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The thermolytic generation of sulfenic acids in synthesis: an account

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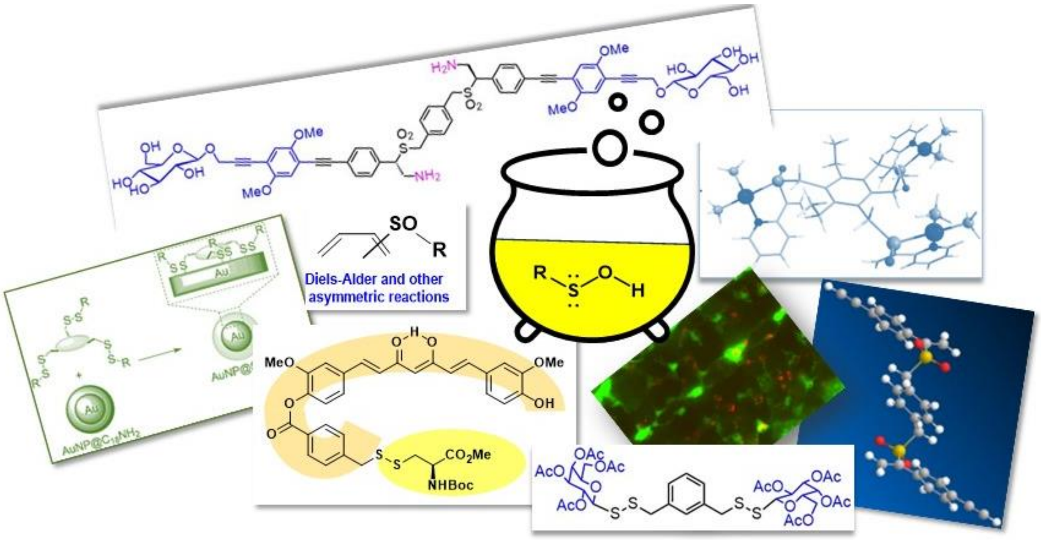
Abstract

Once generated *in situ*, sulfenic acids are transient species that regio- and stereoselectively add to triple and double bonds or condense with thiols to respectively give vinyl and alkyl sulfoxide or unsymmetrically substituted disulfides. This account deals with the use of these versatile intermediates in our preparative chemistry, covering the last decades and spanning from the syntheses of enantiopure carba- and hetero-unsaturated species to be used in stereoselective transformations, getting to cyclophanes, tripodal and amphiphilic species and passing from the generation of biologically relevant residue-decorated sulfenic acids.



Keywords: Sulfenic acid, sulfoxide, disulfide, stereoselectivity, oligofunctionalized sulfur derivatives

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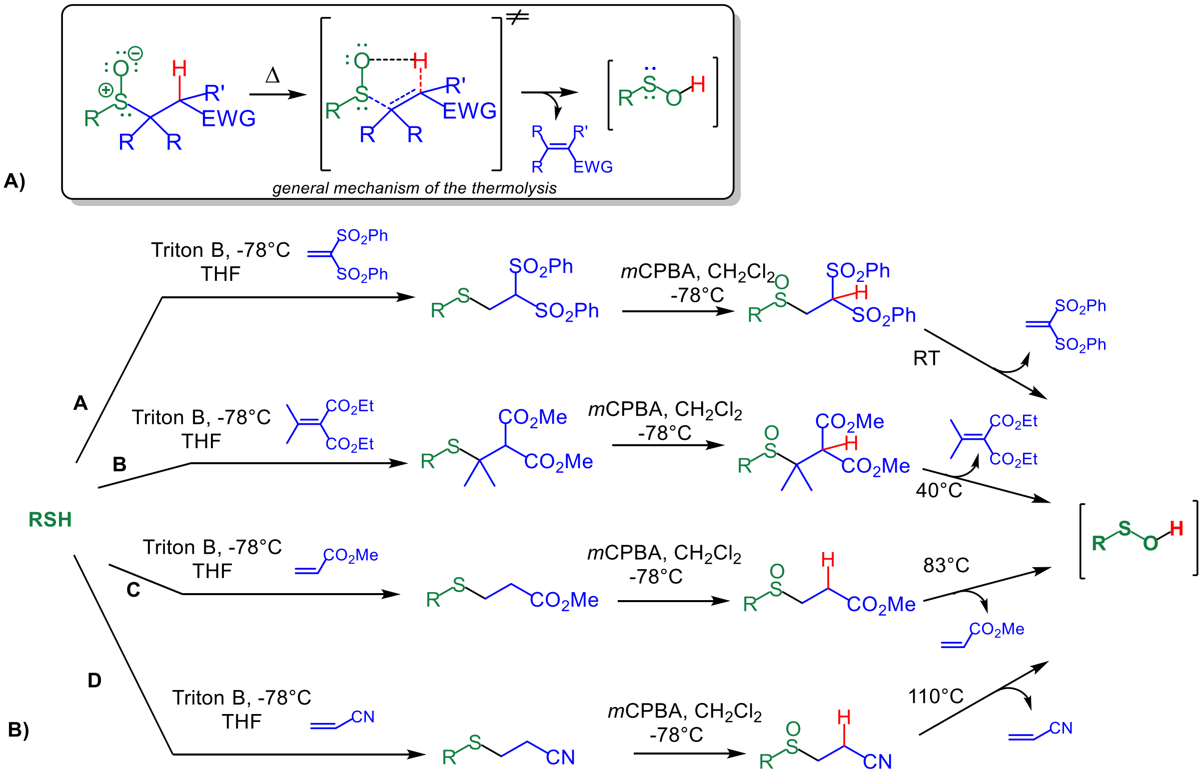
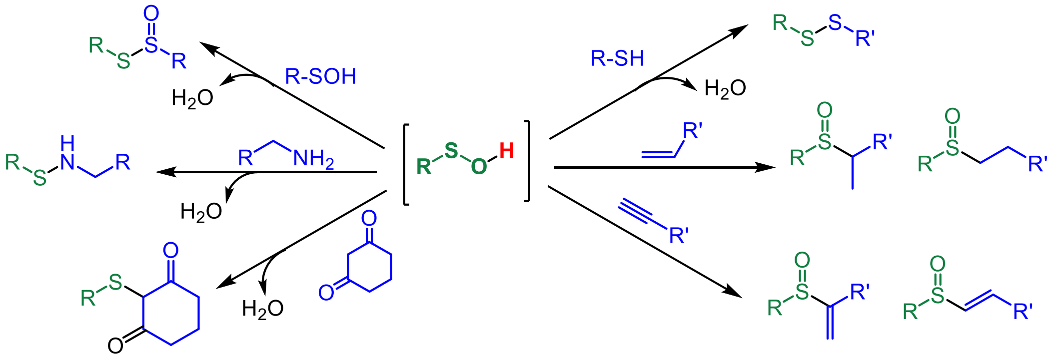
1. Introduction

Transient sulfenic acids (RSOH) are unstable and extremely reactive intermediates implicated in a wide variety of relevant chemical[1] and biochemical reactions.[2] Despite their transient nature, the isolation of few stable ones has been helpful for the comprehension of the structure of the sulfenic moiety and the mechanism of their reactions.[3] Among the others, the insertion of the sulfenic group in a bowl-type environment,[4] that protects the group from any undesired reaction, and the stabilization of the sulfenic moiety via intramolecular hydrogen bonding[5] have been the key methods for their isolation. Sulfenic acids can be synthetically formed with several procedures, most of them involving the hydrolysis at suitable pH of more stable sulfur compounds as disulfides,[6] thiosulfinates,[7] sulfenyl derivatives[8] and *S*-nitrosothiols.[9]



Scheme 1. A) General mechanism of the thermolysis to sulfenic acid; **B)** Schematic routes to the synthesis of the different sulfinyl precursors.

Another method involves the thermolytic concerted syn-β-elimination,[10] involving a five-membered cyclic transition state, of electron-deficient alkenes from suitable sulfoxides, to generate *in situ* specific sulfenic acids. One or two electron-withdrawing groups linked to the β carbon atom and, in one case, sterically demanding groups linked at the α carbon atom, are needed to help and modulate the mobility of the β-H and, consequently the thermolysis temperatures (Scheme 1). The elimination can be also applied for removing the sulfinyl moiety from specific molecules, to form residual alkynes or alkenes with controlled stereochemistry. The sulfoxide precursors synthetic route consists in two steps, with thiols as starting compounds: a nucleophilic conjugated addition in basic conditions of the corresponding thiolate to electron-poor conjugated species gives a sulfide, then oxidized to sulfoxide by means of *m*CPBA in controlled conditions. The tunable experimental conditions, including the absence of acids or bases for their generation, are helpful for the sulfenic acid intermediation in the obtainment of sulfurated products difficult to synthesize. In fact, many papers have been published in the last decades about the sulfenic acids employment in organic synthesis. Their transient character is the key for the involvement of sulfenic acids in a wide range of intermolecular preparative processes that lead to the obtainment of many thio-organic functional groups (Scheme 2): they react with 1,3-dicarbonyl compounds to give thioethers at the central carbon and with amines to obtain sulfenamides, they form non-symmetrically substituted disulfides via condensation with thiols - a general method original from our chemistry - and regioselectively add to alkenes and alkynes, via a concerted syn-addition to give sulfoxides. The unstable nature of sulfenic acids make them react one another, to give unwanted side-products as unstable thiosulfinates, that disproportionates to thiosulfinates and disulfides. Suitable conditions are necessary to give high yields of the desired final products and to avoid undesired reactions, such as auto-condensation. The pericyclic *syn*-addition onto carbon–carbon double or triple bonds furnishes an easy and reproducible method to obtain alkyl and vinyl sulfoxides in mild conditions, without the need of acidic or basic catalysis. The electronic properties of the unsaturated acceptor are responsible of the high regioselectivity[11] of the addition, usually following the Markovnikov's rule while, in the case of enantiopure sulfenic acids the structural features of the R* group linked to the sulfenic moiety have a great influence on the stereoselectivity of the formation of the *S*-epimeric sulfinyl addition products.



Scheme 2. Reactions of sulfenic acids.

The application in synthesis of this pericyclic addition and the condensation of sulfenic acids with thiols to give disulfides, represents a significative branch of our research in the last three decades. In this account we intend to rationally summarize and show our contribution to this field, starting from the utilization of enantiopure sulfenic acids in many stereoselective transformation, until the last years, when this reaction, joint with the obtainment of unsymmetrically substituted disulfides, has been used for the construction of complex molecules, that found applications from biological to material field.

2. Sulfenic Acids from Chiral Pool Derivatives in the Stereoselective Synthesis of Unsaturated Compounds and Their Use in Stereoselective Transformations

The regioselective concerted *syn*-addition of enantiopure sulfenic acids onto triple bonds is an efficient method for the obtainment of the *S*-epimeric mixtures of vinyl sulfoxides with high degree of the stereoselection, depending on the structural features of the R* group linked to the sulfenic moiety. The addition of sulfenic acids to enynes has opened way in our group to the synthesis of enantiopure 2-sulfinyl dienes, not easily accessible and ready to be used in stereoselective transformation. Camphor sulfonic acid and the two commercially available enantiomers of ethyl mandelate were employed as precursors of three starting hydroxy thiols - 10-mercaptoisoborneol, 2-hydroxy-1-phenylethanethiol, 2-hydroxy-2-phenylethanethiol[12] - and the camphor skeleton of 2-bornanethiol[13] (Figure 1). The choice of these chiral auxiliaries was taken to evaluate both the effect of the sterically hindrance and the presence of suitably located hydroxyl groups in the asymmetric induction of the sulfinyldienes formation.

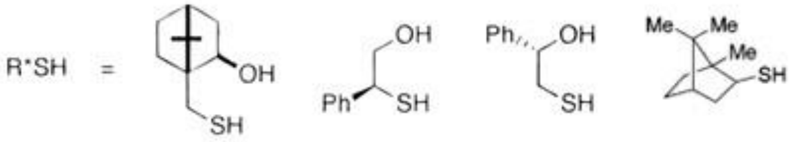


Figure1. Enantiomerically pure residues, being part of the chiral pool, linked to the sulfenic acid function.

Following the method shown in scheme 1 (route D), the sulfinyl precursors of transient sulfenic acids were obtained from the corresponding thiols via a conjugated nucleophilic addition to acrylonitrile in the presence of Triton B as a base and oxidation with *m*CPBA to the epimeric mixture of sulfoxides. Their thermolysis, in the presence of (*E*)- and (*Z*)-1-methoxybut-1-en-3-yne (Figure 2A), gave epimeric mixtures of 2-alkylsulfinyl-1-methoxybuta-1,3-butadienes with high degree of stereoselection, especially for the isoborneol group (R_S/S_S 6/1). A comparison between the proposed mechanisms of the approach of the isoborneol or bornyl sulfenic acids onto the triple bond (Figure 2B) of the enyne was useful to explain the lower stereoselection obtained with the bornyl residue (S_S/R_S 2:1): an intramolecular hydrogen bond in isobornyl sulfenic acid is responsible of the great difference in the sterical hindrance of the two attack faces, while the moderate predominance of one bornyl diene is supposed to be ascribed to the angular methyl near the reactive site, which causes modest differentiation between the two diasterotopic faces. The couples of sulfur epimers are differently mobile in chromatography, so favouring their separation and obtainment of each diastereoisomer in enantiopure form.

From the generation of enantiopure transient sulfenic acids and their *in situ* concerted addition to a wide range of differently substituted alkynes, a library of enantiopure homo- and hetero-sulfinyl dienes [14] was built, and most of them reacted in stereoselective transformation. The enantiopure sulfinyl moiety and the sterically demanding alkyl groups were discriminating for the stereoselectivity of the reactions, including homo-,[15] hetero-Diels Alder[16] cycloadditions and nucleophilic additions to carbonyl groups[17] and for the separation of the obtained diastereomers.

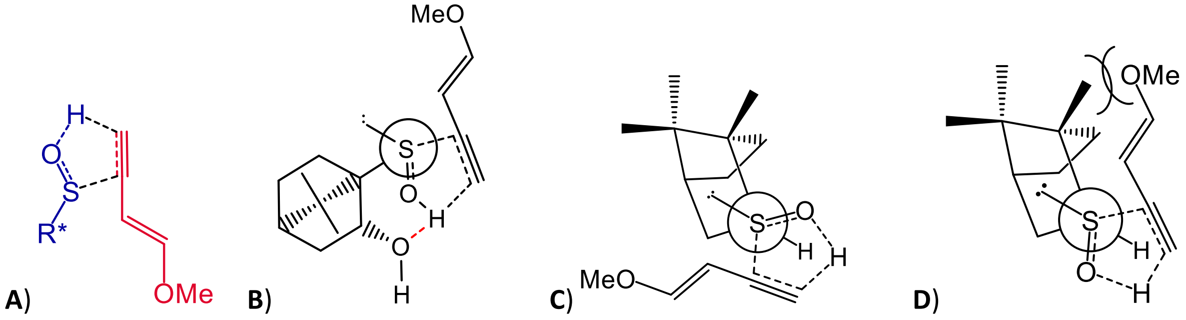
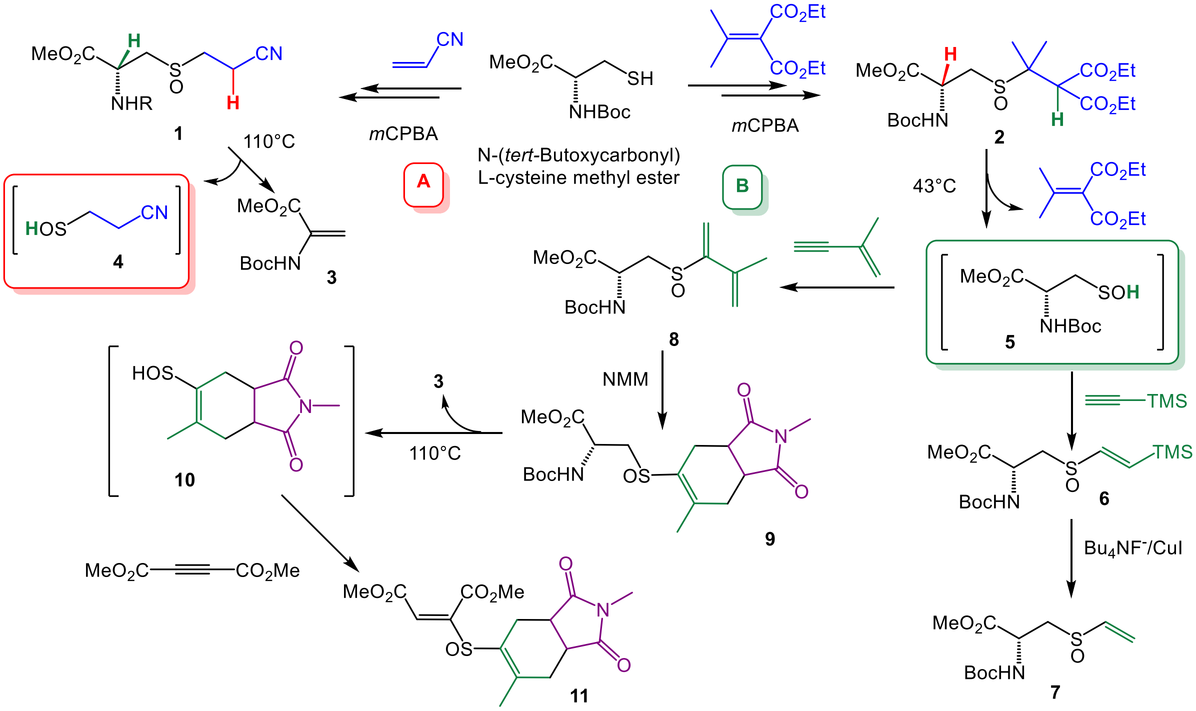


Figure 2. A) regioselective approach to E-1-metoxy-1-buten-3-yne; **B)** stereoselective approach of the enyne on the favourite face of sulfenic acid; **C)** and **D)** approach of E-1-metoxy-1buten-3-yne onto the two faces of sulfenic acid, showing **C**) as the less sterically congested.

3. Sulfenic Acids with Biologically Relevant Residues[18] in the Stereoselective Synthesis of Biologically Significant Compounds

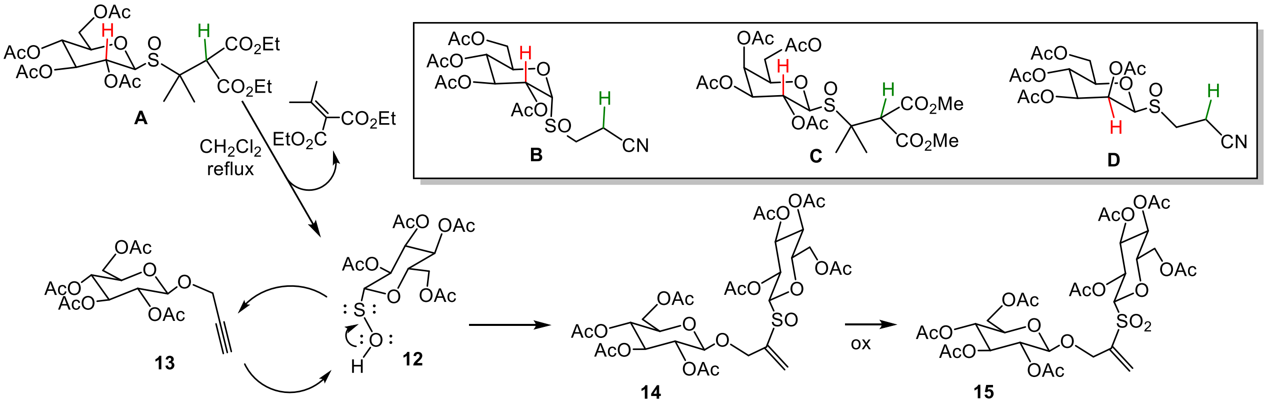
The method for the generation of enantiopure sterically demanding sulfenic acid intermediates described in section 1 was also applied by our group to the generation of transient sulfenylated carbohydrates[19] and amminoacids. Their concerted addition onto triple bonds and the condensation with thiols has been applied to the synthesis of a great variety of derivatives in enantiomerically pure form, with biological applicative interest. Starting from cysteine and monosaccharide thio-derivatives, two different sulfoxide precursors, with two different thermolysis temperatures, were prepared following the general routes described in scheme 1, routes B and D. As already pointed out, their thermolysis and subsequent *in situ* concerted reactions do not imply any acidic or basic conditions, allowing the choice of any protecting group. For what concerns cysteine sulfenic acid, *N*-(tert-butoxycarbonyl)-L-cysteine methyl ester[20] was utilized as starting product for the synthesis of the two different precursors **1** and **2** (Scheme 3, routes A and B). The isolation of carbamate **3** from the first thermolysis crude (route A), conducted at the reflux temperature of toluene, was diagnostic of the formation of undesired sulfenic acid **4**, coming from the unwanted β-elimination involving the more mobile hydrogen of the α-aminoacidic residue. Owing to the presence of the two β-carboxylate groups in sulfoxide **2**, the concerted β-elimination happens in the right direction at lower temperature (43°C), affording intermediate **5**, as proven by the addition product **6** to ethynyltrimethylsilane.

The absence of **3** in the crude reaction product confirmed that, in case of competition in the removal of two β-hydrogens, the modulation of their mobility is the key to avoid the wrong chemoselectivity in the elimination. The concerted addition to different alkynes afforded the stereoselective formation of Alliin analogues. On the other hand, the possibility to remove a second mobile hydrogen was the means to prepare more complex molecules. As an example, addition of cysteine sulfenic acid derivative **5** to 2-methylbuten-3-enyne gave the diene **8**, then reacted in a stereoselective Diels-Alder reaction with *N*-methyl maleimide. The obtained cycloadduct **9** was subjected to a second thermolysis in toluene at 110 °C with the elimination of carbamate **3** and the generation of a second sulfenic acid **10** useful in subsequent transformations to more complex sulfoxides. This last application can be regarded as a further stimulating development of this chemistry. The same synthetic approaches were applied to get D-gluco, D-galacto and D-manno sulfenic acids.[21]



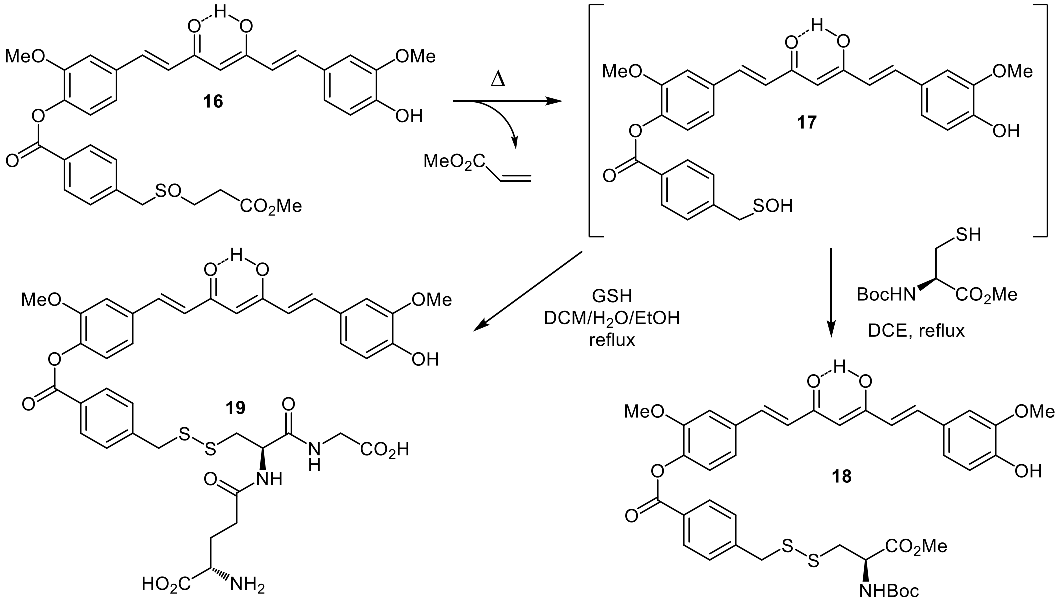
Scheme 3. Synthetic route to the regioselective generation of cysteine sulfenic acid derivative.

Carbohydrates are among the most eclectic compounds in living systems. They are capable to form many different combinatorial structures from relatively small numbers of sugar units and for this reason, their inclusion in a number of synthetic organic structures opens the way to their use in biomedical and material chemistry fields.[22] Thanks to the anti-disposition of the β-glycosyl hydrogen and the sulfinyl function (Scheme 4), thermolysis of the stable and easy handable sulfoxides **B** and **D** could be carried on with total regioselection in the elimination at high temperatures (110°C) and with good yields in the obtainment of the final products.



Scheme 4. Generation of sulfenic acid glycosides and synthesis of target diglycosidic sulfones.

A competition among the two *syn*-β hydrogens (red and green in scheme 4) in β-glucosyl and β-galactosyl precursors in the generation of the sulfenic function led us to use the more reactive **A** and **C** to force the regioselectivity in the formation of the right intermediate. The general method can be used for the stereoselective and regioselective insertion of glycosyl sulfoxides and sulfones in a chosen framework, such as the thiodisaccharides. The concerted addition of a transient beta D-glucopiranosyl sulfenic acid derivative **12** onto the triple bond of tetraacetyl 1-propargyl β-D-glucopyranose **13** afforded, with complete retention of configuration at the anomeric centre, the mixture of sulfinyl epimers **14**, then oxidized to a unique sulfone **15**. The synthesis of the fluorescent precursor of Curcumin sulfenic acid, **16** in scheme 5, was realized following the general synthetic approach showed in scheme 1, route C, using methyl acrylate. Curcumin is a luminescent polyphenolic compound extracted from *Curcuma Longa* L. and extensively studied for its anticancer, antibacterial and antiviral effects, despite its poor solubility that has been bypassed over the years by developing nanotechnologies that emphasize the potential health benefits.[23]

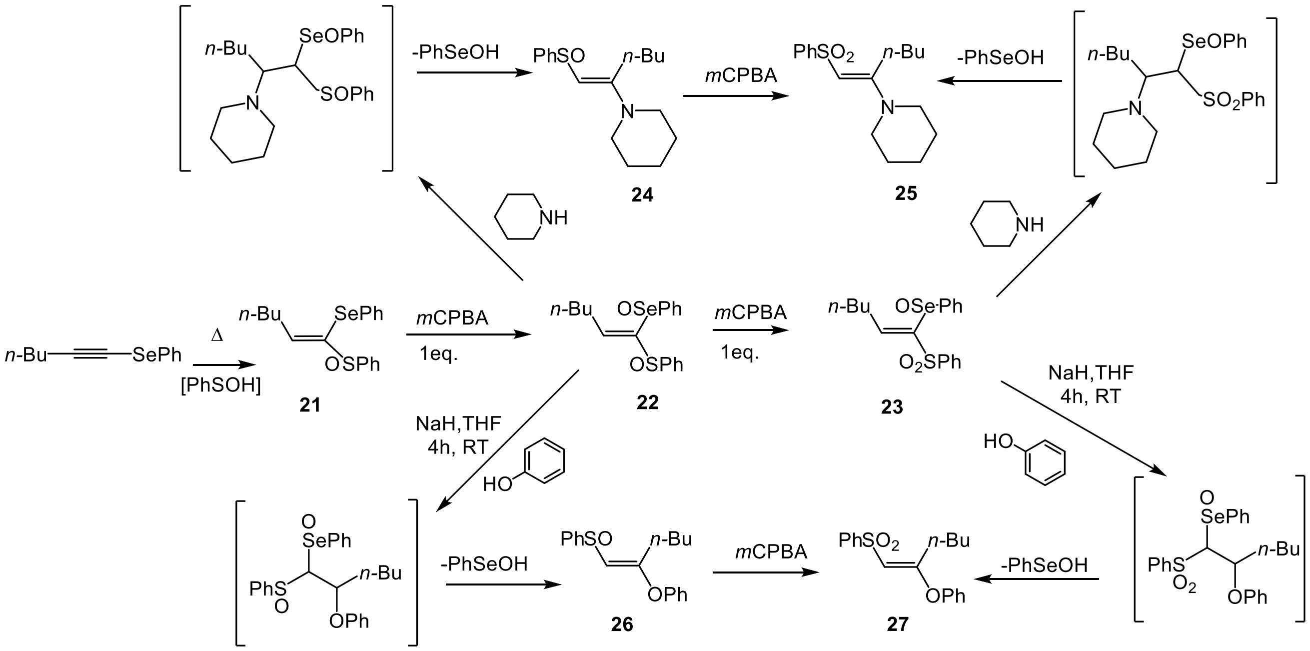


Scheme 5. Generation of a curcumin sulfenic acid and *in situ* reaction with bio-thiols

The scope of the research was to prepare a potential sensor for bio-thiols. Thermolysis of **16** at the reflux temperature of 1,2-dichloroethane (83°C) generated the transient **17**, that *in situ* condensed with cysteine (Cys) or glutathione (GSH) as models of biological thiol targets. The two disulfides **18** and **19** were obtained, both showing no luminescence, even if containing the curcumin residue. The observed quenching[24] of luminescence could favour future application of similar curcumin derivatives as on/off light switching sensors to detect the presence of bio-thiols. Curcumin was also used as platform for the synthesis of a sulfide derivative that was obtained by the reaction of the electrophilic sulfenic function with the nucleophilic central carbon of the curcumin 1,3-diketone moiety, producing a thioether with loss of water.[25] Such compound showed an IC_{50} in a lower molecular range with respect to curcumin on triple negative breast cancer cell lines, and from the analysis of its molecular mechanism of action it appears to be promising for further analysis to demonstrate its real efficacy as a new anticancer agent.

4. Sulfenic Acids in the Synthesis of Mixed Sulfur-Selenium Compounds

The stereospecific *syn*-addition of *in situ*-generated sulfenic acids onto the triple bond of suitable (phenylseleno)acetylenes gave electron-poor 1-(phenylseleno)sulfinyl alkenes with high degree of regioselectivity, depending on the nature of the substituent at the alkyne function. The synthetic interest of the adducts as starting materials for further transformation was experimented through a rational reaction sequence, starting from the *n*-butyl derivative **21** (Scheme 6).[26]

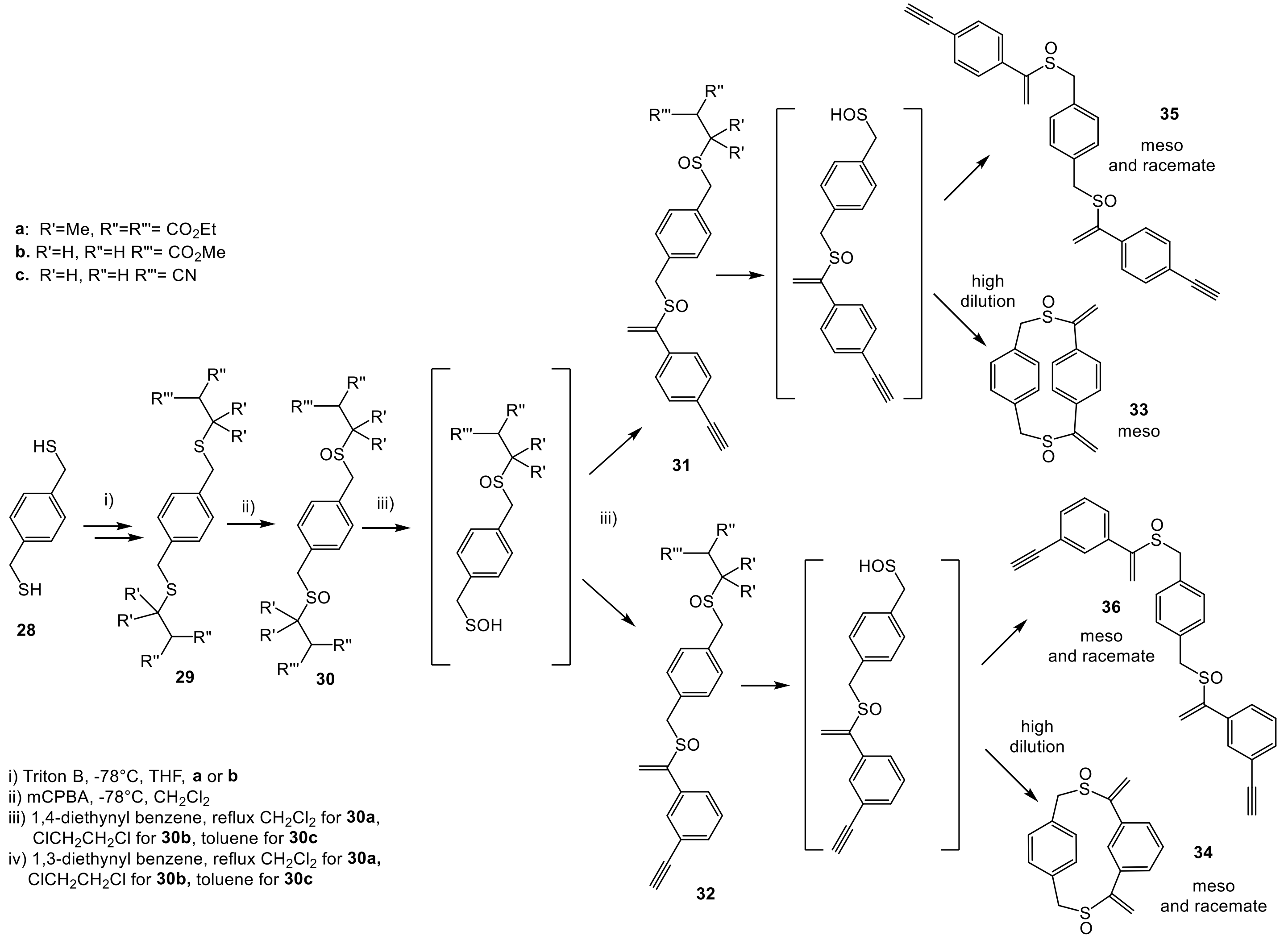


Scheme 6. Synthesis of sulfinyl/sulfonyl enamines and enols involving sulfenic and selenenic acids chemistry.

A chemoselective oxidation of the selenide moiety to selenoxide was obtained with a strictly equimolar amount of *m*CPBA oxidant, and with the obtainance of the (phenylselenenyl)sulfinyl alkene **22** as a mixture of diastereomeric. Longer reaction times and an excess of oxidant afforded α-(phenylselenenyl)sulfonyl alkene **23** as final oxidation products. No traces of the selenone compound were detected. Hard nucleophiles such as piperidine and phenol easily added to the electron-poor double bond of both the oxidation products **22** and **23**. The spontaneous *in situ* β-elimination of selenenic acid from the addition intermediate gave stereospecifically a new class of sulfinyl or sulfonyl enamines (**24** and **25** respectively) and enol eters **26** and **27**. The concerted β–elimination of selenenic and selenonic acid from suitably functionalized precursors also represented an efficient method for the stereoselective synthesis of substituted tetrahydrofurans,[27] tetrahydropyrans and isochromans.[28]

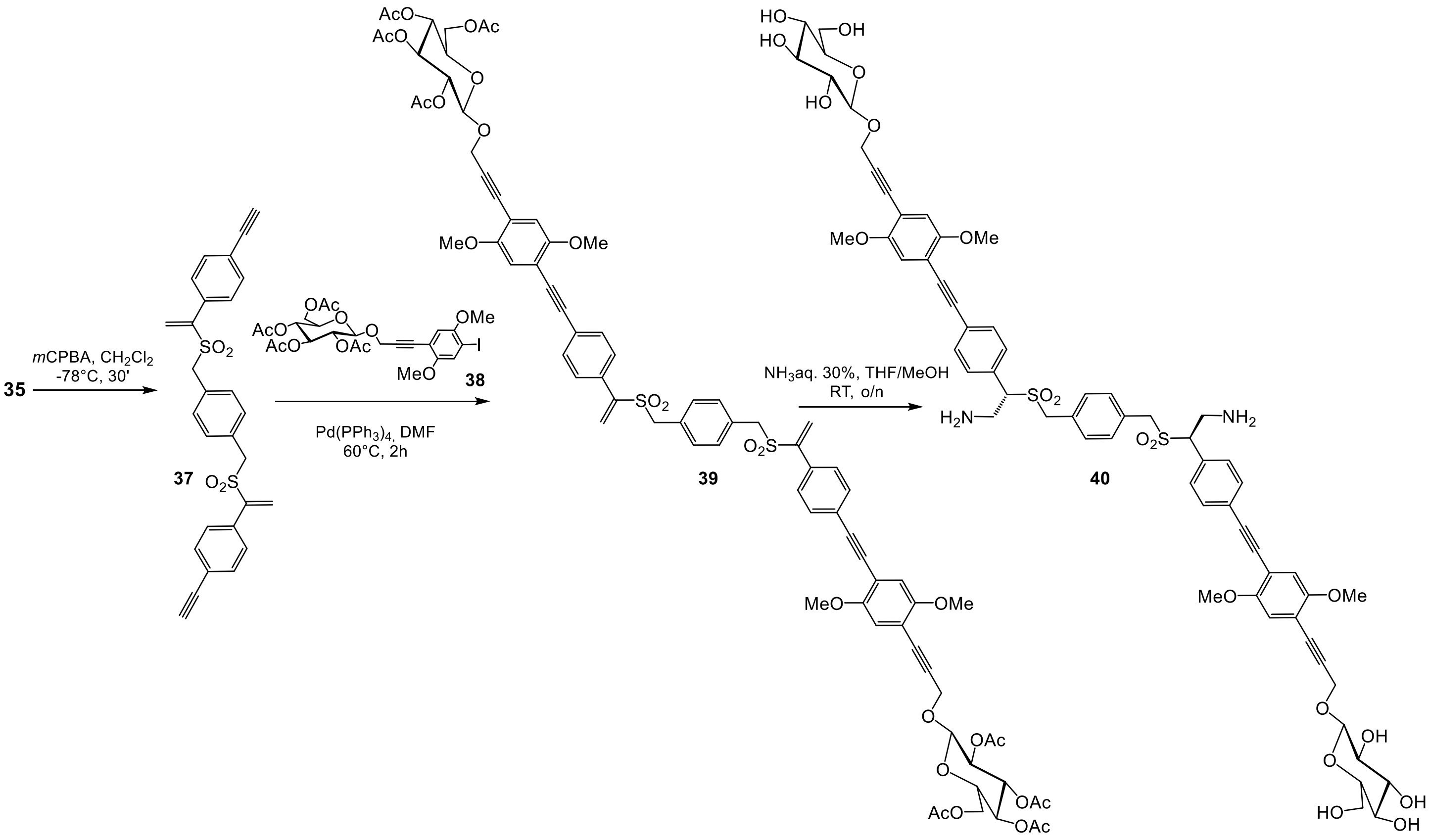
5. Two Sulfenic Acid Moieties in a Skeleton for the Synthesis of bis Sulfur-Functionalized Compounds

One of the extensions of our chemistry has been the ~~employment of bis- or tris-sulfoxides for the *in situ*~~ generation of two or three sulfenic acid functions on the same skeleton to give, in the presence of an excess of the suitable trapper (alkynes or thiols), a large variety of multiarmed sulfur compounds.[29] Michael type conjugate addition of 1,4-benzene dimethanethiol **28**, or other aromatic or benzylic bis and tris-thiolates, onto the electron-deficient unsaturation of diethylisopropylidene malonate (as in route 1B of scheme 1), methyl acrylate (as in route 1C) and acrylonitrile (as in route 1D) and the subsequent oxidation of the obtained bis-sulfides (**29**) by means of *m*CPBA, was the way to create bis sulfoxides **30** (Scheme 7), usable for the generation of two sulfenic acid functions. The thermolysis of bis-sulfoxides **30**, in particular the stable and easy to handle **30b**, has been applied by our group for the obtainment of bis functionalized compounds whose application ranges from the bioorganic to material chemistry.



Scheme 7 Step by-step thermolisys of sulfoxides **30.**

As shown by the isolation of the compounds **31** and **32**, the thermolysis involves a step-by step route leading to a mixture of thia CP S-oxides, (**33** or **34** in scheme 7) together with open-chain disulfinylmethyl arenes (**35** or **36**). The different *syn*-addition products percentage can be modulated by varying the reactant relative *ratios* and the concentration of the reaction solutions: in the presence of a large excess of the diethynyl arene and in very concentrated conditions, **35** or **36** were mainly obtained. Cyclophanes were the main reaction products when the reaction was conducted only in the presence of a strict equimolar amount of the diethynyl reactant, in very high diluted conditions, so favouring the cyclization.[30] Surprisingly, when *p*-diethynylbenzene was employed as sulfenic acid acceptor, the stereoselectivity in the formation of the *meso* dithia[3.3]-paracyclophane S,SO-dioxide **33** was complete. A density functional B3LYP/6-311+G(d,p) theoretical study was conducted on the final *syn*-addition cyclization step from **31b**, demonstrating that it takes place under kinetic control and leads to the exclusive formation of the achiral cyclophane. The quantitative oxidation of Bis-sulfoxides **35** and **36** furnished the corresponding achiral bis-sulfones that are versatile two-site reactive platforms: the electron-poor vinylsulfonyl moities are easily susceptible to conjugated nucleophilic addition, while the two terminal triple bonds can be used in cycloadditions (e.g. Huisgen type) or cross-coupling reactions (e.g. Sonogashira and variations).



Scheme 8. Synthetic route to bolamphiphile **40.**

An example of the double reactivity of the new platforms is given in scheme 8. Copper-free Sonogashira coupling of **37** with a twofold quantity of the iodoaryl glucopyranoside **38**[22] allowed the double-ended glucosyl sulfone **39**. Reaction with an excess of ammonia provided the simultaneous a) nucleophilic addition onto the two vinyl sulfonyl groups and b) deprotection of the acetyl groups, then affording **40** as unique diastereomer. The total stereoselection of the addition to the electron-poor alkene moieties, also when the underivatized platform **37** was directly reacted with other nucleophiles (as piperidine), prompted us to investigate, through theoretical calculations, the nature of the mechanism of the reaction. The π–π interaction of the central aromatic *core* with the peripheral arenes (Figure 3A) or vinyl moieties (Figure3B) forced **40** in two preferred bent conformational state, both impeding the nucleophile approach from the bottom of the electron-poor double bond, leading to the exclusive obtainment of the *meso* adduct. Moreover, the expected bola-amphiphilic character of **40**, for the dual presence of a lipophilic platform containing two vinyl sulfone moieties and two hydrophilic carbohydrate-extremities, was confirmed by its good solubility (figure 3C) both in water (a) and n-octanol (c).

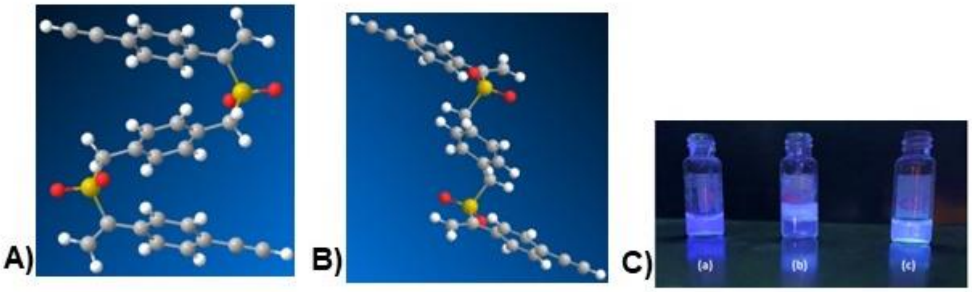
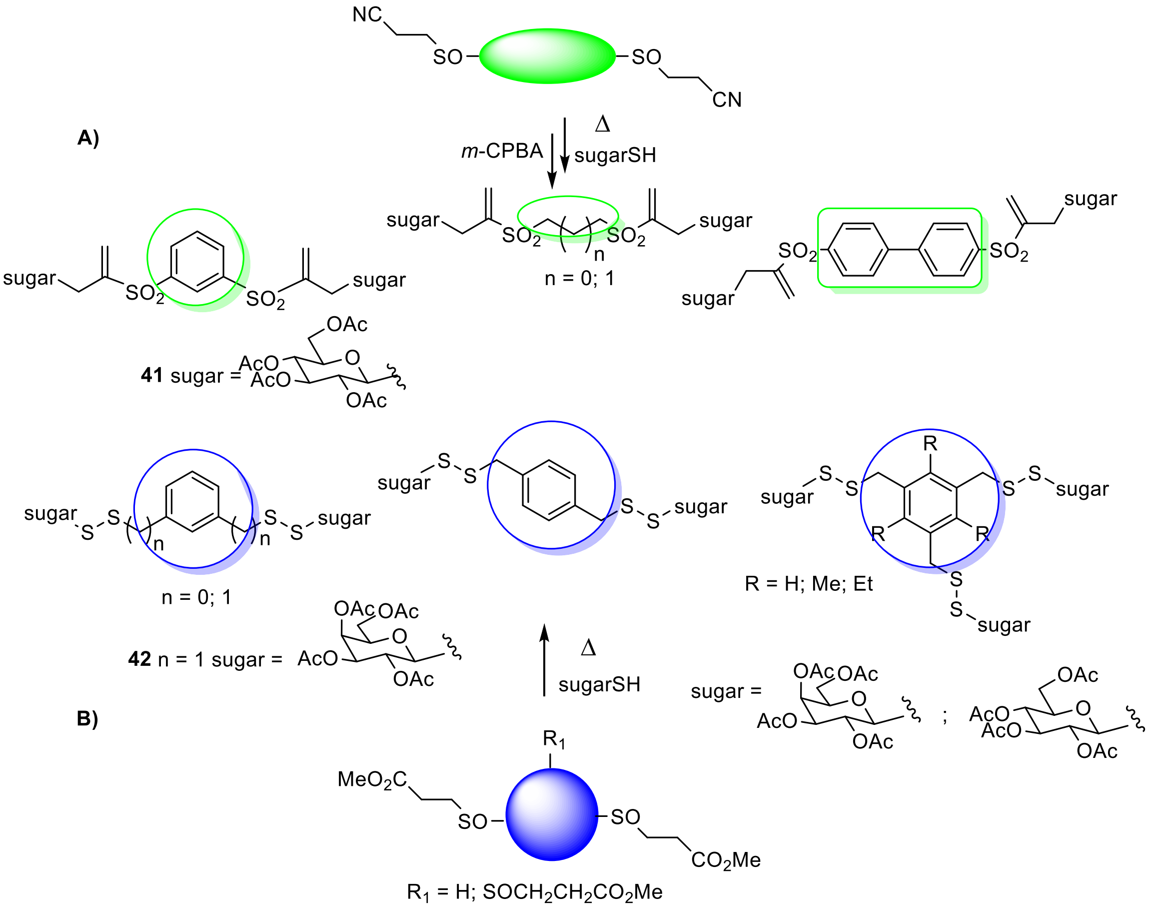


Figure 3. A) and B) bent conformational states of platform **35**; C) solubility tests for compound **40.**

The amphiphilic behaviour, joint with the capability of carbohydrates to specifically target cell membrane glycoreceptors, opens the way for the use of **40** and similarly obtained bolamphiphiles in the biomedics. Two transient sulfenic acid moieties were involved in the synthesis of two families of bis-thioglycoconjugates.[31] The applied synthetic routes allow, in each case: (i) the diversification of the carbohydrate residues within the organic scaffold; (ii) the introduction of sulfurated moieties, as biologically significant functional group; (iii) the modulability of the overall process using suitable and easily accessible thiols.

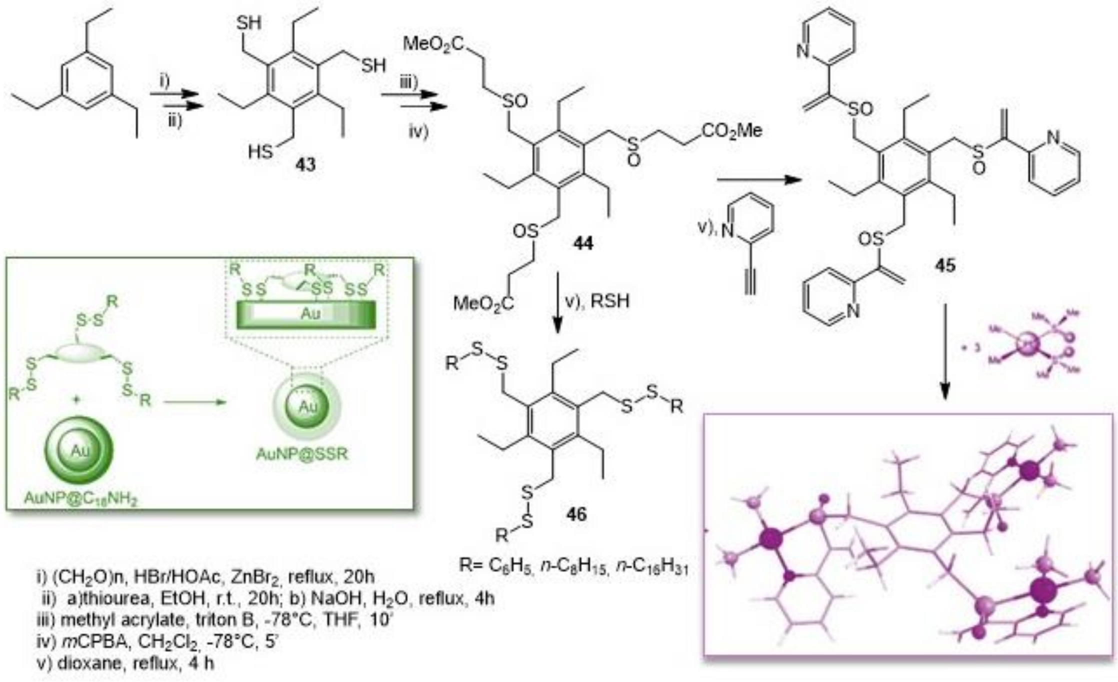


Scheme 9. Synthetic route to bis-thioglycoconjugates.

In the first family, bis-β-D-glucopyranosides, containing thioalkane or thioarene spacers of different lengths and flexibility, have been obtained from a three-step synthesis. The products of such small library, shown in scheme 9a, were involved in biological tests on cell viability and specifically on the ability of the synthesized compounds to induce apoptotic cell death, considering the pivotal role of apoptosis regulation in both the controlled expansion and removal of immune cells and cancer progression and therapy. The investigation of the relationship between molecular structure and biological response directed the research towards sulfurated bis-β-D-glucopyranoside **41** with a central aromatic ring, that appeared a good inductor of cell death by apoptosis. Moreover, the unexpected observation that in the range of 10–50 mM compound **41** stimulated the metabolic activity and the cell growth suggested that the induction of cell death might underline an activation-induced cell death. In the second family of bis-thioglycoconjugates the transient sulfenic acids were used to obtain new sugar molecules where the benzene platform accommodates two or three flexible disulfide arms[32] connecting the saccharide moieties, in analogy to the structural skeleton of compound **41**. Galactose derivatives were used considering the potential of galactose-based small molecules as cancer therapeutics (Scheme 9b). The bis(disulfides), with a thread-like *core* and galactosyl groups at both ends of the molecule, have proven to be cytotoxic, even if at relatively high concentrations, towards a panel of human cancer cells with different levels of malignancy and resistance to chemotherapeutic agents. Bis-thiogalactoconjugate **42** gave the best results. To outline the cellular molecular mechanisms that characterize its apoptosis, experiments using Bcl-2-overexpressing transfectants were conducted, comparing results obtained with U937pMEP (i.e. tumour human monocytes) and U937mBcl2 cells, where the gene for the Bcl2 protein has been inserted. It was demonstrated that Bcl2 protein is involved in the mechanism of apoptosis, at least in the U937 cell model and that therefore the death process determined by thioglycoconjugate **42** follows the normal control mechanisms that regulate apoptosis. Moreover, the apoptotic properties of compound **42** were compared between U297 cancer cells and human healthy cells, showing to be more performing in cancer cells. The two collections of molecules, obtained following the synthetic procedures, involving transient sulfenic acids, may provide a basis for the development of a new series of pharmacologically active carbohydrate-based molecules.

6. Three Sulfenic Acid Moieties in a Skeleton for the Synthesis of tris Sulfur-Functionalized Compounds

The synthetic strategy that was applied to disulfoxide precursors of two transient sulfenic acid moieties (Scheme 8) was also utilized for the non-trivial synthesis of the trisulfoxide analogues, as exploited in the same kind of reaction to trisulfinyl cages or radial trisulfoxides.[29] Modification of the structure at strategic sites, e.g. insertion of three ethyl moieties at the central aryl ring of the sulfinyl precursor, opened to way to the synthesis of trifunctionalised sulfurated architectures[33] (Scheme 10) able to adopt a peculiarly segregated tripodal conformation,[34] bearing three functional substituents alternatively disposed on the same side of the phenyl plane. Tris-thiol precursor **43** was prepared in three steps from the 1,3,5-triethylbenzene: a bromomethylation, nucleophilic substitution by means of thiourea and final hydrolysis of the thiouronium salt in basic media. The corresponding trisulfoxide **44** was obtained in good yields through the route reported in scheme 1C and then thermolized in 1,2-dichloroethane at reflux temperature. Depending on the nature and shape of the trapper of the transient sulfenic acid functions, the resulting tripodal disulfides and sulfoxides found use in nanomaterial,[35] biological,[36] and coordination chemistry.[37] Multiarmed tripodal 1,3,5-tris(alkyl or aryl)-2,4,6-triethylbenzene disulfides **45** were employed as a new class of multifunctional AuNP capping agents. The adopted rigid tripodal conformation helps the three spatially pre-oriented disulfide arms land onto and link almost simultaneously the gold surface, so allowing the control of the ratio between the aryl *core* and peripheral moieties and working against the desorption equilibria involving disulfides. The mixed-functionalized nanoparticles, particularly those mixed with the tripodal tris-triphenyl disulfide derivative **46** (R = C_6H_5, scheme 10), showed to act as sensing nanomaterials for nitro aromatic explosives. On the other hand, the thermolysis of **44** in the presence of 2-ethynyl (or 3-ethynyl) pyridine gave a 1:3 *C3* and non-*C3* racemic mixtures of diastereisomers, bearing three chelating N,S arms that show sulfoxide and pyridine moieties in the appropriate relative position to be finely exploited in coordination chemistry of Pt(II) square planar complexes.



Scheme 10. Synthesis of tripodal disulfides and sulfoxides.

Reaction of tripodal **45** with three equivalents of Pt dimethyl, bis-dimethyl sulfoxide afforded the formation of trinuclear Pt(II) complexes. The tripodal conformation is also suitable to bind metals with an octahedral geometry.

7 Conclusions

The tunability of the conditions of their *in situ* generation, the nature of the alkyl R residue and/or of the reaction counterpart, and the easy chemical modification of the obtained compounds, gave to transient sulfenic acids RSOH a prominent role in synthetic organic chemistry, over the years. The structural relevance of chiral R* residues helps the synthesis of enantiopure sulfinyl dienes and sulfinyl α,β-unsaturated sulfoxides, efficiently exploited in diastereoselective transformations. Thiols easily obtainable from natural substrates *e.g.* thio-glycosides, cysteine, and luminescent curcumin, can be used as starting products for the synthesis of biocompatible disulfides and sulfoxides. Mixed sulfur-selenium compounds having good synthetic potential can be obtained from addition of suitable sulfenic acids onto ethynyl selenoxides. Two or three sulfenic acids functions are efficiently generated on the same residue, helping the formation of multiarmed disulfides and sulfoxides. The involvement of transient sulfenic acids in the reactions that have been described in this review demonstrates that a wide library of sulfur~~ated~~ compounds, useful in synthetic, biomedical and material chemistry can be easily synthesized through their intermediation, with the hope that this chemistry can be of inspiration to younger chemists.

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Paola Maria Bonaccorsi took the Ph. Master in 1987 and in 1996 the Ph. Doctor, at the University of Sheffield, England. Since 1991 she was a researcher of organic chemistry at the University of Messina and from 2001 to 2020 an associate professor at the Department of Chemical, Biological, Pharmaceutical, and Environmental Sciences (ChiBioFarAm) of the University of Messina. Since January 2021, she is Full Professor of organic chemistry (CHIM/06 Organic Chemistry) at the same Department. Research interests: studies on stereoselective syntheses based on the use of enantiopure organosulfurated derivatives and in particular sulfenic acids; design and synthesis of fluorescent molecules with potential applications in the biomedical field. The scientific production of Paola Bonaccorsi includes more than 90 pubblications on international journals, 2 chapters of book, 1 patent, more than 70 communications at congresses and several invited lectures.

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Chiara Maria Antonietta Gangemi received her Ph. Master in organic chemistry in 2012 (110/110 *cum laude*) and Ph.D. in Chemical Science at the University of Catania. She spent six months at Columbia University under the guidance of Prof. Nakanishi and Berova, where she studied the interactions of organic molecules with DNA. Her research is focused on the synthesis and spectroscopic investigations of organic luminescent molecules (e.g., porphyrins, oligophenylene ethynylenes, BODIPY derivatives) and their interactions with biomolecules. Since 2022 she is a researcher in the Department of Chemical, Biological, Pharmaceutical, and Environmental Sciences (ChiBioFarAm) at the University of Messina.

Maura Monforte took the Ph. Master in Chemistry (2022, 110/110 *cum laude*), with a thesis about the synthesis characterization of oligophenylene ethynylene push-pull systems. After a six-month stage in an organic synthesis laboratory working on the synthesis of glyco-conjugated BODIPY, she is now a 1st year Ph.D student in the Chemical Sciences course at the University of Messina, Department of Chemical, Biological, Pharmaceutical, and Environmental Sciences (ChiBioFarAm). Her Ph.D project focuses on the synthesis and characterization of biocompatible luminescent systems for biomedical applications. The scientific production of M.Monforte is represented by one article and a flash communication at congress.

Ester D’Agostino took the Ph. Master in Medicinal Chemistry and Tecnologies (2021, 110/110 *cum laude*), with an experimental thesis in computational chemistry. She started on the same year the PhD in the Chemical Science course at the University of Messina, Department of Chemical, Biological, Pharmaceutical, and Environmental Sciences (ChiBioFarAm). Her research activity concerns the synthesis and characterization of luminescent compounds with potential applications in the biomedical and nano-material fields. Since February 2023, she has spent one year working in Liverpool John Moores University, UK, under the supervision of Prof. F. Giuntini, where her research was focused on peptide synthesis and their conjugation to glyco-porphyrins. During her PhD she also did teaching activities as a tutor in pharmaceutical and organic chemistry at the same Department (University of Messina, ChiBioFarAm). The scientific production of E. D’Agostino is represented by 2 articles, 3 oral communications and 4 poster communications at national and international congresses.

Anna Barattucci took the Ph. Master in Chemistry (1993) and the title of Doctor of Philosophy in Chemistry (1998) at the University of Messina. Since December 2018 she works as Associate Professor (CHIM/06 Organic Chemistry) at the Department of Chemical, Biological, Pharmaceutical, and Environmental Sciences (ChiBioFarAm) of the University of Messina. From 2003 to 2018, she was a researcher at the same Department. The main subjects of her research concern i) transient sulfenic acids in the stereoselective synthesis of sulfoxides and unsymmetrically substituted disulfides, in the synthesis of polyfunctionalized sulfur compounds as cyclophanes, tripodal compounds, bolamphiphiles and ii) synthesis of fluorescent molecules with potential applications in the biomedical field. The scientific production of Anna Barattucci is represented by 79 articles, 2 book chapters, 1 patent, several communications at national and international congresses and 10 invited lectures.

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