A two-site reactive platform in the synthesis of amino-functionalized amphiphilic molecules *via* sulfenic acids†

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The synthesis of some bolaamphiphiles is described. It is a convergent approach that allows the linkage of a glucosyl derivative to a bis-functionalized platform, *via* a copper-free Sonogashira cross-coupling. The central core was obtained from the reaction of a suitably substituted bis-sulfoxide with diethynyl benzenes. The intermediates of such reaction are sulfenyl functions that are easily added to one triple bond of the unsaturated molecules. The functionalization at the central core, through the nucleophilic addition of ammonia or piperidine onto the two vinyl sulfonyl groups already present in the backbones of the molecules, opened the way to the preparation of more complex derivatives. The observation of the formation of new stereogenic carbons with an unexpected significantly high diastereoselectivity was justified and supported by preliminary theoretical calculations. The two ending glucosyl moieties were favourably deprotected to afford the amino-functionalized bolaamphiphilic molecules.

Introduction

Amphiphiles are molecules with at least two covalently bonded components with different affinities for the solvent, one showing a high affinity for polar solvents and another possessing strong affinity for nonpolar solvents. In particular, the term "bolaamphiphiles" (BAs) was first given to "bipolar lipid for ions and molecules which aggregate in water" by Fuhrhop and Fritsch in 1984[1] and 1986[2] papers, although already in 1951 Fuoss and Edelson[3] spoke of a "bolaform electrolyte" (also "bolyte" or "bolion") to indicate a chain of hydrophobic groups connecting two ionic functions. The prefix "bola" refers to the shape of a South American missile weapon: two balls attached to both ends of a cord. Today, the name "bolaamphiphiles" is used to indicate in general amphiphilic molecules containing a hydrophobic skeleton connected with two hydrophilic heads. The most important natural BAs are the membrane lipids of thermophilic and acidophilic archaebacteria, *e.g.*, *Sulfolobus solfataricus*.[4] Synthetic BAs have attracted the attention of researchers for their unique property of self-assembling both at interfaces, such as air/water or liquid/solid, and in solution, forming well defined structures, such as micelles, lamellae vesicles, nanotubes, nanorods, and nanosheets. For this reason, since the nineties, several synthetic methodologies have been developed to obtain BAs and their applications have been extensively studied, including drug delivery,[5] gene delivery,[6] medical imaging,[7] and nanoelectronics.[8] In recent years, supra-amphiphiles[9] and bola-type supra-amphiphiles[10] have been obtained also by the self-assembly of components bearing both hydrophilic and hydrophobic segments held together by noncovalent interactions.[11] Most BAs are easily made by condensation and substitution reactions, using commercial diols or diamines or dicarboxylates as starting materials. Sulfurated molecules are required by all living organisms; therefore, they can be found in a broad range of natural products[12] and pharmaceuticals.[13] This is because of the various sulfur-derived functional groups that possess different properties, from the thiol function and the stable disulfide bond up to the differently oxidized sulfurated molecules. Sulfenic acids (R-SOH), for instance, are intermediates, in nature[14] and in lab-chemistry,[15] which cannot be usually isolated but can be transformed into other stable sulfurated functional groups such as sulfinic and sulfonic acids, sulfoxides, sulfones and disulfides.[16] They have long been studied and their chemistry applied to the synthesis of several sulfur-containing molecules.[17] In this paper we will discuss a nontrivial approach to the synthesis of BAs **1** (Scheme 2) and *O*-acetylated BAs **2** (Scheme 3) composed of a long lipophilic

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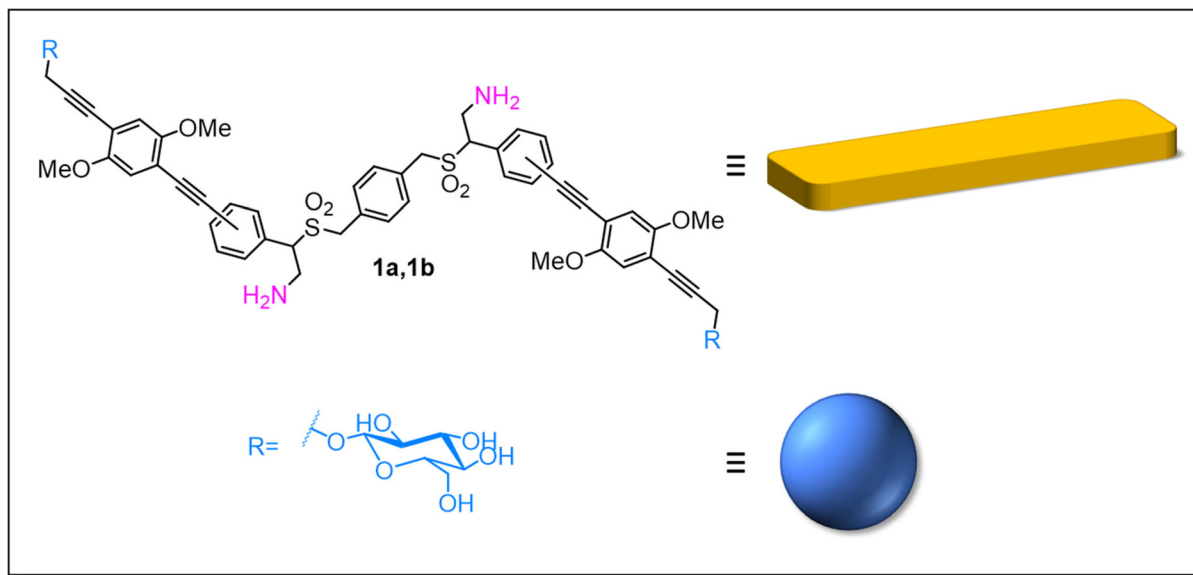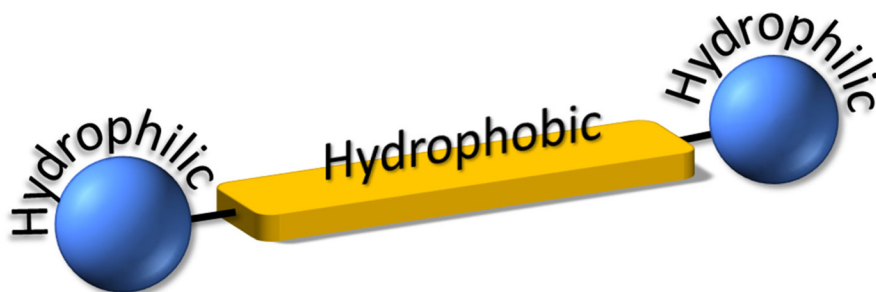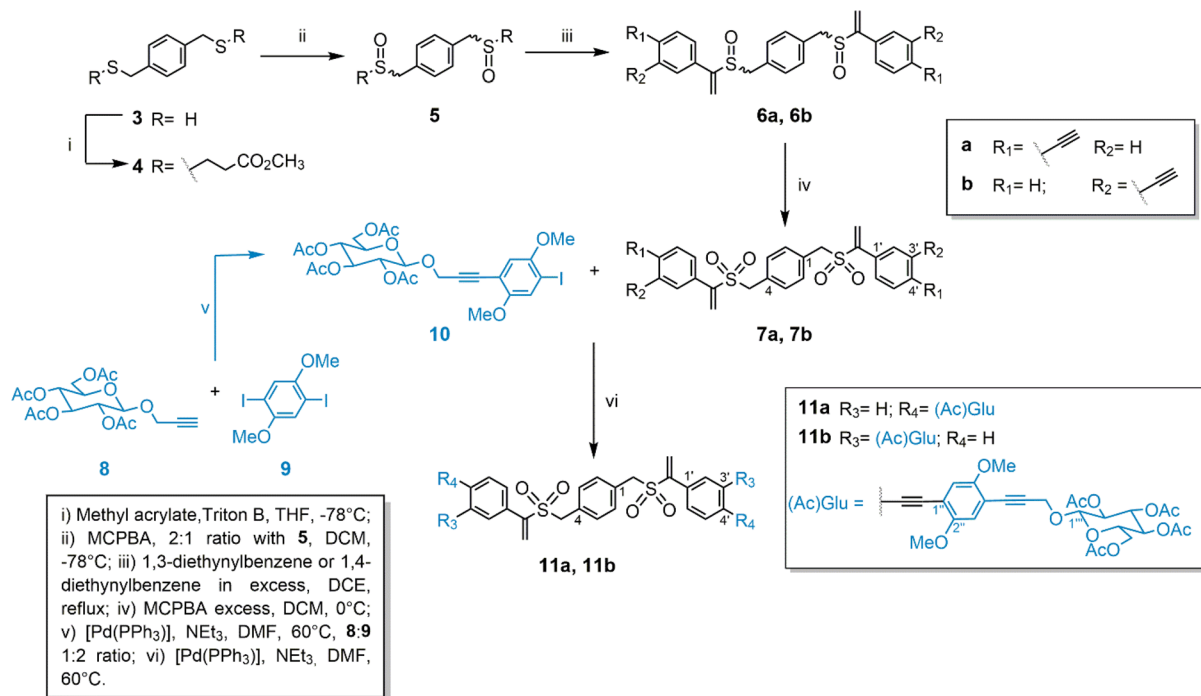†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2ob01266a

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Fig. 1 Schematic representation of bolaamphiphilic molecules synthesized in this paper.

i) Methyl acrylate, Triton B, THF, -78°C;
ii) MCPBA, 2:1 ratio with **5**, DCM,
-78°C; iii) 1,3-diethynylbenzene or 1,4-
diethynylbenzene in excess, DCE,
reflux; iv) MCPBA excess, DCM, 0°C;
v) [Pd(PPh₃)], NEt₃, DMF, 60°C, **8:9**
1:2 ratio; vi) [Pd(PPh₃)], NEt₃, DMF,
60°C.

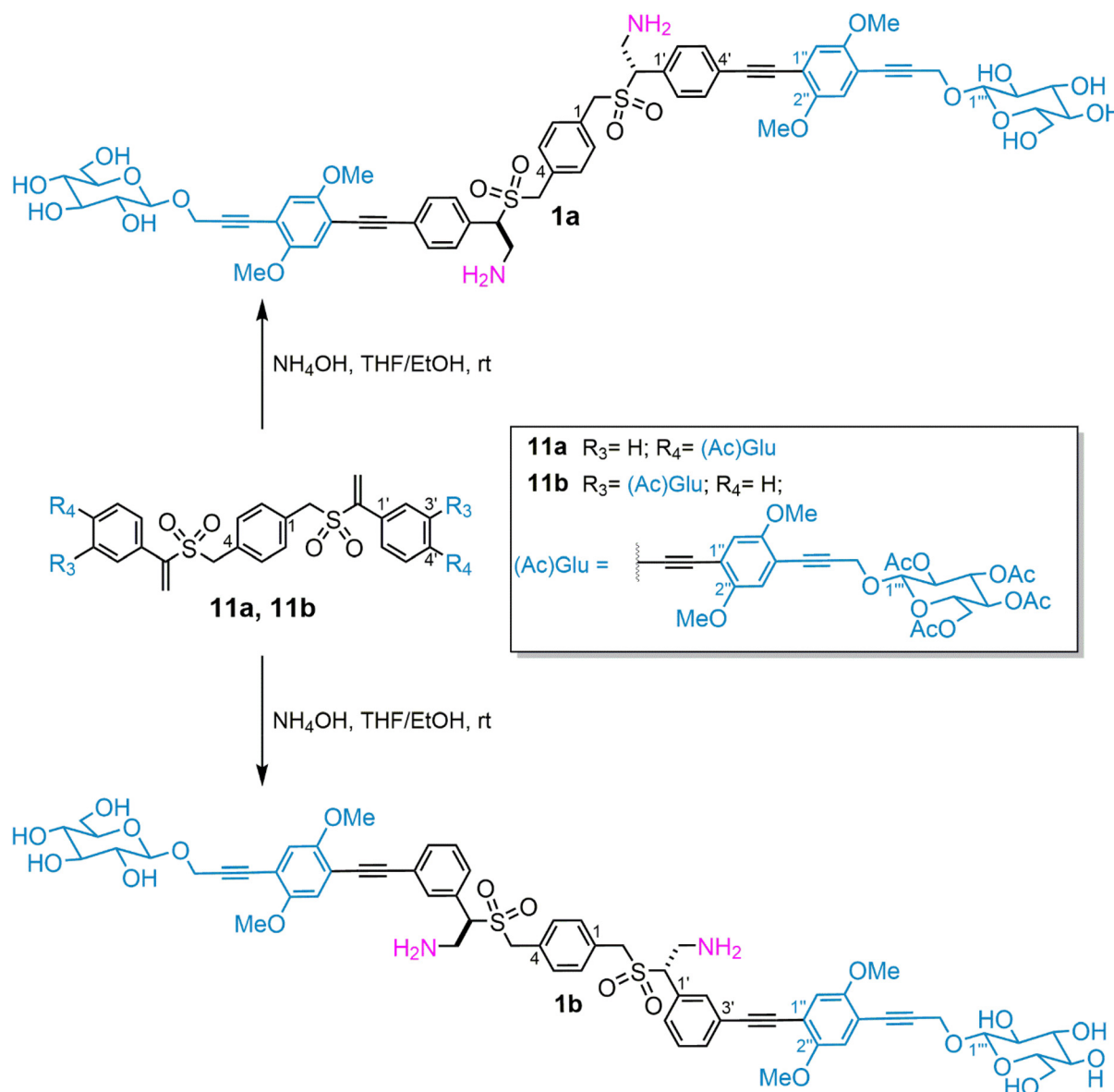**Scheme 1** Synthesis of the "two-sites reactive platform" **7** and its functionalization with glucosyl moieties.

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wire containing two vinyl sulfone moieties, and decorated at the extremities of the chain with glucose terminations (Fig. 1). The two sulfurated functions, introduced by the alkyne/sulfenic acid addition,[18] can be involved in Michael-type additions, while the two carbohydrate-extremities may provide beneficial properties to the bolaamphiphilic molecules. Besides their chirality, non-toxicity and biocompatibility, sugars possess in their skeletons various hydroxyl groups leading to a good hydrophilic environment and multivalent sites that help provide structural diversity during self-assembly.[19] Moreover, carbohydrates can specifically target glycoreceptors in the cellular plasma membrane and can act as ligands in the drug delivery scenario and as target molecules for molecular recognition, adding to the synthesized BAs a biomedical value.

Results and discussion

The synthetic procedure for obtaining BAs is described below. Commercially available 1,4-benzenedimethanthiol (**3**) was reacted with methyl acrylate in the presence of benzyltrimethylammonium hydroxide (TRITON B) as the base (Scheme 1). The obtained bis-thioether **4** underwent oxidation to bis-sulfoxide **5** with *meta*-chloroperbenzoic acid (*m*CPBA) at −78 °C to avoid the formation of the corresponding undesirable bis-sulfone. Thermolysis of compound **5** generated sulfenic acid functionalities that reacted with one of the two triple bonds of *meta*- and *para*-diethynylbenzenes, in a completely regiocontrolled process,[20] leading to the formation of compounds **6a** and **6b**.[21] The electronic nature of the substituents, located at the β position to the sulfinyl groups, is crucial for

Scheme 2 General procedure for amino-bolaamphiphiles **1**.

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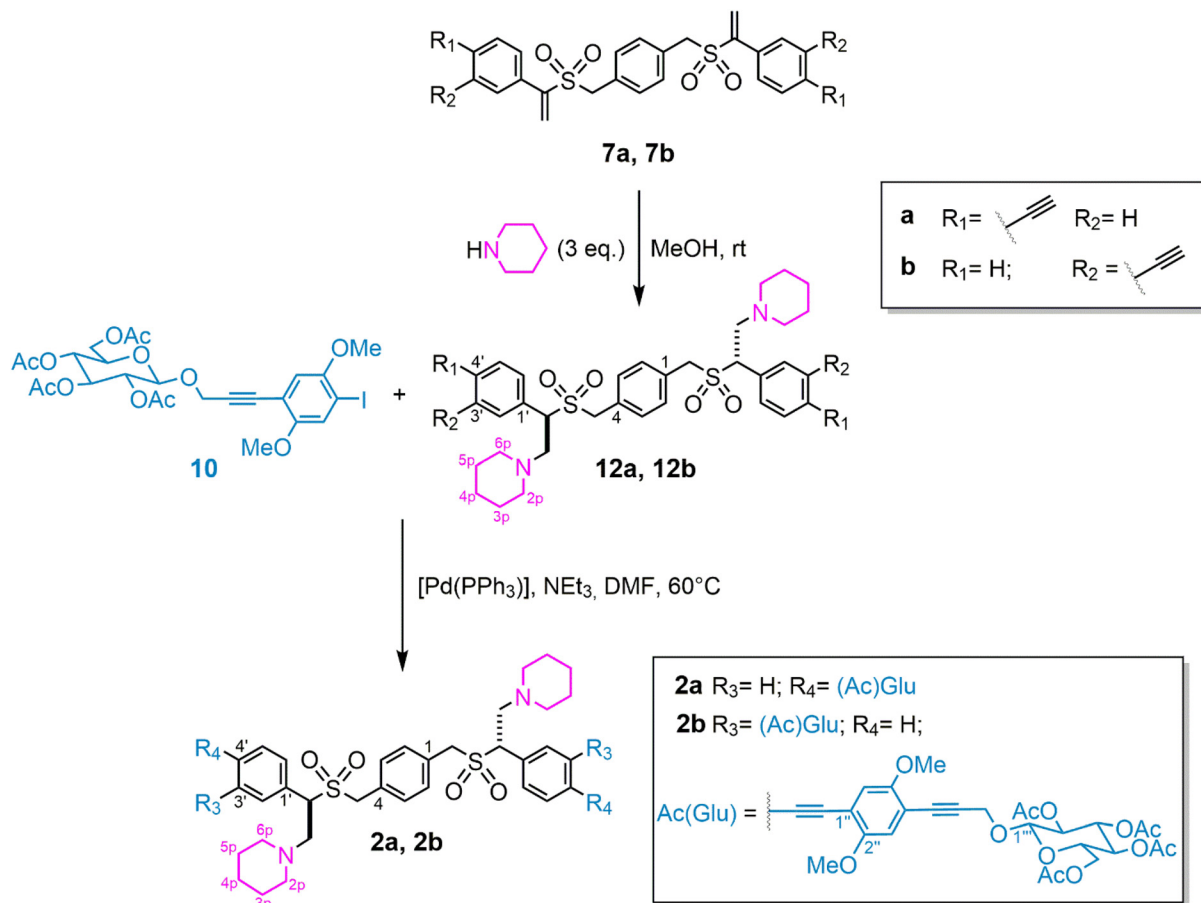This journal is © The Royal Society of Chemistry 2022

the generation of the sulfenyl moieties from bis-sulfoxide **5**, which thermolyzes at 83 °C in 1,2-dichloroethane (DCE), has a good shelf-life and can be easily handled. Methyl acrylate was indeed recognized as the best partner for the Michael-type addition of bis-thiol **3** compared to the previously adopted diethyl isopropylidenemalonate[22] that furnished unstable bis-sulfoxides and low final yield of the desired products. To favour the formation of open-chain compounds **6a** and **6b**, against the already reported cyclophanes (in this case isolated in very small percentages),[23] a large excess of *para-* and *meta-* diethynylbenzenes was used (Scheme 1).

Diastereomeric mixtures (due to the presence of two chiral sulfinyl groups) of **6a** and **6b** were isolated in a 70% total yield and subjected to 0 °C oxidation at the corresponding bis-vinyl sulfones **7a** and **7b**. With the two-site reactive central bricks in hand, the synthesis of the glucosyl arm **10** was performed using 1,4-diiodo-2,5-dimethoxybenzene[24] **9** and 1-(2-prop-1-ynyl)-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[25] **8** in a copper-free Sonogashira cross-coupling, with a 2 : 1 ratio.[26]

Compounds **11a** and **11b** were obtained by reacting separately the central cores **7** with the glucosyl arm **10** by a Sonogashira cross-coupling, again, copper-free to avoid homo-coupling side products and decay of the sugar function

(Scheme 1). Compounds **11a** and **11b** were purified and isolated in 49% and 46% yields, respectively.

Vinyl sulfones are known for their important role as key structural units of many biologically active compounds as well as versatile building blocks for various organic transformations.[27] From a synthetic point of view, they can act as efficient Michael acceptors and 2p donors in cycloaddition reactions. The presence of two vinyl sulfonyl units in the hydrophobic core of compounds **11** allowed us to exploit further modification of their backbones, such as the introduction of new functional groups *via* nucleophilic addition. Ammonia was used for the functionalization, leading to the insertion of two amino groups, which caused the formation of two new stereogenic carbon atoms, in the central region of compounds **11** and the contemporary desired deprotection from acetyl functions of the two glucosyl end-moieties (Scheme 2). Noteworthily, the two amino-functionalized bolaamphiphilic compounds **1a** and **1b** were obtained, simply after several washing steps with MeOH, as almost unique compounds, respectively. Solubility tests were performed to verify the amphiphilic nature of compounds **1** (see page S21 in the ESI†). We could not observe any trace of diastereomeric signals in the ^{1}H NMR spectra of each compound **1**(see the ESI†).

Scheme 3 General procedure for acetylated BAs **2**.

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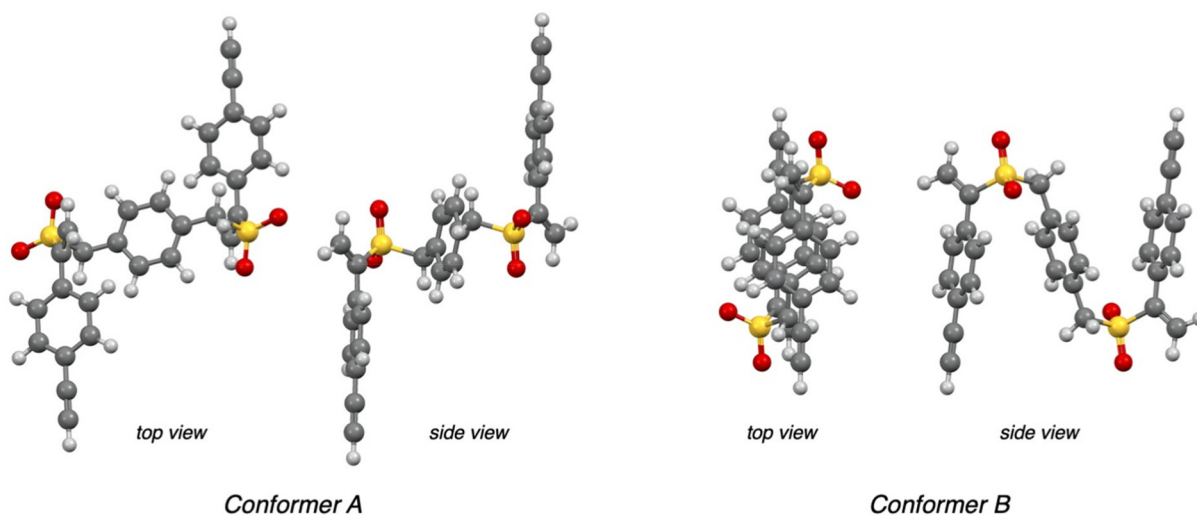*Org. Biomol. Chem.*, 2022, **20**, 7448–7457 | **7451**

Fig. 2 Top and side views of the optimized geometry (DFT, B3LYP/6-311++G(d,p)) of conformers A and B of compound **7a**.

The conformational mobility of platforms **7**, due to the presence of two –CH$_2$– moieties and three symmetrically disposed benzene rings, led us to assume a possible spatial arrangement of molecules **11** that could justify the unexpected stereochemical results. Thinking of a simpler model to study than molecules **11**, we decided to explore the reactivity of platforms **7a** and **7b** by using an excess of piperidine (Scheme 3). Compounds **12a** and **12b** were obtained separately, in quantitative yields, as unique products of the Michael-type reaction

(see the ESI†), requiring no further purification if not the removal of excess piperidine. The reproducibility of the stereochemical results, with a complete diastereoselectivity observed even in the case of compounds **12**, prompted us to investigate by computational methods the conformations of platform **7a** that could explain the preference toward one of the two diastereomeric products **12a**. Compound **7a** was subjected to an unrestricted conformer distribution calculation. Keeping in mind that **7a** possesses limited conformational flexibility,[28]
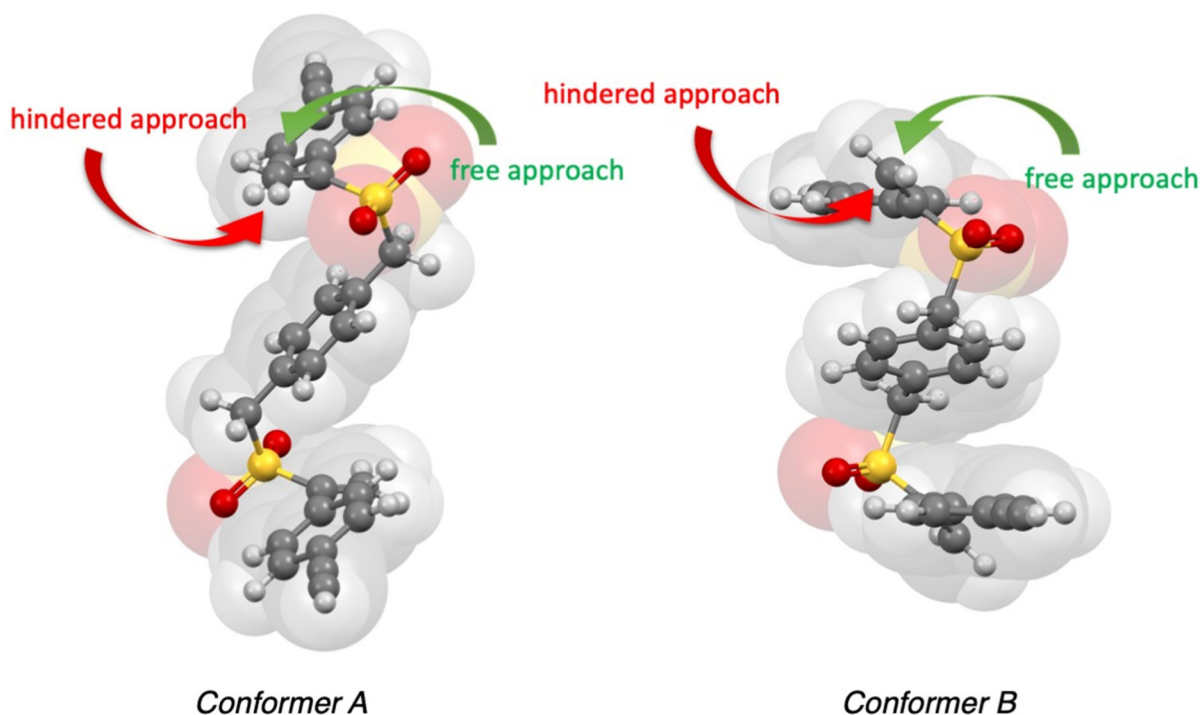

Fig. 3 Top and side views of the optimized geometry (DFT, B3LYP/6-311++G(d,p)) of conformers A and B of compound **7a**.

two relevant conformations emerged from the analysis, a 'zig-zag' (conformer A in Fig. 2) and a 'folded' one (B, Fig. 2). The geometry of these conformers was refined at the DFT level of theory, by using the hybrid B3LYP functional with a 6-311++G (d,p) basis set.

There are some evident differences, but they share a common feature, as in both cases the geometry is driven by internal π-stacking interactions. Conformer B presents the aromatic moieties arranged to maximize – as far as the limited conformational space allows – sandwich-type Ar·····π-stacking (4.20 Å centroid-to-centroid distance and 26.4° interplanar angle, see Fig. S1 in the ESI†). Conversely, alkene–arene π-stacking interactions[29] are predominant in conformer A, with the vinyl group located at 4.3 Å from the central phenylene moiety (59° angle, Fig. S1†). Interestingly, in both conformers the vinyl moiety lies on the same plane as one of the S=O bonds rather than that of the aryl ring, hinting more at a vinylsulfone Michael-type reactivity instead of a styrene-like one. Careful inspection of the two conformers suggests also that the intramolecular stacking interactions fix the position of the vinyl group practically differentiating its two faces (Fig. 3). As a consequence, the approach of a nucleophile (*e.g.*, ammonia and piperidine) should take place preferentially to the unhindered face of the vinyl group determining, once both vinyl moieties have reacted, the exclusive formation of the *meso*-stereoisomer from both conformers. Remarkably, in the recent literature, the facial selectivity of a Diels–Alder reaction between the acrylic ester derivative and cyclopentadiene was demonstrated to depend on an aryl–vinyl π-stacking intramolecular interaction that locked the conformation of one of the reactants.[30]

Pd-Catalysed copper-free Sonogashira cross-coupling was performed between the central bricks **12a** and **12b** and the glucosyl arm **10**, as previously described, leading to compounds **2a** and **2b** in 55% and 62% yields, respectively, demonstrating once again the potential of the reactive platform to be transformed into multifunctionalized BAs. The multivalent nature of BAs **1** and **2**, as well as the synthesis of new BAs through the exploitation of the same platforms, is now under study.

Conclusions

In this paper we have shown an easy, versatile and stereoselective synthetic procedure, to obtain bolaamphiphilic molecules, which couple one of the most applied reactions of sulfenic acids – the concerted addition to triple bonds – to the copper-free Sonogashira cross-coupling, in a convergent synthetic approach often used for the preparation of oligophenylenethynylenes (OPEs).[31]

The synthesis of a two-site reactive central core allows its further functionalization, such as the introduction of the two polar head groups *e.g.* carbohydrate residues – we have used a glucosyl derivative, but many other sugars can be adopted – or the transformation of the two vinyl sulfonyl moieties – we have reacted them with ammonia and piperidine, but any other nucleophiles can be easily introduced. This second synthetic target appears particularly significant if one accounts that the introduction of structural elements, such as a lateral side chains, in the hydrophobic region of BAs can lead to bolapolyphiles (BPs) that can self-assemble into versatile 2D structures, opening the route to new molecules with diverse physical properties and self-assembly characteristics. Finally, the observed stereochemical results make the two-site reactive platforms **7** significant bricks in the synthesis of several other molecular structures. Studies on their applications are ongoing.

Experimental section

Chemicals

Solvents were purified according to standard procedures. All the syntheses were monitored by TLC on commercially available precoated plates (silica gel 60 F254), and the products were visualized with vanillin [1 g dissolved in MeOH (60 mL) and conc. H_2SO_4 (0.6 mL)] and a UV lamp. Silica gel 60 was used for column chromatography.

Instrumentation

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian 500 spectrometer (at 500 MHz for ^1H and 125 MHz for ^{13}C) using $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts are given in parts per million (ppm) (δ relative to the residual solvent peak for ^1H and ^{13}C), coupling constants (J) are given in Hertz, and the attributions are supported by heteronuclear single-quantum coherence (HSQC) and correlation spectroscopy (COSY) experiments. Chemical shifts are reported in ppm relative to the residual $CHCl_3$ peak (7.26 ppm) or residual DMSO *peak* (2.49 ppm). Combustion analyses were carried out on a FISONS EA1108 elemental analyzer, and mass analysis of final products (**1a** and **1b**) was performed with a TSQ-Quantum access Triple Quadrupole Mass Spectrometer (Thermo Fisher Scientific, Waltham, MA, USA), equipped with a HESI (Heated ElectroSpray Ionization) source; analyses were run in positive mode. Mass spectrometer parameters were: sheath gas flow rate, 30 (arbitrary units); aux gas flow rate, 15 (arbitrary units); spray voltage, 5.00 kV; capillary temperature, 250° C; tube lens voltage, 55 V; heater temperature, 270 °C; and scan mode: full scan.

Computational studies

The conformational analysis of compound **7a** was carried out with the classical molecular mechanics force field (MMFF) by using the Monte Carlo method to randomly sample the conformational space. The equilibrium geometries were then calculated at the density functional level of theory (DFT, B3LYP functional) using the 6-311++G(d,p) basis set. All quantum mechanical calculations were performed using Spartan '10 (Wavefunction, Inc., Irvine, CA, USA).

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General procedure for the synthesis of compounds 6

To a solution of **5** (1 eq.) in DCE, commercial 1,4-diethynylbenzene (for compound **6a**) or commercial 1,3-diethynylbenzene (for compound **6b**) (6 eq.) was added and the mixture was stirred at reflux temperature for 24 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (*n*-hexane/ethyl acetate: 80 : 20). The diastereomeric mixtures of compounds **6a** or **6b** were obtained as described in the literature.[22]

General procedure for the synthesis of compounds 7

To a solution of the diastereomeric mixtures of **6a** or **6b** (1 eq.) in DCM, a solution of *m*-CPBA (2.5 eq. 80 wt%) in DCM was slowly added at 0 °C and under an argon atmosphere. The reaction mixture was warmed at r.t. and monitored by TLC (*n*-hexane/DCM 10 : 90) until the disappearance of the reagent. The reaction was quenched with the addition of an equal volume of an aqueous solution of $Na_2S_2O_3$ (10%w/w) and the organics washed with a sat. solution of $NaHCO_3$ (3 times) and brine (twice). The organic phase was dried with Na_2SO_4 and filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (*n*-hexane/DCM: 10 : 90) and **7a** or **7b** was obtained as a white solid.

1,4-Bis{[1-(4-ethynylphenyl)ethenylsulfonyl]methyl}-benzene (7a). (98%). TLC: R_f 0.72 (*n*-hexane/ethyl acetate 50 : 50). δH (500 MHz; CDCl$_3$) 7.55 (8H, m, 2× H-2′, 2× H-3′, 2× H-5′, 2× H-6′), 7.12 (4H, s, H-2, H-3, H-5, H-6), 6.32 and 6.00 (4H, two s, 2× =CH$_2$), 4.10 (4H, s, 2× SCH$_2$), 3.21 (2H, s, 2× ≡CH). δC (125 MHz; CDCl$_3$) 147.3 (q), 132.6 (q), 132.5 and 128.6 (C-2′, C-3′, C-5′, C-6′), 131.1 (C-2, C-3, C-5, C-6), 128.7 and 123.9 (q), 128.2 (=CH$_2$), 82.6 (q), 79.4 (≡CH), 58.5 (SCH$_2$). Anal. Calcd for C$_{28}$H$_{22}$O$_4$S$_2$ (486.60): C, 69.11; H, 4.56. Found: C, 69.07; H, 4.55.

1,3-Bis{[1-(4-ethynylphenyl)ethenylsulfonyl]methyl}-benzene (7b). (98%). TLC: R_f 0.70 (*n*-hexane/ethyl acetate 50 : 50). δH (500 MHz; CDCl$_3$) 7.64 (2H, s, 2× H-2′), 7.59 and 7.56 (4H, dd, $J_{4',5'} = J_{5',6'} = 7.9$, 2× H-4′, 2× H-6′), 7.39 (2H, t, $J_{2',3'} = J_{3',4'} = 7.9$, 2× H-5′), 7.13 (4H, s, H-2, H-3, H-5, H-6), 6.32 and 5.99 (4H, two s, 2× =CH$_2$), 4.10 (4H, s, 2× SCH$_2$), 3.15 (2H, s, 2× ≡CH). δC (125 MHz; CDCl$_3$) 147.2 (q), 133.4 and 129.0 (C-4′, C-5′, C-6′), 132.7 (q), 132.2 (C-2′), 131.1 (C-2, C-3, C-5, C-6), 129.0 and 123.0 (q), 128.2(=CH$_2$), 82.6 (q), 79.4 (≡CH), 58.5 (SCH$_2$). Anal. Calcd for C$_{28}$H$_{22}$O$_4$S$_2$ (486.60): C, 69.11; H, 4.56. Found: C, 68.98; H, 4.54.

General procedure for the synthesis of compounds 11

A solution of compound **11a** or **11b** (1 eq.), compound **10** (2.5 eq.) and [Pd(PPh$_3$)]$_4$ (0.1 eq.) in dry DMF and NEt$_3$ (1 : 1 ratio) was stirred at 60 °C, under an argon atmosphere for 2h, until the disappearance of the reagent by TLC (*n*-hexane/ethyl acetate 25 : 75). The solvent was removed under reduced pressure, the crude product was purified by column chromatography (DCM 100) and the desired product was obtained as a white solid.

Compound 11a. (49%). R_f 0.65 (DCM/ethyl acetate 80 : 20). δH (500 MHz; CDCl$_3$) 7.59 (8H, m, 2× H-2′, 2× H-3′, 2× H-5′, 2× H-6′), 7.10 (4H, s, H-2, H-3, H-5, H-6), 7.02 and 6.95 (4H, two s, 2× H-3″, 2× H-6″), 6.30 e 6.01 (4H, two s, 2× =CH$_2$), 5.25 (2H, t, $J_{2'',3''} = J_{3'',4''} = 9.8$, 2× H-3‴), 5.11 (2H, t, $J_{3'',4''} = J_{4'',5''} = 9.8$, 2× H-4‴), 5.04 (2H, dd, $J_{1'',2''} = 8.3$, $J_{2'',3''} = 9.8$, 2× H-2‴), 4.90 (2H, d, $J_{1'',2''} = 8.3$, 2× H-1‴), 4.65 (4H, s, 2× CH$_2$C≡), 4.26 and 4.16 (2H, split AB system, $J_{5'',6''A} = 4.4$, $J_{6''A,6''B} = 12.8$, 2× H$_2$-6‴), 4.10 (4H, s, 2× SCH$_2$), 3.89 and 3.88 (12H, two s, 4× –OCH$_3$), 3.75 (2H, m, 2× H-5‴), 2.07, 2.04, 2.02, and 2.01 (24H, four s, 8× CH$_3$CO). δC (125 MHz; CDCl$_3$) 170.6, 170.3, 169.4 and 169.3 (4× CO), 154.1 (q), 147.3 (q), 132.1 (q), 132.0 and 128.6 (C-2′, C-3′, C-5′, C-6′), 131.0 (C-2, C-3, C-5, C-6), 128.4 and 124.9 (q), 128.2 (=CH$_2$), 115.7 and 115.5 (C-3″, C-6″), 113.3 and 112.7 (q), 98.3 (C-1‴), 94.0, 89.2, 87.6 and 83.3 (q), 72.8 (C-3‴), 71.9 (C-5‴), 71.1 (C-2‴), 68.3 (C-4‴), 61.8 (C-6″), 58.5 (SCH$_2$), 57.0 (CH$_2$C≡), 56.4 and 56.3 (–OCH$_3$), 20.7, 20.6 and 20.5 (CH$_3$CO). Anal. Calcd for C$_{78}$H$_{78}$O$_{28}$S$_2$ (1527.57): C, 61.33; H, 5.15. Found: C, 61.27; H, 5.17.

Compound 11b. (46%), R_f 0.65 (DCM/ethyl Acetate 80 : 20). δH (500 MHz; CDCl$_3$) 7.74 (2H, s, 2× H-2′), 7.62 and 7.52 (4H, two d, $J_{4',5'} = J_{5',6'} = 7.5$, 2× H-4′, 2× H-6′), 7.40 (2H, t, $J_{4',5'} = J_{5',6'} = 7.5$, 2× H-5′), 7.13 (4H, s, H-2, H-3, H-5, H-6), 7.04 and 6.96 (4H, two s, 2× H-3″, 2× H-6″), 6.34 and 6.02 (4H, two s, 2× =CH$_2$), 5.27 (2H, t, $J_{2'',3''} = J_{3'',4''} = 9.5$, 2× H-3‴), 5.12 (2H, t, $J_{3'',4''} = J_{4'',5''} = 9.6$, 2× H-4‴), 5.05 (2H, dd, $J_{1'',2''} = 8.0$, $J_{2'',3''} = 9.8$, 2× H-2‴), 4.91 (2H, d, $J_{1'',2''} = 8.0$, 2× H-1‴), 4.66 (4H, s, 2× CH$_2$C≡), 4.29 and 4.17 (2H, split AB system, $J_{5'',6''A} = 4.5$, $J_{6''A,6''B} = 12.5$, 2× H$_2$-6‴), 4.13 (4H, s, 2× SCH$_2$), 3.89 (12H, s, 4× OCH$_3$), 3.76 (2H, m, 2× H-5‴), 2.08, 2.05, 2.03, and 2.01 (24H, four s, 8× CH$_3$CO). δC (125 MHz; CDCl$_3$) 170.7, 170.3, 169.5 and 169.4 (4× CO), 154.1 and 153.9 (q), 147.4 (q), 132.9, 128.9 and 128.8 (C-4′, 5′, 6′), 132.7 (q), 131.6 (C-2′), 131.1 (C-2, C-3, C-5, C-6), 128.7 and 124.0 (q), 128.2 (=CH$_2$), 115.7 and 115.6 (C-3″, C-6″), 113.3 and 112.6 (q), 98.3 (C-1‴), 93.9, 89.2, 86.6 and 83.3 (q), 72.8 (C-3‴), 71.9 (C-5‴), 71.1 (C-2‴), 68.3 (C-4‴), 61.8 (C-6‴), 58.6 (SCH$_2$), 57.0 (CH$_2$C≡), 56.5 and 56.4 (–OCH$_3$), 20.7, 20.6 and 20.5 (CH$_3$CO). Anal. Calcd for C$_{78}$H$_{78}$O$_{28}$S$_2$ (1527.57): C, 61.33; H, 5.15. Found: C, 61.55; H, 5.13.

General procedure for the synthesis of compounds 1

Compound **11a** or **11b** (0.2 mmol) was dissolved in THF–MeOH (1 : 1, 40 mL). A large excess of aqueous ammonia (12 mL) was added, and the reaction mixture was continuously stirred at r.t. overnight, until the disappearance of the starting product by TLC (*n*-hexane/ethyl acetate 40 : 60). Solvents were removed under reduced pressure and several washings with Et$_2$O were performed to purify the product from the undesired acetamide.[25]

Compound 1a. (98%) R_f 0.01 (ethyl acetate 100). δH (500 MHz; DMSO-d_6) 7.57 and 7.44 (8H, two d, $J = 8.4$, 2× H-2′, 2× H-3′, 2× H-5′, 2× H-6′), 7.33 (4H, s, H-2, H-3, H-5, H-6), 7.16 and 7.08 (4H, two s, 2× H-3″, 2× H-6″), 5.12 (2H, d, $J = 4.8$, 2× –OH), 4.96 (2H, d, $J = 4.4$, 2× –OH), 4.91 (2H, d, $J = 5.4$, 2× –OH), 4.67 (2H, part A of AB system, d, $J = 15.5$, 2× CH$_2$C≡),

4.6–4.5 (6H, m, 2× CH_2C≡; 2× CH_2S; 2× –OH-6‴), 4.44 (2H, dd, J_{vic} = 5.5, J_{vic} = 4.1, 2× –CHCH$_2$NH$_2$), 4.38–4.32 (4H, m, 2× –CH_2S and 2× H-1‴), 3.82 and 3.81 (12H, two s, 4× –OCH$_3$), 3.71–2.95 (16H, m, 2× H$_2$-6‴, 2× H-5‴, 2× H-4‴, 2× H-3‴, 2× H-2‴, 2× –CHCH_2NH$_2$). δC (125 MHz; DMSO-d_6) 154.1 and 153.9 (q), 133.3 (q), 131.9 and 130.9 (C-2′, C-3′, C-5′, C-6′), 131.7 (C-2, C-3, C-5, C-6), 128.4 and 123.0 (q), 116.3 and 116.0 (C-3″, C-6″), 112.9 and 112.7 (q), 101.6 (C-1‴), 94.6, 91.7, 87.1 and 82.5 (q), 77.5, 77.1, 73.7 and 70.5 (C-2‴, C-3‴, C-4‴, C-5‴), 69.9 (–$\underline{C}$HCH$_2$NH$_2$), 61.6 (C-6‴), 57.6 (–CH$_2$S), 56.6 and 56.2 (–OCH$_3$), 56.2 (–CH$_2$C≡), 41.8 (–CHCH$_2$NH$_2$). Anal. Calcd for C$_{62}$H$_{68}$N$_2$O$_{20}$S$_2$ (1225.34): C, 60.77; H, 5.59; N, 2.29. Found: C, 60.82; H, 5.60; N, 2.29. ESI(+)-MS m/z calcd for C$_{62}$H$_{68}$N$_2$O$_{20}$S$_2$ ([M + H]$^+$) 1226.35, found 1226.32 and 613.23 ([M + 2H]$^{2+}$).

Compound 1b. (98%) R_f 0.01 (ethyl acetate 100). δH (500 MHz; DMSO-d_6) δ 7.54 (4H, br s, 2× H-2′, 2× H-5′), 7.47–7.43 (4H, m, 2× H-4′, 2× H-6′), 7.34 (4H, s, H-2, H-3, H-5, H-6), 7.17 and 7.09 (4H, two s, 2× H-3″, 2× H-6″), 5.14 (2H, br s, 2× OH), 4.92 (2H, br s, 2× OH), 4.69 (2H, br s, 2× OH), 4.68 (2H, part A of AB system, d, J = 15.5, 2× CH_2C≡), 4.60–4.53 (6H, m, 2× CH_2C≡, 2× CH_2S; 2× –OH-6‴), 4.44 (2H, br t, J = 5.5; 2× –CHCH$_2$NH$_2$), 4.38–4.31 (4H, m, 2× –CH_2S and 2× H-1‴), 3.82 and 3.81 (two s, 12H, 4× –OCH$_3$), 3.72–2.98 (16H, m, 2× H$_2$-6‴, 2× H-5‴, 2× H-4‴, 2× H-3‴, 2× H-2‴, 2× –CHCH_2NH$_2$). δC (125 MHz; DMSO-d_6) 153.7 and 153.4 (q), 132.7 (q), 131.4 and 131.3 (C-2′, C-5′, C-2, C-5), 129.1 (C-4′, C-6′) 127.9 and 122.6 (q), 115.8 and 115.6 (C-3″, C-6″), 112.4 and 112.3 (q), 101.1 (C-1‴) 94.1, 91.2, 86.3 and 82.0 (q), 77.0, 76.7, 73.3 and 70.1 (C-2‴, C-3‴, C-4‴, C-5‴), 69.3 (–$\underline{C}$HCH$_2$NH$_2$), 61.2 (C-6‴), 57.2 (–CH$_2$S), 56.2 and 56.1 (–OCH$_3$), 55.8 (–CH$_2$C≡), 41.3 (–CHCH$_2$NH$_2$). Anal. Calcd for C$_{62}$H$_{68}$N$_2$O$_{20}$S$_2$ (1225.34): C, 60.77; H, 5.59; N, 2.29. Found: C, 60.84; H, 5.57; N, 2.29. ESI (+)-MS m/z calcd for C$_{62}$H$_{68}$N$_2$O$_{20}$S$_2$ ([M + H]$^+$) 1226.35, found 1226.26 and 613.24 ([M + 2H]$^{2+}$).

General procedure for the synthesis of compounds 12

To a solution of **7a** or **7b** (1 eq.) in MeOH, piperidine (3.2 eq.) was added and the reaction mixture was stirred at r.t., under an argon atmosphere, until the disappearance of the starting product by TLC (n-hexane/ethyl acetate 50:50). The solvent was evaporated under reduced pressure. The desired product **12a** or **12b** was obtained without requiring any further purification, after removing excess piperidine under vacuum.

Compound 12a. (98%). R_f 0.43 (n-hexane/ethyl acetate 50:50). δH (500 MHz; CDCl$_3$) 7.48 and 7.27 (H, two d, J_{orto} = 7.8, 2× H-2′, 2× H-3′, 2× H-5′, 2× H-6′), 7.41 (4H, s, H-2, H-3, H-5, H-6), 4.47 and 4.38 (4H, AB system, J_{gem} = 13.2, 2× SCH$_2$), 4.19 (2H, part X of ABX system, J_{vic1} = 7.3, J_{vic2} = 4.4, 2× –CHCH$_2$Pi), 3.50 and 2.84 (4H, part A and B of ABX system, J_{gem} = 13.6 J_{vic1} = 7.3 J_{vic2} = 4.4, 2× –CHCH_2Pi), 3.11 (2H, s, 2× ≡CH), 2.47 (8H, m, 2× H$_2$-2p, 2× H$_2$-6p), 1.43 (8H, m, 2× H$_2$-3p, 2× H$_2$-5p), 1.26 (4H, m, 2× H$_2$-4p). δC (125 MHz; CDCl$_3$) 132.8 (q), 132.5 and 129.7 (C-2′, C-3′, C-5′, C-6′), 131.5 (C-2, C-3, C-5, C-6), 128.4 and 122.8 (q), 82.9 (q), 78.3 (≡CH), 65.2 (–CHCH$_2$Pi), 59.2 and 59.1 (SCH$_2$, –CHCH_2Pi), 54.8 (C-2p, C-6p), 26.0 (C-3p, C-5p), 24.0 (C-4p). Anal. Calcd for

C$_{38}$H$_{44}$N$_2$O$_4$S$_2$ (656.90): C, 69.48; H, 6.75; N, 4.26. Found: C, 69.33; H, 6.73; N, 4.25.

Compound 12b. (98%) R_f 0.41 (n-hexane/ethyl acetate 50:50). δH (500 MHz; CDCl$_3$) δ 7.52–7.20 (8H, m, 2× H-2′, 2× H-4′, 2× H-5′, 2× H-6′), 7.42 (4H, s, H-2, H-3, H-5, H-6), 4.48 and 4.41 (4H, AB system, J_{gem} = 14.2, 2× SCH$_2$), 4.19 (2H, part X of ABX system, J_{vic1} = 7.8, J_{vic2} = 4.6, 2× –CHCH$_2$Pi), 3.50 and 2.83 (4H, part A and B of ABX system, J_{gem} = 13.2, J_{vic1} = 7.8, J_{vic2} = 4.6, 2× –CHCH_2Pi), 3.17 (2H, s, 2× ≡CH), 2.47 (8H, m, 2× H$_2$-2p, 2× H$_2$-6p), 1.43 (8H, m, 2× H$_2$-3p, 2× H$_2$-5p), 1.25 (4H, m, 2× H$_2$-4p). δC (125 MHz; CDCl$_3$) 133.3, 132.6, 130.1 and 128.8 (C-2′, C-4′, C-5′, C-6′), 132.5 (q), 131.5 (C-2, C-3, C-5, C-6), 128.5 and 122.8 (q), 82.9 (q), 78.0 (≡CH), 65.0 (–CHCH$_2$Pi), 59.4 and 59.2 (SCH$_2$ and –CHCH_2Pi), 54.8 (C-2p, C-6p), 26.0 (C-3p, C-5p), 24.0 (C-4p). Anal. Calcd for C$_{38}$H$_{44}$N$_2$O$_4$S$_2$ (656.90): C, 69.48; H, 6.75; N, 4.26. Found: C, 69.55; H, 6.76; N, 4.27.

General procedure for the synthesis of compounds 2

Compounds **2** were obtained following the general procedure for the synthesis of compounds **11**. The mixture was reacted until the disappearance of compounds **12** by TLC (n-hexane/ethyl acetate: 40:60). The solvents were removed under reduced pressure and the reaction crude products were purified by column chromatography (n-hexane/ethyl acetate: 40:60). The desired products **2** were obtained as white solids.

Compound 2a. (55% yield) R_f 0.12 (n-hexane/ethyl acetate 40:60). δH (500 MHz; CDCl$_3$) 7.55 and 7.33 (8H, AA′XX′ system, J_{orto} = 8.0, 2× H-2′, 2× H-3′, 2× H-5′, 2× H-6′), 7.41 (4H, s, H-2, H-3, H-5, H-6), 7.00 and 6.93 (4H, two s, 2× H-3″, 2× H-6″), 5.26 (t, $J_{2‴,\,3‴}$ = $J_{3‴,\,4″}$ = 9.0, 2× H-3‴), 5.11 (2H, t, $J_{3‴,\,4″}$ = $J_{4″,\,5‴}$ = 9.0, 2× H-4″), 5.04 (2H, t, $J_{1‴,\,2″}$ = $J_{2″,\,3″}$ = 9.0, 2× H-2‴), 4.90 (2H, d, $J_{1‴,\,2″}$ = 9, 2× H-1‴), 4.64 (4H, s, 2× CH$_2$C≡), 4.48–4.15 (10H, m, 2× SCH$_2$, 2× –CHCH$_2$Pi, 2× H$_2$-6‴), 3.87 (12H, s, 4× OCH$_3$), 3.76 (2H, m, 2× H-5‴), 3.54 and 2.90 (4H, m AB of an ABX system, 2× –CHCH_2Pi), 2.49 (8H, m, 2× H$_2$-2p, 2× H$_2$-6p), 2.07, 2.04, 2.02 and 2.00 (24H, four s, 8× CH$_3$CO), 1.57 (8H, m, 2× H$_2$-3p, 2× H$_2$-5p), 1.42 (4H, m, 2× H$_2$-4p). δC (125 MHz; CDCl$_3$) 170.7, 170.3, 169.5 and 169.4 (4× –CO), 154.1 and 154.0 (q), 132.1 and 129.9 (C-2′, C-3′, C-5′, C-6′), 131.6 (C-2, C-3, C-5, C-6), 128.7, 128.3 and 124.1 (q), 115.7 and 115.6 (C-3″, C-5″), 114.6 and 112.4 (q), 98.2 (C-1‴), 94.3, 89.1, 86.7 and 83.3 (q), 72. 8 (C-3‴), 71.9 (C-5‴), 71.0 (C-2‴), 68.1 (C-4‴), 65.3 (–CHCH$_2$Pi), 61.8 (C-6‴) 59.0 and 58.9 (SCH$_2$, –CHCH_2Pi), 57.1 (–CH$_2$C≡), 56.5 and 56.3 (–OCH$_3$), 54.8 (C-2p, C-6p), 25.5 (C-3p, C-5p), 23.6 (C-4p), 20.8, 20.7, 20.6 and 20.5 (CH$_3$CO). Anal. Calcd for C$_{88}$H$_{100}$N$_2$O$_{28}$S$_2$ (1697.86): C, 62.25; H, 5.94; N, 1.65. Found: C, 62.31; H, 5.93; N, 1.65.

Compound 2b. (62%), R_f 0.13 (n-hexane/ethyl acetate 40:60). δH (500 MHz; CDCl$_3$) 7.67–7.28 (8H, m, 2× H-2′, 2× H-4′, 2× H-5′, 2× H-6′), 7.45 (4H, s, H-2, H-3, H-5, H-6), 7.01 and 6.94 (4H, two s, 2× H-3″, 2× H-6″), 5.27 (2H, t, $J_{2″,\,3‴}$ = $J_{3‴,\,4″}$ = 9.0, 2× H-3‴), 5.12 (2H, t, $J_{3‴,\,4‴}$ = $J_{4″,\,5‴}$ = 9.0, 2× H-4‴), 5.05 (2H, br t, 2× H-2‴), 4.91 (2H, d, $J_{1‴,\,2″}$ = 8.0, 2× H-1‴), 4.65 (4H, s, 2× CH$_2$C≡), 4.53–4.12 (10H, m, 2× SCH$_2$, 2× –CHCH$_2$Pi, 2× H$_2$-6‴), 3.87 (12H, s, 4× OCH$_3$), 3.77 (2H, m, 2× H-5‴), 3.57

and 3.1 (4H, m AB of an ABX system, 2× –CHC*H*$_2$Pi), 2.53 (8H, m, 2× H$_2$-2p, 2× H$_2$-6p), 2.08, 2.05, 2.03 and 2.01 (24H, four s, 8× CH$_3$CO), 1.66 (8H, m, 2× H$_2$-3p, 2× H$_2$-5p), 1.42 (4H, m, 4H, 2× H$_2$-4p). δC (125 MHz; CDCl$_3$) 170.8, 170.4, 169.6 and 169.5 (4× –CO), 154.1 and 153.9 (q), 132.3, 131.8, 128.7 and 128.5 (C-2′, C-3′, C-5′, C-6′, C-2, C-3, C-5, C-6), 130.6, 128.4 and 124.3 (q), 115.9 and 115.8 (C-3″, C-6″), 113.6 and 112.6 (q), 98.2 (C-1″′), 94.3, 89.3, 86.6 and 83.5 (q), 72. 9 (C-3″′), 72.0 (C-5″′), 71.3 (C-2″′), 68.4 (C-4″′), 62.0 (–*C*HCH$_2$Pi), 61.9 (C-6″′), 59.9 (SCH$_2$), 57.1 (*C*H$_2$C≡), 56.6 and 56.5 (–OCH$_3$), 55.1 (C-2p, C-6p), 46.1 (–CHCH$_2$Pi), 29.6 (C-3p, C-5p), 23.5 (C-4p), 21.1 and 20.1 (*C*H$_3$CO). Anal. Calcd for C$_{88}$H$_{100}$N$_2$O$_{28}$S$_2$ (1697.86): C, 62.25; H, 5.94; N, 1.65. Found: C, 62.49; H, 5.92; N, 1.65.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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