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Efficient Synthesis of Unsymmetrical Disulfides through Sulfenic Acids

Maria Chiara Aversa,[a] Anna Barattucci,*[a] and Paola Bonaccorsi[a]

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Unsymmetrical disulfides, some of which are biologically interesting, were prepared by the in situ generation of sulfenic acids from suitable sulfinyl precursors and their coupling with various thiols. This methodology represents an efficient and mild procedure to obtain disulfides in excellent yields. It allows the presence of base/acid and/or thermolabile functional groups in both the sulfenic acid and the thiol on the basis of the choice of suitable sulfenic acid precursors and offers wide chances of modulating the construction of the disulfide bridge between different structural skeletons such as homo- and heteroaromatic, amino acidic and sugar residues.

Introduction

The disulfide bridge plays a pivotal role in the structure and stability of many proteins. The covalent bond between the sulfur atoms of cysteine residues has been studied by biologists to understand how it is formed, how it can be cleaved and how it participates in protein folding.[1] Synthetic chemists have developed different and efficient routes to build the disulfide bond between glycose and peptide residues with the idea of developing straightforward syntheses of hydrolysis-resistant carbohydrate mimics for applications in glycobiology and medicinal research.[2] Replacement of the anomeric oxygen atom by a sulfur atom in glycopeptides leads to modifications that are tolerated by most biological systems and are less susceptible to acid/base or enzyme-mediated hydrolysis. In both cases, the deepened investigation on the disulfide bond has represented a useful tool for the progress of scientific knowledge into secrets of biology.

The synthesis of unsymmetrical disulfides, in particular, has attracted the attention of several research groups, and several methodologies have been developed for the preparation of various types of disulfides.[3] Few of these methods employ mild and efficient conditions that do not require the use of toxic reagents. The most popular approach involves substitution of a sulfenyl derivative with a thiol or its derivative. Herein two recent examples are reported that illustrate this approach. An efficient synthesis of glycopeptides and glycoproteins showing the disulfide linker was conducted by Davis and co-workers[4] by combining site-directed cysteine mutagenesis with the reaction between its thiol residue and glycosyl methane- or benzenethiosulfonate reagents. A new synthetic route to ω-functionalized alkane asymmetric disulfides, involving dialkoxylthiophosphoranesulfenyl halide precursors, has been described.[5] This procedure has been demonstrated to be efficient even in the presence of more nucleophilic groups than the mercaptan function: disulfides bearing acidic and basic terminal moieties as well as groups used in biospecific self-assembly monolayers have been prepared. Few examples of one-pot formations of the disulfide bond are reported. Very recently, the one-pot synthesis of unsymmetrical disulfides by using 1-chlorobenzotriazole was described.[6] 1-Chlorobenzotriazole was used as an environmentally friendly oxidizing source to convert a thiol into a *N*-sulfenyl derivative that could react in situ with a different thiol. Mild conditions were adopted in a one-pot procedure that makes use of diethyl azodicarboxylate to obtain a series of glycosyl disulfides in good to excellent yields.[7]

It is well accepted that oxidation of the cysteine side chain involving disulfide bond formation is initiated by the generation of cysteine sulfenic acid.[8] Sulfenic acids are generally too unstable to be isolated and self-condense to give thiosulfinates.[9] However, Okazaki and Goto[10] synthesized a stable arenesulfenic acid bearing a bowl-shaped macrobicyclic cyclophane skeleton and treated it with a large excess of 1-butanethiol, affording the corresponding disulfide almost quantitatively. The bivalence of this result is very well expressed by the authors who described the event as "reminiscent of the formation of stable sulfenic acid intermediates from cysteine in the active sites of some enzymes, where the structural features of the environment around the SOH group are believed to prevent its self-condensation" and "the first conclusive demonstration of disulfide formation from the reaction of a sulfenic acid with a

[a] Dipartimento di Chimica organica e biologica, Università degli Studi di Messina,
Salita Sperone 31 (vill. S. Agata), 98166 Messina, Italy
Fax: +39-090-393895
E-mail: anna.barattucci@unime.it

thiol". This reaction has been used several times for trapping transient sulfenic acids, owing to the stability of the produced unsymmetrical disulfides,[11] but, to the best of our knowledge, it has never been regarded as a general methodology for the synthesis of disulfides, including unsymmetrical ones bearing bioresidues.

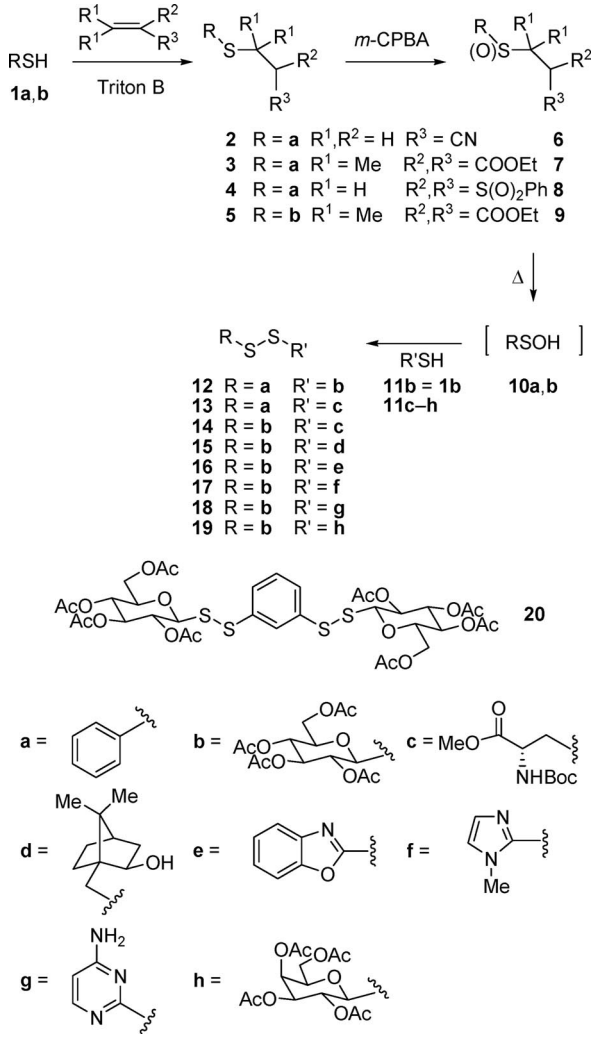
In accordance with our research interests devoted to the development of synthetic procedures that involve sulfenic acids as intermediates,[12] we describe in this paper their in situ generation, from suitable sulfinyl precursors, and their coupling with various thiols in an efficient and mild process to obtain unsymmetrical disulfides in excellent yields, some of which are of biological interest.

Results and Discussion

The synthetic strategy is illustrated in Scheme 1 and the results are shown in Table 1. Two steps were required to convert thiols **1a**,**b** into sulfinyl precursors **6**–**9** of the corresponding sulfenic acids **10a**,**b**, through sulfides **2**–**5**.[12a,12b,12e,12h] Thermolysis of sulfoxides **6**–**9** that generate transient sulfenic acids **10a**,**b** was performed in the presence of thiols **11b**–**h** and 1,3-benzenedithiol (**21**) with an almost 2:1 sulfoxide/thiol group ratio (Table 1). The in situ coupling between intermediates **10a**,**b** and thiols **11b**–**h** or 1,3-benzenedithiol (**21**) led to the formation of unsymmetrical disulfides **12**–**20**, together with minor byproducts coming from sulfenic acid autocondensation, which were easily removed by flash chromatography (see Experimental Section). This last reaction occurs without base or acid promoters at reaction temperatures below 100 °C, allowing the presence of base/acid-sensitive functional groups in both the sulfenic acid and the thiol.

During the last decade, we have gained expertise in the choice and preparation of sulfenic acid precursors.[12b,12h,13] Entries 2–4 in Table 1 show how the use of sulfoxides **6**–**8**, as precursors of sulfenic acid **10a**, in the presence of thiol **11c**, allows the formation of disulfide **12** under different reaction conditions but always in excellent yields. This result can be regarded as indicative of the possible selection of the sulfenic acid precursor, in dependence of the structural demands of the desired disulfide. For example, sulfoxide **8** (Table 1, Entry 4) affords sulfenic acid **10a** at room temperature,[13] as required when temperature-sensitive residues should be included in the disulfide skeleton. Furthermore, the use of 1-thio-β-D-glucopyranose 2,3,4,6-tetraacetate (**1b** = **11b**) either as starting compound **1b** in the synthesis of sulfenic acid precursor **9** (Table 1, Entries 5–11) or as sulfenic acid acceptor **11b** (Table 1, Entry 1) evidences the wide chances that this route offers of modulating the synthesis of unsymmetrical disulfides from thiols.

Most unsymmetrical disulfides obtained with this methodology possess a glucosyl residue and were prepared by thermolysis of sulfoxide **9** in the presence of various thiols, always with the maintenance of the anomeric β-stereochemistry. In particular, the reaction between glucosulfenic acid **10b**, generated from sulfinyl precursor **9**, and *N*-Boc-protected cysteine methyl ester **11c** is reported in Entry 5 (Table 1). The formation of disulfide **14**[14] can be regarded as an alternative to the glycosylation of proteins by the use of glycosyl methane- or benzenethiosulfonates.[4]

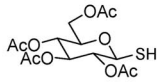
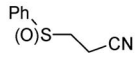
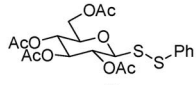
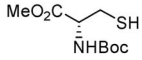
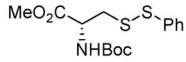
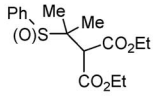
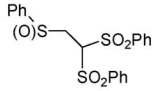
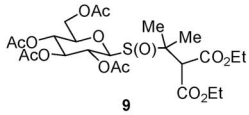
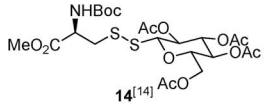
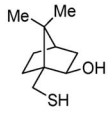
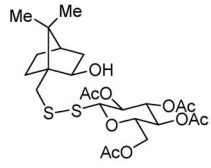
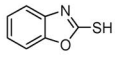
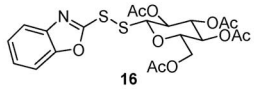
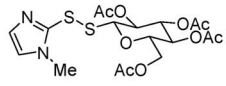
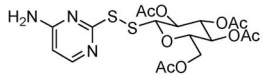
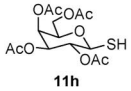
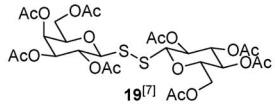
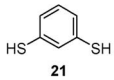
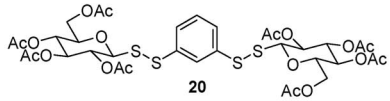


Scheme 1. Synthesis of unsymmetrical disulfides **12**–**20**.

The disulfide bridge has recently been introduced into carbohydrate chemistry as a new interglycosidic linker that offers some advantages in terms of flexibility, increased distance between the two glycosidic components, and opportunity to vary the monosaccharide units.[15] Sulfenic acid/thiol coupling allows the formation of disaccharide mimics such as compound **19** in excellent yield under mild conditions (Table 1, Entry 10).

Benzene-spaced bis-β-D-glucopyranosyl disulfide **20** (Table 1, Entry 11) was obtained as part of our research programme centred on the study of the relationship between molecular structure and biological activity of tailored small molecules containing two glucopyranosyl units separated by thioarene spacers.[16] The biopotentialities of bisdisulfide **20** are under study. Biologically significant heteroaromatic scaffolds have been also linked to the glucosyl resi-

Table 1. Synthesis of unsymmetrical disulfides **12**–**20**.

Entry	Thiol	Sulfenic acid precursor	Reaction conditions[a]	Disulfide	Yield [%]
1	 **1b = 11b**	 **6**	$ClCH_2CH_2Cl$, reflux, overnight	 **12**[7]	>90
2	 **11c**	**6**	$ClCH_2CH_2Cl$, reflux, 40 h	 **13**	80
3	**11c**	 **7**	CH_2Cl_2, reflux, overnight	**13**	85
4	**11c**	 **8**	CH_2Cl_2, r.t., overnight	**13**	85
5	**11c**	 **9**	CH_2Cl_2, reflux, overnight	 **14**[14]	80
6	 **11d**	**9**	CH_2Cl_2, reflux, overnight	 **15**	>90
7	 **11e**	**9**	CH_2Cl_2, reflux, overnight	 **16**	>90
8	 **11f**	**9**	CH_2Cl_2, reflux, overnight	 **17**	>90
9	 **11g**	**9**	MeC(=O)Me, 45 °C, overnight	 **18**	>90
10	 **11h**	**9**	CH_2Cl_2, reflux, overnight	 **19**[7]	82
11	 **21**	**9**	CH_2Cl_2, reflux, overnight	 **20**	50

[a] All the reactions were conducted with a 2:1 molar ratio of sulfenic acid precursor/thiol except for entry 6 (**9**/**21** molar ratio 5:1).

due by the disulfide bridge in compounds **17** and **18** (Table 1, Entries 8 and 9). In particular, disulfide **18**, obtained in excellent yield from the condensation of 2-thiocytosine (**11g**) with sulfenic acid **10b** in acetone at 45 °C, represents a promising candidate to the discovery of new antiviral and anticancer agents.[17]

Conclusions

Although the overall synthetic procedure described in this paper is well known,[9b] to the best of our knowledge, it has never been used before as a general methodology for the preparation of unsymmetrical disulfides. It is a three-

step procedure that offers the possibility of reacting structurally complex thiols. The possible choice among different sulfenic acid precursors, obtained from the same thiol, allows the involvement of starting compounds carrying base/acid-sensitive and thermolabile functional groups. Disulfides **13**, **15**–**18** and **20** have not been described previously in the literature.

Experimental Section

General: Solvents were purified according to standard procedures. Petroleum ether used refers to the fraction boiling at 40–60 °C. All reactions were monitored by TLC on commercially available precoated plates (Aldrich silica gel 60 F_{254}) eluted with light petroleum/ethyl acetate (1:1), and the products were visualized with vanillin [1 g dissolved in MeOH (60 mL) and conc. H_2SO_4 (0.6 mL)]. Silica gel used for column chromatography was Aldrich 60. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury 300 spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$ solutions with $SiMe_4$ as internal standard; the attributions are supported by Attached Proton Test (APT) and homodecoupling experiments; proton and carbon nuclei identified by apex pertain to phenyl group in compound **13**, to isoborneol residue in **15** and to heteroaromatic substituents in **16**–**18**, whereas single and double apex identify proton and carbon nuclei of the two glucose residues in the bisdisulfide **20**.

General Procedure for the Preparation of Disulfides 12–20: Solvents, molar ratios, reaction times, temperatures and yields are indicated in Table 1. A 0.2 M solution of the sulfenic acid precursor was added to a 0.2 M solution of the thiol. The reaction, monitored by TLC, was conducted until the sulfenic acid precursor disappeared. All the obtained disulfides were purified by flash chromatography. The undesired byproducts were always first eluted from the column, and not characterized. Spectral and analytical data were consistent to those reported in the literature for disulfides **12** [241.0 mg, 0.51 mmol, 93% yield, from 200.0 mg, 0.55 mmol, of **1b** (= **11b**),], **14** (406.4 mg, 0.68 mmol, 80% yield, from 200.0 mg, 0.85 mmol, of **11c**) and **19** (327.0 mg, 0.45 mmol, 82% yield, from 200.0 mg, 0.55 mmol, of **11h**).[7,17]

***N*-[(1,1-Dimethylethoxy)carbonyl]-*S*-(phenylthio)-L-cysteine Methyl Ester (13):** Colourless oil [from 200.0 mg, 0.85 mmol, of **11c**, 233.6 mg, 0.68 mmol, 80% yield (Entry 2, Table 1) or 248.1 mg, 0.72 mmol, 85% yield (Entries 3 and 4) of **13** were obtained]. R_f = 0.75. ^{1}H NMR: δ = 7.5–7.2 (m, 5 H, H_{arom}), 5.29 (br. d, 1 H, NH), 4.60 (br. q, 1 H, 2-H), 3.72 (s, 3 H, OMe), 3.18 (m, 2 H, 3-H_2), 1.42 (s, 9 H, CMe_3) ppm. ^{13}C NMR: δ = 171.1 (C-1), 154.6 (NHC=O), 136.6 (C-1′), 129.1, 128.3 and 127.4 (C-2′-6′), 80.2 (*C*Me_3), 52.8 (C-2), 52.6 (OMe), 40.9 (C-3), 28.3 (C*Me*$_3$) ppm. $C_{15}H_{21}NO_4S_2$ (343.46): calcd. C 52.45, H 6.16, N 4.08; found C 52.49, H 6.15, N 4.10.

1-[(1*S*)-Isoborneol-10-dithio]-1-deoxy-β-D-glucopyranose 2,3,4,6-Tetraacetate (15): White crystals, m.p. 128–130 °C (559.6 mg, 1.02 mmol, 95% yield, from 200.0 mg, 1.07 mmol, of **11d**). R_f = 0.61. ^{1}H NMR: δ = 5.21 (m, 2 H, 2-H and 3-H), 5.08 (m, 1 H, 4-H), 4.57 (d, $J_{1,2}$ = 9.2 Hz, 1-H), 4.17 (m, 2 H, 6-H_2), 3.96 (m, 1 H, 2′-H), 3.77 (m, 1 H, 5-H), 3.26 (AB d, $J_{10'A,10'B}$ = 12.0 Hz, 1 H, 10′-H_A), 2.76 (AB d, 1 H, 10′-H_B), 2.60 (br. s, 1 H, OH), 2.15, 2.02, 2.01 and 1.99 [4 s, 12 H, 4× C(O)Me], 1.8–1.1 (m, 7 H, 3′-H_2, 4′-H, 5′-H_2, and 6′-H_2), 0.98 and 0.78 (2 s, 6 H, 8′-H_3 and 9′-H_3) ppm. ^{13}C NMR: δ = 170.6, 170.2, 169.3 and 169.2 [4× *C*(O)Me], 88.1 (C-1), 76.2, 75.9, 73.7, 69.1 and 68.0 (C-2,2′,3,4,5), 62.0 (C-6), 53.2 (C-1′), 48.0 (C-7′), 45.1 (C-4′), 40.0 and 39.2 (C-3′,10′), 30.3 and 27.0 (C-5′,6′), 20.7, 20.58, 20.55, 20.51, 19.8 [C-8′,9′ and 4× C(O)*Me*] ppm. $C_{24}H_{36}O_{10}S_2$ (548.67): calcd. C 52.54, H 6.61; found C 52.51, H 6.60.

1-(2-Benzoxazolyldithio)-1-deoxy-β-D-glucopyranose 2,3,4,6-Tetraacetate (16): White crystals, m.p. 157–159 °C (621.4 mg, 1.21 mmol, 92% yield, from 200.0 mg, 1.32 mmol, of **11e**). R_f = 0.54. ^{1}H NMR: δ = 7.6–7.3 (m, 4 H, H_{arom}), 5.26 (m, 2 H, 2-H and 3-H), 5.07 (m, 1 H, 4-H), 4.75 (d, $J_{1,2}$ = 9.6 Hz, 1-H), 4.01 (AB dd, $J_{6A,6B}$ = 12.3 Hz, $J_{5,6A}$ = 4.7 Hz, 1 H, 6-H_A), 3.96 (AB dd, $J_{5,6B}$ = 2.3 Hz, 1 H, 6-H_B), 3.72 (m, 1 H, 5-H), 2.04, 1.99 and 1.81 (3 s, 12 H, 4× Me) ppm. ^{13}C NMR: δ = 170.4, 170.1, 169.24 and 169.21 (4× C=O), 161.8 (C-2′), 152.2 (C-7a′), 141.8 (C-3a′), 125.1 and 124.7 (C-5′,6′), 119.5 (C-4′), 110.2 (C-7′), 86.4 (C-1), 76.0, 73.5, 69.2 and 67.7 (C-2–5), 61.6 (C-6), 20.6, 20.53, 20.48 and 20.3 (4× Me) ppm. $C_{21}H_{23}NO_{10}S_2$ (513.54): calcd. C 49.12, H 4.51, N 2.73; found C 49.08, H 4.49, N 2.74.

1-[2-(1-Methyl)imidazolyldithio]-1-deoxy-β-D-glucopyranose 2,3,4,6-Tetraacetate (17): Colourless oil (776.7 mg, 1.63 mmol, 93% yield, from 200.0 mg, 1.75 mmol, of **11f**). R_f = 0.20. ^{1}NMR: δ = 7.09 and 7.03 (2 d, $J_{4',5'}$ = 1.5 Hz, 2 H, 4′-H and 5′-H), 5.24 (t, $J_{2,3}$ = $J_{3,4}$ = 9.2 Hz, 1 H, 3-H), 5.08 (m, 2 H, 2-H and 4-H), 4.89 (d, $J_{1,2}$ = 9.9 Hz, 1-H), 4.26 (AB dd, $J_{6A,6B}$ = 12.5 Hz, $J_{5,6A}$ = 4.4 Hz, 1 H, 6-H_A), 4.05 (AB dd, $J_{5,6B}$ = 2.6 Hz, 1 H, 6-H_B), 3.81 (m, 1 H, 5-H), 3.77 (s, 3 H, NMe), 2.07, 2.01, 1.99 and 1.94 [4 s, 12 H, 4× C(O)Me] ppm. ^{13}C NMR: δ = 170.4, 169.9, 169.25 and 169.21 (4× C=O), 139.9 (C-2′), 130.0 and 124.2 (C-4′,5′), 88.8 (C-1), 75.9, 73.6, 69.7 and 67.8 (C-2–5), 61.7 (C-6), 34.1 (NMe), 20.6–20.4 [4× C(O)*Me*] ppm. $C_{18}H_{24}N_2O_9S_2$ (476.52): calcd. C 45.37, H 5.08, N 5.88; found C 45.43, H 5.06, N 5.87.

1-[2-(4-Amino)pyrimidyldithio]-1-deoxy-β-D-glucopyranose 2,3,4,6-Tetraacetate (18): White crystals, m.p. 69–71 °C (704.9 mg, 1.44 mmol, 92% yield, from 200.0 mg, 1.57 mmol, of **11g**). R_f = 0.22. ^{1}H NMR: δ = 8.05 (d, $J_{5',6'}$ = 5.6 Hz, 1 H, 6′-H), 6.20 (d, 1 H, 5′-H), 5.32 (br. s, 2 H, NH_2), 5.20 (m, 2 H, 2-H and 3-H), 5.06 (m, 1 H, 4-H), 4.64 (d, $J_{1,2}$ = 9.6 Hz, 1-H), 4.08 (m, 2 H, 6-H_2), 3.68 (m, 1 H, 5-H), 2.05, 1.98 and 1.96 (3 s, 12 H, 4× Me) ppm. ^{13}C NMR: δ = 170.6, 170.2, 169.33, 169.30 and 169.2 (C-2′ and 4× C=O), 162.8 (C-4′), 156.1 (C-6′), 102.5 (C-5′), 86.4 (C-1), 75.8, 73.8, 69.7 and 61.8 (C-2–5), 60.3 (C-6), 20.7–20.5 (4× Me) ppm. $C_{18}H_{23}N_3O_9S_2$ (489.52): calcd. C 44.16, H 4.74, N 8.58; found C 44.20, H 4.73, N 8.56.

1,3-Bis-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)dithio]benzene (20): White crystals, m.p. 169–171 °C (606.9 mg, 0.70 mmol, 50% yield, from 200.0 mg, 1.41 mmol, of **21**). R_f = 0.48. ^{1}H NMR: δ = 7.80 (t, J_{meta} = 1.8 Hz, 1 H, 2-H), 7.45 (dd, J_{ortho} = 7.7 Hz, 2 H, 4-H and 6-H), 7.19 (t, 1 H, 5-H), 5.24 (m, 4 H, 2′-H, 2′′-H, 3′-H and 3′′-H), 5.08 (m, 2 H, 4′-H and 4′′-H), 4.60 (m, 2 H, 1′-H and 1′′-H), 4.15 (AB dd, $J_{5A,5B}$ = 12.5 Hz, $J_{5A,6}$ = 4.4 Hz, 2 H, 6′-H_A and 6′′-H_A), 4.08 (AB dd, $J_{5B,6}$ = 2.5 Hz, 2 H, 6′-H_B and 6′′-H_B), 3.74 (m, 2 H, 5′-H and 5′′-H), 2.03, 2.00, 2.02 and 2.01 (4 s, 24 H, 8× Me) ppm. ^{13}C NMR: δ = 170.5, 170.1, 169.3 and 169.1 (8× C=O), 137.8 (C-1,3), 129.0, 127.6 and 127.1 (C-2,4–6), 87.7 (C-1′,1′′), 76.1, 73.7, 69.3 and 67.9 (C-2′-5′ and C-2′′-5′′), 61.9 (C-6′,6′′), 20.64, 20.61, 20.55 and 20.51 (8× Me) ppm. $C_{34}H_{42}O_{18}S_4$ (866.95): calcd. C 47.10, H 4.88; found C 47.04, H 4.89.

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