hz, 1H; H-1), 4.76 (s, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 7.33 ppm (d, *J* = 9.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 27.1 (4C; 2CMe_2), 55.6, 69.3, 72.0, 74.9, 80.6, 80.7, 80.8, 113.7, 129.3, 130.7, 130.8, 159.6 ppm; MS (FAB): *m/z*: 381.30 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{20}H_{29}O_7$: 381.1968; found: 381.1913 $[M+H]^+$.

4′-*O*-Benzyl-1′-*O*-[(1-*O*-*p*-methoxybenzyl-2,3:5,6-di-*O*-isopropylidene-*scyllo*-inositol)carbonyloxy]-2′,3′:5′,6′-di-*O*-isopropylidene-*scyllo*-inositol (16): A solution of **15** (43 mg, 0.11 mmol) and NaH (2.7 mg, 0.11 mmol) in dry THF (2.5 mL) at 0 °C was stirred for 30 min, and then added to a solution containing **13** (50 mg, 0.11 mmol) in dry THF (2.1 mL). After stirring for 1 h at 0–5 °C, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with a saturated solution of NH_4Cl. The organic layer was dried, filtered, and concentrated to give the crude product, which was purified by using column chromatography on silica gel to obtain **16** as a colorless solid (53 mg, 62%). R_f = 0.46 (EtOAc/*n*Hex 1:2); m.p. 244–246 °C; ^{1}H NMR ($CDCl_3$): δ = 1.43, 1.47 (2s, 6H each; 2CMe_2), 3.66–3.88 (m, 13H), 4.47 (s, 2H), 4.83 (s, 2H), 5.12 (t, *J* = 9.3 Hz, 2H; H-6, H-6′), 6.88 (d, *J* = 8.7 Hz, 2H), 7.27–7.42 ppm (m, 7H); ^{13}C NMR ($CDCl_3$): δ = 27.1 (4C; 2CMe_2); 55.7, 69.4, 72.1, 74.1, 74.6, 74.9, 75.0, 75.3, 77.0, 80.5 (inositol ring carbon atoms); 80.6, 80.8, 113.4, 114.2, 127.87, 127.94 (2C), 128.2 (2C), 128.6 (2C), 129.9, 130.6, 138.5, 153.3, 159.7, 171.4 ppm; MS (FAB): *m/z*: 757.43 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{40}H_{53}O_{14}$: 757.3523; found: 757.3435 $[M+H]^+$; *m/z* calcd for $C_{40}H_{52}O_{14}Na$: 779.3423; found: 779.3218 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-[(1-*O*-*p*-methoxybenzyl-*myo*-inositol)carbonyloxy]-*myo*-inositol (17): A solution of **7** (2.21 g, 3.70 mmol) and *p*-TSA (286.1 mg, 1.46 mmol) in CH_2Cl_2/MeOH (50 mL, 1:9) was stirred at RT for 14 h. The solid was filtered off, and the liquor washed with CH_2Cl_2/MeOH (19:1, 100 mL) to remove the *p*-TSA. The residue was concentrated and dried under vacuum to afford **17** as a colorless solid (1.45 g, 83%). R_f = 0.15 (CH_2Cl_2/MeOH 9:1); m.p. 169 °C; ^{1}H NMR ($CDCl_3$ with drops of [D_6]DMSO): δ = 3.11–3.24 (m, 4H), 3.35–3.48 (m, 5H), 3.74 (s, 3H), 3.90–3.97 (m, 3H), 4.25–4.33 (m, 2H), 4.70–4.74 (m, 2H), 4.77–4.81 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 2H; Ph), 7.21–7.35 (m, 5H; Ph), 7.43 ppm (d, *J* = 7.1 Hz, 2H; Ph); ^{13}C NMR ($CDCl_3$ with drops of [D_6]DMSO): δ = 55.1, 69.4, 69.5, 69.6, 70.2, 70.3, 70.5, 70.91, 71.86, 72.1, 72.6, 72.8, 74.7, 78.0, 78.2, 79.6, 79.7, 81.6, 113.4, 127.0, 127.6, 127.9, 129.2, 131.1, 139.9, 154.58, 154.62, 158.5 ppm; MS (FAB): *m/z*: 619.09 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{28}H_{37}O_{14}$: 597.2205; found: 597.2183 $[M+H]^+$; *m/z* calcd for $C_{28}H_{36}O_{14}Na$: 619.2105; found: 619.1951 $[M+Na]^+$.

A representative peracylation with *N*-Boc-protected aminocarboxylic acid: A solution of **7** (60 mg, 0.10 mmol), 6-aminocaproic acid (558 mg, 2.41 mmol), EDC (463 mg, 2.41 mmol), and DMAP (18.4 mg, 0.15 mmol) in DMF (6.5 mL) was stirred at RT for 24 h under N_2, treated with EtOAc, and washed several times with saturated $NaHCO_3$, water, and brine. The organic phase was dried and concentrated to give the crude product, which was purified by column chromatography on silica gel to afford **19** as a sticky solid (190 mg, 82%).

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-*p*-methoxybenzyl-2,3,5,6-*O*-(4-Boc-aminobutanoyl)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(4-Boc-aminobutanoyl)-*myo*-inositol (18): Colorless, sticky solid (166 mg, 62%); R_f = 0.43 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.35 (brs, 72H), 1.58–1.79 (m, 16H), 2.01–2.49 (m, 16H), 2.99–3.01 (m, 16H), 3.50–3.57 (m, 1H), 3.71 (s, 3H), 3.86–3.93 (m, 1H), 4.44–4.55 (m, 4H), 4.75–5.64 (m, 18H), 6.77 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 7.10–7.26 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 25.35, 25.43, 25.6, 25.8, 25.9, 28.77, 28.82, 31.4, 31.5, 31.7, 31.8, 40.1, 55.6, 67.1, 67.2, 68.3, 68.4, 69.1, 69.4, 69.9, 70.3, 70.7, 71.4, 71.6, 72.0, 73.7, 75.4, 75.5, 77.7, 79.5, 114.4, 127.67, 127.72, 128.2, 128.8, 129.1, 138.1, 138.2, 153.3, 153.4, 156.4, 156.5, 160.1, 172.0, 172.1, 172.3, 172.4, 172.5, 172.7 ppm; MALDI-TOF MS: *m/z* calcd for $C_{100}H_{156}N_8O_{38}Na$: 2101.0554; found: 2100.0781 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-*p*-methoxybenzyl-2,3,5,6-*O*-(6-Boc-aminohexanoyl)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(6-Boc-aminohexanoyl)-*myo*-inositol (19): Colorless, sticky solid (190 mg, 82%); R_f = 0.62 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.13–1.32 (m, 16H), 1.36 (brs, 72H), 1.45–1.57 (m, 32H), 2.06–2.15 (m, 16H), 2.95–3.02 (m, 16H), 3.76 (s, 3H), 3.85–3.91 (m, 1H), 4.22 (dd, *J* = 1.9, 9.3 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 2H), 4.55 (d, *J* = 18.4 Hz, 2H), 4.60–5.68 (m, 18H), 6.76 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.10–7.26 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 24.6, 24.7, 25.1, 26.3, 26.4, 28.8, 28.9, 30.1, 30.3, 33.8, 34.1, 34.2, 34.4, 40.7, 55.6, 66.7, 68.1, 69.1, 70.2, 71.3, 71.9, 72.2, 73.6, 73.7, 74.5, 75.1, 75.4, 79.28, 79.34, 114.2, 127.3, 127.5, 128.1, 128.8, 129.4, 129.8, 153.5, 156.4, 156.5, 159.8, 172.2, 172.3, 172.5, 172.7, 172.8, 172.9, 173.1 ppm; MALDI-TOF MS: *m/z* calcd for $C_{116}H_{188}N_8O_{38}Na$: 2325.3058; found: 2324.6021 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-*p*-methoxybenzyl-2,3,5,6-*O*-(8-Boc-aminooctanoyl)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(8-Boc-aminooctanoyl)-*myo*-inositol (20): Colorless, sticky solid (220 mg, 82%); R_f = 0.55 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.14–1.21 (m, 48H), 1.35 (s, 72H), 1.48–1.56 (m, 32H), 2.03–2.37 (m, 16H), 2.95–3.00 (m, 16H), 3.70 (s, 3H), 4.53 (dd, *J* = 11.7, 17.4 Hz, 4H), 4.63–5.67 (m, 20H), 6.73 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 7.08–7.24 ppm (m, 5H; Ph); ^{13}C NMR ($CDCl_3$): δ = 24.85, 24.93, 25.2, 25.4, 26.9, 27.0, 28.8, 29.2, 29.3, 29.4, 29.7, 30.0, 30.4, 33.8, 34.2, 34.3, 34.4, 41.0, 55.6, 66.8, 67.9, 68.4, 69.1, 69.8, 70.7, 72.7, 75.5, 76.2, 113.4, 115.4, 119.5, 123.1, 124.7, 126.9, 127.57, 127.64, 128.4, 129.3, 130.5, 132.66, 132.72, 138.9, 151.5, 153.7, 158.0, 159.7, 162.4, 170.7, 171.4, 172.0, 172.4, 172.7 ppm; MALDI-TOF MS: *m/z* calcd for $C_{132}H_{220}N_8O_{38}Na$: 2549.5562; found: 2548.3932 $[M+Na]^+$.

A representative procedure for the removal of the PMB protecting group: CAN (20.2 mg, 0.37 mmol) was added to a solution of **19** (170 mg,

0.07 mmol) in a mixture of CH_3CN, toluene, and water (18:5:5), and the mixture was stirred at 0 °C for 2 h and at RT for 10 h. The reaction mixture was diluted with EtOAc and subjected to the standard extraction work-up procedure to give the crude product, which was purified by using column chromatography on silica gel to afford **22** as a colorless, foamy solid (126 mg, 78 %).

(+)-4′-*O*-Benzyl-1′-*O*-{[2,3,5,6-*O*-(4-Boc-aminobutanoyl)-*myo*-inositol]-carbonyloxy}-2′,3′,5′,6′-*O*-(4-Boc-aminobutanoyl)-*myo*-inositol (21): Off-white, foamy solid (89 mg, 58 %); $R_f = 0.14$ (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): $\delta = 1.36$ (brs, 72H), 1.56–1.81 (m, 16H), 2.02–2.54 (m, 16H), 2.98–3.18 (m, 16H), 3.80–3.94 (m, 2H), 4.56 (dd, $J = 12.3$, 18.0 Hz, 2H), 4.73–5.57 (m, 18H), 7.11–7.28 ppm (m, 5H; Ph); ^{13}C NMR ($CDCl_3$): $\delta =$ 24.4, 24.7, 25.1, 25.3, 26.3, 26.6, 28.6, 30.1, 33.8, 34.0, 34.1, 34.5, 40.7, 68.0, 68.9, 70.0, 70.5, 71.2, 72.8, 73.7, 75.2, 79.6, 127.3, 127.5, 128.8, 138.1, 153.5, 156.5, 172.3, 172.49, 172.54, 172.9, 173.2 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{92}H_{148}N_8O_{37}Na$: 1980.9979; found: 1980.0722 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[2,3,5,6-*O*-(6-Boc-aminohexanoyl)-*myo*-inositol]-carbonyloxy}-2′,3′,5′,6′-*O*-(6-Boc-aminohexanoyl)-*myo*-inositol (22): Colorless, foamy solid (126 mg, 78 %); $R_f = 0.33$ (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): $\delta = 1.17$–1.26 (m, 16H), 1.37 (brs, 72H), 1.41–1.53 (m, 32H), 2.07–2.41 (m, 16H), 2.94–3.05 (m, 16H), 3.86–3.92 (m, 2H), 4.31–5.56 (m, 20H), 7.11–7.27 ppm (m, 5H; Ph); ^{13}C NMR ($CDCl_3$): $\delta = 24.9$, 25.2, 25.7, 25.8, 28.8, 29.6, 30.4, 31.0, 31.5, 31.7, 32.2, 34.1, 40.1, 68.2, 69.4, 70.7, 71.8, 72.6, 73.6, 75.6, 79.5, 80.1, 126.3, 127.5, 128.7, 128.8, 138.1, 153.4, 156.5, 156.6, 172.0, 172.3, 172.95, 173.00 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{108}H_{180}N_8O_{37}Na$: 2205.2483; found: 2204.8119 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[2,3,5,6-*O*-(8-Boc-aminooctanoyl)-*myo*-inositol]-carbonyloxy}-2′,3′,5′,6′-*O*-(8-Boc-aminooctanoyl)-*myo*-inositol (23): Colorless, foamy solid (132 mg, 70 %); $R_f = 0.11$ (EtOAc/*n*Hex 2:1, three times); ^{1}H NMR ($CDCl_3$): $\delta = 1.15$–1.21 (m, 48H), 1.36 (brs, 72H), 1.49–1.59 (m, 32H), 2.07–2.40 (m, 16H), 2.96–3.02 (m, 16H), 4.54 (dd, $J = 12.0$, 17.7 Hz, 2H), 4.63–5.54 (m, 20H), 7.09–7.24 ppm (m, 5H; Ph); ^{13}C NMR ($CDCl_3$): $\delta = 24.6$, 25.0, 25.4, 26.9, 28.8, 29.5, 30.0, 33.7, 34.0, 34.4, 40.9, 68.7, 68.9, 69.1, 70.5, 71.1, 72.3, 73.8, 79.3, 127.5, 128.1, 128.7, 138.1, 153.5, 156.4, 172.4, 172.5, 172.8, 173.0, 173.2 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{124}H_{212}N_8O_{37}Na$: 2429.4987; found: 2429.0366 $[M+Na]^+$.

A representative dansylation procedure: DMAP (14 mg, 0.114 mmol) and 5-dimethylamino-α-naphthalenesulfonyl chloride (31 mg, 0.114 mmol) were added to a solution of **22** (125 mg, 0.057 mmol) in CH_3CN (4 mL). The reaction mixture was stirred for 15 h at RT and quenched with EtOAc and then saturated NH_4Cl. The standard extraction work-up procedure gave the crude product, which was purified by using column chromatography on silica gel to afford the dansylated compound **25** as a light-yellowish, sticky solid (122 mg, 88 %).

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(4-Boc-aminobutanoyl)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(4-Boc-aminobutanoyl)-*myo*-inositol (24): Light-yellowish, sticky solid (110 mg, 52 %); $R_f = 0.23$ (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): $\delta = 1.36$–1.40 (m, 72H), 1.49–1.67 (m, 16H), 1.85–2.34 (m, 16H), 2.84 (s, 6H), 2.92–2.98 (m, 16H), 3.88 (t, $J = 9.7$ Hz, 1H), 4.54 (dd, $J = 12.1$, 16.0 Hz, 2H), 4.74–5.49 (m, 19H), 7.10–7.24 (m, 6H; aromatic), 7.49 (dd, $J = 7.5$, 14.1 Hz, 2H), 8.00 (d, $J = 8.4$ Hz, 1H), 8.15 (d, $J = 7.2$ Hz, 1H), 8.58 ppm (d, $J = 6.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 24.7$, 25.1, 25.2, 25.6, 25.8, 28.6, 29.6, 30.4, 31.2, 31.7, 33.1, 40.0, 45.8, 68.0, 69.1, 69.6, 70.4, 71.2, 72.2, 72.8, 73.8, 75.2, 79.3, 79.6, 127.3, 128.1, 128.8, 138.1, 153.5, 156.5, 172.3, 172.4, 172.5, 172.8, 173.2, 173.7 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{104}H_{159}N_9O_{39}SNa$: 2214.0490; found: 2214.1921 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(6-Boc-aminohexanoyl)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(6-Boc-aminohexanoyl)-*myo*-inositol (25): Light-yellowish, sticky solid (122 mg, 88 %); $R_f = 0.29$ (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): $\delta = 1.21$ (s, 16H), 1.38 (brs, 72H), 1.53–1.59 (m, 32H), 1.99–2.33 (m, 16H), 2.83 (s, 6H), 2.94–3.04 (m, 16H), 3.89 (t, $J = 9.77$ Hz, 1H), 4.56 (dd, $J = 11.8$, 18.6 Hz, 2H), 4.62 (d, $J = 12.5$ Hz, 1H), 4.69–5.54 (m, 19H), 7.11–7.29 (m, 6H), 7.50 (dd, $J = 8.4$, 16.5 Hz, 2H), 8.03 (d, $J = 7.5$ Hz, 1H), 8.18 (d, $J = 7.2$ Hz, 1H), 8.61 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 24.2$, 24.5, 24.7, 26.2, 26.3, 28.8, 29.7, 30.1, 30.3, 34.1, 34.2, 40.7, 41.8, 46.2, 67.9, 68.4, 69.2, 69.7, 72.1, 73.8, 74.7, 77.7, 79.3, 127.3, 128.1, 128.8, 130.6, 138.1, 153.4, 156.4, 156.5, 171.6, 171.8, 172.4, 172.5, 172.7 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{120}H_{191}N_9O_{39}SNa$: 2438.9024; found: 2438.1826 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(8-Boc-aminooctanoyl)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(8-Boc-aminooctanoyl)-*myo*-inositol (26): Light-yellowish, sticky solid (162 mg, 66 %); $R_f = 0.33$ (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): $\delta = 1.11$–1.16 (m, 48H), 1.32 (brs, 104H), 1.80–2.22 (m, 16H), 2.79 (s, 6H), 2.97 (brs, 16H), 3.83 (t, $J = 9.8$ Hz, 1H), 4.56 (d, $J = 12.1$ Hz, 1H), 4.60 (d, $J =$ 12.6 Hz, 1H), 4.60–5.48 (m, 19H), 7.05–7.20 (m, 5H), 7.24 (s, 1H), 7.42 (dd, $J = 8.3$, 16.3 Hz, 2H), 7.49 (d, $J = 8.6$ Hz, 1H), 8.10 (d, $J = 7.3$ Hz, 1H), 8.49 ppm (d, $J = 8.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 24.4$, 24.8, 25.0, 25.5, 28.8, 29.1, 29.3, 29.5, 30.0, 33.5, 33.7, 34.2, 34.4, 41.0, 45.7, 67.9, 68.0, 69.1, 70.5, 70.9, 73.9, 74.0, 74.5, 75.3, 75.4, 77.7, 79.2, 115.8, 119.3, 123.5, 127.5, 128.1, 128.7, 130.1, 130.2, 132.3, 138.1, 153.3, 153.4, 156.4, 171.4, 172.1, 172.3, 172.6 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{136}H_{223}N_9O_{39}SNa$: 2662.3277; found: 2662.2875 $[M+Na]^+$.

A representative procedure for the *N*-Boc deprotection: Compound **25** (120 mg, 0.054 mmol) was added to a solution of gaseous HCl in saturated EtOAc (5 mL) at 0 °C, and the solution was stirred for 3 h. The precipitate was separated and dried under vacuum to give the colorless hydrochloride salt **28** (80 mg, quant.).

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(4-aminobutanoyl hydrochloride)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(4-aminobutanoyl hydrochloride)-*myo*-inositol (27): Off-white solid (48 mg, quant.); ^{1}H NMR (CD_3OD): $\delta = 1.77$–1.90 (m, 16H), 2.18–2.62 (m, 16H), 2.95–3.13 (m, 16H), 3.28–3.30 (m, 1H), 3.47 (s, 6H), 3.81 (t, $J = 9.7$ Hz, 1H), 4.50 (dd, $J = 12.1$, 17.5 Hz, 2H), 4.95–5.62 (m, 11H), 7.23–7.34 (m, 5H; Ph), 7.93 (m, 2H), 8.19 (brs, 1H), 8.52 (d, $J =$ 7.2 Hz, 1H), 8.57 (d, $J = 7.8$ Hz, 1H), 8.97 ppm (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CD_3OD): $\delta = 22.3$, 22.7, 22.8, 23.2, 29.5, 30.2, 30.5, 30.8, 31.0, 39.0, 39.2, 46.7, 68.0, 69.0, 69.3, 69.7, 69.9, 71.4, 73.9, 75.2, 75.7, 78.0, 119.9, 126.6, 127.3, 128.5, 129.1, 131.9, 153.3, 153.4, 171.3, 171.7, 171.8, 172.1, 172.4 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{64}H_{95}N_9O_{23}SNa$: 1412.6262; found: 1412.6842 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(6-aminohexanoyl hydrochloride)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(6-aminohexanoyl hydrochloride)-*myo*-inositol (28): Colorless solid (80 mg, quant.); ^{1}H NMR (CD_3OD): $\delta = 1.31$–1.78 (m, 48H), 2.23–2.38 (m, 16H), 2.94–3.18 (m, 16H), 3.28–3.30 (m, 1H), 3.44 (s, 6H), 4.71 (brs, 2H), 4.95–5.62 (m, 11H), 7.21–7.30 (m, 5H), 7.87–7.98 (m, 2H), 8.14 (brs, 1H), 8.53 (dd, $J = 8.4$, 15.0 Hz, 2H), 8.95 ppm (t, $J = 8.4$ Hz, 1H); ^{13}C NMR (CD_3OD): $\delta = 23.9$, 24.2, 24.9, 25.9, 26.0, 26.1, 27.2, 29.4, 29.6, 33.2, 33.6, 33.8, 39.6, 39.7, 46.5, 68.0, 69.3, 69.4, 70.4, 72.1, 74.9, 76.0, 77.7, 119.2, 124.7, 126.1, 127.5, 127.7, 128.5, 128.9, 129.7, 133.1, 138.5, 153.5, 153.6, 171.78, 171.83, 172.2, 172.7, 172.9 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{80}H_{127}N_9O_{23}SNa$: 1636.8766; found: 1636.4102 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(8-aminooctanoyl hydrochloride)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(8-aminooctanoyl hydrochloride)-*myo*-inositol (29): Colorless solid (105 mg, quant.); ^{1}H NMR (CD_3OD): $\delta = 1.63$–2.03 (m, 80H), 2.41–2.58 (m, 16H), 3.19–3.26 (m, 16H), 3.57 (s, 6H), 4.07–4.20 (m, 1H), 4.81–4.90 (m, 2H), 5.11–5.84 (m, 11H), 7.10–7.19 (m, 5H), 7.68–7.92 (m, 4H), 8.24 (d, $J = 7.8$ Hz, 2H), 8.66 ppm (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CD_3OD): $\delta = 22.7$, 24.3, 24.5, 25.0, 25.1, 25.2, 26.4, 27.1, 27.46, 27.52, 28.9, 29.0, 33.4, 33.9, 39.8, 39.9, 68.0, 68.2, 68.6, 69.6, 69.9, 70.7, 70.8, 74.7, 75.1, 77.7, 119.4, 125.2, 126.3, 127.8, 128.4, 128.9, 131.4, 134.9, 153.4, 153.6, 168.3, 172.0, 172.3, 172.6, 172.89, 172.94, 173.0 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{96}H_{159}N_9O_{23}SNa$: 1862.1303; found: 1861.3469 $[M+Na]^+$.

A representative procedure for guanidinylation: Et_3N (0.16 mL, 1.15 mmol) and *N*,*N*′-di-Boc-*N*″-trifluoromethanesulfonylguanidine (454 mg, 1.15 mmol) were sequentially added to a solution of **28** (78 mg, 0.048 mmol) in dry DMF (4.5 mL), and the reaction mixture was stirred at RT for 3 d. The mixture was diluted with EtOAc, and washed with 1 N $NaHSO_4$, saturated $NaHCO_3$, and brine. The organic layer was separated, dried, and concentrated to give the crude product, which was purified by using column chromatography on neutral alumina to afford **31** as a colorless, foamy solid (105 mg, 61 %).

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminobutanoylguanidine)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminobutanoylguanidine)-*myo*-inositol (30): Colorless, foamy solid (71 mg, 56%); R_f=0.64 (EtOAc/*n*Hex 2:1, two times); ^{1}H NMR ($CDCl_3$): δ=1.72 (brs, 144H), 1.84–1.96 (m, 16H), 2.20–2.58 (m, 16H), 2.81 (s, 6H), 3.31 (m, 16H), 3.92 (brs, 1H), 4.52–5.49 (m, 13H), 7.13–7.24 (m, 6H; aromatic), 7.52 (m, 2H), 7.99 (d, J=8.1 Hz, 1H), 8.18 (d, J=7.2 Hz, 1H), 8.28 (brs, 8H), 8.55 (d, J=7.8 Hz, 1H), 11.44 ppm (brs, 8H); ^{13}C NMR ($CDCl_3$): δ=24.3, 24.4, 24.6, 25.1, 28.17, 28.21, 28.7, 29.5, 31.3, 32.2, 40.3, 45.7, 67.8, 69.7, 69.9, 70.5, 71.2, 72.2, 72.7, 73.0, 73.5, 75.6, 75.9, 79.4, 79.8, 83.3, 83.7, 116.0, 119.4, 127.8, 128.1, 128.2, 128.5, 128.9, 129.4, 132.2, 132.6, 138.1, 153.2, 153.9, 156.5, 157.1, 171.7, 171.8, 172.0, 172.1, 172.4 ppm.

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminohexanoylguanidine)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminohexanoylguanidine)-*myo*-inositol (31): Colorless, foamy solid (105 mg, 61%); R_f=0.53 (EtOAc/*n*Hex 2:1, developed three times); ^{1}H NMR ($CDCl_3$): δ=1.13–1.65 (m, 192H), 1.60–2.31 (m, 16H), 2.82 (s, 6H), 3.24–3.36 (m, 16H), 3.88 (t, J=9.9 Hz, 1H), 4.56–5.51 (m, 13H), 7.11–7.29 (m, 6H), 7.51 (dd, J=8.4, 16.2 Hz, 2H), 7.99 (d, J=8.7 Hz, 1H), 8.17 (d, J=7.5 Hz, 1H), 8.22–8.28 (m, 8H), 11.46 ppm (brs, 8H); ^{13}C NMR ($CDCl_3$): δ=24.3, 24.4, 24.6, 25.2, 26.6, 26.9, 28.5, 28.7, 29.1, 29.2, 33.9, 34.0, 34.2, 35.9, 41.0, 45.7, 67.7, 68.0, 68.4, 69.1, 69.5, 70.0, 70.5, 72.4, 73.7, 74.8, 75.4, 75.9, 77.6, 79.5, 83.29, 83.34, 115.8, 119.5, 123.5, 127.0, 127.5, 128.1, 128.8, 129.2, 132.4, 132.5, 138.1, 152.3, 153.4, 153.7, 156.4, 171.2, 171.2, 172.1, 172.2, 172.4 ppm; MALDI-TOF MS: m/z calcd for $C_{169}H_{271}N_{25}O_{55}SNa$: 3574.8932; found: 3572.6201 $[M+Na-2]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminooctanoylguanidine)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminooctanoylguanidine)-*myo*-inositol (32): Colorless, foamy solid (107 mg, 64%); R_f=0.41 (EtOAc/*n*Hex 2:1, two times); ^{1}H NMR ($CDCl_3$): δ=1.21–1.49 (m, 224H), 2.05–2.18 (m, 16H), 2.88 (s, 6H), 3.42 (brs, 16H), 3.94 (t, J=9.7 Hz, 1H), 4.57–5.63 (m, 13H), 7.17–7.30 (m, 6H), 7.50–7.60 (m, 2H), 8.05 (d, J=8.3 Hz, 1H), 8.22 (d, J=7.3 Hz, 1H), 8.41 (brs, 8H), 8.61 (d, J=8.5 Hz, 1H), 11.51 ppm (brs, 8H); ^{13}C NMR ($CDCl_3$): δ=21.2, 23.0, 23.3, 24.5, 24.7, 24.9, 26.97, 27.00, 27.08, 27.12, 28.4, 28.7, 29.1, 29.2, 29.3, 29.6, 30.4, 31.6, 32.2, 33.9, 34.0, 34.2, 34.3, 34.4, 41.2, 41.3, 45.7, 53.7, 65.8, 67.9, 68.3, 69.2, 69.4, 70.5, 72.3, 73.9, 75.3, 75.4, 77.6, 78.2, 79.1, 83.5, 115.7, 119.6, 123.4, 127.2, 128.1, 128.7, 129.1, 131.1, 138.1, 152.3, 153.7, 156.4, 164.0, 171.7, 172.0, 172.2, 172.4, 172.6 ppm; MALDI-TOF MS: m/z calcd for $C_{184}H_{303}N_{25}O_{55}SNa$: 3800.1469; found: 3798.7681 $[M+Na-2]^+$.

A representative procedure for the *N*-Boc deprotection of the guanidine moiety: A TFA/CH_2Cl_2 mixture (1:1, 2 mL) was added to a solution of compound **31** (35 mg, 0.01 mmol) in CH_2Cl_2 (1 mL) at RT, and the solution was stirred for 5 h. Samples from the reaction were analyzed by using TLC, and after the starting-material spot had completely disappeared, the solution was concentrated. The residue was washed with a mixture of diethyl ether and MeOH (20:1), and thoroughly dried under vacuum. The residue was dissolved in deionized water, filtered through a polytetrafluoroethylene (PTFE) syringe filter, and lyophilized to give the TFA salt **34** as a light-brownish, foamy solid (17.1 mg, 89%).

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(aminobutanoylguanidinium)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(aminobutanoylguanidinium)-*myo*-inositol·8TFA (33): Light-brownish, glassy solid (11.2 mg, 83%); UV (H_2O): λ_{max} (ε): 336.80 nm (3460 $cm^{-1}M^{-1}$); ^{1}H NMR (CD_3OD): δ=1.71–1.78 (m, 16H), 2.20–2.48 (m, 16H), 2.87 (s, 6H), 3.15–3.27 (m, 16H), 3.92–4.34 (m, 3H), 4.92–5.22 (m, 11H), 7.21–7.29 (m, 6H; aromatic), 7.55–7.62 (m, 2H), 8.02 (d, J=8.1 Hz, 1H), 8.18–8.22 (m, 1H), 8.65 ppm (d, J=7.9 Hz, 1H); ^{13}C NMR (CD_3OD): δ=24.8, 25.0, 25.3, 26.5, 26.6, 29.1, 29.8, 33.8, 41.4, 41.5, 44.8, 67.9, 68.05, 68.07, 69.1, 69.5, 70.7, 72.1, 75.1, 75.57, 75.60, 75.8, 115.7, 119.3, 123.5, 127.4, 128.4, 130.0, 130.1, 130.5, 132.2, 138.4, 152.4, 157.6, 161.7, 162.2, 172.2, 172.5, 172.9, 173.0 ppm; MALDI-TOF MS: m/z calcd for $C_{72}H_{111}N_{25}O_{23}SNa$: 1748.8005; found: 1748.5223 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(aminohexanoylguanidinium)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(aminohexanoylguanidinium)-*myo*-inositol·8TFA (34): Light-brownish, glassy solid (17.1 mg, 89%); UV (H_2O): λ_{max} (ε)=336.40 nm (2700 $cm^{-1}M^{-1}$); ^{1}H NMR (CD_3OD): δ=1.13–1.35 (m, 16H), 1.42–1.57 (m, 32H), 2.13–2.43 (m, 16H), 2.88 (s, 6H), 3.02–3.16 (m, 16H), 4.01 (t, J=9.6 Hz, 1H), 4.64 (dd, J=11.9, 18.7 Hz, 2H), 5.01–5.61 (m, 11H), 7.16–7.28 (m, 6H; aromatic), 7.52–7.66 (m, 2H), 8.00 (d, J=8.6 Hz, 1H), 8.27 (d, J=7.3 Hz, 1H), 8.64 ppm (d, J=8.5 Hz, 1H); ^{13}C NMR (CD_3OD): δ=24.0, 24.2, 24.4, 24.7, 26.0, 28.47, 28.54, 28.6, 33.2, 33.3, 33.7, 41.3, 44.8, 68.1, 68.6, 69.2, 70.0, 70.2, 72.2, 74.1, 75.6, 77.6, 115.3, 115.8, 119.1, 123.1, 123.5, 126.3, 127.5, 128.4, 129.0, 130.3, 130.4, 132.3, 138.4, 152.6, 153.6, 157.8, 161.9, 162.4, 172.0, 172.1, 172.3, 172.6, 172.9 ppm; MALDI-TOF MS: m/z calcd for $C_{88}H_{143}N_{25}O_{23}SNa$: 1973.0509; found: 1972.8712 $[M+Na]^+$.

(+)-4′-*O*-Benzyl-1′-*O*-{[1-*O*-(5-dimethylamino-α-naphthalenesulfonyl)-2,3,5,6-*O*-(aminooctanoylguanidinium)-*myo*-inositol]carbonyloxy}-2′,3′,5′,6′-*O*-(aminooctanoylguanidinium)-*myo*-inositol·8TFA (35): Light-brownish, foamy solid (21.7 mg, 87%); UV (H_2O): λ_{max} (ε)=360 nm (3100 $cm^{-1}M^{-1}$); ^{1}H NMR (CD_3OD): δ=1.25–1.35 (m, 48H), 1.50 (brs, 32H), 2.17–2.37 (m, 16H), 2.89 (s, 6H), 3.14 (brs, 16H), 3.40 (brs, 1H), 4.62–4.64 (m, 2H), 5.13–5.60 (m, 11H), 7.21–7.26 (m, 5H; aromatic), 7.47–7.64 (m, 3H), 8.02 (d, J=7.1 Hz, 1H), 8.26 (brs, 1H), 8.64 ppm (d, J=7.6 Hz, 1H); ^{13}C NMR (CD_3OD): δ=23.1, 23.2, 23.9, 25.1, 27.4, 27.5, 27.6, 27.8, 28.0, 31.9, 32.1, 32.5, 43.5, 67.8, 68.0, 68.2, 69.5, 70.9, 72.7, 73.6, 74.3, 76.3, 113.9, 114.5, 117.4, 126.1, 126.5, 127.6, 128.6, 129.9, 130.8, 130.9, 137.0, 151.1, 152.1, 152.2, 156.5, 159.9, 160.4, 170.8, 171.0, 171.2, 171.3, 171.5, 171.7 ppm; MALDI-TOF MS: m/z calcd for $C_{104}H_{175}N_{25}O_{23}SNa$: 2198.3047; found: 2198.9236 $[M+Na]^+$.

4-*O*-Allyl-1-*O*-benzoyl-2,3:5,6-di-*O*-isopropylidene-*scyllo*-inositol (36): Ag_2O (2.22 g, 9.61 mmol), allyl bromide (0.84 mL, 9.61 mmol), and a catalytic amount of TBAI (150 mg) were added to a solution of **8** (1.4 g, 3.84 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred for 3 h at RT, and then filtered through a short bed of Celite. The filtrate was concentrated and purified by using column chromatography on silica gel to obtain **36** as a colorless solid (1.46 mg, 94.5%). M.p. 214–216°C; R_f=0.34 (EtOAc/*n*Hex 1:4); ^{1}H NMR ($CDCl_3$): δ=1.44 (s, 12H; 2CMe_2), 3.75–3.88 (m, 5H), 4.31 (dd, J=6.9, 1.2 Hz, 2H), 5.22 (dd, J=1.5, 10.1 Hz, 1H), 5.35 (dd, J=1.5, 18.1 Hz, 1H), 5.57 (t, J=8.7 Hz, 1H), 5.92–6.02 (m, 1H), 7.47 (t, J=9.0 Hz, 2H), 7.57 (t, J=6.0 Hz, 1H), 8.08 ppm (d, J=9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=27.08 (2C; CMe_2), 27.11 (2C; CMe_2), 70.1, 71.7, 74.8, 78.8, 80.7, 113.6, 118.0, 126.3, 128.7, 130.1, 130.4, 133.6, 134.9, 165.7 ppm; MS (FAB): m/z: 405.19 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{22}H_{29}O_7$: 405.1901; found: 405.1909 $[M+H]^+$.

1-*O*-Allyl-2,3:5,6-di-*O*-isopropylidene-*scyllo*-inositol (37): NaOMe (0.32 mL, 1.38 mmol) was added to a solution of **36** (1.40 g, 3.46 mmol) in MeOH (35 mL), and the reaction mixture was placed at reflux for 3 h. After cooling to RT, the mixture was filtered through silica gel. The filtrate was concentrated, and the residue was washed with 5% EtOAc in *n*-hexane, and dried under vacuum to give **37** as a colorless solid (957 mg, 92%). M.p. 200–202°C; R_f=0.35 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ=1.46 (s, 12H; 2CMe_2), 2.45 (d, J=2.7 Hz, 1H; OH), 3.57–3.68 (m, 4H), 3.83 (t, J=8.1 Hz, 1H), 4.05 (t, J=7.9 Hz, 1H), 4.28 (dd, J=7.0, 1.2 Hz, 2H), 5.21 (d, J=10.2 Hz, 1H), 5.33 (dd, J=1.5, 18.1 Hz, 1H), 5.95 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ=27.1 (4C; 2CMe_2), 69.4, 71.7, 75.0, 77.0, 80.5, 80.7, 113.5, 118.0, 134.9 ppm; MS (FAB): m/z: 301.17 $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{15}H_{25}O_6$: 301.1700 found 301.1650 $[M+H]^+$.

1-*O*-(2-Oxoethyl)-2,3:5,6-diisopropylidene-*scyllo*-inositol (38): A solution of **37** (940 mg, 3.13 mmol) and $NaHCO_3$ (395 mg, 4.7 mmol) in CH_2Cl_2/MeOH (6:1, 210 mL) was treated with ozone at −78°C until the blue color persisted. Nitrogen was bubbled through the solution until the blue color was discharged. Triphenylphosphine (928 mg, 3.54 mmol) was added and the solution was stirred at RT for 12 h. The reaction mixture was concentrated and purified by using column chromatography on silica gel to give **38** as a colorless solid (814 mg, 86%). M.p. 145–147°C; R_f=0.33 (EtOAc/*n*Hex 2:1); ^{1}H NMR ($CDCl_3$): δ=1.46 (s, 12H; 2CMe_2), 2.45 (brs, 1H; OH), 3.60–3.79 (m, 7H), 3.87 (t, J=6.2 Hz, 1H), 9.72 ppm (s, 1H; CHO); ^{13}C NMR ($CDCl_3$): δ=26.1 (4C; 2CMe_2), 69.6, 70.4, 72.0,

75.2, 76.8, 80.2, 89.3, 112.7 ppm; MS (FAB): *m/z*: 303.13 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{14}H_{23}O_7$: 303.1530; found: 303.1444 $[M+H]^+$.

1-*O*-(*N*,*N*-Dibenzylaminoethyl)-2,3:5,6-diisopropylidene-*scyllo*-inositol (39): Dibenzylamine (0.76 mL, 3.97 mmol) was added to a solution of **38** (800 mg, 2.65 mmol) in dry dichloroethane (DCE; 45 mL) at 0 °C. After 10 min at 0 °C, $NaBH(OAc)_3$ (898 mg, 4.23 mmol) was added and the stirring was continued for 12 h at RT. The mixture was subjected to the standard extraction work-up procedure using CH_2Cl_2 to give the crude product, which was purified by using column chromatography on silica gel to yield **39** as a colorless solid (972 mg, 76 %). M.p. 144–145 °C; R_f = 0.42 (EtOAc/*n*Hex 2:1); ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 12H; 2 CMe_2), 2.70 (brs, 1H; OH), 2.74 (t, *J* = 6.0 Hz, 2H), 3.54–3.59 (m, 4H), 3.64 (s, 4H), 3.73–3.77 (m, 1H), 3.87 (t, *J* = 6.2 Hz, 2H), 4.0 (t, *J* = 6.0 Hz, 1H), 7.19–7.39 ppm (m, 10H); ^{13}C NMR ($CDCl_3$): δ = 27.2 (4C; 2 CMe_2), 42.6, 53.2, 59.0, 62.3, 69.0, 75.8, 80.6, 113.0, 127.3, 128.5, 128.6, 129.0, 129.2, 140.3 ppm; MS (FAB): *m/z*: 484.26 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{28}H_{38}NO_6$: 484.2738; found: 484.2701 $[M+H]^+$.

4-*O*-(2-Dibenzylaminoethyl)-2,3:4,5-diisopropylidene-1-*O*-(methoxycarbonylmethyl)-*scyllo*-inositol (40): Ag_2O (1.0 g, 4.32 mmol), methyl bromoacetate (0.41 mL, 4.32 mmol), and TBAI (135 mg) were sequentially added to a solution of **39** (950 mg, 1.96 mmol) in CH_2Cl_2 (30 mL). After stirring at RT for 12 h, the reaction mixture was filtered through Celite and washed with CH_2Cl_2 (150 mL). The filtrate was concentrated and purified by using column chromatography on silica gel to give **40** as a colorless solid (1.02 g, 94 %). M.p. 130–132 °C; R_f = 0.38 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 12H; 2 CMe_2), 2.72 (t, *J* = 6.3 Hz, 2H), 3.56 (t, *J* = 9.3 Hz, 2H), 3.63–3.89 (m, 13H), 4.36 (s, 2H), 7.21–7.40 ppm (m, 10H); ^{13}C NMR ($CDCl_3$): δ = 27.1 (4C; 2 CMe_2), 52.2, 53.2, 59.0, 67.7, 69.1, 75.6, 77.0, 79.9, 80.6, 113.5, 127.3, 128.5, 129.29, 140.3, 171.1 ppm; MS (FAB): *m/z*: 556.19 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{31}H_{42}NO_8$: 556.2922; found: 556.2913 $[M+H]^+$; *m/z* calcd for $C_{31}H_{41}NO_8Na$: 578.2822; found: 578.2794 $[M+Na]^+$.

4-*O*-(2-Aminoethyl)-1-*O*-(methoxycarbonylmethyl)-2,3:5,6-diisopropylidene-*scyllo*-inositol (41): A solution of **40** (400 mg, 0.719 mmol) in a mixed solvent (CH_2Cl_2/MeOH 1:9, 30 mL) was hydrogenated (40 psi) at RT over 10 % Pd/C (100 mg). After 3 h, the catalyst was filtered and the filtrate was evaporated. The crude product was recrystallized from methanol/dichloromethane to give **41** as an off-white solid (270 mg, quant.). M.p. 193–195 °C; R_f = 0.22 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (CD_3OD): δ = 1.40 (s, 12H; 2 CMe_2), 3.10 (t, *J* = 5.9 Hz, 2H), 3.27 (dd, *J* = 6.5, 1.8 Hz, 2H), 3.69–3.90 (m, 11H), 4.28 ppm (s, 2H); ^{13}C NMR (CD_3OD): δ = 27.1 (4C; 2 CMe_2), 46.2, 52.8, 58.8, 67.9, 68.8, 75.6, 76.8, 77.0, 79.7, 80.5, 82.9, 113.7, 127.4, 128.6, 129.4, 139.5, 162.1, 173.4 ppm; MS (FAB): *m/z*: 376.26 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{17}H_{30}NO_8$: 376.2012; found: 376.1987 $[M+H]^+$.

4-*O*-(2-*N*,*N*-Dibenzylaminoethyl)-1-*O*-(methoxycarboxyl)-2,3:5,6-diisopropylidene-*scyllo*-inositol (42): NaOH (136 mg, 3.4 mmol) was added to a solution of **40** (540 mg, 0.971 mmol) in methanol (25 mL). After being stirred at RT for 12 h the reaction mixture was concentrated under vacuum and the residue was dissolved in water (25 mL). The aqueous solution was washed with diethyl ether (2 × 10 mL) to remove the nonpolar impurities, and then carefully acidified with 10 % aqueous AcOH to pH 6.0–6.5. The standard extraction workup with EtOAc gave **42** as colorless, foamy solid (485 mg, 92 %). R_f = 0.32 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR ($CDCl_3$): δ = 1.41, 1.44 (2 s, 6H each; 2 CMe_2), 2.77 (t, *J* = 5.9 Hz, 2H), 3.35–3.83 (m, 10H), 3.89 (t, *J* = 5.9 Hz, 2H), 4.37 (s, 2H), 7.20–7.40 ppm (m, 10H; aromatic); ^{13}C NMR ($CDCl_3$): δ = 25.9 (2C), 26.0 (2C; 2 CMe_2), 40.0, 51.3, 66.6, 67.2, 76.2, 76.4, 79.8, 113.3, 171.6 ppm; MS (FAB): *m/z*: 542.30 $[M+H]^+$, 564.25 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{30}H_{40}NO_8$: 542.2778; found: 542.2749 $[M+H]^+$; *m/z* calcd for $C_{30}H_{39}NO_8Na$: 564.2778; found: 564.2702 $[M+Na]^+$.

4-*O*-[(2-*N*,*N*-dibenzylaminoethyl)-4′-*O*-{(methoxycarbonylmethyl)-2′,3′:5′,6′-di-*O*-isopropylidene-*scyllo*-inositol}-1′-*O*-ethyl-1-*O*-methylamido]-2,3:5,6-di-*O*-isopropylidene-*scyllo*-inositol (43): Triethylamine (0.04 mL, 0.276 mmol), HOBT (27.4 mg, 0.202 mmol), and EDC (38.9 mg, 0.202 mmol) were sequentially added to the equimolar solution of **41** (69.3 mg, 0.184 mmol) and **42** (100 mg, 0.184 mmol) in dry DMF (5 mL) at RT under N_2. After stirring for 22 h, the reaction mixture was diluted with EtOAc (35 mL) and washed with aqueous NH_4Cl (1 × 10 mL), saturated $NaHCO_3$ (2 × 10 mL), and water (3 × 15 mL). The standard extraction workup gave the crude product, which was purified by using column chromatography on silica gel (EtOAc/*n*Hex 1:2 to 1:1) to afford **43** as a colorless, foamy solid (109 mg, 65 %). R_f = 0.36 (EtOAC/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.40, 1.43 (2s, 12H each; 4 CMe_2), 2.72 (t, *J* = 6.1 Hz, 2H), 3.35–3.88 (m, 25H), 4.23 (s, 2H), 4.36 (s, 2H), 7.02 (t, *J* = 6.0 Hz, 1H; CONH), 7.19–7.39 ppm (m, 10H; aromatic); ^{13}C NMR ($CDCl_3$): δ = 27.1 (4C; 2 CMe_2), 27.2 (4C; 2 CMe_2), 39.3, 52.2, 53.1, 59.0, 67.7, 69.1, 69.6, 70.2, 75.5, 76.2, 76.9, 79.8, 79.9, 80.4, 80.6, 113.5, 113.6, 127.2, 128.5, 129.2, 140.2, 170.1, 171.1 ppm; MS (FAB): *m/z*: 899.48 $[M+H]^+$, 921.42 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{47}H_{67}N_2O_{15}$: 899.4534; found: 899.4530 $[M+H]^+$; *m/z* calcd for $C_{47}H_{66}N_2O_{15}Na$: 921.4534; found: 921.4488 $[M+Na]^+$.

4-*O*-{(2-*N*,*N*-Dibenzylaminoethyl)-4′-*O*-[(methoxycarbonylmethyl)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-*scyllo*-inositol (44): *p*-TSA monohydrate (21 mg, 0.116 mmol) was added in portions to a solution of **43** (90 mg, 0.097 mmol) in CH_2Cl_2 and MeOH (9:1, 3.3 mL) at RT under N_2. After 10 h, the solution mixture was concentrated. The residue was washed several times with a mixture of CH_2Cl_2 and MeOH (19:1) to remove excess *p*-TSA, and dried to give **44** as a colorless, sticky solid (72 mg, quant.). R_f = 0.22 (CH_2Cl_2/MeOH 3:1); ^{1}H NMR (CD_3OD): δ = 2.91–3.11 (m, 4H), 3.22–3.38 (m, 15H), 3.82 (dist. t, *J* = 6.8 Hz, 2H), 4.05 (t, *J* = 7.2 Hz, 2H), 4.24 (s, 2H), 4.35 (s, 2H), 4.30–4.44 (m, 4H), 7.39–7.36 ppm (m, 10H; aromatic); ^{13}C NMR (CD_3OD): δ = 39.7, 52.3, 57.60, 66.0, 69.3, 71.3, 71.5, 74.1, 74.2, 74.3, 83.0, 83.4, 84.2, 84.8, 126.0, 126.3, 128.9, 129.5, 129.7, 130.2, 131.5, 140.7, 142.6, 172.9, 173.8 ppm; MS (FAB): *m/z*: 739.42 $[M+H]$, 761.42 $[M+Na]^+$; HRMS (FAB): *m/z* calcd for $C_{35}H_{50}N_2O_{15}Na$: 761.3211; found: 761.2807 $[M+Na]^+$.

4-*O*-{(2-*N*,*N*-Dibenzylaminoethyl)-4′-*O*-[(methoxycarboxylmethyl)-2′,3′:5′,6′-*O*-(4-Boc-aminobutanoyl)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(4-Boc-aminobutanoyl)-*scyllo*-inositol (45): Colorless, sticky solid (100 mg, 55 %); R_f = 0.29 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.42 (brs, 72H), 1.68–1.70 (m, 16H), 2.10–2.25 (m, 18H), 3.11 (brs, 16H), 3.55–3.71 (m, 14H), 4.01–4.19 (m, 5H), 4.99–5.32 (m, 16H), 6.98 (brs, 1H; CONH), 7.22–7.34 ppm (m, 10H; aromatic); ^{13}C NMR ($CDCl_3$): δ = 24.7, 24.8, 26.7, 28.8, 30.1, 34.2, 34.2, 40.8, 53.2, 59.1, 60.7, 68.5, 71.2, 71.7, 71.8, 72.2, 72.4, 77.0, 78.0, 78.8, 79.3, 127.3, 128.6, 129.0, 139.8, 156.36, 156.40, 168.9, 169.7, 172.4, 172.5, 172.8 ppm; MALDI-TOF MS: *m/z* calcd for $C_{107}H_{170}N_{10}O_{39}Na$: 2243.1660; found: 2243.1539 $[M+Na]^+$.

4-*O*-{(2-*N*,*N*-Dibenzylaminoethyl)-4′-*O*-[(methoxycarboxylmethyl)-2′,3′:5′,6′-*O*-(6-Boc-aminohexanoyl)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(6-Boc-aminohexanoyl)-scyllo-inositol (46): Colorless, sticky solid (189 mg, 81 %); R_f = 0.35 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.28–1.59 (m, 120H), 2.15–2.31 (m, 16H), 2.51 (brs, 2H), 3.07 (brs, 16H), 3.36 (brs, 2H), 3.62–3.81 (m, 12H), 4.04–4.21 (m, 5H), 4.84–5.39 (m, 16H), 6.98 (brs, 1H; CONH), 7.21–7.30 ppm (m, 10H; aromatic); ^{13}C NMR ($CDCl_3$): δ = 24.2, 26.2, 28.3, 31.3, 34.1, 53.1, 59.0, 67.1, 71.8, 71.9, 72.4, 76.1 78.4, 79.5, 127.1, 128.4, 129.3, 156.2, 159.3, 169.9, 170.7, 172.2, 173.4 ppm; MALDI-TOF MS: *m/z* calcd for $C_{123}H_{202}N_{10}O_{39}Na$: 2467.9636; found: 2467.5435 $[M+Na]^+$.

4-*O*-{(2-*N*,*N*-Dibenzylaminoethyl)-4′-*O*-[(methoxycarboxylmethyl)-2′,3′:5′,6′-*O*-(8-Boc-aminooctanoyl)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(8-Boc-aminooctanoyl)-*scyllo*-inositol (47): Colorless, sticky solid (186 mg, 76 %); R_f = 0.39 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.25–1.59 (m, 152H), 2.21–2.23 (m, 16H), 2.56 (brs, 2H), 3.09–3.15 (m, 16H), 3.33 (brs, 2H), 3.50–3.67 (m, 14H), 4.05–4.20 (m, 5H), 4.71–5.11 (m, 8H), 5.16–5.41 (m, 8H), 6.95 (brs, 1H; CONH), 7.21–7.30 ppm (m, 10H; aromatic); ^{13}C NMR ($CDCl_3$): δ = 21.3, 24.9, 24.95, 25.00, 27.0, 28.8, 29.30, 29.34, 29.37, 29.41, 30.4, 34.3, 34.4, 41.0, 52.0, 53.2, 59.1, 60.6, 71.0, 71.6, 71.8, 72.3, 78.1, 79.2, 79.4, 127.3, 128.5, 128.9, 139.7, 156.3, 156.4, 168.8, 169.7, 172.46, 172.52, 172.8 ppm; MALDI-TOF MS: *m/z* calcd for $C_{139}H_{234}N_{10}O_{39}Na$: 2691.6668; found: 2691.6768 $[M+Na]^+$.

**4-*O*-{(2-*N*,*N*-Dibenzylaminoethyl)-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(4-aminobutanoyl hydrochloride)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(4-aminobutanoyl hydrochloride)-*scyllo*-ino-

sitol (48): Colorless solid (HCl salt, 54 mg, quant.); ^{1}H NMR (CD_3OD): δ = 1.23–1.26 (m, 16H), 2.53–2.61 (m, 16H), 2.93–3.00 (m, 16H), 3.41–3.88 (m, 14H), 4.10–4.23 (m, 5H), 5.11–5.38 (m, 8H), 7.28–7.43 ppm (m, 10H; aromatic); ^{13}C NMR (CD_3OD): δ = 24.4, 26.0, 27.1, 31.3, 39.7, 49.2, 57.2, 67.7, 72.2, 72.8, 78.2, 79.8, 127.2, 128.7, 129.0, 131.7, 171.3, 172.9, 173.0 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{67}H_{108}N_{10}O_{23}Na$: 1443.7589; found: 1443.9495 $[M+Na]^+$.

4-*O*-{(2-*N*,*N*-Dibenzylaminoethyl)-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(6-aminohexanoyl hydrochloride)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(6-aminohexanoyl hydrochloride)-*scyllo*-inositol (49): Colorless solid (HCl salt, 142 mg, quant.); ^{1}H NMR (CD_3OD): δ = 1.32–1.68 (m, 48H), 2.21–2.45 (m, 16H), 2.93 (brs, 16H), 3.19–3.80 (m, 14H), 4.02–4.36 (m, 5H), 5.15–5.36 (m, 8H), 7.48–7.53 ppm (m, 10H; aromatic); ^{13}C NMR (CD_3OD): δ = 19.9, 24.3, 25.3, 27.2, 33.8, 39.6, 48.6, 48.9, 57.3, 60.5, 71.9, 72.3, 74.1, 78.6, 79.0, 129.5, 130.2, 131.7, 131.9, 172.0, 172.4, 173.0, 173.5 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{83}H_{140}N_{10}O_{23}Na$: 1668.00; found: 1667.50 $[M+Na]^+$.

4-*O*-{(2-*N*,*N*-Dibenzylaminoethyl)-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(8-aminooctanoyl hydrochloride)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-O-(8-aminooctanoyl hydrochloride)-*scyllo*-inositol (50): Colorless solid (HCl salt, 143 mg, 99%); ^{1}H NMR (CD_3OD): δ = 1.27–1.64 (m, 80H), 2.37 (brs, 16H), 2.93–2.96 (m, 16H), 3.41–3.88 (m, 14H), 4.11 (brs, 5H), 4.22 (s, 2H), 5.27–5.48 (m, 8H), 7.54–7.63 ppm (m, 10H; aromatic); ^{13}C NMR (CD_3OD): δ = 24.7, 24.9, 26.4, 26.5, 27.49, 27.51, 28.95, 29.03, 29.1, 34.1, 39.8, 39.9, 48.7, 51.7, 57.3, 60.6, 71.8, 72.1, 72.4, 78.8, 129.6, 130.3, 131.8, 170.5, 171.9, 172.9, 173.0, 173.1, 173.3 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{99}H_{170}N_{10}O_{23}Na$: 1891.2472; found: 1891.2677 $[M+Na]^+$.

4-*O*-{(2-*N*,*N*-Dibenzylaminoethyl)-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminobutanoylguanidine)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-O-(*N*,*N*′-bis-Boc-*N*″-aminobutanoylguanidine)-*scyllo*-inositol (51): Colorless, foamy solid (68 mg, 51%); R_f = 0.38 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.48 (brs, 144H), 1.74–1.85 (m, 16H), 2.33–2.36 (m, 16H), 3.36–3.68 (m, 30H), 4.08–4.15 (m, 5H), 4.93–5.22 (m, 8H), 7.26–7.37 (m, 10H; aromatic), 8.34 (brs, 8H), 11.48 ppm (brs, 8H); ^{13}C NMR ($CDCl_3$): δ = 24.6, 24.8, 28.2, 28.36, 28.44, 28.7, 30.1, 31.8, 36.9, 40.3, 77.8, 83.6, 83.8, 86.2, 86.4, 117.5, 121.8, 128.8, 149.3, 151.8, 152.4, 153.6, 156.6, 163.0, 163.9 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{155}H_{250}N_{26}O_{55}Na$: 3378.7565; found: 3376.4721 $[M+Na-2]^+$.

4-*O*-{(2-*N*,*N*-Dibenzylaminoethyl)-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminohexanoylguanidine)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminohexanoylguanidine)-*scyllo*-inositol (52): Off-white, foamy solid (129 mg, 67%); R_f = 0.44 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.25–1.53 (m, 192H), 2.24–2.30 (m, 16H), 2.34 (app. t, J = 6.7 Hz, 2H), 3.36–3.50 (m, 18H), 3.64–3.89 (m, 15H), 4.10 (brs, 2H), 4.22 (brs, 2H), 5.14–5.43 (m, 8H), 6.90 (brs, 1H), 7.27–7.34 (m, 10H; aromatic), 8.29 (brs, 8H), 11.58 ppm (brs, 8H); ^{13}C NMR ($CDCl_3$): δ = 24.7, 24.8, 24.9, 26.79, 26.83, 28.2, 28.5, 28.7, 29.2, 34.2, 34.4, 41.1, 71.7, 72.2, 77.9, 79.5, 83.3, 83.4, 127.4, 128.7, 129.0, 139.7, 153.7, 156.5, 164.0, 172.35, 172.42, 172.6, 172.7 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{171}H_{282}N_{26}O_{55}Na$: 3604.0103; found: 3603.1566 $[M+Na]^+$.

4-*O*-{(2-*N*,*N*-Dibenzylaminoethyl)-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminooctanoylguanidine)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminooctanoylguanidine)-*scyllo*-inositol (53): Colorless, foamy solid (125 mg, 72%); R_f = 0.42 (EtOAc/*n*Hex 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.24–1.53 (m, 224H), 2.22–2.30 (m, 18H), 2.34 (app. t, J = 7.3 Hz, 2H), 3.00 (m, 2H), 3.36–3.89 (m, 32H), 5.11–5.43 (m, 8H), 7.27–7.29 (m, 10H; aromatic), 8.29 (brs, 8H), 11.50 ppm (brs, 8H); ^{13}C NMR ($CDCl_3$): δ = 21.3, 24.95, 25.02, 25.1, 27.1, 28.2, 28.5, 28.7, 28.8, 29.4, 30.0, 34.3, 34.5, 41.3, 52.1, 53.2, 59.1, 60.7, 71.2, 71.8, 71.9, 72.3, 79.4, 83.3, 126.3, 127.3, 128.6, 129.0, 139.7, 153.7, 156.5, 164.0, 168.8, 169.6, 171.3, 172.5, 172.7 ppm; MALDI-TOF MS: *m*/*z*: calcd for $C_{187}H_{315}N_{26}O_{55}$: 3807.6353; found: 3807.2341 $[M+H]^+$; calcd for $C_{187}H_{314}N_{26}O_{55}Na$: 3829.6353; found: 3829.7262 $[M+Na]^+$.

A representative procedure for debenzylation of the terminal dibenzylamine moiety: A mixture of **52** (125 mg, 0.035 mmol) and 10% Pd/C (65 mg, 10 mol%) in a mixed solvent of CH_2Cl_2 and MeOH (4 mL, 1:9) was hydrogenated by using a balloon (1 atm). After stirring for 22 h at RT, the catalyst was filtered and the filtrate was evaporated to give the crude product, which was recrystallized from a MeOH/CH_2Cl_2 mixture to afford **55** as a colorless, sticky solid (88 mg, 74%).

4-*O*-{(2-Aminoethyl)-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminobutanoylguanidine)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminobutanoylguanidine)-*scyllo*-inositol (54): Colorless, sticky solid (50 mg, 83%); R_f = 0.19 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (CD_3OD); δ = 1.49–1.54 (m, 160H), 1.92 (brs, 16H), 2.46 (brs, 16H), 3.22–3.79 (m, 30H), 4.02–4.23 (m, 5H), 5.13–5.33 ppm (m, 8H); MALDI-TOF MS: *m*/*z*: calcd for $C_{141}H_{240}N_{26}O_{55}$ 3176.6726; found: 3176.4531 $[M+H]^+$; calcd for $C_{141}H_{239}N_{26}O_{55}Na$: 3198.6626; found: 3198.8276 $[M+Na]^+$.

4-*O*-{(2-Aminoethyl)-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminohexanoylguanidine)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminohexanoylguanidine)-*scyllo*-inositol (55): Colorless, sticky solid (88 mg, 74%); R_f = 0.22 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (CD_3OD): δ = 1.30–1.61 (m, 192H), 2.35–2.37 (m, 16H), 3.28–3.33 (m, 32H), 4.01–4.29 (m, 5H), 5.24–5.38 ppm (m, 8H); MALDI-TOF MS: *m*/*z* calcd for $C_{154}H_{270}N_{26}O_{55}Na$: 3424.9649; found: 3424.2172 $[M+Na]^+$.

4-*O*-{(2-Aminoethyl)-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminooctanoylguanidine)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminooctanoylguanidine)-*scyllo*-inositol (56): Colorless, sticky solid (78 mg, 89%); R_f = 0.23 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (CD_3OD): δ = 1.36–1.57 (m, 224H), 2.35 (brs, 16H), 2.81 (brs, 2H), 3.05 (dist. t, 2H), 3.33–3.43 (m, 26H), 3.89–4.20 (m, 8H), 5.24–5.35 ppm (m, 8H); MALDI-TOF MS: *m*/*z* calcd for $C_{173}H_{302}N_{26}O_{55}Na$: 3625.1668; found: 3625.2019 $[M+Na]^+$.

A representative procedure for the FITC-I attachment: Fluorescein-5-isothiocyanate (1.2 mg, 0.03 mmol) and TEA (10 μL, 0.07 mmol) were added to a solution of **55** (80 mg, 0.023 mmol) in a mixed solvent of THF and absolute ethanol (3:2, 4 mL). The reaction mixture was stirred for 24 h at RT in the dark, and then concentrated. The crude product was purified by means of column chromatography by using a long, thin column of flash silica gel to afford **58** as a light-greenish-yellow, sticky mass (56 mg, 63%).

4-*O*-{[2-(*N*-Fluoresceinyl-5-thioureido)-ethyl]-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminobutanoylguanidine)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminobutanoylguanidine)-*scyllo*-inositol (57): Light-greenish-yellow, sticky solid (26 mg, 46%); R_f = 0.32 (CH_2Cl_2/MeOH 9:2); ^{1}H NMR ($CDCl_3$): δ = 1.48–1.60 (m, 160H), 2.31–2.34 (m, 18H), 3.40–4.20 (m, 35H), 5.24–5.39 (m, 8H), 6.62–6.80 (m, 6H), 7.23–7.33 (m, 2H), 8.35 (brs, 9H), 11.47 ppm (brs, 8H); MALDI-TOF MS: *m*/*z* calcd for $C_{162}H_{249}N_{27}O_{60}SNa$: 3588.7017; found: 3587.6681 $[M+Na]^+$.

4-*O*-{[2-(*N*-Fluoresceinyl-5-thioureido)ethyl]-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminohexanoylguanidine)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminohexanoylguanidine)-*scyllo*-inositol (58): Light-greenish, sticky solid (56 mg, 63%); R_f = 0.39 (CH_2Cl_2/MeOH 9:2); ^{1}H NMR ($CDCl_3$): δ = 1.25–1.55 (m, 192H), 2.27 (brs, 16H), 3.38–3.40 (m, 16H), 3.49–3.69 (m, 14H), 4.01–4.21 (m, 5H), 5.11–5.30 (m, 8H), 6.68–6.89 (m, 5H), 7.29 (brs, 2H), 8.30–8.39 (m, 9H), 11.56 ppm (brs, 8H); MALDI-TOF MS: *m*/*z*: calcd for $C_{178}H_{282}N_{27}O_{60}S$ 3790.9621; found: 3790.6613 $[M+H]^+$; calcd for $C_{178}H_{281}N_{27}O_{60}SNa$: 3812.9521; found: 3812.3281.

4-*O*-{[2-(*N*-Fluoresceinyl-5-thioureido)ethyl]-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminooctanoylguanidine)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminooctanoylguanidine)-*scyllo*-inositol (59): Light-yellowish, sticky solid (35 mg, 58%); R_f = 0.38 (CH_2Cl_2/MeOH 9:2); ^{1}H NMR ($CDCl_3$): δ = 1.26–1.53 (m, 224H), 2.24 (brs, 18H), 3.67 (m, 16H), 3.88–4.21 (m, 22H), 5.54–5.71 (m, 8H), 6.62–6.80 (m, 6H), 8.33 (brs, 9H), 11.44 ppm (brs, 8H); MALDI-TOF MS: *m*/*z*: calcd for $C_{194}H_{314}N_{27}O_{60}SNa$: 4014.2002; found: 4013.0459 $[M+H]^+$; calcd for $C_{194}H_{313}N_{27}O_{60}SNa$: 4036.1992; found: 4035.8321 $[M+Na]^+$.

A representative procedure for the *N*-Boc deprotection from the guanidine moiety: EtOAc (4 mL) saturated with gaseous HCl was added to a solution of **58** (30 mg, 0.008 mmol) in EtOAc (1 mL) at RT. After being stirred for 20 h, the solution was concentrated and the residue was washed with a mixture of diethyl ether and MeOH (20:1) to remove less polar impurities. The residue was dried and purified by using MPLC on reverse-phase C-8 silica gel (H_2O/CH_3CN 1:1 to 1:2 with 0.1% TFA). The purified product was dissolved in deionized water, filtered through a PTGE syringe filter, and lyophilized to give **61** as a light-greenish-yellow, foamy solid (HCl salt, 12.6 mg, 73%).

4-*O*-{[2-(*N*-Fluoresceinyl-5-thioureido)ethyl]-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(aminobutanoylguanidinium)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(aminobutanoylguanidinium)-*scyllo*-inositol·8 HCl (60): Light-yellowish, foamy solid (HCl salt, 9.6 mg, 76%); UV (H_2O): λ_{max} (ε) = 495 nm (15700 $cm^{-1}M^{-1}$); ^1H NMR (CD_3OD): δ = 1.86 (brs, 16H), 2.14–2.16 (m, 2H), 2.44 (brs, 16H), 3.22–3.31 (m, 23H), 3.68–4.28 (m, 10H), 5.20–5.34 (m, 8H), 6.65–7.01 (m, 6H), 7.19–7.22 (m, 2H), 8.30 ppm (brs, 1H); MALDI-TOF MS: *m/z* calcd for $C_{82}H_{121}N_{27}O_{28}SNa$: 1989.08; found: 1989.03 $[M+Na]^+$; analytical HPLC (BU-300): t_R = 3.79 min (flow rate: 1 mL min^{-1}; UV: λ = 215 nm; CH_3CN/H_2O 40:60), purity 95+%.

4-*O*-{[2-(*N*-Fluoresceinyl-5-thioureido)ethyl]-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(aminohexanoylguanidinium)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(aminohexanoylguanidinium)-*scyllo*-inositol·8 HCl (61): Light-yellowish, foamy solid (HCl salt, 12.6 mg, 73%); UV (H_2O): λ_{max} (ε) = 490 nm (19400 $cm^{-1}M^{-1}$); ^1H NMR (CD_3OD): δ = 1.39–1.61 (m, 48H), 2.35–2.45 (m, 18H), 3.16–3.31 (m, 24H), 3.67–4.28 (m, 11H), 5.28–5.44 (m, 8H), 6.65–6.93 (m, 6H), 7.20–24 (m., 2H), 8.26 ppm (brs, 1H); ^{13}C NMR (CD_3OD): δ = 24.6, 24.9, 26.3, 27.3, 28.7, 34.1, 41.4, 61.3, 67.9, 70.2, 72.3, 126.3, 127.9, 128.1, 130.7, 157.6, 162.1, 171.6, 172.0, 173.1, 175.8 ppm; MALDI-TOF MS: *m/z*: calcd for $C_{98}H_{154}N_{27}O_{28}S$: 2190.50; found: 2190.39 $[M+H]^+$; calcd for $C_{98}H_{153}N_{27}O_{28}SNa$: 2212.49; found: 2212.53 $[M+Na]^+$; analytical HPLC (BU-300): t_R = 3.69 min (flow rate:1 mL min^{-1}; UV: λ = 215 nm; CH_3CN/H_2O 40:60), purity 99+%.

D,L-4-*O*-{[2-(*N*-Fluoresceinyl-5-thioureido)ethyl]-4′-*O*-[(methoxycarbonyl-methyl)-2′,3′:5′,6′-*O*-(aminooctanoylguanidinium)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(aminooctanoylguanidinium)-*scyllo*-inositol·8 HCl (62): Light-yellowish, foamy solid (HCl salt, 13.2 mg, 80%); UV (H_2O): λ_{max} (ε) = 488 nm (16600 $cm^{-1}M^{-1}$); ^1H NMR (CD_3OD): δ = 1.30–1.61 (m, 96H), 2.30–2.43 (m, 16H), 2.86 (brs, 2H), 3.20–3.39 (m, 14H), 3.67–4.18 (m, 10H), 5.20–5.34 (m, 8H), 6.65–6.79 (m, 6H), 7.11 (brs, 2H), 8.30 ppm (brs, 1H); ^{13}C NMR (CD_3OD): δ = 25.1, 25.4, 26.2, 27.0, 27.9, 28.7, 29.4, 34.8, 42.2, 44.6, 46.2, 62.1, 68.5, 69.0, 70.7, 72.4, 121.3, 121.9, 126.3, 126.6, 127.2, 128.3, 130.4, 157.6, 162.1, 162.6, 171.0, 172.1, 172.5, 173.2 ppm; MALDI-TOF MS: *m/z* calcd for $C_{114}H_{186}N_{27}O_{28}S$: 2414.92; found: 2414.72 $[M+H]^+$; analytical HPLC (BU-300): t_R = 3.57 min (flow rate: 1 mL min^{-1}; UV: λ = 215 nm; CH_3CN/H_2O 40:60), purity 95+%.

4-*O*-{[2-(*N*-Cbz-L-serineamido)ethyl]-4′-*O*-[(methoxycarbonylmethyl)-2′,3′:5′,6′-*O*-(*N*,*N*′-bis-Boc-*N*″-aminooctanoylguanidine)-*scyllo*-inositol]-1′-*O*-ethyl-1-*O*-methylamido}-2,3:5,6-*O*-(*N*,*N*′-bis-Boc-*N*″-aminooctanoylguanidine)-*scyllo*-inositol (63): EDC (3.2 mg, 0.0168 mmol) and HOBT (2.3 mg, 0.0168 mmol) were added to a solution of **56** (51 mg, 0.014 mmol) and *N*-Cbz-protected L-serine (4 mg, 0.0168 mmol) in dry DMF (2 mL) at RT under N_2. After stirring for 22 h, the reaction mixture was subjected to the standard extraction workup using EtOAc to give the crude product, which was purified by using column chromatography on silica gel (CH_2Cl_2/MeOH 10:1 to 6:1) to afford **63** as a colorless, sticky solid (39 mg, 72%). R_f = 0.38 (CH_2Cl_2/MeOH 10:1); ^1H NMR ($CDCl_3$): δ = 1.32–1.49 (m, 224H), 2.26 (brs, 16H), 2.81 (brs, 2H), 3.39 (brs, 16H), 3.69–3.89 (m, 20H), 5.13–5.16 (m, 10H), 7.28–7.37 (m, 5H), 8.29 (brs, 8H), 11.5 ppm (brs, 8H); ^{13}C NMR ($CDCl_3$): δ = 23.1, 25.2, 27.2, 28.5, 28.7, 28.9, 29.4, 30.1, 32.3, 34.4, 41.3, 72.1, 77.0, 79.6, 83.4, 128.5, 128.7, 129.0, 153.7, 156.5, 164.0, 172.1, 172.7, 173.1 ppm.

Doxorubicin conjugate 64: Pyridine (18.2 μL, 0.0224 mmol) was added to a solution of **63** (28 mg, 0.0045 mmol) and *p*-nitrochloroformate (2.7 mg, 0.0131 mmol) in CH_2Cl_2 (2.5 mL) at 0°C. The solution was stirred at RT for 3 h, and concentrated under high vacuum. To the residue dissolved in dry DMF (2 mL) and TEA (3.5 μL, 0.023 mmol), doxorubicin-hydrochloride (3.1 mg, 0.0056 mmol) was added, and the resulting solution was stirred at RT under dark for 24 h. The reaction mixture was concentrated and purified by using column chromatography on silica gel (CH_2Cl_2/MeOH 10:1 to 5:1) to afford **64** as a reddish, sticky solid (23.6 mg, 77%). R_f = 0.33 (CH_2Cl_2/MeOH 10:1); ^1H NMR ($CDCl_3$): δ = 1.25–1.68 (m, 224H), 2.26 (brs, 20H), 3.37–3.73 (m, 26H), 4.76–4.86 (m, 4H), 4.90–5.45 (m, 12H), 7.24–7.26 (m, 5H), 7.60–7.68 (m, 1H), 7.72–7.81 (m, 1H), 7.88–7.94 (brs, 1H), 8.28 (brs, 8H), 11.48 ppm (brs, 8H); ^{13}C NMR ($CDCl_3$): δ = 24.3, 25.1, 25.3, 27.5, 28.2, 28.8, 29.1, 30.3, 31.9, 33.8, 41.0, 43.6, 49.0, 65.4, 71.2, 76.9, 80.3, 83.9, 123.2, 125.3, 127.8, 128.1, 128.7, 153.5, 155.3, 165.6, 171.9, 172.4, 172.5, 182.3 ppm.

HCl salt of the doxorubicin conjugate 65: Light-reddish, glassy solid (11.6 mg, 76%); UV (H_2O): λ_{max} (ε): 490 nm (10000 $cm^{-1}M^{-1}$); ^1H NMR (CD_3OD): δ = 1.30–1.60 (m, 80H), 2.38 (brs, 16H), 3.19 (brs, 16H), 3.21–342 (m, 14H), 3.53–3.72 (m, 18H), 3.78 (brs, 5H), 3.89–4.21 (m, 10H), 5.18–5.34 (m, 8H), 7.31–7.59 ppm (m, 3H); MALDI-TOF MS: *m/z*: calcd for $C_{132}H_{213}N_{28}O_{39}$ 2814.56; found: 2815.93 $[M+H]^+$; calcd for $C_{132}H_{212}N_{28}O_{39}Na$: 2836.55; found: 2835.67 $[M+Na]^+$; analytical HPLC (BU-300): t_R = 3.77 min (flow rate: 1 mL min^{-1}; UV: λ = 215 nm; CH_3CN/H_2O 40:60), purity 95+%.

Cellular uptake studies

Peptide synthesis and fluorescence labeling: Dansyl-Arg9 and Fl-Arg9 were custom synthesized by PEPTRON, Inc. Daejeon, South Korea, and satisfactorily characterized by means of HPLC and mass spectrometric analyses.

Cell culture: COS-7 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) and 10% (v/v) fetal bovine serum without antibiotics. The subculture was conducted every 3–4 d using the cells grown to subconfluence. RAW264.7 cells were cultivated according to a literature procedure.[17] HeLa cells derived from human cervical cancer cells were cultured as exponentially growing subconfluent monolayers on 60 mm dishes in alpha-minimum essential medium (α-MEM) supplemented with 10% (v/v) calf serum. A subculture was performed every 3–4 d.

Confocal laser scanning microscopy (CLSM): Each kind of cells was placed into 35 mm glass-bottomed dishes and cultured for 48 h. After removing the medium, the COS-7 cells were washed with PBS (×1). The cells were incubated for 3 min at RT in the presence of dansyl-R9 and compounds **33**, **34**, and **35** at 10 μM concentration in DMEM. After incubation, the cells were washed with PBS (×1), and CLSM was performed by using a Carl Zeiss LSM 510 Meta Confocal Microscope with a 40× objective lens. FITC fluorescence was excited with the λ = 458 nm line of an argon laser (Figure 1A). After removing the medium, the RAW 264.7 cells were washed with PBS (×1). The cells were incubated for 3 min at RT in the presence of dansyl-R9 and compounds **34** and **72** at a concentration of 10 μM in DMEM. After incubation, the cells were washed with PBS (×1), and then ethanol. CLSM was performed in the same manner as described above (Figure 1B). After removing the medium, the HeLa cells were washed with PBS (×2). The cells were incubated for 15 min at 37°C in the presence of R9-Fl and compounds **60**, **61**, and **62** at a concentration of 10 μM in DMEM. After incubation, the cells were washed with cold PBS (×5), and CLSM was performed by using a Carl Zeiss LSM 510 Meta Confocal Microscope with a 40× objective lens. FITC fluorescence was excited with the λ = 488 nm line of an argon laser (Figure 1C).

Protocols for the organ biodistribution study were previously described.[33]

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