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Synthesis of Unsymmetrical Thioethers Using an Uncommon Base-Triggered 1,5-Thiol Transfer Reaction of 1-Bromo-2-alkylthiolcarbonates

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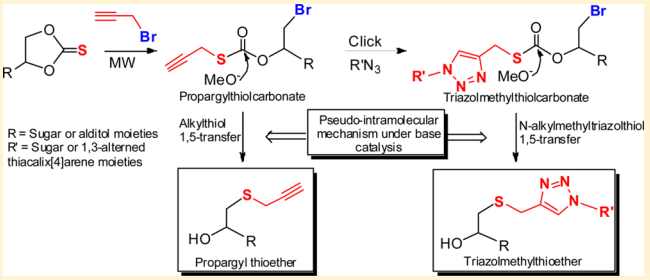
Supporting Information

ABSTRACT: Described herein is a convenient, odorless, metal-free, one-pot strategy for the synthesis of unsymmetrical thioethers. The key step in this new strategy is a base-catalyzed 1,5-thiol transfer reaction via a pseudointramolecular mechanism of a 1-bromo-2-alkylthiolcarbonate, which is itself obtained through a straightforward microwave-assisted thioalkylation of a 1,2-cyclic-thionocarbonate precursor with an appropriate alkyl bromide. The starting 1,2-cyclic-thionocarbonates are easily obtained from the corresponding diols. When a propargylthiolcarbonate constitutes the key alkylthiolcarbonate 1,5-shift precursor, a copper-mediated dipolar cycloaddition reaction ("click") with azide partners is rendered possible. This increases the versatility of the approach, as a very large variety of complex triazole-tethered substrates can potentially be integrated into the target unsymmetrical thioether final products. As an example of the scope of the reaction, four 1,5-shift reactions have been triggered simultaneously from a sugar-derived tetrathiolcarbonate precursor using base catalysis, to allow four 6-thioglucose moieties to be installed (78% yield for each sugar unit) onto a 1,3-alternate thiacalix[4]arene scaffold in a one-pot transformation.



INTRODUCTION

Organosulfur chemistry has a rich and illustrious history and an established place in biology, chemistry, and materials science.[1] Nevertheless, the synthesis of carbon−sulfur bonds is far less straightforward than either their carbon−oxygen or carbon−nitrogen counterparts. This difference might be attributed in part to the repugnant odor invariably associated with thiols, common precursors in classical routes to thioethers, that has possibly deterred their extensive study. Consequently, over the past years a number of thiol-free syntheses of thioethers have been proposed. For instance, reagents such as native sulfur S(0), $Na_2S_2O_3$, thiourea, or trialkylsilyl-protected thiols have been efficiently reacted with alkyl and/or aryl halides, with or without metal catalysis, to obtain the target unsymetrical alkyl or arylthioether derivatives.[2]

In a project related to the investigation of bacterial adhesion events we required a convenient synthesis of a number of sugar-derived unsymmetrical thioethers and in particularly of sugar-functionalized thiacalix[4]erene such as the tetravalent glucose analogue described herein (Figure 1). Although several disconnections evoking various sulfur sources might be proposed to access such a tetravalent construct, we were particular drawn to developing a method exploiting as a key step the thiolcarbonate (RSC(O)OR) function.[3] This particular functional motif has rarely been identified in natural compounds,[4] but its presence in certain antimalarial compounds appears to lead to an enhancement in these analogues of the antiplasmodium effect.[5] The thiolcarbonate function has had wider use as an intermediate in organic chemistry where it has been encountered as an aglycone in glycosyl donors[6] or

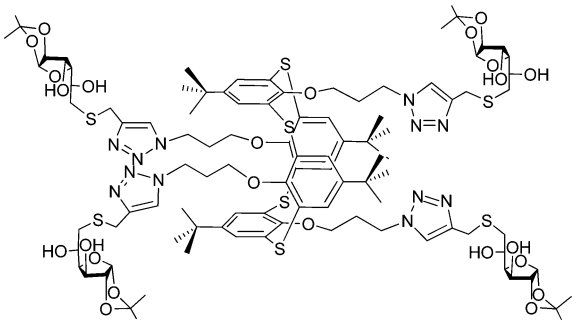


Figure 1. Targeted 1,3-alternate thiacalix[4]arene glucoconjugate.

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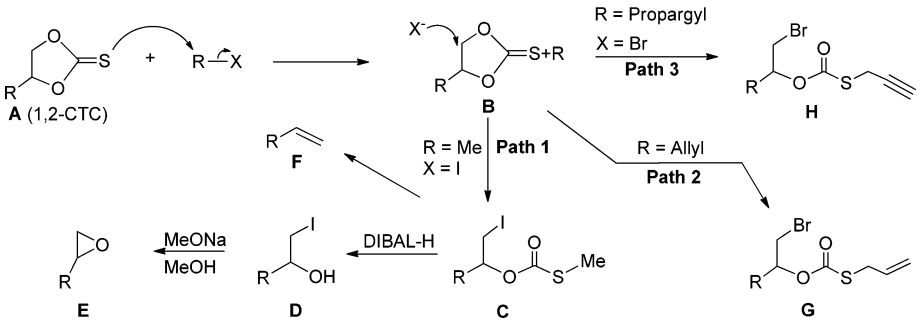
Scheme 1. Haloalkylation of 1,2-CTC Function A to Halothiolcarbonates C, G, and H

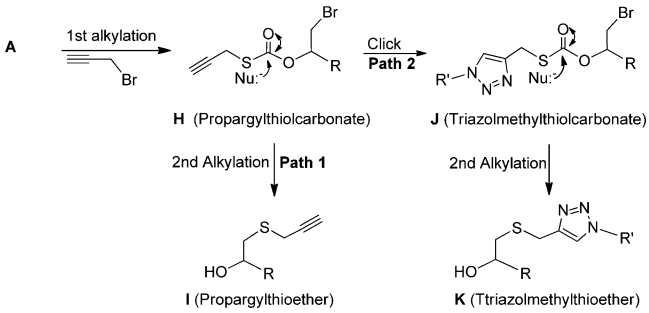


used in intramolecular S-glycosylations assisted by palladium catalysis,[7] as a spacer group fragment,[8] and in a route to carbamates.[9] It potential as an odorless sulfur source (thiol or thiolate ion) is arguably the most attractive feature of thiolcarbonates, and its inter- and intramolecular reactions with various electrophiles have indeed been explored in the synthesis of thioethers.[6,10−12] For example, Rich et al. have shown that the reaction of cysteine-*S*-Fmoc with a tertiary amine as base gives the corresponding fluorenylthioether derivative in good yield albeit as a side unwanted product.[11] The mechanism of this side-reaction was proposed to be due to *β*-elimination of fluorenylene with concomitant release of the cysteine thiolate and with subsequent in situ coupling of these two moieties to give the corresponding thioether. A sister mechanism was proposed by Zard et al. for the synthesis of various trifluoromethylthioethers from the corresponding trifluoromethylthiolcarbonate analogues.[12]

The thiolcarbonates at the core of the present investigation are generated through the reaction of corresponding 1,2-cyclic thionocarbonate (1,2-CTC) **A** with an appropriate alkyl halide (Scheme 1). For example, treatment of **A** with methyl iodide results in deoxyiodination of the primary alcohol substituent with concomitant installation of a thiolcarbonate unit at the adjacent secondary alcohol moiety to give **C** via sulfonium intermediate **B**.[13] Subsequent removal of the thiolcarbonate unit in **C** gave the iodohydrin **D**. The deoxyiodo alcohol analogue **D** allowed access to the target epoxide **E**.[14] The formation of alkene **F** through elimination in **C** has also been reported.[15] We have reported that the use of alkyl halides other than methyl iodide including, for example, allyl or propargyl bromide in this type of transformation gives successfully the corresponding sugar-derived allylthiolcarbonate **G** (path 2) and propargylthiolcarbonate **H** (path 3), respectively.[16]

It occurred to us that the synthetic potential of such thiolcarbonate analogues would be greatly increased if appropriate reaction conditions could be developed for their transformation into the corresponding propargylthioether analogues through an intra- or intermolecular 1,5-thiol transfer reaction. Reported strategies to unsymmetrical propargylthioethers of carbohydrates remain rather scarce and usually require the prior preparation, by a classical route, of the required thiosugar precursor followed subsequently by its reaction with propargyl bromide.[17] We describe the successful application of a 1,5-thiol transfer strategy to obtain unsymmetrical propargylthioether analogues such as **I** (Scheme 2, path 1). We also describe the reaction of propargylthiolcarbonates with azido analogues to give the corresponding triazolethiolcarbonate derivatives **J** (path 2), which can also be made to undergo the 1,5-thiol displacement to obtain the

Scheme 2. Thiol 1,5-Shift of l-Bromo-2-alkylthiolcarbonate



corresponding triazolethioether **K**, further enlarging the versatility of thiolcarbonates as useful intermediates in organic synthesis and also the scope of the newly described strategy for the synthesis of unsymmetrical thioethers.

RESULTS AND DISCUSSION

The feasibility of the proposed intramolecular 1,5-thiol transfer methodology was initially tested, employing the known D-glucose propargylthiolcarbonate **3**[18] as substrate (Scheme 3a). This thiolcarbonate smoothly underwent the expected propargylthiol transfer under MeONa catalysis, to give the expected glucopropargylthioether **4** in an isolated yield of 77% after purification by silica gel chromatography. The structure of the newly formed thioether **4** is fully supported by its spectral data. Of particular significance is the absence of signals at 169.5 and 169.0 ppm corresponding to carbonyl moieties of thiolcarbonate and acetate units, respectively, in the ^{13}C NMR spectrum of thioether **4**. Thioether formation was further evidenced from the expected upfield shift of signals corresponding to the H-6 methylene protons in the ^{1}H NMR spectrum of product **4** (3.09 and 2.82 ppm, SCH_2) compared with those in the spectrum of the starting sugar **3** (3.79 and 3.64 ppm, $BrCH_2$).

Mechanistically two routes might be plausibly evoked to rationalize the observed transformation: concerted or the stepwise (Scheme 3b). Insights into these routes were indirectly garnered using the data of electrospray mass spectroscopy (ESI-MS). Monitoring of the reaction by ESI-MS indicated the rapid initial formation of a signal at $m/z = 71$ ($[M - 1]^-$) suggesting the intermediacy of the propargylthiolate species. There was no trace of signal suggesting the formation of compound **7** expected from deprotection of OH-3 and OH-5 in path 2. However, detection of the ion at $m/z = 225$ ($[M + Na]^+$) suggests the possible intermediacy of the 3,6- or 5,6-anhydro derivatives **8** and **9**, respectively. The rapid disappearance of the signal at $m/z = 225$ ($[M + Na]^+$) followed

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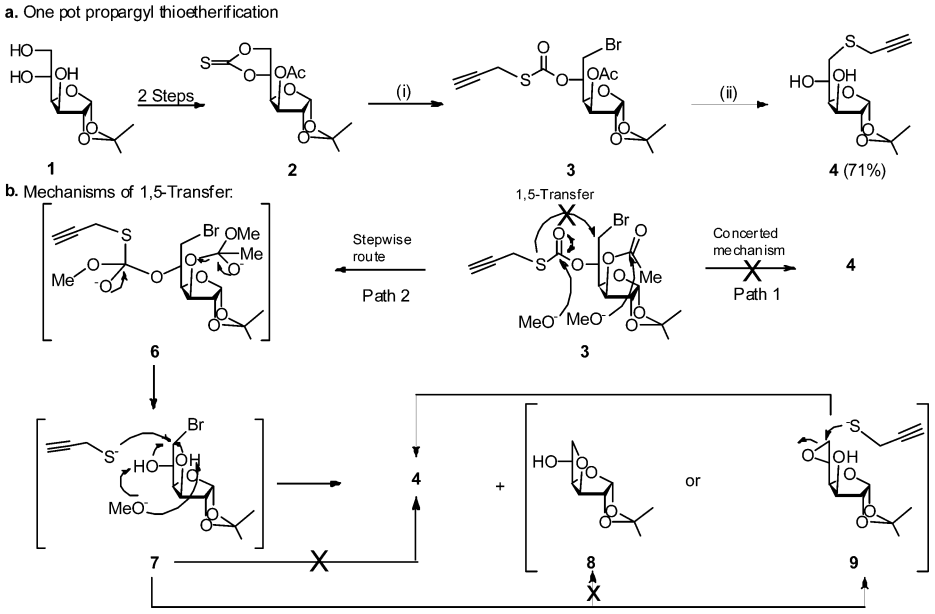
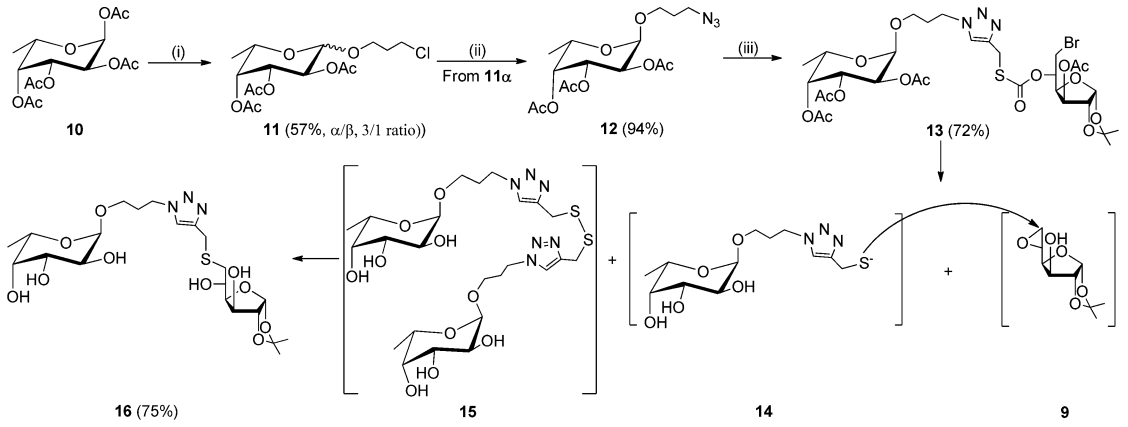
Scheme 3. Synthesis of Compound 4 and Involved Mechanism



Scheme 4. Synthesis of Thiolcarbonate 13 and Its Corresponding Thioether 16



by the appearance of another corresponding to the propargylthioether derivative **4** (m/z = 297) ($[M + Na]^+$), however, correlates with the presence of oxirane **9**, expected to be only fleetingly formed under the reaction conditions.

The stage was set to investigate if this same intramolecular 1,5-thiol transfer reaction might be effective also from a triazole rather than a propargylthiolcarbonate substrate. The required triazole could in principle be obtained from the corresponding propargylthiolcarbonate via its copper-catalyzed Huisgen–Meldal–Sharpless cycloaddition (CuAAC)[19] reaction with any selected azido compound ("click" reaction). The O-glycosylated azido-α-L-*fuco* derivative **12** obtained in two steps from the peracetylated α-L-fucose **10** (Scheme 4) was chosen as azide partner. The choice motivated by the possibility to furnish a fucosyl mimetic using the intramolecular 1,5-thiol transfer strategy: the frequency of L-fucosyl linkages in glycoconjugates and the key role of fucosyl epitopes in numerous biological functions, including the recognition by host glycans by LecB from *Pseudomonas aeruginosa* Gram (−) bacteria,[20] has seen the proposition of a multitude of fucosyl glycan mimetics as potential therapeutic leads. The click reaction between thiolcarbonate **3** and the fucoside **12** was conducted in a mixture of tBuOH/H_2O/THF with a catalytic amount of $CuSO_4$ and L-ascorbic acid sodium salt at 60 °C. Despite the need to heat the reaction mixture under basic conditions, to facilitate the desired 1,3-dipolar cycloaddition, the thiolcarbonate unit proved resistant to cleavage and the expected pseudodisaccharide **13** was formed in an acceptable yield (72%). The structure of compound **13** was supported by its spectral data. Of particular significance were the signals at 7.54 and 122.6 in their ^1H and ^{13}C NMR spectra, respectively, characteristic of the 1,4-disubstituted 1,2,3-triazole ring.[21]

The thiolcarbonate **13** when subjected to our base-catalyzed 1,5-thiol transfer methodology gave smoothly the desired triazolethioether **16** in 75% yield after column chromatography on silica gel. Again ESI-MS of the reaction with time allowed its evolution to be monitored. Formation of the postulated thiolate ion **14** and the epoxide **9** intermediates were evidenced from signals appearing at m/z = 318 ($[M - 1]^-$) and m/z = 201 ($[M - 1]^-$), respectively. These latter peaks subsequently disappear with the gradual appearance of a signal at m/z = 544 ($[M + Na^+]$) corresponding to the triazolethioether pseudodisaccharide **16**. Note that the presence of a signal at m/z = 559 ($[M + Na]^+$) corresponding to the disulfide species **15** most likely emanates from autoxidation of thiolate ion **14.** Assignment of the structure of product **16** was possible from its NMR

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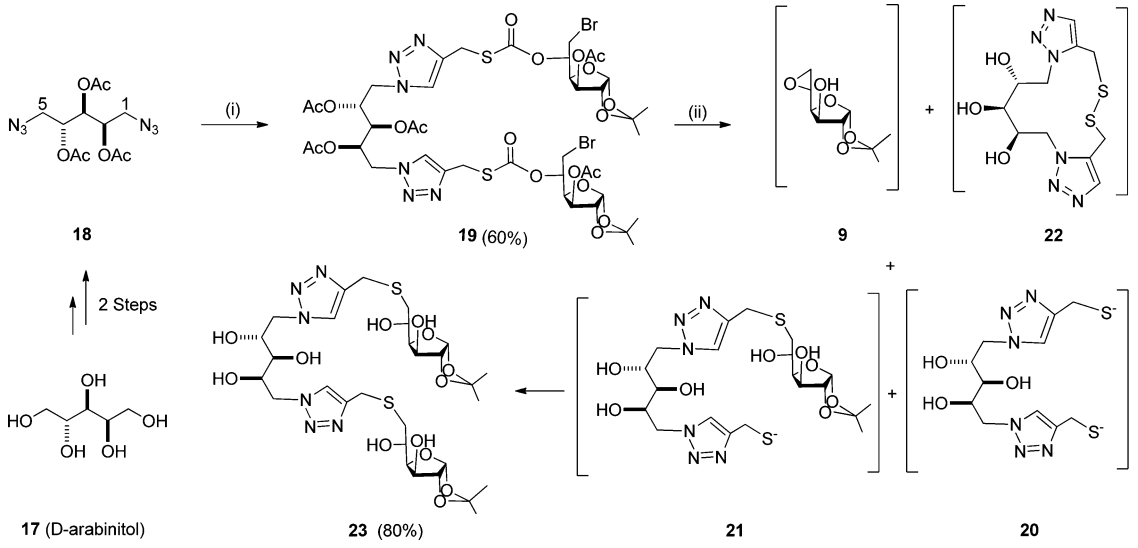
Scheme 5. Synthesis of Bis-thiolcarbonate 19 and Its Corresponding Bis-thioether 23



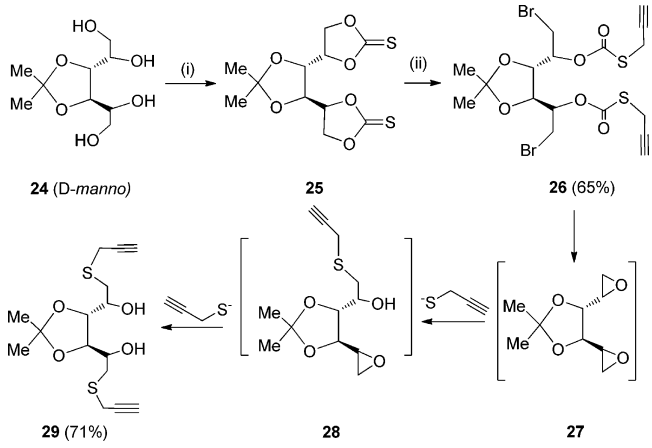
spectroscopic data. Of particular significance are the signals at 112.7 ppm in its ^{13}C NMR spectrum assigned to quaternary carbon of the isopropylidene function and the signal at 16.6 ppm corresponding to the C-6 carbon atom of the L-fucosyl moiety.

In both the latter examples of the intramolecular 1,5-transfer reaction, a monothiolate intermediate was seen to be generated and to react spontaneously with the electrophilic primary atom (C-6) of the substrate to give the corresponding thioether analogues. To further extend the scope of this transformation, the feasibility of performing two simultaneous 1,5-transfer reactions from an appropriate bis-thiolcarbonate precursor, with a view to generate the corresponding bis-thioether product, was examined. The desired precursor was obtained by "clicking" together analogue **3** and the bis-azido derivative **18**,[22] an easily available acyclic polyhydroxylated system featuring the D-*arabino* configuration (Scheme 5). This click reaction took place smoothly under the previously developed conditions to give the target pseudotrisaccharide **19** in 60% yield. Application of the base-catalyzed 1,5-transfer reaction protocol to the precursor **19** led to its smooth transformation into the expected triazoledithioether derivative **23** in an isolated yield of 80%. As expected, the ^{13}C NMR spectra of both pseudotrisaccharides **19** and **23** are characterized by two sets of signals corresponding to their respective C-1/C-5 alditol-derived carbon atoms (50.4 and 49.9 ppm for **19**, and 54.9 and 54.7 ppm for **23**).

The ESI-MS data supports that the dithiolate **20** is the first intermediate formed (m/z = 345 $[M - 1]^-$). However, its presence in the medium is brief, as it is quickly transformed into the corresponding pseudodisaccharide thiolate intermediate **21**, evidenced by the rapid appearance of ions at m/z = 547 ($[M - 1]^-$) and 571 ($[M + Na]^+$). A second S-alkylation of intermediate **21** by its reaction with **9** then takes place to give the bis-thioether **23**. A trace of an ion corresponding to the oxidized compound **22** is also present in the spectrum (m/z = 367 $[M + Na]^+$). However, this latter compound was not isolated.

Thus far it has been demonstrated that either a propargylthiol analogue or propargylthiol-clicked triazole derivative may serve as substrates in the base-catalyzed 1,5-thiol transfer reaction and in each case gave their expected thioether products in good to excellent yield. To test the scope of this methodology further we thought to apply it to alternative substrates featuring two propargylthiolcarbonate units such as the D-*manno* analogue **26** (Scheme 6).

Scheme 6. Synthesis of Bispropargylthiolcarbonate 26 and Its Corresponding Bispropargylthioether 29



The required precursor was obtained from the commercially available 3,4-*O*-isopropylidene-D-mannitol **24** in two straightforward chemical steps. Thus, transformation of the mannitol analogue into the corresponding 1,2:5,6-bis-cyclicthionocarbonate derivative **25** proceeded as described[23] and, when subsequently reacted with propargyl bromide under microwave irradiation, gave the target bis-propargylthiolcarbonate **26** in 65% yield. The latter compound gives spectral data consistent with its proposed structure. Of particular significance is the absence of any resonance in its ^{13}C NMR spectrum corresponding to a carbonyl function expected for a thiolcarbonyl group (appearing at 192 ppm in the starting precursor) and instead the presence of a peak at 169 ppm characteristic of a carbonyl carbon in a thiocarbonate moiety.

The thus-obtained bis-propargylthiolcarbonate precursor **26** was then subjected to the 1,5-thiol transfer reaction, triggered as before by catalytic base. The double 1,5-thiol transfer proceeded cleanly to give, after purification on silica gel, the

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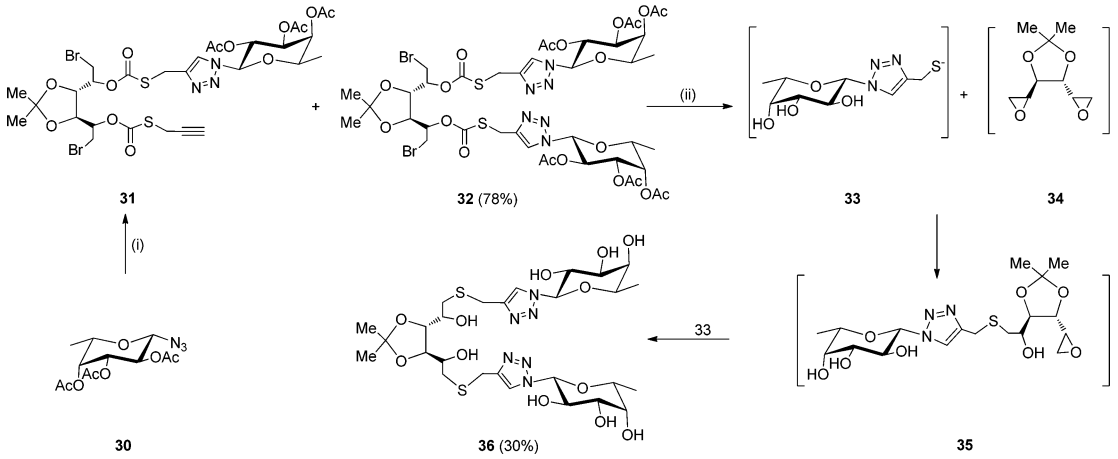
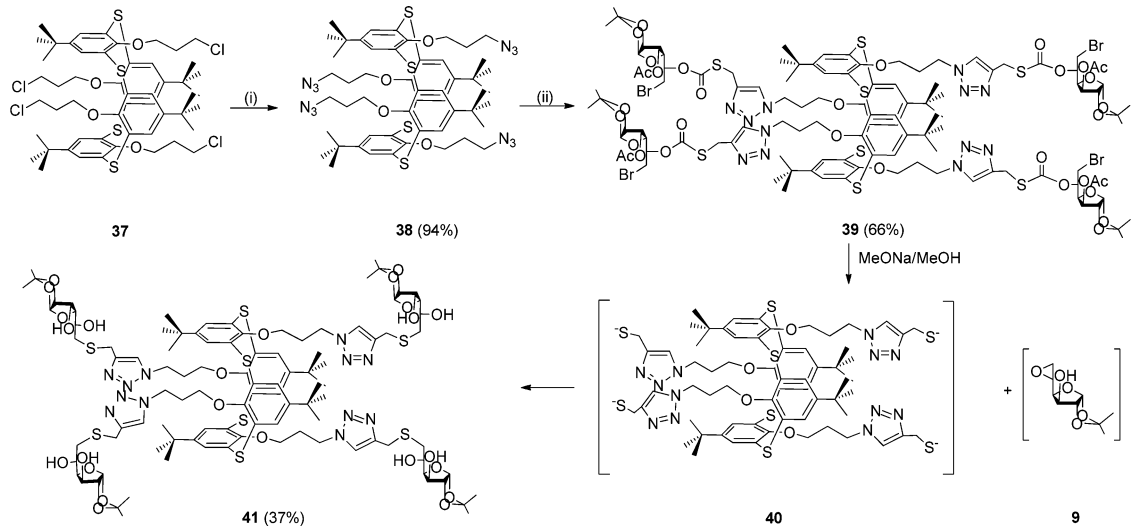
Scheme 7. Synthesis of Bis-fucothiolcarbonate 32 and Its Corresponding Bis-fucothioether 36



Scheme 8. Synthesis of Glucoconjugate 1,3-Alternate Thiacalix[4]arene Tetrathiolcarbonate 39 and Its Corresponding Tetrathioether 41



expected bis-propargylthioether **29** in a yield of 71%. Monitoring of the reaction by ESI-MS revealed the presence of an intense ion at m/z = 281 in addition to two others of lower intensity at m/z = 209 and m/z = 353. The data supports that the bis-epoxide **27** (m/z = 281 ($[M + Na]^+$)) is the first intermediate formed which rapidly transforms into the monoepoxide **28** (m/z = 281$[M + Na]^+$) presumably via nucleophilic attack by the in situ-generated propargylthiolate ion. Subsequently, attack by a second thiolate ion leads to the expected thioether product **29** (m/z = 353 ($[M + Na]^+$)).

As a further example of its scope, we examined exploitation of the reaction to obtain the bis-*β*-L-*fuco*-triazolethioether **36** (Scheme 7). The desired precursor required that the bis-propargylthiol **26** be clicked with two moieties of the easily available 1-azido-*β*-L-fucose analogue **30**.[24] This transformation proceeded under the usual click conditions to give the bis-fucosyltriazolethiol **32** as the major component in 78% yield after isolation by chromatography on silica gel. Monitoring of the reaction by ESI-MS indicated the formation of the monofucosyltriazolethiolcarbonate **31** (m/z = 882 ($[M + Na]^+$) and m/z = 1740 ($[2\times M + Na]^+$), respectively), which disappeared with time to give only the pseudotrisaccharide **32** (m/z = 1197 ($[M + Na]^+$)).

The tandem bis-1,5-thiol transfer reaction of precursor **32** proceeded under base catalysis to give the expected bis-*β*-L-*fuco*-triazolethioether **36** in 30% yield. Both the adducts **32** and **36** were fully characterized by NMR spectroscopy. Data consistent with the formation of **36** include the absence of the four signals at 172.1, 171.6, 171.3, and 170.6 ppm assigned to the carbonyl carbon atoms in the ^{13}C NMR spectrum of **32**. Furthermore, due to the C_2-symmetry axis of adduct **36**, only one signal at 36.7 ppm is present in its ^{13}C NMR spectrum, which corresponds to the thioetherified C-1/C-6 carbon of the D-mannitol unit, and a single signal at 16.8 ppm assigned to the C-6 carbons atoms of its pair of L-fucosyl units. The bis-1,5-transfer reaction is thus less efficient with bis-triazolethiolcarbonates substrates than with the alternative bis-propargylthiolcarbonate substrates, at least with these substrates, possibly due to differences in steric constraints between them.

We were now ready to apply the newly developed 1,5-thiol transfer reaction to the synthesis of the sugar functionalized thiacalix[4]rene at the origin of the present work. This would require that an appropriate tetrathiolcarbonate undergo four 1,5-transfer reactions simultaneously to install the four sugar thioether functions required on the central thiacalix[4]rene core (Scheme 8).

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Thiacalix[4]arenes are a subclass of "third generation" calixarenes and exhibit a number of interesting features compared to the oxygenated counterparts, such as enlarged ring size and differing metal complexation potential, due to the presence of its bridging sulfur atoms. In addition the scaffold offers the possibility for functionalization not only at its upper and lower rims but also at its bridging thiosulfide groups. Modified thiacalixarenes have been used for many applications such as the detection and separation of biologically important cations, anions, and bioanalytes. They aslo allow the mimicking of logic gates and devices and the construction of self-assembled coordination cages, multinuclear complexes, magnetic materials, and luminescent materials.[25] We were particularly interested in synthesizing sugar-functionalized thiacalixarenes such as the tetravalent glucose analogue **41** in a project related to designing chemical tools to modulate bacterial adhesion events. The key intermediate is the 1,3-alternate tetrachlorothiacalix[4]arene **37** obtained as described in the literature.[26] Its transformation into the tetraazido derivative **38** was achieved by reaction with NaN_3 in DMF at 80 °C. The tetraazido analogue was thereupon reacted with the propargylthiolcarbonate analogue **3** to give after purification on silica gel the target tetraglucothiolcarbonate thiacalix[4]arene **39** in 66% yield. The structure of the precursor was supported by its NMR spectral data. The symmetry of the thiacalix[4]-arene scaffold renders the analysis relatively straightforward. In particular the ^{13}C NMR spectrum of **39** shows a signal at 32.7 ppm assigned to the C-6 carbon of its D-glucosyl unit and another at 26.1 ppm assigned to the bridged methylene carbon linked to both the C-4 carbon atom of its triazole ring and the sulfur atom of its thiolcarbonate function. The four methyl carbons of the acetyl groups in **39** give a single resonance (20.7 ppm) in its ^{13}C NMR spectrum. Similarly, all four methyl functions of the tBu groups in **39** gave a single peak (31.1 ppm).

Pleasingly, this substrate also undergoes the key 1,5-thiol transfer reaction to give the target tetrathioether thiacalix[4]-arene **41** in a yield of 37% after chromatography on silica gel. Characterization of the sugar-conjugated thiacalixerene product was possible from its NMR spectral data. For example, in its ^{13}C NMR spectrum, the signals corresponding to the sugar ring units all appear at between 106.2 and 69.7 ppm. The signals corresponding to the CH_2OAr carbon atoms is assigned to the resonance at 67.3 ppm. The thiacalixarene scaffold gives, in addition to the signals typical of aromatic carbon in its ^{13}C NMR spectrum, an additional peak at 31.8 ppm corresponding to the 12 methyl carbon atoms of its tBu groups. All carbonyl signals present in the ^{13}C NMR spectrum of the tetrathiolcarbonate **39** are absent in the corresponding ^{13}C NMR spectrum of **41**. In addition, the presence of the triazole function in product **41** is evidenced by typical resonances at 145.0 ppm corresponding to a quaternary carbon and another at 122.9 ppm to a tertiary carbon.

The modest yield reflects the molecular complexity of the precursor and also that four separate 1,5-thiol transfer reactions must take place to give the product. Considered as the sum of four separate 1,5-transfer reactions, a relative yield of 78% may be computed for each. A multitude of potential side-reactions such as intra- and intermolecular autoxidations of thiolate ion intermediates could in principle ensue, but unfortunately ESI-MS proved to be of limited use in monitoring the reaction. Only the parent ion of the expected product **41** was observed at m/z = 1098 ($[M + 2Na]^{2+}/2$).

CONCLUSION

To summarize, we have described a new and straightforward protocol for the synthesis of unsymmetrical thioethers featuring an unusual base-triggered 1,5-thiol transfer reaction of 1-bromo-2-propargylthiolcarbonates. The method is shown to be odorless and metal free and provides a convenient one-pot strategy to the desired targets. We further demonstrate that this same intramolecular 1,5-transfer reaction is also effective starting from the corresponding triazole precursors, themselves obtained efficiently from the reaction of a chosen azido analogue with an appropriate propargylthiolcarbonate substrate under copper-catalyzed "click" conditions. A number of pertinent examples are given to demonstrate the potential of the method starting from both sugar-derived 1-bromo-2-propargylthiolcarbonate precursors as well as the corresponding sugar-derived 1-bromo-2-triazolethiolcarbonate precursors.

As an example of the scope of the reaction, four 1,5-thiol transfer reactions have been triggered simultaneously from a sugar-derived tetrathiolcarbonate precursor using base catalysis, to allow four 6-thioglucose moieties to be installed on a 1,3-alternate thiacalix[4]arene scaffold in a one-pot transformation in 78% yield (for each sugar unit).

EXPERIMENTAL SECTION

General Methods. Syntheses under microwave irradiation were performed under pressure with "CEM Discover", a single-mode apparatus (2450 MHz) using an external reaction temperature sensor. ^1H and ^{13}C NMR spectra were recorded on a 300 and 600 WB spectrometer in appropriate deuterated solvents; chemical shifts are reported in δ(ppm). All ^{13}C NMR signals were assigned through C−H correlated HSQC spectra. TLC was performed on silica gel 60 F254, 230 mesh (E. Merck) with cyclohexane−EtOAc or EtOAc−MeOH, and spots were detected by vanillin−H_2SO_4 reagent. Preparative column chromatography was performed using 230−400 mesh Merck silica gel (purchased from Sigma). Optical rotations were determined with a polarimeter 1 mL cell. Low resolution electrospray mass spectra (ESI-MS) in the positive or negative ion mode were obtained on a ZQ quadripole instrument equipped with an electrospray (Z-spray) ion source. High resolution electrospray experiments (ESI-HRMS) were performed on a Q-TOF Ultima Global hybrid quadrupole time-of-flight instrument, equipped with an electrospray (Z-spray) ion source. Infrared spectra were recorded on an FTIR spectrometer.

General Procedure for Click Chemistry Reaction (A). The synthesis took place under Cu(I)-mediated conditions. Azido derivative (1 equiv), alkyne (1.2 equiv), $CuSO_4{\cdot}5H_2O$ (0.5 equiv), and sodium ascorbate (1 equiv) were dissolved in THF/tBuOH/water solvent mixture (1/1.5/1.5, v/v/v) and stirred 3 h at 60 °C. After cooling to room temperature, the solvent was evaporated under reduced pressure. The crude product obtained was diluted in CH_2Cl_2 and washed two-fold with brine. The organic layer was dried on $MgSO_4$. The crude product was purified by column chromatography on silica gel to afford the desired glycoadducts.

General Procedure for Thioetherification via Base-Catalyzed 1,5-Shift Conditions (B). Thioether compounds were prepared by treating a solution of thiolcarbonate derivatives in anhydrous MeOH at room temperature with catalytic MeONa. The reaction was stirred at rt and followed by TLC and ESI-MS until total disappearance of substrates. After concentration, the residues were purified by column chromatography on silica gel, affording the desired compounds.

6-S-Propargyl-1,2-O-isopropylidene-α-D-glucofuranose (4). Obtained as a pale yellow oil (75 mg, 77% yield), following general procedure B: Compound **3**[18] (0.15 g, 3.543 mmol) was reacted with sodium (catalytic amount) in MeOH (3 mL). Isolation by column chromatography on silica gel (cyclohexane/EtOAc: 2/1) gave pure compound. R_f = 0.25 (SiO_2, cyclohexane/EtOAc: 2/1); $[\alpha]_D^{20} = -3$ (*c* 0.11, acetone); ESI-MS: m/z = 297.1 $[M + Na]^+$. ^1H NMR (MeOD, 600 MHz), δ (ppm): 5.90 (d, 1H, H-1, $J_{1,2}$ = 3.7 Hz), 4.51 (d, 1H, H-

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2, $J_{2,1}$ = 3.7 Hz), 4.24 (d, 1H, H-3, J = 2.5 Hz), 4.12−4.01 (m, 2H, H-4/H-5), 3.41 (dd, 2H, $CH_2C{\equiv}CH$, ^4J = 2.6 Hz, ^2J = 1.1 Hz), 3.39 (s, 1H, OH), 3.09 (dd, 1H, H-6a, $J_{6a,6b}$ = 14.1 Hz, $J_{6a,5}$ = 2.8 Hz), 2.82 (dd, 1H, H-6b, $J_{6b,6a}$ = 14.1 Hz, $J_{6b,5}$ = 7.1 Hz), 2.58 (t, 1H, ($CH_2C{\equiv}CH$), ^4J = 2.6 Hz), 1.49 (s, 3H, $C(CH_3)_2$), 1.33 (s, 3H, $C(CH_3)_2$). ^{13}C NMR (MeOD, 150 MHz), δ (ppm): 112.7 ($C(CH_3)_2$), 106.3 (C-1), 86.7 (C-2), 82.8 (C-4), 81.3 ($CH_2C{\equiv}CH$), 75.2 (C-3), 72.0 ($CH_2C{\equiv}CH$), 69.1 (C-5), 37.5 (C-6), 27.1 $C(CH_3)_2$, 26.5 $C(CH_3)_2$, 20.6 ($CH_2C{\equiv}CH$). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{18}O_5SNa$: 297.0773; found 297.0773.

*2,3,4-Tri-O-acetyl-1-O-[3-chloropropyl]-α-L-fucopyranoside (**11α**/**11β**).* Peracetylated α-L-fucopyranose **10** (2 g, 6.015 mmol), $BF_3{\cdot}Et_2O$ (3.42 g, 24.07 mmol), and 3-chloropropanol (2.275 g, 24.07 mmol) in CH_2Cl_2 (4 mL) were introduced into a microwave vial (8 mL). The vial was closed with a septum cap and heated at 70 °C for 20 min under 100 W microwave irradiation. After cooling for 5 min, the solvent was evaporated. Purification by flash chromatography on silica gel (cyclohexane/EtOAc) afforded **11α** and **11β** anomers in 45% and 12% yields, respectively.

*2,3,4-Tri-O-acetyl-1-O-[3-chloropropyl]-α-L-fucopyranoside (**11α**).* Obtained as a colorless oil (1.185 g, 45% yield). R_f = 0.55 (SiO_2, cyclohexane/EtOAc: 4/2). $[\alpha]_D^{20}$ = −131 (c 0.215, CH_2Cl_2). ESI-MS: m/z = 389.0 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 300 MHz), δ(ppm): 5.29 (dd, 1H, H-3, $J_{3,2}$ = 10.6 Hz, $J_{3,4}$ = 3.4 Hz), 5.24 (dd, 1H, H-4, $J_{4,3}$ = 3.4 Hz, $J_{4,5}$ = 1.2 Hz), 5.07 (dd, 1H, H-2, $J_{2,3}$ = 10.6 Hz, $J_{2,1}$ = 3.7 Hz), 5.01 (d,1H, H-1, $J_{1,2}$ = 3.7 Hz), 4.18−4,05 (dq, 1H, H-5, $J_{5,4}$ = 1.2 Hz, $J_{5,6}$ = 6.6 Hz), 3.83 (dt, 1H, CH_2O, J = 10.0 Hz, J = 5.6 Hz), 3.70−3.56 (m, 2H, CH_2Cl), 3.50 (dt, 1H, CH_2O, J = 10.0 Hz, J = 5.6 Hz), 2.12 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.01 (m, 2H, ($OCH_2(CH_2)CH_2Cl$), 1.94 (s, 3H, CH_3), 1.10 (d, 3H, H-6, $J_{6,5}$ = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 170.6, 170.4, 170.1 (C═O), 96.4 (C-1), 71.2 (C-4), 68.3 (C-2), 68.1 (C-3), 64.6 (CH_2O), 64.5 (C-5), 41.1 (CH_2Cl), 32.1 ($OCH_2(CH_2)CH_2Cl$), 20.7, 20.7, 20.6 (CH_3), 15.9 (C-6). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{15}H_{23}ClO_8Na$: 389.0979; found 389.0997.

*2,3,4-Tri-O-acetyl-1-O-[3-chloropropyl]-β-L-fucopyranoside (**11β**).* Obtained as a colorless oil (0.313 g, 12% yield). R_f = 0.46 (SiO_2, cyclohexane/EtOAc: 4/2). $[\alpha]_D^{20}$ = −9 (c 0.115, CH_2Cl_2). ESI-MS: m/z = 389.0 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 5.19 (dd, 1H, H-4, $J_{4,3}$ = 3.4 Hz, $J_{4,5}$ = 1.0 Hz), 5.13 (dd, 1H, H-2, $J_{2,3}$ = 10.5 Hz, $J_{2,1}$ = 7.9 Hz), 4.98 (dd, 1H, H-3, $J_{3,4}$ = 3.4 Hz, $J_{3,2}$ = 10.5 Hz), 4.40 (d, 1H, H-1, $J_{1,2}$ = 7.9 Hz), 3.97 (dt, 1H, (OCH_2), J = 9.9 Hz, J = 5.1 Hz), 3.78 (dq, 1H, H-5, $J_{5,6}$ = 6.4 Hz, $J_{5,4}$ = 1.0 Hz), 3.63 (dt, 1H, (OCH_2), J = 9.9 Hz, J = 5.1 Hz), 3.57 (m, 2H, (CH_2Cl)), 2.12 (s, 3H, CH_3), 2.01 (m, 5H, CH_3/($OCH_2(CH_2)CH_2Cl$)), 1.93 (s, 3H, CH_3), 1.18 (d, H-6, $J_{6,5}$ = 6,4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 170.7, 170.2, 169.6 (C═O), 71.3 (C-3), 70.3 (C-4), 69.1 (C-2/C-5), 66.2 (CH_2O), 41.47 (CH_2Cl), 32.3 ($OCH_2(CH_2)CH_2Cl$), 20.8, 20.7, 20.7 (CH_3), 16.1 (C-6). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{15}H_{23}ClO_8Na$: 389.0979; found 389.0997.

*2,3,4-Tri-O-acetyl-1-O-[3-azidopropyl]-α-L-fucopyranoside (**12**).* To a stirred solution of **11α** (1.084 g, 2.955 mmol) in DMF (25 mL) was added NaN_3 (0.480 g, 7.388 mmol). After 12 h at 85 °C and evaporation, the crude product was extracted with CH_2Cl_2 and washed with brine. The organic layer was dried on $MgSO_4$ and concentrated. Compound **12** was obtained as a colorless oil (1.103 g, 94% yield) and used without further purification. R_f = 0.4 (SiO_2, cyclohexane/EtOAc: 2/1). ESI-MS: m/z = 395.9 [M + Na]$^+$. $[\alpha]_D^{20}$ = −103 (c 0.385, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 5.25 (dd, 1H, H-3, $J_{3,2}$ = 10.6 Hz; $J_{3,4}$ = 3.4 Hz), 5.20 (dd, 1H, H-4, $J_{4,3}$ = 3.4 Hz, $J_{4,5}$ = 1.2 Hz), 5.03 (dd, 1H, H-2, $J_{2,3}$ = 10.6 Hz, $J_{2,1}$ = 3.7 Hz), 4.96 (d, 1H, H-1, $J_{1,2}$ = 3.7 Hz), 4.06 (m, 1H, H-5), 3.71 (dt, 1H, CH_2O, J = 10.1 Hz, J = 5.8 Hz), 3.39 (dt, 1H, CH_2O, J = 10.1 Hz, 5.8 Hz), 3.33 (m, 2H, CH_2N_3), 2.08 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 1.80 (m, 2H, $OCH_2(CH_2)CH_2N_3$), 2.92 (d, 3H, H-6, $J_{6,5}$ = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 170.4, 170.2, 169.91 (C═O), 96.4 (C-1), 71.0 (C-4), 68.0 (C-2), 67.9 (C-3), 64.7 (CH_2O), 64.4 (C-5), 48.0 (CH_2N_3), 28.7 ($OCH_2(CH_2)CH_2N_3$), 20.6, 20.6, 20.5 (CH_3), 15.8 (C-6). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{15}H_{23}N_3O_8Na$: 396.1383; found 396.1375.

*2,3,4-Tri-O-acetyl-1-O-[1′-(3″-O-acetyl-6″-bromo-6″-deoxy-1″,2″-O-isopropylidene-α-D-glucofuranose)-1′H-1′,2′,3′-triazol-4′-yl)-thiocarbonyl]-propyl-α-L-fucoside (**13**).* Obtained as a white foam (0.136 g, 72%) following general procedure A: Compound **3**[18] (0.1 g, 0.236 mmol), 3-azidopropyl-α-L-*fuco* derivative **12** (0.105 g, 0.283 mmol), $CuSO_4{\cdot}5H_2O$ (0.029 g, 0.118 mmol), and sodium ascorbate (0.046 g, 0.236 mmol) in THF, tBuOH, and water solvent mixture (2.5 mL/3.75 mL/3.75 mL). R_f = 0.31 (SiO_2, cyclohexane/EtOAc/acetone: 4/1/1); $[\alpha]_D^{20}$ = −81 (c 0.125, CH_2Cl_2); ESI-MS: m/z = 820.2 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 600 MHz), δ(ppm): 7.54 (s, 1H, $CH_{triazole}$), 5.86 (d, 1H, H-1_{Glc}, $J_{1,2Glc}$ = 3.5 Hz), 5.32 (m, 1H, H-5_{Glc}), 5.30−5.25 (m, 2H, H-3_{Fuc}/H-4_{Fuc}), 5.21 (d, 1H, H-3_{Glc}, $J_{3,4Glc}$ = 2.9 Hz), 5.11 (dd, 1H, H-2_{Fuc}, $J_{2,3Fuc}$ = 10.9 Hz, $J_{2,1Fuc}$ = 3.7 Hz), 4.99 (d, 1H, H-1_{Fuc}, $J_{1,2Fuc}$ = 3.7 Hz), 4.44 (m, 3H, CH_2N/H-2_{Glc}), 4.34 (dd, 1H, H-4_{Glc}, $J_{4,5Glc}$ = 9.1 Hz, $J_{4,3Glc}$ = 2.9 Hz), 4.2−4.06 (m, 3H, CH_2S/H-5_{Fuc}), 3.75 (dd, 1H, H-$6a_{Glc}$, $J_{6a,6bGlc}$ = 11.6 Hz, $J_{6a,5Glc}$ = 2.6 Hz), 3.70 (dt, 1H, CH_2O, J = 10.3 Hz, 5.9 Hz), 3.57 (dd, 1H, H-$6b_{Glc}$, $J_{6b,6aGlc}$ = 11.6 Hz, $J_{6b,5Glc}$ = 6.5 Hz), 3.35 (dt, 1H, CH_2O, J = 10.3 Hz, 5.9 Hz), 2.16 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.48 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$), 1.11 (d, 3H, H-6_{Fuc}, $J_{6,5}$ = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz), δ(ppm): 170.6, 170.5, 170.1, 170.0, 169.5 (C═O), 144.5 ($C_{triazole}$), 122.6 ($CH_{triazole}$), 112.9 ($C(CH_3)_2$), 105.1 (C-1_{Glc}), 96.46(C-1_{Fuc}), 83.3, 78.1, 74.7, 71.5, 71.2, 68.1, 68.1, 64.7 (C_{Glc} + C_{Fuc}), 64.6 (CH_2O), 47.1 (CH_2N), 32.7 (C-6_{Glc}), 22.9 ($OCH_2(CH_2)$-CH_2N), 26.8, 26.3 ($C(CH_3)_2$), 26.0 (CH_2S), 20.8, 20.7, 20.7, 20.6 (CH_3), 15.9 (C-6_{Fuc}). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{30}H_{42}BrN_3O_{15}SNa$: 818.1418; found 818.1395.

*1-O-[1′-(1″,2″-O-Isopropylidene-6″-S-α-D-glucofuranose)-1′H-1′,2′,3′-triazol-4′-yl)-propyl-α-L-fucoside (**16**).* Obtained as yellow pale foam (0.039 g, 75%) following general procedure B: Compound **13** (0.08 g, 0.100 mmol), sodium (catalytic amount) in MeOH (2 mL). The product was purified by column chromatography on silica gel (9/2: EtOAc/MeOH), yielding pure compound. R_f = 0.20 (SiO_2, EtOAc/MeOH: 9/2). $[\alpha]_D^{20}$ = −43 (c 0.18, MeOH). ESI-MS: m/z = 544.2 [M + Na]$^+$. ^{1}H NMR (MeOD, 300 MHz), δ (ppm): 8.06 (s, 1H, $CH_{triazole}$), 5.95 (d, 1H, H-1_{Glc}, $J_{1,2Glc}$ = 3.6 Hz), 4.82 (d, 1H, H-1_{Fuc}, $J_{1,2Fuc}$ = 2.7 Hz), 4.63 (t, 2H, CH_2N, J = 6.7 Hz), 4.57 (d, 1H, H-2_{Glc}, $J_{2,1Glu}$ = 3.6 Hz), 4.28−4.10 (m, 3H, H-4_{Fuc}/H-5_{Glc}/H-4_{Glc}), 3.99 (m, 3H, SCH_2N/H-5_{Fuc}), 3.82−3.38 (m, 5H, H-2_{Fuc}/H-3_{Fuc}/H-3_{Glc}/CH_2O), 2.98 (m, 2H, H-$6a_{Glc}$), 2.73 (m, 2H, H-$6b_{Glc}$), 2.31 (m, 2H, ($OCH_2(CH_2)CH_2N$)), 1.52 (s, 3H, $C(CH_3)_2$), 1.37 (s, 3H, $C(CH_3)_2$), 1.27 (d, 3H, H-6_{Fuc}, $J_{6,5Fuc}$ = 6.6 Hz). ^{13}C NMR (MeOD, 75 MHz), δ (ppm): 146.5 ($C_{triazole}$), 124.7 ($CH_{triazole}$), 112.7 ($C(CH_3)_2$), 106.3 (C-1_{Glc}), 100.6 (C-1_{Fuc}), 86.6 (C-2_{Glc}), 83.2 (C-4_{Glc}), 75.2 (C-4_{Fuc}), 73.6 (C-3_{Fuc}), 69.9 (C-2_{Fuc}), 69.0 (C-3_{Glc}), 67.6 (C-5_{Glc}), 65.4 (C-5_{Fuc}), 64.0 (CH_2O), 47.1 (CH_2N), 37.5 (C-6_{Glc}), 31.0 ($OCH_2(CH_2)CH_2N$), 27.2 (SCH_2N), 27.2, 26.5 ($C(CH_3)_2$), 16.6 (C-6_{Fuc}). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{21}H_{35}N_3O_{10}SNa$: 544.1941; found 544.1932.

*1,5-Di-[4′-(3″-O-acetyl-6″-bromo-6″-deoxy-1″,2″-O-isopropylidene-α-D-glucofuranose)-1′H-1′,2′,3′-triazol-4′-yl)-methylthiocarbonyl]-D-arabinitol (**19**).* Obtained as a white foam (0.149, 59%) following general procedure A: Compounds **3**[18] (0.2 g, 0.472 mmol) and **18**[22] (0.070 g, 0.214 mmol) were allowed to react in the presence of $CuSO_4{\cdot}5H_2O$ (0.053 g, 0.214 mmol) and sodium ascorbate (0. 085 g, 0.429 mmol) in THF, tBuOH, and water as solvent mixture (3 mL:4.5 mL:3.5 mL). R_f = 0.094 (SiO_2, cyclohexane/EtOAc/acetone: 4/1/1). $[\alpha]_D^{20}$ = −10 (c 0.13, CH_2Cl_2). ESI-MS: m/z = 1197.2 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 300 MHz), δ(ppm): 7.57 (s, 1H, $CH_{triazole}$), 7.55 (s, 1H, $CH_{triazole}$), 5.88 (d, 2H, H-1_{Glc}, $J_{1,2Glc}$= 3.5 Hz), 5.61−5.10 (m, 6H, H-4_{Ara}/H-5_{Glc}/H-2_{Ara}/H-3_{Glc}), 4.45 (m, 9H, (H-1, H-5)$_{Ara}$/H-2_{Glc}/H-3_{Ara}/H-4_{Glc}), 4.14 (m, 4H, SCH_2), 3.82 (m, 2H, H-$6a_{Glc}$), 3.62 (m, 2H, H-$6b_{Glc}$), 2.23 (s, 3H, CH_3), 2.06 (s, 6H, CH_3), 2.00 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.51 (s, 3H, $C(CH_3)_2$), 1.27 (s, 3H, $C(CH_3)_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ(ppm): 169.99, 169.87, 169.64, 169.46, 169.37 (C═O), 144.7 ($C_{triazole}$), 123.5 ($CH_{triazole}$), 112.9 ($C(CH_3)_2$), 105.1 (C-1_{Glc}), 83.2, 77.8, 74.6, 71.4, 68.7, 68.5, 65.8 (C-2,3,4,5,6$_{Glc}$+C-2,3,4$_{Ara}$), 50.5, 50.0 (C-1/C-5$_{Ara}$), 32.6 (C-6_{Glc}), 26.8 ($C(CH_3)_2$), 26.2 ($C(CH_3)_2$), 25.9 (CH_2S), 20.7, 20.6, 20.4 (CH_3).

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HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{41}H_{54}Br_2N_6O_{20}S_2Na$: 1195.1099; found 1195.1115.

*1,5-Di-[4′-(1″,2″-O-isopropylidene-6″-S-α-D-glucofuranose)-1′H-1′,2′,3′-triazol-4′-yl)methyl]-D-arabinitol (**23**).* Obtained as a white foam (0.051 g, 80%) following general procedure B: Compound **19** (0.1 g, 0.085 mmol), sodium (catalytic amount) in MeOH (2 mL). The product was purified by column chromatography on silica gel (9/2: EtOAc/MeOH), yielding pure compound. R_f = 0.14 (SiO_2, EtOAc/MeOH:9/1). $[\alpha]_D^{20}$ = +4 (c 0.11, MeOH). ESI-MS: m/z = 773.3 [M + Na]$^+$. ^{1}H NMR (MeOD, 600 MHz), δ (ppm): 8.02 (2s, 2H, $CH_{triazole}$), 5.96−5.86 (m, 2H, H-1_{Glc}), 4.86 (m, 2H, (H-1, H-5)$_{Ara}$), 4.54 (m, 4H, H-2_{Glc}/(H-1, H-5)$_{Ara}$), 4.25(d, H-2/H-4_{Ara}, 2H, J = 2. 1 Hz), 4.23−3.98 (m, 3H, H-5_{Glc}/H-3_{Ara}), 3.95 (s, 4H, CH_2S), 3.40 (s, 2H, H-4_{Glc}), 2.94 (m, 2H, H-6a$_{Glc}$), 2.75 (m, 2H, H-6b$_{Glc}$), 1.47 (s, 6H, C(CH_3)$_2$), 1.34 (s, 6H, C(CH_3)$_2$). ^{13}C NMR (MeOD, 150 MHz), δ(ppm): 146.3 ($C_{triazole}$), 125.7 ($CH_{triazole}$), 125.4 ($CH_{triazole}$), 112.7 ($C(CH_3)_2$), 106.3 (C-1_{Glc}), 86.6 (C-2_{Glc}), 83.1 (C-5_{Glc}), 75.2 (C-3_{Glc}), 73.2 (C-4_{Glc}), 71.2, 70.2, 69.1 (C-2,3,4)$_{Ara}$, 54.9, 54.8 (C-1/C-5_{Ara}), 37.5 (C-6_{Glc}), 27.3 (CH_2S), 27.1 (C(CH_3)$_2$), 26.4 (C(CH_3)$_2$). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{29}H_{46}N_6O_{13}S_2Na$: 773.2462; found 773.2455.

*1,6-Dibromo-1,6-dideoxy-3,4-O-isopropylidene-2,4-di-O-propargylthiocarbonyl-D-mannitol (**26**).* Obtained from **25**[23] (0.37 g, 1.207 mmol) and propargyl bromide (2.54 g, 21 mmol) under pressure and MW irradiation (250 W) at 120 °C for 30 min. After cooling, the solvent was evaporated. Purification by column chromatography on silica gel (cyclohexane/EtOAc: 7/0.5) afforded pure compound **26** (0.334 g, 65%) as a yellow oil. R_f = 0.57 (SiO_2, cyclohexane/EtOAc: 3/1). $[\alpha]_D^{20}$ = +10 (c 0.17, CH_2Cl_2). ESI-MS: m/z = 567.0 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 300 MHz), δ(ppm): 5.26−5.03 (m, 2H, H-2/H-5), 4.31−4.13 (m, 2H, H-3/H-4), 3.73−3.54 (m, 8H, CH_2C≡CH/H-6a), 2.27 (t, 2H, CH_2C≡CH, ^4J = 2.7 Hz), 1.42 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ(ppm): 169.6 (C═O), 111.9 ($C(CH_3)_2$), 78.2 (CH_2C≡CH), 77.7 (C-3/C-4), 76.0 (C-2/C-5), 72.1 (CH_2C≡CH), 30.5 (C-1 = C-6), 27.5 (CH_3), 19.9 (CH_2C≡CH)). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{20}Br_2O_6S_2Na$: 564.8966; found 564.8973.

*3,4-O-Isopropylidene-1,6-di-S-propargyl-D-mannitol (**29**).* Obtained as a yellow oil (0. 043 g, 71%) following general procedure B: **26** (0.1 g, 0.0183 mmol), sodium (catalytic amount) in MeOH (2 mL). The product was purified by column chromatography on silica gel (cyclohexane/EtOAc: 7/1), yielding pure compound. R_f = 0.06 (SiO_2, cyclohexane/EtOAc: 7/1). $[\alpha]_D^{20}$ = +68 (c 0.105, acetone). ESI-MS: m/z = 353.0 [M + Na]$^+$. ^{1}H NMR (acetone-d_6, 300 MHz), δ(ppm): 3.91 (m, 4H, (H-2/H-5)/(H-3/H-4)), 3.42 (d, 4H, CH_2C≡CH, J = 2.6 Hz), 3.09 (dd, 2H, H-1a = H-6a, $J_{1a,1b}$ = 14.1 Hz, $J_{1a,2}$ = 2.8 Hz), 2.76 (dd, 2H, H-1b = H-6b, $J_{1b,1a}$ = 14.1 Hz, $J_{1b,2}$ = 7.3 Hz), 2.67 (t, 2H, CH_2C≡CH, J = 2.6 Hz), 1.35 (s, 6H, CH_3). ^{13}C NMR (acetone-d_6, 75 MHz), δ(ppm): 109.0 ($C(CH_3)_2$), 81.8 (C-2/C-5), 80.5 (CH_2C≡CH), 72.6 (C-3/C-4), 71.4 (CH_2C≡CH), 35.8 (C-1/C-6), 26.5 (CH_3), 19.5 (CH_2C≡CH). HRMS (ESI-TOF) m/z: [M + Na] $^+$calcd for $C_{15}H_{22}O_4S_2Na$: 353.0857; found 353.0847.

*1,6-Dibromo-1,6-dideoxy-3,4-O-isopropylidene-2,4-di-O-[1′-(2″,3″,4″-tri-O-acetyl-β-L-fucofuranose)-1′H-1′,2′,3′-triazol-4′-yl)-methylthiocarbonyl]-D-mannitol (**32**).* Obtained as a white solid (0.252 g, 78%) following general procedure A: Compounds **26** (0.15 g, 0.28 mmol) and **30** (0.208 g, 0.661 mmol) react in the presence of $CuSO_4{\cdot}5H_2O$ (0.068 g, 0.0755 mmol) and sodium ascorbate (0.109 g, 0.5511 mmol) in THF/tBuOH/water solvent mixture (6 mL/9 mL/9 mL). R_f = 0.08 (SiO_2, cyclohexane/EtOAc/acetone: 4/1/1). $[\alpha]_D^{20}$ = +30 (c 0.14, CH_2Cl_2). ESI-MS: m/z = 1197.3 [M + Na]$^+$. ^{1}H NMR (MeOD, 300 MHz), δ(ppm): 8.14 (s, 2H, $CH_{triazole}$), 6.07 (d, 2H, H-1_{Fuc}, $J_{1,2}$ = 9.2 Hz), 5.64 (m, 2H, H-2_{Fuc}), 5.51−5.38 (m, 4H, H-3/H-4_{Fuc}), 5.37−5.21 (m, 2H, H-2/H-5_{Mann}), 4.43−4.32 (m, 4H, H-5_{Fuc}/H-3/H-4_{Mann}), 4.28 (d, 4H, CH_2S, J = 8.9 Hz), 3.83 (dd, 4H, H-6a, $J_{6a,6b}$ = 11.5 Hz, $J_{6a,5}$ = 3.4 Hz), 3.67 (dd, 4H, H-6b, $J_{6b,6a}$ = 11.5 Hz, $J_{6b,5}$ = 6.7 Hz), 2.3 (s, 6H, CH_{3Ac}), 2.04 (s, 6H, CH_{3Ac}), 1.91 (s, 6H, CH_{3Ac}), 1.45 (s, 6H, C(CH_3)$_2$), 1.31 (d, 6H, CH_{3Fuc}, J = 6.4 Hz). ^{13}C NMR (MeOD, 75 MHz), δ(ppm): 172.2, 171.6, 171.3 (C═O), 146.0 ($C_{triazole}$), 123.5 ($CH_{triazole}$), 112.8 ($C(CH_3)_2$), 87.2 (C-1_{Fuc}), 79.0 (C-3/C-4_{Mann}), 77.3 (C-2/C-5_{Mann}), 73.7 (C-5_{Fuc}), 72.6, 71.6 (C-3/C-4_{Fuc}), 69.6 (C-2_{Fuc}), 31.7 (C-6_{Mann}), 27.6 (C(CH_3)$_2$), 25.8 (CH_2S), 20.6, 20.5, 20.3 (CH_3), 16.4 (H-6_{Fuc}). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{41}H_{54}Br_2N_6O_{20}S_2Na$: 1195.1099; found 1195.1129.

*3,4-O-Isopropylidene-1,6-di-S-[1′-(β-L-fucofuranose)-1′H-1′,2′,3′-triazol-4′-yl)-methyl]-D-mannitol (**36**).* Obtained as a white solid (0.024 g, 30%) following general procedure B: Compound **32** (0.137g, 1.162 mmol), sodium (catalytic amount) in MeOH (4 mL). The product was purified by column chromatography on silica gel (EtOAc/MeOH: 9/1.5), yielding pure compound. R_f = 0.19 (SiO_2, EtOAc/MeOH: 9/3). $[\alpha]_D^{20}$ = +10 (c 0.12, MeOH). ESI-MS: m/z = 731.3 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 300 MHz), δ(ppm): 8.19 (s, 2H, $CH_{triazole}$), 5.57 (d, 2H, H-1_{Fuc}, $J_{1,2}$ = 9.2 Hz), 4.14 (m, 2H, H-2_{Fuc}), 4.05−3.95 (m, 8H, H-5_{Fuc}/(H-4/H-3)$_{Mann}$/SCH_2), 3.88−3.81 (m, 4H, H-4_{Fuc}/(H-2/H-5)$_{Mann}$), 3.76 (dd, 2H, H-3_{Fuc}, $J_{3,2}$ = 9.5 Hz, $J_{3,4}$ = 3,3 Hz), 2. 95 (dd, 2H, (H-1 = H-6)$_{Mann}$, $J_{1a,1b}$ = 14.0 Hz, $J_{1a,2}$ = 2.9 Hz), 2.71 (dd, 2H, (H-1 = H-6)$_{Mann}$, $J_{1b,1a}$ = 14.0 Hz, $J_{1b,2}$ = 7.6 Hz), 1.39 (s, 6H, C(CH_3)$_2$), 1.35 (d, 6H, C-6_{Fuc}, $J_{6,5}$ = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 146.9 ($C_{triazole}$), 123.0 ($CH_{triazole}$), 90.1 (C-1_{Fuc}), 82.7 (C-3/C-4_{Mann}), 75.4 (C-5/C-3_{Mann}), 73.5 (C-4_{Fuc}), 73.0 (C-2/C-5_{Mann}), 71.2 (C-2_{Fuc}), 36.7 (C-1/C-6_{Mann}), 27.5 (C(CH_3)$_2$), 27.3 (CH_2S), 16.8 (C-6_{Fuc}). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{27}H_{44}N_6O_{12}S_2Na$: 731.2357; found 731.2341.

*Tetra-3-azidopropylthiacalix[4]arene **38**.* To a stirred solution of **37**[26] (0.56 g, 0.545 mmol) in DMF (11 mL) was added NaN_3 (0.425 g, 6.542 mmol). The mixture was stirred for 12 h at 85 °C. The solvent was evaporated. The reaction mixture was diluted with $CHCl_3$, and the obtained solution was washed with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Compound **38** was obtained as pale yellow solid (0.539 g, 94%) and used without further purification. R_f 0.54 (SiO_2, cyclohexane/CH_2Cl_2: 5/3). ESI-MS: m/z = 1075.5 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.35 (s, 8H, H_{Ar}), 3.94 (t, 8H, OCH_2, J = 7.1 Hz), 2.99 (t, 8H, CH_2N_3, J = 7.1 Hz), 1.27 (m, 44H, NC$H_2CH_2CH_2O$/CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 156.6 (ArCS), 146.4 (ArCtBu), 128.2 (ArCO), 127.6 (ArCH), 66.0 (CH_2O), 48.5 (CH_2N_3), 34.5 ($C(CH_3)_3$), 31.4 (CH_3), 28.6 (CH_2O). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{52}H_{68}N_{12}O_4S_4Na$: 1075.4268 found; 1075.4272.

*Tetrathiolcarbonylthiacalix[4]arene **39**.* Obtained as a white solid (0. 257 g, 66%) following general procedure A: From compounds **3** (0.265 g, 0.625 mmol) and **38** (0.15 g, 0.142 mmol) in the presence of $CuSO_4{\cdot}5H_2O$ (0.071 g, 0.289 mmol) and sodium ascorbate (0.113 g, 0.568 mmol) in THF, tBuOH, and water (5.5 mL:7.75 mL:7.75 mL). R_f = 0.11 (SiO_2, cyclohexane/EtOAc/acetone: 6/1/1). $[\alpha]_D^{20}$ = −11 (c 0.115, CH_2Cl_2). ESI-MS: m/z = 1396.2 [M + 2Na]$^{2+}$/2. ^{1}H NMR ($CDCl_3$, 300 MHz), δ(ppm): 7.26 (s, 4H, $CH_{triazole}$), 6.94 (s, 8H, H_{Ar}), 5.55 (d, 4H, H-1, $J_{1,2}$ = 3.5 Hz), 5.00 (m, 4H, H-5), 4.93 (d, 4H, H-3, $J_{3,4}$ = 2.9 Hz), 4.15 (d, 4H, H-2, $J_{2,1}$ = 3.5 Hz), 4.06 (dd, 4H, H-4, $J_{4,3}$ = 2.9 Hz, $J_{4,5}$ = 9.1 Hz), 3.84 (s, 8H, CH_2S), 3.76 (t, 8H, CH_2N, J = 5.6 Hz), 3.65 (t, 8H, CH_2O, J = 7.0 Hz), 3.44 (dd, 4H, H-6a, $J_{6a,6b}$ = 11.6 Hz, $J_{6a,5}$ = 2.6 Hz), 3.27 (dd, 4H, H-6b, $J_{6b,6a}$ = 11.6 Hz, $J_{6b,5}$ = 6.1 Hz), 1.72 (s, 12H, CH_3), 1.34 (m, 8H, NC$H_2CH_2CH_2$O), 1.17 (s, 12H, C(CH_3)$_2$), 0.96 (s, 12H, C(CH_3)$_2$), 0.74 (s, 36H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 170.1, 169.5 (C═O), 156.5 (ArCS), 146.5 (ArCtBu), 143.7 ($C_{triazole}$), 128.2 (ArCO), 127.5 (CHAr), 122.9 ($CH_{triazole}$), 112.9 ($C(CH_3)_2$), 105.1 (C-1), 83.3 (C-2), 78.0 (C-4), 74.7 (C-3), 71.4 (C-5), 66.2 (CH_2O), 47.9 (CH_2N), 34.3 ($C(CH_3)_3$, 32.7 (C-6), 31.2 (CH_3), 26.9 (C(CH_3)$_2$), 26.4 (C(CH_3)$_2$), 26.2 (CH_2S), 20.8 (CH_3). HRMS (ESI-TOF) m/z: [M + 2Na]$^{2+}$/2 calcd for $C_{112}H_{142}Br_4N_{12}O_{32}S_8Na_2$: 1393.2147; found 1393.2125.

*Tetrathioether Thiacalix[4]arene **41**.* Obtained as a white solid (0.043 g, 37%) following general procedure B: Compound **39** (0.15 g, 0.0545 mmol), sodium (catalytic amount) in MeOH (3 mL). The product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH: 10/0.3) to yield pure compound. R_f = 0.076 (SiO_2, CH_2Cl_2/MeOH: 10/0.3). $[\alpha]_D^{20}$ = −8 (c 0.12, acetone). ESI-MS: m/z = 1098.5 [M + 2Na]$^{2+}$/2. ^{1}H NMR ((CD_3)$_2$CO, 600 MHz), δ (ppm): 7.91 (s, 4H, $CH_{triaozle}$), 7.40 (s, 8H, H_{Ar}), 5.85 (d, 4H, H-1, $J_{1,2}$ = 2.5 Hz), 4.49 (d, 4H, H-2, $J_{2,1}$ = 2.5 Hz), 4.27 (m, 12H, CH_2N/H-4), 4.15−4.02 (m, 16H, H-5/H-3/CH_2O), 3.93 (s, 8H, CH_2S), 2.92

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(dd, 4H, H-6a, $J_{6a,6b}$ = 14 Hz, $J_{6a,5}$ = 1.2 Hz), 2.70 (dd, 4H, H-6b, $J_{6b,6a}$ = 14 Hz, $J_{6b,5}$ = 7.2 Hz), 1.80−1.61 (m, 8H, $NCH_2CH_2CH_2O$), 1.41 (s, 12H, $C(CH_3)_2$), 1.26 (s, 12H, $C(CH_3)_2$), 1.14 (s, 36H, CH_3). ^{13}C NMR ($(CD_3)_2CO$, 150 MHz), δ(ppm): 156.5 (ArCS), 146.6 (ArCtBu), 145.2 ($C_{triazole}$), 128.1 (ArCO), 127.3 (CHAr), 123.0 ($CH_{triazole}$), 111.0 ($C(CH_3)_2$), 105.0 (C-1), 85.4 (C-2), 81.6 (C-3), 74.1 (C-4), 68.5 (C-5), 66.1 (CH_2O), 44.5 (CH_2N), 36.4 (C-6), 34.0 ($C(CH_3)_3$), 30.6 (CH_3), 29.4 ($NCH_2CH_2CH_2O$), 25.8 (CH_2S), 25.8 ($C(CH_3)_2$), 25.0 ($C(CH_3)_2$). HRMS (ESI-TOF) m/z: $[M + 2Na]^{2+}/2$ calcd for $C_{100}H_{140}N_{12}O_{24}S_8Na_2$: 1097.3827; found 1097.3855.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for compounds **4**−**41** and IR spectra of compounds **13**, **16**, **23**, **26**, **29**, **32**, **36**, **39**, and **41**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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