Maleimide and Cyclooctyne Based Hexakis-Adducts of Fullerene: Multivalent Scaffolds for Copper-Free Click Chemistry on Fullerenes

Javier Ramos-Soriano,[a,b,e] *José J. Reina,*[b,c,e] *B. M. Illescas,*,*[a] *Javier Rojo,*,*[b] *Nazario Martín.*,*[a,d]

[a] Departamento de Química Orgánica, Facultad de Química, Universidad Complutense de Madrid, E-28040-Madrid, Spain.

E-mail: beti@ucm.es, nazmar@ucm.es

[b] Instituto de Investigaciones Químicas (IIQ), CSIC – Universidad de Sevilla, Américo Vespucio 49, 41092 Seville, Spain

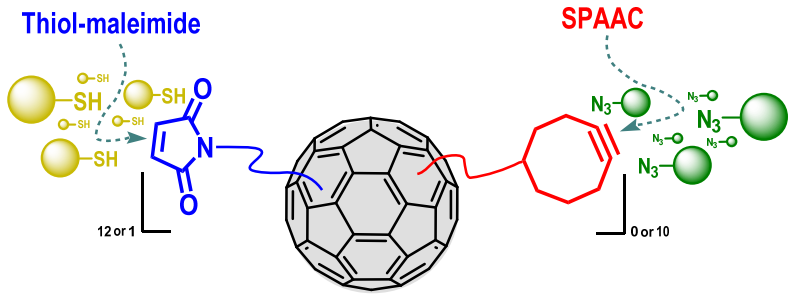
E-mail: javier.rojo@iiq.csic.es

[c] Current address: Singular Research Centre in Chemical Biology and Molecular Materials (CIQUS), Organic Chemistry Department, University of Santiago de Compostela (USC), Santiago de Compostela, Spain

[d] IMDEA-Nanoscience, C/ Faraday, 9, Campus de Cantoblanco, E-28049-Madrid, Spain

[e] These authors contributed equally to this work

TABLE OF CONTENTS



ABSTRACT

The synthesis of multivalent systems based on hexakis-adducts of [60]fullerene employing a biocompatible copper-free click chemistry strategy has been accomplished. A symmetric hexakis-adduct of fullerene bearing 12 maleimide units **3** is reported and it has been employed to carry out the thiol-maleimide Michael addition. To achieve orthogonal click addition, an asymmetric derivative bearing one maleimide and ten cyclooctynes has been synthesized. The sequential and one-pot transformations of the two clickable groups have been explored, finding the best results in the case of the one-pot experiment. This route has been used to obtain a biocompatible hexakis-adduct appended with two different biomolecules, carbohydrates and amino acids.

INTRODUCTION

Multivalency has a crucial role in many biological processes, such as cell-cell, cell adhesion or cell-virus interactions.[1-3] It may be described as a strategy to achieve strong non-covalent interactions through multiple otherwise weak interactions between ligands and receptors. It is strongly related with biomolecular recognition where the resulting global interaction is stronger than the sum of the interactions of a monovalent ligand. Different supramolecular processes as chelation, clustering, subsite rebinding or statistical rebinding seem to be involved in the multivalent effect giving rise to stronger and highly selective recognition events.[2] Hence, in the last years there has been an interest in the formation of multivalent systems for the presentation of ligands to different receptors.[3] For the achievement of this goal, different platforms have been employed that allow the formation of multivalent clusters,[4] such as dendrimers,[5,6] nanoparticles,[7] aromatics,[8] polymers,[9] liposomes,[10] graphene,[11,12] nanotubes[13,14] or fullerenes[15-17] among others.

Their remarkable features make [60]fullerene hexakis-adducts suitable platforms for the construction of multivalent systems, including their monodisperse globular disposition of the ligands, due to a T_h octahedral symmetry.[18] It is important to note that size and shape are important issues to address in the presentation of multivalent systems. Actually, they can even

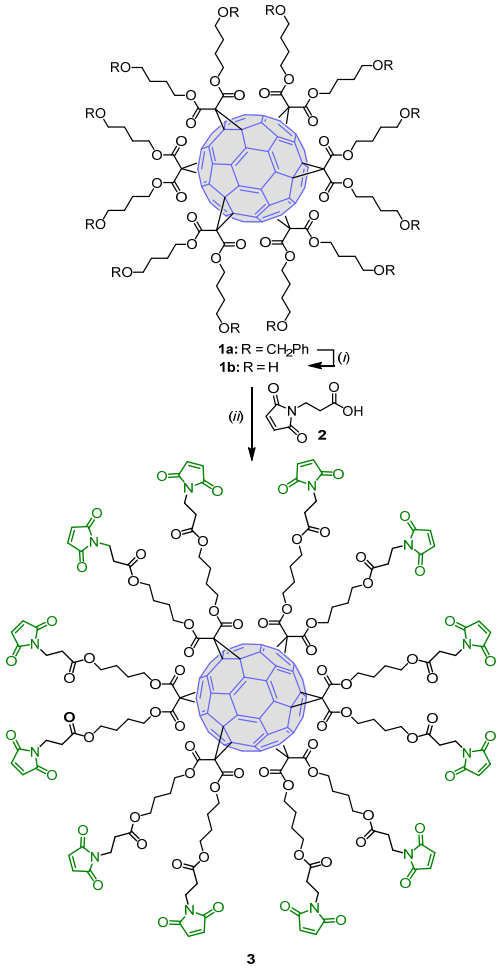
play a most significant role than multivalency itself. In this regard, the previously synthesized polyvalent bacteriophage-based glycodendrinanoparticle displaying 1620 copies of mannose on its surface[19] exhibited around 18 times less efficiency (IC50 value) than a tridecafullerene having 120 mannoses.[15] The synthesis of these derivatives was first reported by Hirsch[20] and later modified by Sun[21] and is carried out in one-step by the Bingel addition of the corresponding malonates. This route, however, is limited by the steric effects of the functionalized malonates, usually proceeding with moderate to low yields. To circumvent this limitation, a two-step procedure is usually carried out, functionalizing in the first step the C_{60} surface with simple malonates which are lately post-functionalized in the second step.[22-26] Nierengarten and our own group have developed a two-step click-chemistry approach to obtain complex hexakis-adducts.[27-29] In the first step, an alkyne or azide functionalized malonate is added to the C_{60} core, obtaining the hexakis-adduct which is then chemically modified by the Cu(I)-catalyzed alkyne azide 1,3-dipolar cycloaddition (CuAAC). This methodology has led to derivatives for applications in different areas, such as materials science[30,31] and especially for biological applications.[32-35] However, the employ of copper is a serious drawback for the biocompatibility of the obtained products. Generally, an additional purification step is needed to eliminate the residual copper. Moreover, when the obtained molecules have copper chelating groups, a small amount of this metal remains chelated to the molecule after several purification steps.[36] This is more noticeable in the case of multivalent systems in which there are many of those chelating groups which, in some cases, could affect to the click reaction, lowering the yields and even, in some cases, inhibiting the reaction.

Recently, we have reported the synthesis of a [60]fullerene hexakis-adduct appended with cyclooctynes to carry out copper-free strain promoted alkyne-azide cycloadditions (SPAAC).[37] In the present work, we describe the synthesis of a new derivative for the copper-free click chemistry on hexakis-adducts of fullerene, a system bearing 12 maleimide units. Although the thiol-ene click reaction had already been employed in the post-functionalization of hexa-adducts of [60]fullerene by the introduction of up to twelve methacrylate subunits, the yields

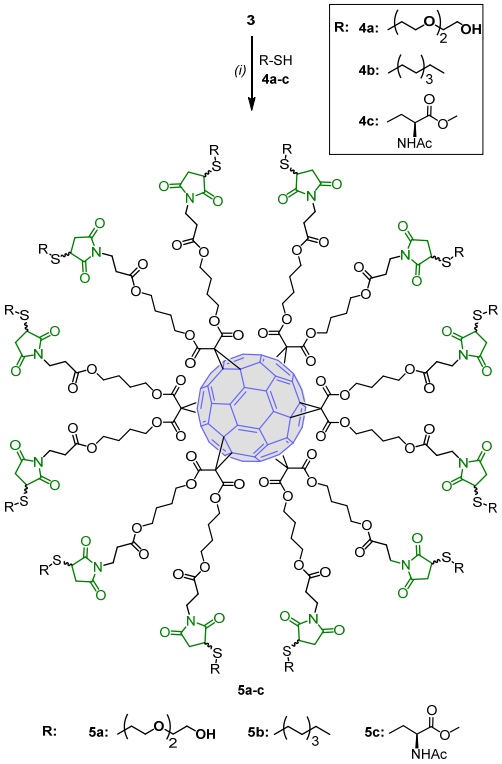
obtained in the addition of different thiols (AIBN, benzene, 80ºC) were moderate (35-52%).[38] Using the thiol-maleimide Michael addition, the scope of this procedure has been tested with some thiols of different nature and the yields were above 95% in all cases under mild conditions. Then, the introduction of the two mentioned clickable units, a maleimide and ten cyclooctyne units in the same molecule to achieve orthogonal click chemistry has been explored. Two different sequential routes and the one-pot approach have been studied to carry out both click transformations on the same molecule, opening the way to interesting hexakis-adducts of fullerene with two different functionalities obtained by a copper-free methodology. As a proof of concept, two kinds of biomolecules, as carbohydrates and amino acids, have been successfully clicked following this biocompatible approach.

RESULTS AND DISCUSSION

The synthesis of maleimide hexakis-adduct of [60]fullerene was carried out as depicted in Scheme 1.



Scheme 1. *Reagents and conditions:* (*i*) H_2, Pd-C, DCM/MeOH, r.t., overnight (100%); (*ii*) DMAP/DCC, DCM/DMF, r.t., overnight (99%).



Scheme 2. *Reagents and conditions: (i)* DMF, r.t., 30 min (96-100 %).

As previously observed for the cyclooctyne appended hexakis-adduct,[37] direct addition of the corresponding malonate by Bingel reaction under the conditions reported by Sun yielded a complex mixture of different products owing to bromination of the maleimide unit. Therefore, we followed a three steps strategy involving formation of the hexakis-adduct with protected alcohols **1a**,[37] deprotection to yield **1b** and esterification with 3-maleimidepropionic acid (**2)** in the presence of DCC and DMAP (Scheme 1). Purification of the hexakis-adduct **3** was developed by size-exclusion chromatography using Sephadex (DCM:MeOH 1:1). Employing the thiol-maleimide click reaction, we proved the platform for the conjugation of different thiols, as non-polar 1-octanethiol (**4a**), polar 2-(2-(2-mercaptoethoxy)ethoxy)ethan-1-ol (**4b**) and the protected amino acid *N*-acetyl-L-cysteine methyl ester (**4c**) (Scheme 2). A mixture of **3** (1 eq) and the corresponding thiol (1.5 eqs per maleimide unit) in DMF was kept at room temperature for 30 min. After purification using Sephadex, derivatives **5a-c** were obtained in excellent yields.

The structure of compounds **5a-c** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. DEPT, COSY and HSQC experiments were carried out for all new compounds synthesized to confirm the proposed structures (see ESI). The ^{1}H NMR spectra of these conjugates clearly show completion of the addition of the thiols by the disappearance of the characteristic signal of the olefinic protons of the maleimide at δ 6.71. The addition of the thiol generates a new asymmetric centre per maleimide unit, leading to a complex mixture of diastereoisomers owing to the multivalent presentation of the systems. However, the high symmetry of these hexakis-adducts provides NMR spectra simpler than those we can expect. For **5a** and **5b**, the signals for the proton of the new stereogenic centre are indistinguishable for the two possible isomers and only one signal is observed at 3.72 and 3.94 ppm, respectively. For compound **5c**, on the other side, a diastereomeric mixture per maleimide unit is formed upon addition of the thiol, and therefore the signals of the cysteine and the maleimide moieties appear duplicated (see ESI). ^{13}C NMR spectra of **5a-c** also confirm the structure showing the presence of only two

signals for the sp^2 carbons of [60]fullerene at ~ 145 and 141 ppm and the loss of the signal of the olefinic carbons of the maleimide observed at ~ 134 ppm (Figure 1).

Once we had prepared the symmetric adduct **3**, we were interested in obtaining an asymmetric derivative for the simultaneous addition of different addends to the C_{60} scaffold. To improve the biocompatibility of the resulted systems, we thought of an orthogonal copper-free click reaction. Thus, maleimide and cyclooctyne units were introduced in the same molecule by following the synthetic pathway depicted in Scheme 3. Monoadduct **8** was first synthesized under typical Bingel addition conditions, adding malonate **7** (1 eq), I_2 (3.5 eqs) and DBU (2.5 eqs) to a solution of C_{60} (2 eqs). Formation of the asymmetric hexakis-adduct was carried out by addition of the malonate **9** with orthogonal protection of the alcohol group (10 eqs) in the presence of a large excess of CBr_4 (80 eqs) and DBU (20 eqs). Hydrogenation at atmospheric pressure of compound **10** led to quantitative deprotection of the benzyl groups to yield compound **11**, which was submitted to esterification with the cyclooctyne carboxylic acid **12** in the presence of DCC and DMAP. The deprotection of the TBDPS was achieved by the HF/pyridine complex in the presence of AcOH and a final esterification with maleimide carboxylic acid **2** yielded compound **15**.

Characterization by ^1H NMR and ^{13}C NMR of all derivatives confirmed the proposed structures. Even for the asymmetric hexakis-adducts of C_{60} **10-15**, only two signals were observed in the ^{13}C NMR spectrum for the 48 sp^2 carbons of the fullerene core in the compounds, showing the high local symmetry of these derivatives, as previously reported (Figure 2).[29,39,40]

Then, the reactivity of compound **15** was explored either in a stepwise sequence (routes A and B, Scheme 4) or in a one-pot process (route C, Scheme 4)). First, the SPAAC addition of 2-(2-(2-azidoethoxy)ethoxy)ethan-1-ol to the cyclooctyne moieties was carried out. The previously reported conditions for this addition (DMSO, MW, 50°C) were avoided to prevent reaction of the azide with the maleimide, which can take place at high temperature. Thus, the SPAAC reaction was accomplished in DMSO at room temperature overnight and led quantitatively to

compound **16** after size-exclusion chromatography with Sephadex LH-20. Completion of the reaction was confirmed by the absence of the signals of the alkyne functionality of the cyclooctyne units in the ^{13}C NMR spectrum (Figure 2). Additionally, the characteristic formation of two regioisomers was observed, with several duplicated signals present in the ^{1}H NMR (see ESI).

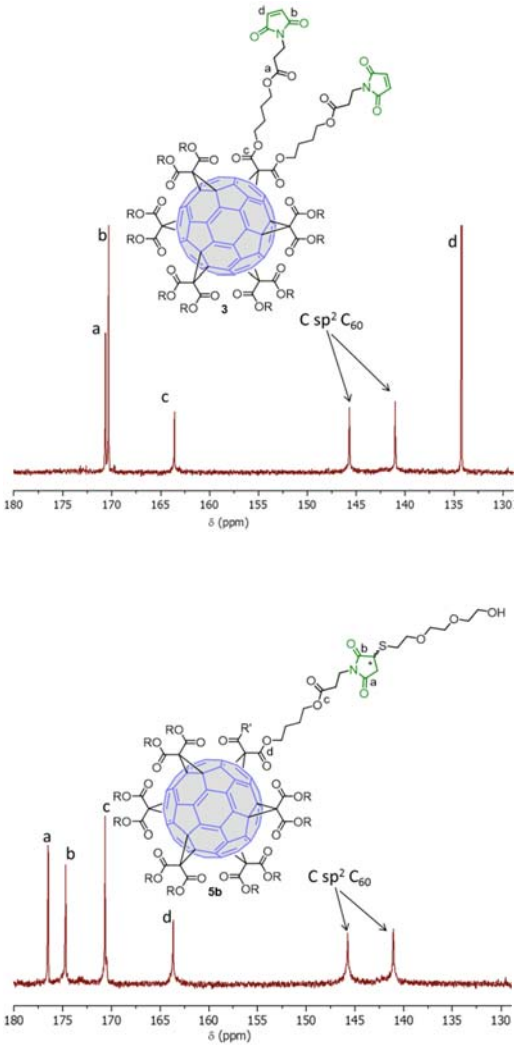
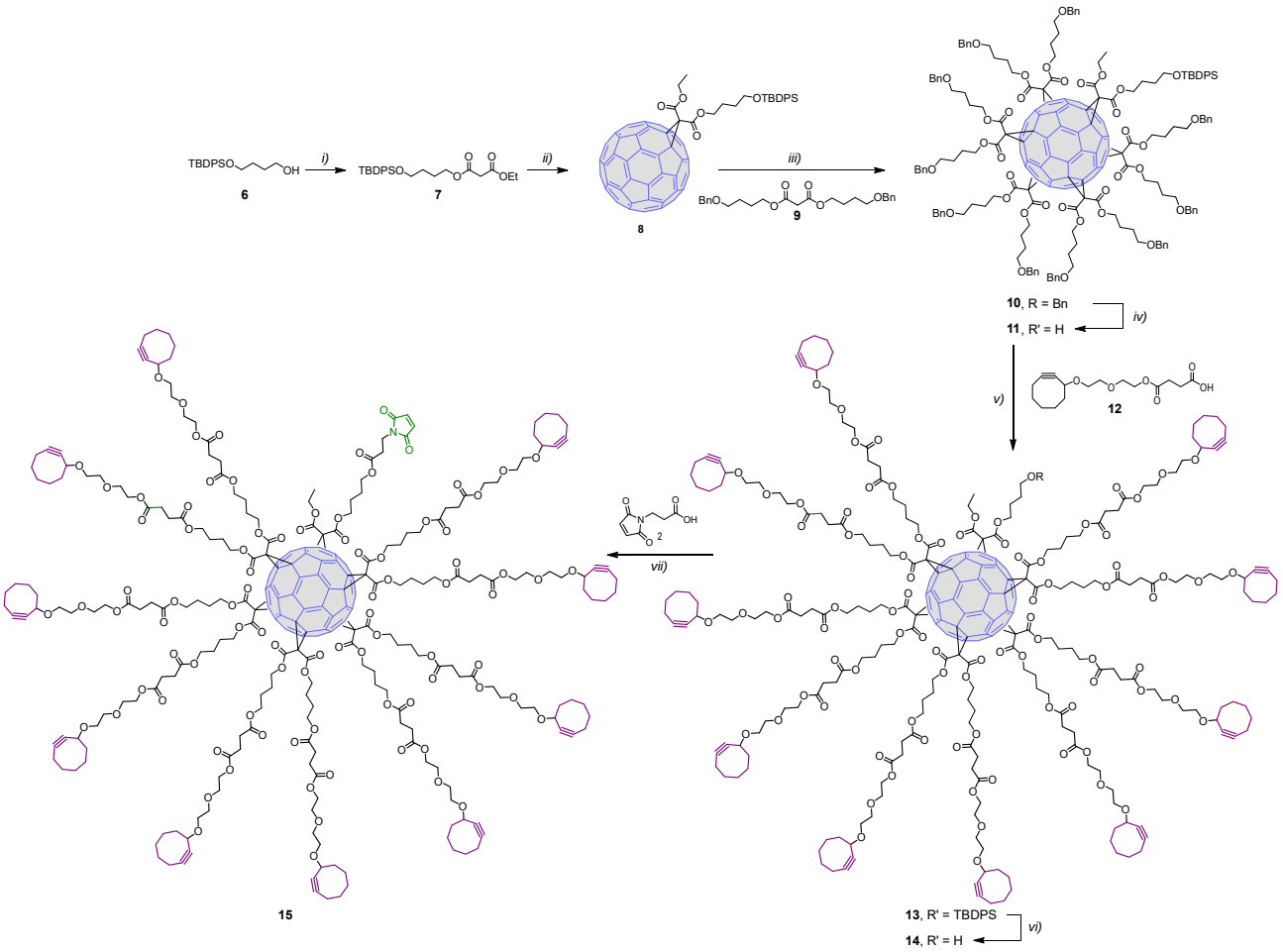


Figure 1. ^{13}C NMR spectra of symmetric hexakis-adducts **3** and **5b** ($CDCl_3$, 125.8 MHz).



Scheme 3. *Reagents and conditions*: *i)* ethyl malonyl chloride, Et_3N, DMAP, DCM, r.t., overnight (quant.); *ii)* C_{60}, DBU, I_2, ODCB, 0 ºC, 4h (69%); *iii)* DBU, CBr_4, ODCB, r.t., 72h (48%); *iv)* H_2, Pd/C, EtOAc/MeOH, r.t., overnight (quant); *v)* DMAP, DCC; DCM/DMF, r.t., overnight (99%); *vi)* HF/py, AcOH, TFH, r.t., overnight (99%); *vii)* DMAP, DCC, DCM, r.t., overnight (quant.).

The signals corresponding to the two carbons of the triazole rings were also duplicated, appearing at δ ~ 145 and 135 for the major isomer and δ ~ 144 and 133 for the minor isomer. Importantly, the signals of the olefinic carbons of the maleimide unit were also present at δ ~ 134, which confirms the exclusive functionalization of the cyclooctyne moieties under these conditions (Figure 2). Treatment of compound **16** with 1-octanethiol in DMF at room temperature, under the same conditions employed for the synthesis of **5a-c**, did not lead to the quantitative conversion to **17a**, as the signal corresponding to the maleimide protons was present in the ^{1}H NMR spectrum. Therefore, temperature and time reaction were increased (24

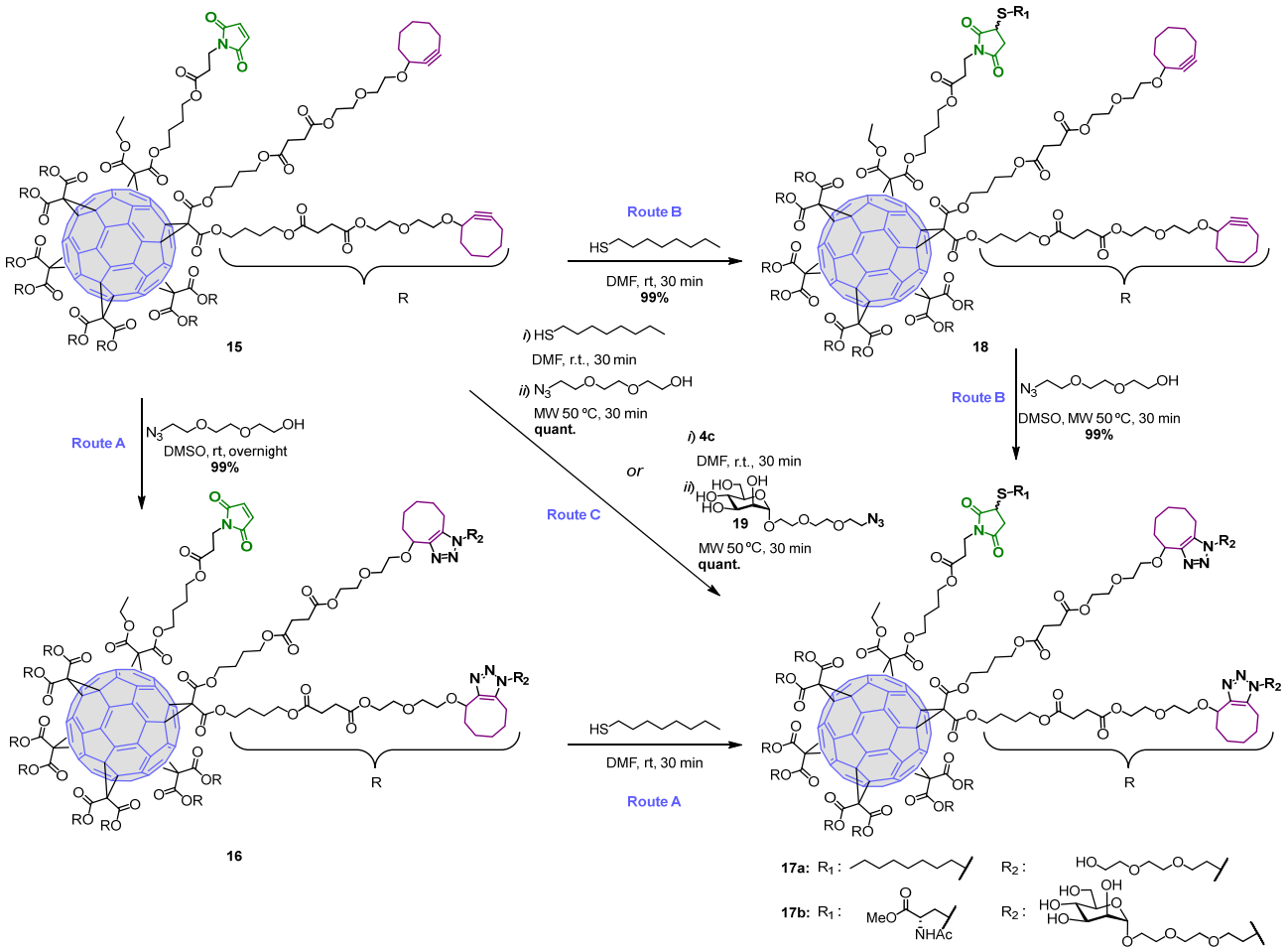
h, 50ºC) and an excess of thiol was added (10 eqs). Even under these conditions, the maleimide unit remained unreacted.

Therefore, we went through route B (Scheme 4). Compound **15** was submitted to the thiol-maleimide coupling reaction, yielding quantitatively compound **18**. The ^{1}H NMR spectrum showed the presence of the signals corresponding to the generated asymmetric centre and the diastereotopic protons of the methylene unit close to the chiral carbon. In addition, the signals of the alkyne carbons of the cyclooctynes were still present at $\delta \sim 100$ and 93, evidencing the chemoselectivity of the reaction (Figure 2). Then, reaction of **18** with 2-(2-(2-azidoethoxy)ethoxy)ethan-1-ol was carried out under microwave irradiation for 30 min and led to compound **17a** in quantitative yield. In this case, the reaction could be run under microwave irradiation as it was not necessary to avoid the side reaction of the azide with the maleimide unit. The ^{13}C NMR spectrum shows the signals of the new triazole rings for the two regioisomers formed, as well as the absence of the signals of the triple bond, thus showing the completion of the SPAAC addition. Consequently, route B allowed the formation of derivative **17a** with excellent yield and complete orthogonality of the two clickable units.

Finally, we explored the one-pot approach to the synthesis of **17a**, employing the same solvent for the two reactions (DMF) and avoiding the purification of the intermediate compound **18**. According to the previous results, it is important to add first the thiol derivative. Hence, we treated a solution of **15** in DMF with 1-octanethiol and, after 30 min, 2-(2-(2-azidoethoxy)ethoxy)ethan-1-ol was added and the mixture was submitted to MW irradiation for 30 min. After size-exclusion chromatography, compound **17a** was obtained in quantitative yield. In conclusion, route C seems to be the more adequate to the preparation of derivatives bearing two different addends around the C_{60} scaffold.

As a proof of concept to check the scope of this methodology with more complex derivatives, we synthesized compound **17b**, in which an amino acid and ten carbohydrate units have been clicked to the fullerene scaffold using the route C. A solution of compound **15** in DMF was treated with the cysteine derivative **4c** and, after 30 min, the azide mannose **19** was added and

the mixture submitted to MW irradiation at 50°C for 30 min. After purification with G-25, compound **17b** was obtained quantitatively. The ^{13}C NMR spectrum of the isolated product revealed the absence of the signals of the alkyne groups or the olefinic carbons of the maleimide, as well as the characteristic signal for the anomeric carbon of the mannose at δ ~ 100 (Figure 2)



Scheme 4. Explored conditions for the sequential or one-pot copper-free click functionalization of asymmetric hexakis-adduct **15**.

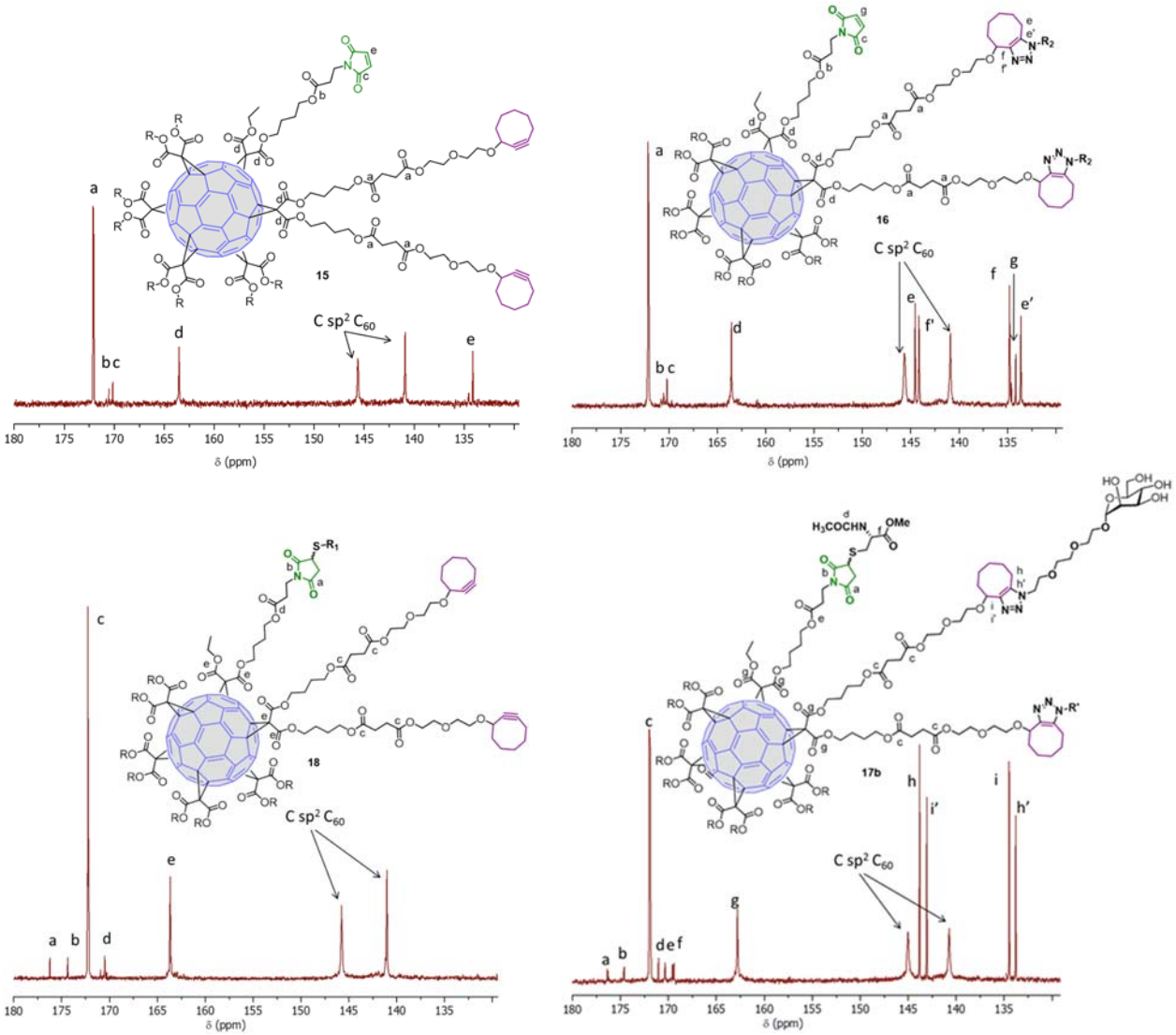


Figure 2. ^{13}C NMR spectra of compounds **15**, **16**, **18** and **17b** (125.8 MHz)

CONCLUSIONS

In conclusion, in this work we have prepared two highly versatile building blocks for the synthesis of new hexakis-adducts of [60]fullerene under copper-free click chemistry conditions. Firstly, we have obtained a symmetric maleimide derivative **3** which results useful for the thiol-maleimide Michael addition. Secondly, we have synthesized an asymmetric hexakis-adduct endowed with two orthogonal clickable moieties. Compound **15** contains a maleimide unit and ten cyclooctyne units that can be independently modified in a stepwise or a one-pot process. Remarkably, the one-pot procedure allows the preparation of the orthogonally clicked adducts in an effective way without the need to purify the intermediate products. The scope of the methodology has been tested with biologically interesting addends,

as carbohydrates and amino acids, allowing to get mixed adducts with these two types of compounds. Moreover, the two processes are carried out in the absence of copper as catalyst, which is a key point for the biocompatibility of the new conjugates. This kind of derivatives could be of interest for several biological applications for which carbohydrates should be added as recognition motifs to address and facilitate the internalization of the appropriate epitope depending on the biological target.

EXPERIMENTAL SECTION

General. Reagents and solvents were purchased as reagent grade and used without further purification. Compounds **1a-b**,[37] 3-maleimidopropionic acid (**2**),[41] 2-[2'-(2''-mercaptoethoxy)ethoxy]ethanol (**4a**),[42] 4-((tert-butyldiphenylsilyl)oxy)butan-1-ol (**7**),[43] bis (4-(benzyloxy)butyl) malonate (**9**),[37] cyclooctyne derivative **12**,[37] 2-[2'-(2''-azidoethoxy)ethoxy]ethanol[44] and compound **19**[45] were prepared according to previously reported procedures. For column chromatography silica gel 60 (230-400 mesh, 0.040-0.063 mm) was purchased from E. Merck or by Sephadex LH20 or G25 (GE Healthcare, Barcelona, Spain) gel filtration. Thin Layer Chromatography (TLC) was performed on aluminium sheets coated with silica gel 60 F_{254} purchased from E. Merck, visualization by UV light. IR spectra (cm^{-1}) were measured on an ATI Mattson Genesis Series FTIR instrument. NMR spectra were recorded on a Bruker AC 400 or AC 500 with solvent peaks as reference. ^{1}H and ^{13}C NMR spectra were obtained for solutions in CD_3OD, $CDCl_3$ and DMSO-d_6. All the assignments were confirmed by one- and two-dimensional NMR experiments (COSY, HSQC and DEPT). Some signals appear duplicated due to the mixture of isomers and are indicated in the list by mj. for major and mi. for minor isomers. MALDI-TOF-mass spectra were carried out on a Bruker BIFLEXTM matrix-assisted laser desorption time-of-flight mass spectrometer using dithranol or 2-[(*E*)-3-(4-*tert*-butylphenyl)-2methylprop-2-enylidene]propanedinitrile (DCTB) as matrix. ESI-mass spectra were recorded with an Esquire 6000 ESI-Ion Trap from Bruker Daltonics using CH_2Cl_2/MeOH as solvent system. Melting points were measured with a Gallenkamp (Sanyo) melting point apparatus. Microwave irradiation experiments

were performed using a Monowave 300 (Anton Pear) apparatus. The temperature in the sealed reaction vessel was monitored by an external surface sensor.

Synthesis and Characterization

Compound 3. To a solution of **1b** (100 mg, 45.48 μmol) and 3-maleimidopropionic acid (**2**) (138 mg, 0.82 mmol) in a mixture dry CH_2Cl_2/DMF (20:1, 4.2 mL) under Ar atmosphere, a solution of DCC (171 mg, 0.82 mmol) in dry CH_2Cl_2 (2 mL) and DMAP (3.5 mg, 27.29 μmol) were sequentially added. The reaction mixture was stirred at room temperature overnight. Once the reaction was completed, the dicyclohexylurea was filtered off in a fritted glass filter and washed with CH_2Cl_2. The crude product was purified by size-exclusion chromatography (Sephadex LH-20, MeOH/CH_2Cl_2 1:1), to give **3** (180 mg, 44.87 μmol, 99%) as a red oil. FTIR: 2958, 1703, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.71 (s, 24H, $H_{maleimide}$), 4.29 (t, 24H, $J_{H,H}$ = 6.3, OC*H*$_2$CH$_2$), 4.08 (t, 24H, $J_{H,H}$ = 6.0, CH$_2$C*H*$_2$OCO), 3.81 (t, 24H, $J_{H,H}$ = 7.0, NC*H*$_2$CH$_2$), 2.64 (t, 24H, $J_{H,H}$ = 7.0, NCH$_2$C*H*$_2$), 1.76 (m, 24H, OCH$_2$C*H*$_2$), 1.69 (m, 24H, C*H*$_2$CH$_2$OCO); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 170.6 (CO_{ester}), 170.3 ($CO_{maleimide}$), 163.6 (CO), 145.7 ($C_{sp2,fullerene}$), 141.0 ($C_{sp2,fullerene}$), 134.2 ($CH_{maleimide}$), 69.0 ($C_{sp3,fullerene}$), 66.4 (O*C*H$_2$CH$_2$), 64.0 (CH$_2$*C*H$_2$OCO), 45.3 (C_q), 33.6 (N*C*H$_2$CH$_2$), 32.8 (NCH$_2$*C*H$_2$), 25.1 (OCH$_2$*C*H$_2$) 25.0 (*C*H$_2$CH$_2$OCO); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{210}H_{168}N_{12}O_{72}Na$ 4034.7; Found 4034.1.

Thiol-maleimide conjugation

General procedure.

To a solution of maleimide [60]fullerene hexakis adduct **3** (80 mg, 19.96 μmol) in DMF (2 mL), compound **4a-c** (1.5 eq. per maleimide group) was added. After 30 min of stirring at room temperature, the solution was purified by size-exclusion chromatography (Sephadex LH-20, CH_2Cl_2/MeOH 1:1), furnishing the compound **5a-c**.

Compound 5a. Following the general procedure and using 1-octanethiol (**4a**) (53 mg, 0.36 mmol) as starting material, compound **5a** (110 mg, 19.09 μmol, 96%) was obtained as a red oil. FTIR:

2927, 2855, 1778, 1702, 1190, 728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.30 (m, 24H, OCH_2CH_2), 4.08 (m, 24H, CH_2CH_2OCO), 3.79 (m, 24H, NCH_2CH_2), 3.72 (m, 12H, CH_{cycle}), 3.14 (m, 12H, CH_{cycle}), 2.85 (m, 12H, SCHH), 2.72 (m, 12H, SCHH), 2.62 (m, 24H, NCH_2CH_2), 2.51 (m, 12H, CH_{cycle}), 1.91-1.53 (m, 72H, SCH_2CH_2, OCH_2CH_2, CH_2CH_2OCO), 1.44-1.19 (m, 120H, $CH_{2,aliphatic\ chain}$), 0.87 (t, 36H, $J_{H,H}$ = 6.7, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 176.3 (CO_{cycle}), 174.5 (CO_{cycle}), 170.5 (CO_{ester}), 163.7 (CO), 145.8 ($C_{sp2,fullerene}$), 141.1 ($C_{sp2,fullerene}$), 69.1 ($C_{sp3,fullerene}$), 66.5 (OCH_2CH_2), 64.2 (CH_2CH_2OCO), 45.4 (C_q), 39.1 (CH_{cycle}), 36.2 ($CH_{2,cycle}$), 34.7 (NCH_2CH_2), 31.9 (NCH_2CH_2), 31.8 (SCH_2, $CH_{2,aliphatic\ chain}$), 29.1 ($CH_{2,aliphatic\ chain}$), 29.0 (SCH_2CH_2), 28.8 ($CH_{2,aliphatic\ chain}$), 25.2 (OCH_2CH_2) 25.1 (CH_2CH_2OCO), 22.6 ($CH_{2,aliphatic\ chain}$), 14.1 (CH_3); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{306}H_{384}N_{12}O_{72}S_{12}Na$ 5790.2; Found 5790.4.

Compound 5b. Following the general procedure and using 2-[2'-(2''-mercaptoethoxy)ethoxy]ethanol (**4b**) (60 mg, 0.36 mmol) as starting material, compound **5b** (118 mg, 19.66 μmol, 98%) was obtained as a red oil. FTIR: 3466, 2927, 1700, 1195, 725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.26 (m, 24H, OCH_2CH_2), 4.04 (m, 24H, CH_2CH_2OCO), 3.94 (m, 12H, CH_{cycle}), 3.80-3.49 (m, 144H, SCH_2CH_2O, NCH_2CH_2, CH_2O, OCH_2CH_2OH, OCH_2CH_2OH), 3.20-3.04 (m, 24H, CH_{cycle}, SCHH), 2.82 (m, 12H, SCHH), 2.65-2.45 (m, 36H, NCH_2CH_2, CH_{cycle}), 1.82-1.55 (m, 48H, OCH_2CH_2, CH_2CH_2OCO); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 176.5 (CO_{cycle}), 174.7 (CO_{cycle}), 170.7 (CO_{ester}), 163.7 (CO), 145.7 ($C_{sp2,fullerene}$), 141.1 ($C_{sp2,fullerene}$), 72.5 (OCH_2CH_2OH), 70.9 (SCH_2CH_2O), 70.3 (CH_2O), 69.1 ($C_{sp3,fullerene}$), 66.5 (OCH_2CH_2), 64.1 (CH_2CH_2OCO), 61.7 (OCH_2CH_2OH), 45.3 (C_q), 39.5 (CH_{cycle}), 36.3 ($CH_{2,cycle}$), 34.7 (NCH_2CH_2), 31.9 (NCH_2CH_2), 31.3 (SCH_2), 25.1 (OCH_2CH_2) 25.0 (CH_2CH_2OCO); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{282}H_{336}N_{12}O_{108}S_{12}Na$ 6029.5; Found 6029.0.

Compound 5c. Following the general procedure and using *N*-acetyl-L-cysteine methyl ester (**4c**) (64 mg, 0.36 mmol) as starting material, compound **5c** (122 mg, 19.89 μmol, quant.) was obtained as a red oil. FTIR: 3368, 2957, 1778, 1701, 1204 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.82 (m, 12H, both isomers, CHNHAc), 4.26 (m, 24H, OCH_2CH_2), 4.04 (m, 24H, CH_2CH_2OCO), 3.88 (m, '12H', both isomers, CH_{cycle}), 3.82-3.61 (m, 60H, NCH_2CH_2, $CH_{3,COOMe}$ + '12H', both isomers, CH_{cycle}), 3.44,

3.36 (2m, 12H, both isomers, SC*H*H), 3.20-3.05 (m, 12H, both isomers, C*H*H_{cycle} + '12H', both isomers, SCH*H*), 2.95 (m, '12H', both isomers, SCH*H*), 2.70-2.50 (m, 24H, NCH_2CH_2 + '12H', both isomers, CH*H*$_{cycle}$), 2.43 (m, '12H', both isomers, CH*H*$_{cycle}$), 2.01 (s, 36H, $CH_{3,NHAc}$), 1.83-1.55 (m, 48H, OCH_2CH_2, CH_2CH_2OCO); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 176.7, 176.4 (CO_{cycle}, both isomers), 174.2, 174.0 (CO_{cycle}, both isomers), 171.1, 171.0 (CO_{NHAc}, both isomers), 170.6 (CO_{ester}), 170.4, 170.3 (CO_{COOMe}, both isomers), 163.7 (CO), 145.7 ($C_{sp2,fullerene}$), 141.1 ($C_{sp2,fullerene}$), 69.1 ($C_{sp3,fullerene}$), 66.5 (OCH_2CH_2), 64.2 (CH_2CH_2OCO), 52.9, 52.8 ($CH_{3,COOMe}$, both isomers), 52.2, 51.4 (*C*HNHAc, both isomers), 45.4 (C_q), 40.2, 38.8 (CH_{cycle}, both isomers), 36.3, 35.7 ($CH_{2,cycle}$, both isomers), 34.9 (NCH_2CH_2), 34.5, 33.9 (SCH_2, both isomers), 31.8 (NCH_2CH_2), 25.1 (OCH_2CH_2) 25.0 (CH_2CH_2OCO), 23.0 ($CH_{3,NHAc}$); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{282}H_{300}N_{24}O_{108}S_{12}Na$ 6159.3; Found 6159.6.

4-((Tert-butyldiphenylsilyl)oxy)butyl ethyl malonate (7). Ethyl malonyl chloride (450 μL, 3.51 mmol) was added dropwise to a solution of 4-((tert-butyldiphenylsilyl)oxy)butan-1-ol (**6**) (1.27 g, 3.87 mmol), Et_3N (539 μL, 3.87 mmol) and DMAP (17 mg, 0.14 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C under Ar atmosphere. After 30 min, the mixture was allowed to slowly warm to room temperature, and stirred for 12 h. Then, the solution was diluted with CH_2Cl_2 and washed with 1M HCl and brine. The organic layer was dried with anh. $MgSO_4$, filtered and concentrated. The resulting crude was purified by silica gel column chromatography (EtOAc/*n*-hexane, 1:10), to give **7** (1.55 g, 3.51 mmol, quant.) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (m, 4H, H-Ar$_{TBDPS}$), 7.40 (m, 6H, H-Ar$_{TBDPS}$), 4.20 (q, 2H, $J_{H,H}$ = 7.1, CH_2CH_3), 4.16 (t, 2H, $J_{H,H}$ = 6.6, OCH_2CH_2), 3.38 (t, 2H, $J_{H,H}$ = 6.1, CH_2CH_2OTBDPS), 3.35 (s, 2H, H$_{malonate}$), 1.76 (m, 2H, CH_2CH_2OTBDPS), 1.61 (m, 2H, OCH_2CH_2), 1.27 (t, 3H, $J_{H,H}$ = 7.1, CH_2CH_3), 1.05 (s, 9H, $C(CH_3)_{3,TBDPS}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7 (CO), 166.6 (CO), 135.6 (C-Ar$_{TBDPS}$), 133.9 (C_{ipso}-Ar$_{TBDPS}$), 129.7 (C-Ar$_{TBDPS}$), 127.7 (C-Ar$_{TBDPS}$), 65.5 (OCH_2CH_2), 63.3 (CH_2CH_2OTBDPS), 61.6 (CH_2CH_3), 41.7 ($CH_{2malonate}$), 28.9 (CH_2CH_2OTBDPS), 26.9 ($C(CH_3)_{3,TBDPS}$), 25.2 (OCH_2CH_2), 19.3 ($C(CH_3)_{3,TBDPS}$), 14.2 (CH_2CH_3); MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{34}O_5SiNa$ 465.2; Found 465.3; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{34}O_5SiNa$ 465.2068; Found 465.2060.

Compound 8. DBU (388 μL, 2.26 mmol) was added to a solution of fullerene C_{60} (1.30 g, 1.80 mmol), malonate **7** (400 mg, 0.90 mmol) and I_2 (803 mg, 3.17 mmol) in dry toluene (300 mL) at 0 °C under Ar atmosphere. The resulting solution was stirred at 0 °C for 4 h. After this time, $Na_2S_2O_3$ sat. aq. soln. (50 mL) was added, and the organic layer was successively washed with 0.5 M HCl, and brine, dried over anh. $MgSO_4$, filtered and concentrated. The resulting crude was purified by silica gel column chromatography (CH_2Cl_2/*n*-hexane, 1:1), furnishing monoadduct **8** (720 mg, 0.62 mmol, 69%) as a brown solid. mp = 100 ºC (desc); FTIR: 3474, 3067, 2929, 2858, 2329, 1744, 1235 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.69 (m, 4H, H-Ar_{TBDPS}), 7.42 (m, 6H, H-Ar_{TBDPS}), 4.55 (q, 2H, $J_{H,H}$ = 7.1, C*H*$_2$CH$_3$), 4.53 (t, 2H, $J_{H,H}$ = 6.7, OC*H*$_2$CH$_2$), 3.75 (t, 2H, $J_{H,H}$ = 6.2, CH$_2$C*H*$_2$OTBDPS), 1.98 (m, 2H, C*H*$_2$CH$_2$OTBDPS), 1.77 (m, 2H, OCH$_2$C*H*$_2$), 1.48 (t, 3H, $J_{H,H}$ = 7.1, CH$_2$C*H*$_3$), 1.08 (s, 9H, C(CH$_3$)$_{3,TBDPS}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 163.7 (CO), 163.6 (CO), 145.5 ($C_{sp2,fullerene}$), 145.4 ($C_{sp2,fullerene}$), 145.3 ($C_{sp2,fullerene}$), 145.2 ($C_{sp2,fullerene}$), 145.1 ($C_{sp2,fullerene}$), 145.0 ($C_{sp2,fullerene}$), 144.9 ($C_{sp2,fullerene}$), 144.8 ($C_{sp2,fullerene}$), 144.7 ($C_{sp2,fullerene}$), 144.6 ($C_{sp2,fullerene}$), 143.9 ($C_{sp2,fullerene}$), 143.3 ($C_{sp2,fullerene}$), 143.2 ($C_{sp2,fullerene}$), 143.1 ($C_{sp2,fullerene}$), 143.0 ($C_{sp2,fullerene}$), 142.3 ($C_{sp2,fullerene}$), 142.0 ($C_{sp2,fullerene}$), 141.9 ($C_{sp2,fullerene}$), 141.0 ($C_{sp2,fullerene}$), 140.9 ($C_{sp2,fullerene}$), 139.2 ($C_{sp2,fullerene}$), 139.0 ($C_{sp2,fullerene}$), 135.6 (C-Ar_{TBDPS}), 133.8 (C_{ipso}-Ar_{TBDPS}), 129.8 (C-Ar_{TBDPS}), 127.8 (C-Ar_{TBDPS}), 71.7 ($C_{sp3,fullerene}$), 67.3 (O*C*H$_2$CH$_2$), 63.5 (*C*H$_2$CH$_3$), 63.3 (CH$_2$*C*H$_2$OTBDPS), 52.3 (C_q), 29.0 (*C*H$_2$CH$_2$OTBDPS), 27.0 (C(*C*H$_3$)$_{3,TBDPS}$), 25.4 (OCH$_2$*C*H$_2$), 19.3 (*C*(CH$_3$)$_{3,TBDPS}$), 14.4 (CH$_2$*C*H$_3$); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{85}H_{32}O_5SiNa$ 1183.2; Found 1183.2.

Compound 10. DBU (902 μL, 6.03 mmol) was added to a solution of monoadduct **8** (350 mg, 0.30 mmol), malonate **9** (1.29 g, 3.02 mmol) and CBr_4 (8.20 g, 24.13 mmol) in dry ODCB (60 mL) under Ar atmosphere. The mixture was stirred for 72 h at room temperature and evaporated. The resulting crude was purified by silica gel column chromatography (toluene/acetone, 30:1 → 15:1), yielding hexakis-adduct **10** (480 mg, 0.15 mmol, 48%) as a red oil. FTIR: 2928, 2858, 1744, 1215 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.66 (m, 4H, H-Ar_{TBDPS}), 7.38 (m, 6H, H-Ar_{TBDPS}), 7.35-7.21

(m, 50H, H-Ar), 4.46 (s, 20H, $CH_{2,Bn}$), 4.36-4.13 (m, 24H, OCH_2CH_2, CH_2CH_3), 3.68 (t, 2H, $J_{H,H}$ = 5.9, $CH_2CH_2OTBDPS$), 3.45 (t, 20H, $J_{H,H}$ = 6.0, CH_2CH_2OBn), 1.77 (m, 22H, OCH_2CH_2), 1.71-1.58 (m, 22H, CH_2CH_2OBn, $CH_2CH_2OTBDPS$), 1.25 (t, 3H, $J_{H,H}$ = 7.1, CH_2CH_3), 1.05 (s, 9H, $C(CH_3)_{3,TBDPS}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 163.6 (CO), 145.7 ($C_{sp2,fullerene}$), 141.0 ($C_{sp2,fullerene}$), 138.4 (C_{ipso}-Ar), 135.4 (C-Ar_{TBDPS}), 133.6 (C_{ipso}-Ar_{TBDPS}), 129.5 (C-Ar_{TBDPS}), 128.2 (C-Ar), 127.6 (C-Ar_{TBDPS}), 127.4 (C-Ar), 127.3 (C-Ar), 72.7 ($CH_{2,Bn}$), 69.3 (CH_2CH_2OBn), 69.0 ($C_{sp3,fullerene}$), 66.6 (OCH_2CH_2), 63.0 (CH_2CH_3), 62.7 ($CH_2CH_2OTBDPS$), 45.4 (C_q), 28.6 ($CH_2CH_2OTBDPS$), 26.8 ($C(CH_3)_{3,TBDPS}$), 25.9 (CH_2CH_2OBn), 25.2 (OCH_2CH_2), 24.9 (OCH_2CH_2), 19.1 ($C(CH_3)_{3,TBDPS}$), 13.9 (CH_2CH_3); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{210}H_{182}O_{35}SiNa$ 3216.8; Found 3316.1.

Compound 11. A solution of **10** (480 mg, 0.15 mmol) in a mixture of EtOAc/MeOH (16 mL, 3:1) was hydrogenated under atmospheric pressure at room temperature overnight using Pd-C (10%) as catalyst. Then, the solution was filtered through Celite, and the catalyst was washed with MeOH. The filtered solution was concentrated, furnishing **11** (350 mg, 0.15 mmol, quant.) as a red solid. mp = 98 ºC (desc.); FTIR: 3347, 2929, 2861, 1737, 1214 cm^{-1}; ^1H NMR (500 MHz, CD_3OD + ε$CDCl_3$) δ: 7.66 (m, 4H, H-Ar_{TBDPS}), 7.41 (m, 6H, H-Ar_{TBDPS}), 4.46-4.18 (m, 24H, OCH_2CH_2, CH_2CH_3), 3.71 (t, 2H, $J_{H,H}$ = 6.0, $CH_2CH_2OTBDPS$), 3.56 (m, 20H, CH_2CH_2OH), 1.78 (m, 22H, OCH_2CH_2), 1.69-1.51 (m, 22H, CH_2CH_2OH, $CH_2CH_2OTBDPS$), 1.29 (t, 3H, $J_{H,H}$ = 7.1, CH_2CH_3), 1.04 (s, 9H, $C(CH_3)_{3,TBDPS}$); ^{13}C-NMR (125.8 MHz, CD_3OD + ε$CDCl_3$) δ: 164.6 (CO), 146.6 ($C_{sp2,fullerene}$), 142.4 ($C_{sp2,fullerene}$), 136.5 (C-Ar_{TBDPS}), 134.7 (C_{ipso}-Ar_{TBDPS}), 130.8 (C-Ar_{TBDPS}), 128.7 (C-Ar_{TBDPS}), 70.4 ($C_{sp3,fullerene}$), 68.1 (OCH_2CH_2), 64.2 ($CH_2CH_2OTBDPS$, CH_2CH_3), 62.2 (CH_2CH_2OH), 47.3 (C_q), 29.8 (CH_2CH_2OH), 29.6 ($CH_2CH_2OTBDPS$), 27.4 ($C(CH_3)_{3,TBDPS}$), 26.1 (OCH_2CH_2), 20.0 ($C(CH_3)_{3,TBDPS}$), 14.6 (CH_2CH_3); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{140}H_{122}O_{35}SiNa$ 2414.7; Found 2414.7.

Compound 13. To a solution of **11** (170 mg, 71.11 μmol), cyclooctyne derivative **12** (333 mg, 1.07 mmol) in a mixture of dry CH_2Cl_2/DMF (3.4 mL, 7.5:1) under Ar atmosphere, a solution of DCC (171 mg, 0.82 mmol) in dry CH_2Cl_2 (2 mL) and DMAP (4.4 mg, 35.55 μmol) were sequentially added. The reaction mixture was stirred at room temperature overnight. Once the reaction was complete, the

dicyclohexylurea was filtered off in a fritted glass filter and washed with CH_2Cl_2. The crude product was purified by size-exclusion chromatography (Sephadex LH-20, MeOH/CH_2Cl_2 1:1), to give **13** (377 mg, 70.70 μmol, quant.) as a red oil. FTIR: 2927, 2857, 1734, 1213 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.64 (m, 4H, H-Ar_{TBDPS}), 7.38 (m, 6H, H-Ar_{TBDPS}), 4.33-4.25 (m, 24H, OC*H*$_2$CH$_2$, C*H*$_2$CH$_3$), 4.25-4.17 (m, 30H, H-1, CH_2O), 4.10 (m, 20H, CH_2CH_2OCO), 3.74-3.65 (m, 32H, C*H*HO, CH_2O, $CH_2CH_2OTBDPS$), 3.63 (m, 20H, CH_2O), 3.48 (m, 10H, CH*H*O), 2.68-2.56 (m, 40H, $CH_{2,succ.}$), 2.23 (m, 10H, H-6a), 2.18-2.06 (m, 20H, H-2a, H-6b), 2.00-1.86 (m, 20H, H-2b, H-5a), 1.85-1.62 (m, 72H, H-3a, H-4a, H-5b, OCH_2CH_2, CH_2CH_2OCO), 1.62-1.53 (m, 12H, H-4b, $CH_2CH_2OTBDPS$), 1.41 (m, 10H, H-3b), 1.26 (t, 3H, $J_{H,H}$ = 7.1, CH_2CH_3), 1.03 (s, 9H, $C(CH_3)_{3,TBDPS}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 171.9 (CO_{succ}), 171.8 (CO_{succ}), 163.3 (CO), 145.5 ($C_{sp2,fullerene}$), 140.8 ($C_{sp2,fullerene}$), 135.2 (C-Ar_{TBDPS}), 133.4 (C_{ipso}-Ar_{TBDPS}), 129.4 (C-Ar_{TBDPS}), 127.4 (C-Ar_{TBDPS}), 99.7 (C-7), 92.5 (C-8), 72.4 (C-1), 70.1 (CH_2O), 68.8 ($C_{sp3,fullerene}$), 68.7 (CH_2O), 68.2 (CH_2O), 66.1 (OCH_2CH_2), 63.6 (CH_2CH_2OCO), 63.5 (CH_2O), 62.9 (CH_2CH_3), 62.7 ($CH_2CH_2OTBDPS$), 45.0 (C_q), 42.0 (C-2), 34.0 (C-5), 29.5 (C-4), 28.8 ($CH_{2,succ.}$, $CH_2CH_2OTBDPS$), 26.6 ($C(CH_3)_{3,TBDPS}$), 26.1 (C-3), 24.8 ($OCH_2CH_2CH_2CH_2OCO$), 20.4 (C-6), 18.9 ($C(CH_3)_{3,TBDPS}$), 13.8 (CH_2CH_3); MS (MALDI-ToF) m/z*:* $[M+Na]^+$ Calcd for $C_{300}H_{342}O_{85}SiNa$ 5358.1; Found 5358.1.

Compound 14. A cold solution of HF-pyridine complex (375 μL), was slowly added to a mixture of compound **13** (375 mg, 70.33 μmol) and AcOH (90 μL) in THF (2 mL). The reaction mixture was stirred at room temperature overnight. The crude product was purified by size-exclusion chromatography (Sephadex LH-20, MeOH/CH_2Cl_2 1:1), to give **14** (355 mg, 69.69 μmol, 99%) as a red oil. FTIR: 2928, 2857, 1735, 1214 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 4.37-4.26 (m, 24H, OC*H*$_2$CH$_2$, C*H*$_2$CH$_3$), 4.26-4.17 (m, 30H, H-1, CH_2O), 4.10 (m, 20H, CH_2CH_2OCO), 3.75-3.66 (m, 30H, C*H*HO, CH_2O), 3.66-3.58 (m, 22H, CH_2O, CH_2CH_2OH), 3.49 (m, 10H, CH*H*O), 2.69-2.57 (m, 40H, $CH_{2,succ.}$), 2.24 (m, 10H, H-6a), 2.19-2.07 (m, 20H, H-2a, H-6b), 2.01-1.87 (m, 20H, H-2b, H-5a), 1.86-1.63 (m, 72H, H-3a, H-4a, H-5b, OCH_2CH_2, CH_2CH_2OCO), 1.63-1.54 (m, 12H, H-4b, CH_2CH_2OH), 1.42 (m, 10H, H-3b), 1.32 (t, 3H, $J_{H,H}$ = 7.1, CH_2CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 172.2 (CO_{succ}), 172.1 (CO_{succ}), 163.6 (CO), 145.7 ($C_{sp2,fullerene}$), 141.0 ($C_{sp2,fullerene}$), 100.0 (C-7), 92.7

(C-8), 72.7 (C-1), 70.3 (CH_2O), 69.0 ($C_{sp3,fullerene}$), 68.9 (CH_2O), 68.4 (CH_2O), 66.4 (OCH_2CH_2), 63.9 (CH_2CH_2OCO), 63.8 (CH_2O, CH_2CH_3), 61.9 (CH_2CH_2OH), 45.3 (C_q), 42.2 (C-2), 34.2 (C-5), 29.7 (C-4), 28.9 ($CH_{2,succ.}$), 26.3 (C-3), 25.1 ($OCH_2CH_2CH_2CH_2OCO$, CH_2CH_2OH), 20.6 (C-6), 14.0 (CH_2CH_3); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{284}H_{324}O_{85}Na$ 5120.6; Found 5120.0.

Compound 15. To a solution of **14** (340 mg, 66.74 μmol) and 3-maleimidopropionic acid (**5**) (22.6 mg, 0.13 mmol) in dry CH_2Cl_2 (3 mL) under Ar atmosphere, a solution of DCC (42 mg, 0.20 mmol) in dry CH_2Cl_2 (1 mL) and DMAP (0.8 mg, 6.67 μmol) were sequentially added. The reaction mixture was stirred at room temperature overnight. Once the reaction was complete the dicyclohexylurea was filtered off in a fritted glass filter and washed with CH_2Cl_2. The crude product was purified by size-exclusion chromatography (Sephadex LH-20, MeOH/CH_2Cl_2 1:1), to give **15** (349 mg, 66.54 μmol, quant.) as a red oil. FTIR: 2928, 2857, 1733, 1212 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.70 (s, 2H, $H_{maleimide}$), 4.37-4.25 (m, 24H, OCH_2CH_2, CH_2CH_3), 4.25-4.17 (m, 30H, H-1, CH_2O), 4.10 (m, 22H, CH_2CH_2OCO), 3.81 (t, 2H, $J_{H,H}$ = 6.9, NCH_2CH_2), 3.74-3.66 (m, 30H, CHHO, CH_2O), 3.63 (m, 20H, CH_2O), 3.49 (m, 10H, CHHO), 2.70-2.55 (m, 42H, $CH_{2,succ.}$, NCH_2CH_2), 2.23 (m, 10H, H-6a), 2.19-2.07 (m, 20H, H-2a, H-6b), 2.00-1.87 (m, 20H, H-2b, H-5a), 1.86-1.63 (m, 74H, H-3a, H-4a, H-5b, OCH_2CH_2, CH_2CH_2OCO), 1.58 (m, 10H, H-4b), 1.42 (m, 10H, H-3b), 1.31 (t, 3H, $J_{H,H}$ = 7.1, CH_2CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 172.1 (CO_{succ}), 172.0 (CO_{succ}), 170.5 (CO_{ester}), 170.2 ($CO_{maleimide}$), 163.5 (CO), 145.6 ($C_{sp2,fullerene}$), 140.9 ($C_{sp2,fullerene}$), 134.2 ($CH_{maleimide}$), 99.9 (C-7), 92.6 (C-8), 72.6 (C-1), 70.2 (CH_2O), 68.9 ($C_{sp3,fullerene}$), 68.8 (CH_2O), 68.3 (CH_2O), 66.3 (OCH_2CH_2), 63.8 (CH_2CH_2OCO), 63.7 (CH_2O, CH_2CH_3), 45.2 (C_q), 42.1 (C-2), 34.2 (C-5), 33.5 (NCH_2CH_2), 32.8 (NCH_2CH_2), 29.6 (C-4), 28.8 ($CH_{2,succ.}$), 26.2 (C-3), 25.0 ($OCH_2CH_2CH_2CH_2OCO$), 20.6 (C-6), 14.0 (CH_2CH_3); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{291}H_{329}NO_{88}Na$ 5271.7; Found 5271.1.

Compound 16. To a solution of hexakis adduct **15** (100 mg, 19.07 μmol) in DMSO (2 mL), 2-(2-(2-azidoethoxy)ethoxy)ethan-1-ol (50 mg, 0.29 mmol) was added. The reaction mixture was stirred at room temperature overnight. The solution was purified by size-exclusion chromatography (Sephadex LH-20, CH_2Cl_2/MeOH 1:1), furnishing compound **16** (132 mg, 18.87 μmol, 99%) as a red oil. FTIR: 3459, 2925, 2862, 1735, 1216 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.64 (s, 2H, $H_{maleimide}$),

4.76 (m, 10H, both isomers, H-1), 4.52 (m, '20H', mi., OCH_2CH_2N), 4.30 (m, '20H', mj., OCH_2CH_2N), 4.27-4.18 (m, 24H, OCH_2CH_2, CH_2CH_3), 4.14 (m, 20H, CH_2O), 4.02 (m, 22H, CH_2CH_2OCO), 3.84 (m, 20H, OCH_2CH_2N), 3.73 (m, 2H, NCH_2CH_2), 3.67-3.38 (m, 140H, OCH_2CH_2OH, OCH_2CH_2OH, CH_2O), 3.01, 2.74, 2.62 (3m, 20H, both isomers, H-6), 2.59-2.48 (m, 42H, $CH_{2,succ.}$, NCH_2CH_2), 2.10 (m, '20H', both isomers, H-2a), 1.93 (m, '20H', mi., H-2b), 1.79-1.37 (m, 84H, OCH_2CH_2, CH_2CH_2OCO, H-3, H-5 + '20H', both isomers, H-4 + '20H', mj., H-2b), 1.23 (m, 3H, CH_2CH_3), 1.16, 0.94 (2m, '20H', both isomers, H-4); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 172.2 (CO_{succ}), 172.1 (CO_{succ}), 170.6 (CO_{ester}), 170.2 ($CO_{maleimide}$), 163.6 (CO), 145.7 ($C_{sp2,fullerene}$), 144.6 (C-7, mj.), 144.2 (C-8, mi.), 140.9 ($C_{sp2,fullerene}$), 134.8 (C-8, mj.), 134.2 ($CH_{maleimide}$), 133.6 (C-7, mi.), 74.5 (C-1, mj.), 72.4 (OCH_2CH_2OH), 71.9 (C-1, mi.), 70.6 (CH_2O), 70.5 (CH_2O), 70.4 (CH_2O), 70.3(CH_2O), 70.2 (CH_2O), 70.0, 69.7 (OCH_2CH_2N, both isomers), 68.9, 68.8 (CH_2O, both isomers, $C_{sp3,fullerene}$), 67.7, 67.4 (CH_2O, both isomers), 66.3 (OCH_2CH_2), 63.8-63.6 (CH_2CH_2OCO, CH_2CH_3 + CH_2O, both isomers), 61.5 (OCH_2CH_2OH), 48.4 (OCH_2CH_2N, mi.), 47.3 (OCH_2CH_2N, mj.), 45.2 (C_q), 35.4 (C-2, mj.), 33.5 (NCH_2CH_2), 32.8 (NCH_2CH_2), 30.8 (C-2, mi.), 28.8 ($CH_{2,succ.}$), 28.7 ($CH_{2,succ.}$), 28.0 (C-5, mi.), 26.9 (C-5, mj.), 25.4 (C-4, mj.), 25.0 ($OCH_2CH_2CH_2CH_2OCO$), 24.4 (C-4, mi.), 24.2 (C-6, mi.), 22.8 (C-3, mi.), 20.7 (C-3, mj.), 19.9 (C-6, mj.), 14.0 (CH_2CH_3); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{351}H_{459}N_{31}O_{118}Na$ 7022.6; Found 7022.8.

Compound 18. To a solution of hexakis adduct **15** (100 mg, 19.07 μmol) in DMF (2 mL), 1-octanethiol (5.8 mg, 38.14 μmol) was added. After 30 min of stirring at room temperature, the solution was purified by size-exclusion chromatography (Sephadex LH-20, CH_2Cl_2/MeOH 1:1), furnishing compound **18** (102 mg, 18.92 μmol, 99%) as a red oil. FTIR: 2926, 2854, 1732, 1210 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.32-4.22 (m, 24H, OCH_2CH_2, CH_2CH_3), 4.22-4.14 (m, 30H, H-1, CH_2O), 4.06 (m, 22H, CH_2CH_2OCO), 3.86-3.72 (m, 3H, NCH_2CH_2, CH_{cycle}), 3.70-3.62 (m, 30H, CHO, CH_2O), 3.60 (m, 20H, CH_2O), 3.45 (m, 10H, CHO), 3.09 (m, 1H, CH_{cycle}), 2.82 (m, 1H, SCH), 2.69 (m, 1H, SCH), 2.64-2.53 (m, 42H, $CH_{2,succ.}$, NCH_2CH_2), 2.46 (m, 1H, CH_{cycle}), 2.20 (m, 10H, H-6a), 2.15-2.03 (m, 20H, H-2a, H-6b), 1.96-1.84 (m, 20H, H-2b, H-5a), 1.82-1.60 (m, 74H, H-3a, H-4a, H-5b, OCH_2CH_2, CH_2CH_2OCO), 1.60-1.50 (m, 12H, H-4b, SCH_2CH_2), 1.38 (m, 10H, H-3b), 1.30-1.17

(m, 13H, $CH_{2,aliphatic\ chain}$, CH_2CH_3), 0.83 (m, 3H, $CH_{3,aliphatic\ chain}$); ^{13}C NMR(125.8 MHz, $CDCl_3$) δ: 176.2 (CO_{cycle}), 174.4 (CO_{cycle}), 172.3 (CO_{succ}), 172.2 (CO_{succ}), 170.5 (CO_{ester}), 163.7 (CO), 145.8($C_{sp2,fullerene}$), 141.0 ($C_{sp2,fullerene}$), 100.1 (C-7), 92.8 (C-8), 72.8 (C-1), 70.4 (CH_2O), 69.1 ($C_{sp3,fullerene}$), 69.0 (CH_2O), 68.5 (CH_2O), 66.4 (OCH_2CH_2), 63.9 (CH_2CH_2OCO), 63.8 (CH_2O, CH_2CH_3), 45.3 (C_q), 42.3 (C-2), 39.0 (CH_{cycle}), 36.1 ($CH_{2,cycle}$), 34.7 (NCH_2CH_2), 34.3 (C-5), 31.9 (NCH_2CH_2), 31.8 (SCH_2), 31.7 ($CH_{2,aliphatic\ chain}$), 29.7 (C-4), 29.6 (SCH_2CH_2), 29.1 ($CH_{2,aliphatic\ chain}$), 29.0 ($CH_{2,succ.}$, $CH_{2,aliphatic\ chain}$), 28.8 ($CH_{2,aliphatic\ chain}$), 26.4 (C-3), 25.1 ($OCH_2CH_2CH_2CH_2OCO$), 22.6 ($CH_{2,aliphatic\ chain}$), 20.7 (C-6), 14.1 (CH_2CH_3, $CH_{3,aliphatic\ chain}$); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{299}H_{347}NO_{88}SNa$ 5417.1; Found 5417.3.

Compound 17a.

*From **18***: Hexakis adduct **18** (100 mg, 18.55 μmol) and 2-(2-(2-azidoethoxy)ethoxy)ethan-1-ol (49 mg, 0.28 mmol) were dissolved in DMSO (1 mL) in a sealed microwave vial. The solution was heated at 50 °C in a microwaves oven for 30 min. The solution was purified by size-exclusion chromatography (Sephadex LH-20, CH_2Cl_2/MeOH 1:1), furnishing compound **17a** (131 mg, 18.34 μmol, 99%) as a red oil.

Consecutive approach: To a solution of hexakis adduct **15** (100 mg, 19.07 μmol) in DMF (1 mL) in a sealed microwave vial, 1-octanethiol (5.8 mg, 38.14 μmol) was added. After 30 min of stirring at room temperature, 2-(2-(2-azidoethoxy)ethoxy)ethan-1-ol (50 mg, 0.29 mmol) was added. The reaction mixture was heated at 50 °C in a microwaves oven for 30 min. The solution was purified by size-exclusion chromatography (Sephadex LH-20, CH_2Cl_2/MeOH 1:1), furnishing compound **17a** (136 mg, 19.04 μmol, quant.) as a red oil. FTIR: 3468, 2925, 2863, 1733, 1218 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 4.77 (m, 10H, both isomers, H-1), 4.54 (m, '20H', mi., OCH_2CH_2N), 4.32 (m, '20H', mj., OCH_2CH_2N), 4.28-4.19 (m, 24H, OCH_2CH_2, CH_2CH_3), 4.15 (m, 20H, CH_2O), 4.04 (m, 22H, CH_2CH_2OCO), 3.85 (m, 20H, OCH_2CH_2N), 3.77-3.70 (m, 3H, NCH_2CH_2, CH_{cycle}), 3.68-3.39 (m, 140H, OCH_2CH_2OH, OCH_2CH_2OH, CH_2O), 3.12-2.95 (m, 1H, CHH_{cycle} + '20H', both isomers, H-6), 2.76, 2.64 (2m, 2H, SCH_2 + '20H', both isomers, H-6), 2.61-2.50 (m, 42H, $CH_{2,succ.}$, NCH_2CH_2), 2.44 (m, 1H, CHH_{cycle}), 2.11 (m, '20H', both isomers, H-2a), 1.94 (m, '20H', mi., H-2b), 1.81-1.40

(m, 86H, OCH_2CH_2, CH_2CH_2OCO, H-3, H-5, SCH_2CH_2 + '20H', both isomers, H-4 + '20H', mj., H-2b), 1.36-1.09 (m, 13H, $CH_{2,aliphatic\ chain}$, CH_2CH_3 + '20H', both isomers, H-4), 0.96 (m, '20H', both isomers, H-4), 0.80 (m, 3H, $CH_{3,aliphatic\ chain}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 176.2 (CO_{cycle}), 174.4 (CO_{cycle}), 172.2 (CO_{succ}), 172.1 (CO_{succ}), 170.5 (CO_{ester}), 163.6 (CO), 145.7 ($C_{sp2,fullerene}$), 144.6 (C-7, mj.), 144.2 (C-8, mi.), 141.0 ($C_{sp2,fullerene}$), 134.8 (C-8, mj.), 133.7 (C-7, mi.), 74.5 (C-1, mj.), 72.4 (OCH_2CH_2OH), 71.9 (C-1, mi.), 70.6 (CH_2O), 70.5 (CH_2O), 70.4 (CH_2O), 70.3 (CH_2O), 70.2 (CH_2O), 70.0, 69.8 (OCH_2CH_2N, both isomers), 69.0, 68.8 (CH_2O, both isomers, $C_{sp3,fullerene}$), 67.7, 67.4 (CH_2O, both isomers), 66.4 (OCH_2CH_2), 63.9, 63.8, 63.7 (CH_2CH_2OCO, CH_2CH_3 + CH_2O, both isomers), 61.5 (OCH_2CH_2OH), 48.4 (OCH_2CH_2N, mi.), 47.4 (OCH_2CH_2N, mj.), 45.2 (C_q), 39.0 (CH_{cycle}), 36.1 ($CH_{2,cycle}$), 35.5 (C-2, mj.), 34.6 (NCH_2CH_2), 33.8 (NCH_2CH_2), 31.8 (SCH_2), 31.7 ($CH_{2,aliphatic\ chain}$), 30.8 (C-2, mi.), 29.6 (SCH_2CH_2), 29.0 ($CH_{2,aliphatic\ chain}$), 28.9, 28.8 ($CH_{2,succ.}$, $CH_{2,aliphatic\ chain}$), 28.7 ($CH_{2,aliphatic\ chain}$), 28.1 (C-5, mi.), 26.9 (C-5, mj.), 25.5 (C-4, mj.), 25.0 ($OCH_2CH_2CH_2CH_2OCO$), 24.4 (C-4, mi.), 24.3 (C-6, mi.), 22.9 (C-3, mi.), 22.6 ($CH_{2,aliphatic\ chain}$), 20.8 (C-3, mj.), 19.9 (C-6, mj.), 14.0 (CH_2CH_3, $CH_{3,aliphatic\ chain}$); MS (MALDI-ToF) m/z: $[M+Na]^+$ Calcd for $C_{359}H_{477}N_{31}O_{118}SNa$ 7169.9; Found 7169.1.

Compound 17b. To a solution of hexakis adduct **15** (100 mg, 19.07 μmol) in DMF (2 mL) in a sealed microwave vial, *N*-acetyl-L-cysteine methyl ester (**4c**) (7.5 mg, 38.14 μmol) was added. After 30 min of stirring at room temperature, compound **19** (97 mg, 0.29 mmol) was added. The reaction mixture was heated at 50 °C in a microwaves oven for 30 min. The solution was purified by size-exclusion chromatography (Sephadex G-25, H_2O/MeOH 9:1), furnishing compound **17b** (136 mg, 19.04 μmol, quant.) as a red oil. FTIR: 3377, 2926, 1731, 1239, 1023 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 4.85 (m, '10H', mi., H-1), 4.72 (m, '10H', mj., H-1), 4.62 (m, 10H, H-1_{man}), 4.60-4.46 (m, 1H, both isomers, CHNHAc + '20H', mi., OCH_2CH_2N), 4.39 (m, '20H', mj., OCH_2CH_2N), 4.35-4.19 (m, 24H, OCH_2CH_2, CH_2CH_3), 4.11 (m, 20H, CH_2O), 4.06-3.93 (m, 23H, both isomers, CH_{cycle}, CH_2CH_2OCO), 3.78 (m, 20H, OCH_2CH_2N), 3.68-3.34 (m, 195H, NCH_2CH_2, $CH_{3,COOMe}$, CH_2O, H-2_{man}, H-3_{man}, H-5_{man}, H-6_{man}), 3.33-3.27 (m, 11H, both isomers, SCHH, H-4_{man}), 3.07-2.87 (m, 2H, both isomers, CHH$_{cycle}$, both isomers, SCHH + '20H', both isomers, H-6), 2.74 (m, '20H', both

isomers, H-6), 2.59-2.51 (m, 42H, $CH_{2,succ.}$, NCH_2CH_2), under DMSO-d_6 (m, 1H, both isomers, CHH_{cycle}), 2.13 (m, '20H', mi., H-2a), 1.99 (m, '20H', mj., H-2a), 1.92 (m, '20H', mi., H-2b), 1.86 (m, 3H, $CH_{3,NHAc}$), 1.78-1.36 (m, 84H, OCH_2CH_2, CH_2CH_2OCO, H-3, H-5 + '20H', both isomers, H-4 + '20H', mj., H-2b), 1.22 (m, 3H, CH_2CH_3), 1.13, 0.98 (2m, '20H', both isomers, H-4); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ: 176.4, 176.3 (CO_{cycle}, both isomers), 174.7, 174.6 (CO_{cycle}, both isomers), 172.0 (CO_{succ}), 171.9 (CO_{succ}), 171.1, 171.0 (CO_{NHAc}, both isomers), 170.4 (CO_{ester}), 169.6, 169.4 (CO_{COOMe}, both isomers), 162.8 (CO), 145.0 ($C_{sp2,fullerene}$), 143.8 (C-7, mj.), 143.1 (C-8, mi.), 140.7 ($C_{sp2,fullerene}$), 134.5 (C-8, mj.), 133.8 (C-7, mi.), 100.0 (C-1_{man}), 73.9 (C-4_{man}, C-1, mj.), 71.0 (C-3_{man}), 70.7 (C-1, mi.), 70.3 (C-2_{man}), 69.9-69.5 (CH_2O), 69.4, 69.3 (OCH_2CH_2N, both isomers), 68.7 ($C_{sp3,fullerene}$), 68.3, 68.2 (CH_2O, both isomers), 67.3, 67.1 (CH_2O, both isomers), 67.0 (C-5_{man}), 66.7 (OCH_2CH_2), 65.7 (CH_2O), 63.5 (CH_2O), 63.4 (CH_2CH_2OCO, CH_2CH_3), 61.3 (C-6_{man}), 52.2, 52.1 ($CH_{3,COOMe}$, both isomers), 52.0, 51.5 (*C*HNHAc, both isomers), 47.9 (OCH_2CH_2N, mi.), 47.0 (OCH_2CH_2N, mj.), 45.6 (C_q), under DMSO-d_6 (CH_{cycle}, both isomers), 35.8, 35.6 ($CH_{2,cycle}$, both isomers), 35.0 (C-2, mj.), 33.5 (NCH_2CH_2), 32.2, 32.1 (SCH_2, both isomers), 31.4 (NCH_2CH_2), 30.3 (C-2, mi.), 28.5 ($CH_{2,succ.}$), 27.9 (C-5, mi.), 26.4 (C-5, mj.), 25.3 (C-4, mj.), 24.6 ($OCH_2CH_2CH_2CH_2OCO$), 23.9 (C-4, mi.), 23.6 (C-6, mi.), 22.3 ($CH_{3,NHAc}$), 22.2 (C-3, mi.), 20.8 (C-3, mj.), 19.5 (C-6, mj.), 13.7 (CH_2CH_3); MS (MALDI-ToF) m/z: $[M]^+$ Calcd for $C_{417}H_{590}N_{32}O_{171}S$ 8819.4; Found: high level of occurring fragmentation avoided the observation of the expected molecular ion peak.

ACKNOWLEDGEMENTS

Financial support from the European Research Council (ERC-320441-Chiralcarbon), the Ministerio de Economía y Competitividad (MINECO) of Spain (projects CTQ2014-52045-R and CTQ2014-52328-P) and Comunidad de Madrid (FOTOCARBON Project S2013/MIT-2841) is acknowledged. JJR thanks CSIC for a JAEdoc contract, and JRS thanks MINECO for a FPI fellowship.

SUPPORTING INFORMATION

Spectroscopic data, 1H, 13C, COSY, HSQC and DEPT NMR; MALDI-TOF and ESI MS spectra. This material is avalaible free of charge via the Internet at http://pubs.acs.org.

REFERENCES

(1) Fasting, C.; Schalley, C. A.; Weber, M.; Seitz, O.; Hecht, S.; Koksch, B.; Dernedde, J.; Graf, C.; Knapp, E. W.; Haag, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 10472.

(2) Kanfar, N.; Bartolami, E.; Zelli, R.; Marra, A.; Winum, J.-Y.; Ulrich, S.; Dumy, P. *Org. Biomol. Chem.* **2015**, *13*, 9894.

(3) Bhatia, S.; Camacho, L. C.; Haag, R. *J. Am. Chem. Soc.* **2016**, *138*, 8654.

(4) Bernardi, A.; Jimenez-Barbero, J.; Casnati, A.; De Castro, C.; Darbre, T.; Fieschi, F.; Finne, J.; Funken, H.; Jaeger, K.-E.; Lahmann, M.; Lindhorst, T. K.; Marradi, M.; Messner, P.; Molinaro, A.; Murphy, P. V.; Nativi, C.; Oscarson, S.; Penades, S.; Peri, F.; Pieters, R. J.; Renaudet, O.; Reymond, J.-L.; Richichi, B.; Rojo, J.; Sansone, F.; Schaffer, C.; Turnbull, W. B.; Velasco-Torrijos, T.; Vidal, S.; Vincent, S.; Wennekes, T.; Zuilhof, H.; Imberty, A. *Chem. Soc. Rev.* **2013**, *42*, 4709.

(5) Lasala, F.; Arce, E.; Otero, J. R.; Rojo, J.; Delgado, R. *Antimicrob. Agents Chemother.* **2003**, *47*, 3970.

(6) Röglin, L.; Lempens, E. H. M.; Meijer, E. W. *Angew. Chem. Int. Ed.* **2011**, *50*, 102.

(7) Arosio, D.; Chiodo, F.; Reina, J. J.; Marelli, M.; Penadés, S.; van Kooyk, Y.; Garcia-Vallejo, J. J.; Bernardi, A. *Bioconjug. Chem.* **2014**, *25*, 2244.

(8) Chabre, Y. M.; Roy, R. *Chem. Soc. Rev.* **2013**, *42*, 4657.

(9) Lin, K.; Kasko, A. M. *ACS Macro Letters* **2014**, *3*, 652.

(10) Jayaraman, N.; Maiti, K.; Naresh, K. *Chem. Soc. Rev.* **2013**, *42*, 4640.

(11) Ragoussi, M.-E.; Casado, S.; Ribeiro-Viana, R.; Torre, G. d. l.; Rojo, J.; Torres, T. *Chemical Science* **2013**, *4*, 4035.

(12) Cheng, C.; Li, S.; Thomas, A.; Kotov, N. A.; Haag, R. *Chem. Rev.* **2017**, *117*, 1826.

(13) Chen, Y.; Star, A.; Vidal, S. *Chem. Soc. Rev.* **2013**, *42*, 4532.

(14) Chen, Y.; Vedala, H.; Kotchey, G. P.; Audfray, A.; Cecioni, S.; Imberty, A.; Vidal, S.; Star, A. *ACS Nano* **2012**, *6*, 760.

(15) Muñoz, A.; Sigwalt, D.; Illescas, B. M.; Luczkowiak, J.; Rodríguez-Pérez, L.; Nierengarten, I.; Holler, M.; Remy, J.-S.; Buffet, K.; Vincent, S. P.; Rojo, J.; Delgado, R.; Nierengarten, J.-F.; Martín, N. *Nat. Chem.* **2016**, *8*, 50.

(16) Nierengarten, I.; Nierengarten, J.-F. *Chem. Asian J.* **2014**, *9*, 1436.

(17) Illescas, B. M.; Rojo, J.; Delgado, R.; Martín, N. *J. Am. Chem. Soc.* **2017**, *139*, 6018.

(18) Hirsch, A.; Vostrowsky, O. *Eur. J. Org. Chem.* **2001**, *2001*, 829.

(19) Ribeiro-Viana, R.; Sánchez-Navarro, M.; Luczkowiak, J.; Koeppe, J. R.; Delgado, R.; Rojo, J.; Davis, B. G. *Nat. Commun.* **2012**, *3*, 1303.

(20) Lamparth, I.; Maichle–Mössmer, C.; Hirsch, A. *Angew. Chem. Int. Ed.* **1995**, *34*, 1607.

(21) Li, H.; Haque, S. A.; Kitaygorodskiy, A.; Meziani, M. J.; Torres-Castillo, M.; Sun, Y.-P. *Org. Lett.* **2006**, *8*, 5641.

(22) Campisciano, V.; La Parola, V.; Liotta, L. F.; Giacalone, F.; Gruttadauria, M. *Chemistry (Weinheim an der Bergstrasse, Germany)* **2015**, *21*, 3327.

(23) Pierrat, P.; Réthoré, C.; Muller, T.; Bräse, S. *Chem. Eur. J.* **2009**, *15*, 11458.

(24) Beuerle, F.; Hirsch, A. *Chem. Eur. J.* **2009**, *15*, 7434.

(25) Constant, C.; Albert, S.; Zivic, N.; Baczko, K.; Fensterbank, H.; Allard, E. *Tetrahedron* **2014**, *70*, 3023.

(26) Fensterbank, H.; Baczko, K.; Constant, C.; Idttalbe, N.; Bourdreux, F.; Vallée, A.; Goncalves, A.-M.; Méallet-Renault, R.; Clavier, G.; Wright, K.; Allard, E. *J. Org. Chem.* **2016**, *81*, 8222.

(27) Nierengarten, J.-F.; Iehl, J.; Oerthel, V.; Holler, M.; Illescas, B. M.; Muñoz, A.; Martín, N.; Rojo, J.; Sánchez-Navarro, M.; Cecioni, S.; Vidal, S.; Buffet, K.; Durka, M.; Vincent, S. P. *Chem. Commun.* **2010**, *46*, 3860.

(28) Iehl, J.; Pereira de Freitas, R.; Delavaux-Nicot, B.; Nierengarten, J.-F. *Chem. Commun.* **2008**, 2450.

(29) Iehl, J.; Nierengarten, J.-F. *Chem. Eur. J.* **2009**, *15*, 7306.

(30) Iehl, J.; Nierengarten, J.-F.; Harriman, A.; Bura, T.; Ziessel, R. *J. Am. Chem. Soc.* **2012**, *134*, 988.

(31) Guerra, S.; Iehl, J.; Holler, M.; Peterca, M.; Wilson, D. A.; Partridge, B. E.; Zhang, S.; Deschenaux, R.; Nierengarten, J.-F.; Percec, V. *Chem. Sci.* **2015**, *6*, 3393.

(32) Compain, P.; Decroocq, C.; Iehl, J.; Holler, M.; Hazelard, D.; Mena-Barragán, T.; Ortiz-Mellet, C.; Nierengarten, J.-F. *Angew. Chem. Int. Ed.* **2010**, *122*, 5889.

(33) Rísquez-Cuadro, R.; García-Fernández, J. M.; Nierengarten, J.-F.; Ortiz-Mellet, C. *Chem. Eur. J.* **2013**, *19*, 16791.

(34) Sánchez-Navarro, M.; Muñoz, A.; Illescas, B. M.; Rojo, J.; Martín, N. *Chem. Eur. J.* **2011**, *17*, 766.

(35) Luczkowiak, J.; Muñoz, A.; Sánchez-Navarro, M.; Ribeiro-Viana, R.; Ginieis, A.; Illescas, B. M.; Martín, N.; Delgado, R.; Rojo, J. *Biomacromolecules* **2013**, *14*, 431.

(36) Ornelas, C.; Broichhagen, J.; Weck, M. *J. Am. Chem. Soc.* **2010**, *132*, 3923.

(37) Ramos-Soriano, J.; Reina, J. J.; Pérez-Sánchez, A.; Illescas, B. M.; Rojo, J.; Martín, N. *Chem. Commun.* **2016**, *52*, 10544.

(38) Iehl, J.; Nierengarten, J. F. *Chem.Commun.* **2010**, *46*, 4160.

(39) Sigwalt, D.; Caballero, R.; Holler, M.; Strub, J.-M.; Van Dorsselaer, A.; Nierengarten, J.-F. *Eur. J. Org. Chem.* **2016**, *2016*, 2882.

(40) Herzog, A.; Hirsch, A.; Vostrowsky, O. *Eur. J. Org. Chem.* **2000**, *2000*, 171.

(41) Song, H. Y.; Ngai, M. H.; Song, Z. Y.; MacAry, P. A.; Hobley, J.; Lear, M. J. *Org. Biomol. Chem.* **2009**, *7*, 3400.

(42) Dechtrirat, D.; Gajovic-Eichelmann, N.; Wojcik, F.; Hartmann, L.; Bier, F. F.; Scheller, F. W. *Biosens.Bioelectron.* **2014**, *58*, 1.

(43) Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 6187.

(44) Li, J.; Zacharek, S.; Chen, X.; Wang, J.; Zhang, W.; Janczuk, A.; Wang, P. G. *Bioorg. Med. Chem.* **1999**, *7*, 1549.

(45) Kong, N.; Shimpi, M. R.; Park, J. H.; Ramström, O.; Yan, M. *Carbohydr. Res.* **2015**, *405*, 33.