Applications, Properties and Synthesis of ￼-Functionalized n-Alkanethiols and Disulfides – the Building Blocks of Self-Assembled Monolayers

Dariusz Witt[1], Rafal Klajn[2], Piotr Barski[1,2] and Bartosz A. Grzybowski[2*]

[1] *ProChimia Poland, ul. Zacisze 2, 81-850 Sopot, Poland*

[2] *Northwestern University, Department of Chemical and Biological Engineering, 2145 Sheridan Rd. Evanston IL 06208, USA*

Abstract: Self-assembled monolayers (SAMs) of alkane thiols on gold and other metals are versatile constructs with which to study interfacial phenomena and reactions at surfaces. Surface properties of SAMs – e.g., wettability, stability in diverse environments, propensity to interact with or to resist adsorption of macromolecules -- depend on and can be controlled flexibly by the properties of the functional (head) groups in the ￼ position of the alkyl chain. SAMs provide a basis for many important scientific and technological applications, ranging from micropatterning methods, through sensing, to biological recognition. Despite their importance, the literature on SAMs and the synthesis of molecules that constitute them remains scattered and often conflicting. The purpose of this *Review* is (i) to summarize the applications and physical properties of SAMs and (ii) to systematize the strategies of synthesis of ￼-functionalized alkane thiols. Generic retrosynthetic scheme is developed that allows efficient synthetic planning. Issues related to the selection of appropriate protecting groups and the ways of introduction of the thiol functionality are discussed in detail, and illustrated with examples of syntheses of several complex alkane thiols.

1. INTRODUCTION

Over the last decade, self-assembled monolayers (SAMs) of thiols and disulfides on gold [1-3] (and, to a lesser degree on Ag [4], Pt [5], Cu [6], Pd [7], Hg [8]) have emerged as one of the most important classes of surface coatings. In particular, alkyl thiols (ATs) and disulfides (ADs) are widely used to prepare highly ordered monolayers whose properties can be adjusted by changing the chemical nature of the terminal groups [9-11]. SAMs of alkyl thiols and disulfides are used in modern micro- and nano-fabrication [12,13], in biomaterials and biological assays [14], in molecular electronics, [15] in analytical [16] and sensory applications [17], and as molecular lubricants [18], protective coatings [19], or templates for crystal nucleation and growth [20]. As the number of publications on SAMs steadily increases (273 in 1996, 562 in 1998, 721 in 2000 and 946 in 2002), new applications are likely to be developed and new types of thiols and disulfides synthesized. Yet, despite the importance of these classes of compounds and sometimes non-trivial aspects of their synthesis and purification, the literature on their preparation remains scattered and fragmentary. In our academic and business practice, we have found that the published synthetic procedures are often inefficient, incomplete or in some cases even wrong. The logic of some published syntheses is unclear and there is no available compendium that would help a practicing organic chemist to learn about the important aspects/caveats of synthesis of different structural subclasses [159].

The current *Review* is intended to fill this gap and become an accessible reference on the broad applications, structural properties and synthetic aspects of ATs and ADs. Since it is impossible to discuss all the ATs and ADs that have been made, we will focus on the most important,

technologically relevant structural sub-classes. With this objective, we will first review the applications in which alkyl thiols and disulfides are used, and will tabulate the most representative compounds. Next, we will summarize the general characteristics of thio- and disulfide groups emphasizing their reactivities, ways of their protection/deprotection, spectroscopic characteristics, and propensities to form monolayers. We will then discuss (i) synthetic strategies for the introduction of thiol/disulfide groups onto alkane chains in the absence of other functionalities and (ii) general schemes for the synthesis of functionalized ATs and ADs. We will suggest a logical approach to the synthesis of these compounds that is based on the categorization of functional head-groups. We will conclude by providing several illustrative syntheses of important ATs and ADs.

2. APPLICATION OF ALKANE THIOLS AND DISULFIDES

2.1. Micro- and Nanofabrication

Arguably, the most important application of alkane thiols is in soft lithography [21-23]. This technique, developed by the Whitesides group, uses elastomeric stamps micropatterned in bas relief to locally deliver thiols onto metallic (usually, gold) surfaces. The stamp is first inked with an ethanolic solution of a thiol, rinsed, dried, and gently placed onto the gold surface. Thiols transfer from the raised portions of the stamp onto the metal. The resulting SAM micropattern can be used to either protect the portions of the metal or to tailor surface properties. In the first case, the unprotected (i.e., bare) gold can be etched away to leave behind a metallic microstructure. Usually, simple methyl-terminated alkane thiols (~10-18 carbons long) are used in these etching procedures; interested readers can find a list of surface-specific etchants in Reference 1. Tailoring of surface properties is achieved by using appropriate chemistries at the ￼ position of the n-alkyl thiols. Surfaces can be made hydrophilic by introduction of polar groups [24, 26] (X=OH,

*Address correspondence to this author at the Northwestern University, Dept. of Chemical & Biological Eng. 2145 Sheridan Rd. Evanston IL 06208 USA; Tel: 847-491-3024; Fax: 847-491-3728; E-mail: grzybor@northwestrn.edu or chemistry@prochimia.com

COOH or CONH$_2$); non-polar head-groups groups give hydrophobic surfaces (X= CH$_3$, [4] OCH$_2$CF$_2$CF$_3$ [25] or O(CH$_2$)$_m$CH$_3$, m=3,4 [26]). By using more complex functionalities, SAMs can be made (bio)chemically reactive, adhesive [27] or biologically inert (cf. Sections 2.3, 2.4).

2.2. Studies of Surface Reactions

Owing to their stability, the ease of preparation/modification and high degree of order, SAMs of alkanethiols on gold are interesting constructs with which to study reactions and reactivities at surfaces. Since this interesting area has been recently reviewed [28], we will only briefly summarize the most important -- in our view -- aspects of ongoing research, and will give examples of some thiols used (cf. Table **1**). Interested readers are directed for more information to Reference [28].

(i) Most synthetically useful reactions on SAMs are performed on monolayers containing thiols terminated in carboxyl, amino or hydroxyl groups. These groups can be modified either prior to or after the formation of the monolayers. Activation of COOH groups is usually achieved by treatment with carbodiimides [29] such as dicyclohexyl-carbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), by reaction with ethyl chloroformate [30], or by exposure [31, 32] to gaseous SOCl$_2$; active esters are prepared usually by EDC-mediated coupling with N-hydroxysulfosuccinimide (NHSS) [33] or N-hydroxy-succinimide (NHS) [34]. Monolayers with terminal amine groups were reacted with acylating reagents such as active esters [35, 36], acid chlorides [37] or quinones [38]. Monolayers with terminal hydroxyl groups can be acylated by reaction with acid chlorides or anhydrides to produce esters [39]. The methods of surface activation are important in immobilization of biomolecules onto SAMs, all will be further discussed in Section 2.4.

(ii) The head groups of the SAM can react with one another to give a polymerized monolayer. N-pyrrolylalkanethiols adsorbed on the surface of a gold electrode undergo electropolymerization [40, 41] similar to that occurring in the bulk. Thiols containing terminal diacetylene groups are polymerized by UV irradiation [42]. Hydrolysis of the monolayers of (3-mercaptopropyl)-trimethoxysilane, HS(CH$_2$)$_3$Si(OMe)$_3$, produces a siloxane polymer [43] (cf. Section 2.9). Monolayers terminated in anthracene [44] and coumarin [45] undergo reversible photodimerization. SAMs can also be used to initiate the growth of surface attached polymers [46]. For example, Paul *et al.* synthesized grafted polyacrylonitrile (PAN) brushes from SAMs containing modified AIBN head groups by irradiation at 300 nm.

(iii) Thiols terminated in photoswitchable groups can be used to prepare mixed SAMs whose surface properties change reversibly upon irradiation. Monolayers of cis- and trans-cyanostilbene-terminated thiols [47] have different wetting properties: the contact angle of water on cis-cyanostilbene is 60°, while that on trans-cyanostilbene is 45°. In monolayers with terminal azobenzenes [48], the changes in wettability are smaller in magnitude, and it is the trans-conformation that gives a more hydrophobic surface.

2.3. Surfaces Inert to Protein and Cellular Adhesion

Controlling the interaction of proteins, biomolecules, and cells with surfaces of synthetic materials is important for the development of new biocompatible materials. When synthetic materials are exposed to a biological fluid, proteins are adsorbed on their surfaces. These proteins, in turn, harbor specific bacteria that can cause an infection [49, 50].

SAMs made of alkane thiols have proven to be useful model systems with which to study protein adsorption onto surfaces [51,52]. In particular, lot's of effort has been devoted to preparing monolayers that would resist protein adsorption. Recently, Whitesides' [53-57] and later Mrksich's [58] groups studied surfaces systematically to determine the molecular characteristics that impart resistance. They identified several molecular functionalities that, when presented at surfaces, resisted the adsorption of representative proteins in a manner comparable to surfaces decorated with poly(ethylene glycol). The molecular groups identified as part of this screen shared four characteristics: (i) absence of hydrogen bond donor groups; (ii) presence of hydrogen bond accepting groups; (iii) polar characteristics; (iv) overall charge neutrality. Examples of the most resistant groups are given in (Table **1**).

2.4. Immobilization of Biomolecules

It is sometimes necessary to attach biomolecules to synthetic surfaces; applications include sensors, biocatalytic electrodes and arrays for high-throughput screening. Biomolecules can be linked to functionalized SAMs covalently or by coordination/electrostatic interactions.

2.4.1. Covalent Immobilization

Patel *et al.* used mixed SAMs formed from 3-mercaptopropanoic acid and 11-mercaptoundecanoic acid to immobilize catalase using NHS/EDC chemistry; the resulting orientation of the protein could not be specified *a priori* [59]. NHS-activated carboxy-terminated thiols were also used to immobilize -galactosidase [60], collagen V and horseradish peroxidase [61]. Biebuyck *et al.* have used thiols terminated with active NHS esters for covalent attachment of antibodies to SAMs for the development of immunosensors [62]. Deckert's group studied the attachment of myoglobin to surfaces terminated in mesylate, chloride or bromide [63]. Corn and coworkers [64,65] designed a method for reversible protection and reactive patterning of amine and hydroxyl-terminated SAMs and used it to fabricate several biopolymer arrays. Maleimide-terminated mixed disulfides [66] were used to capture thiol-terminated peptide and carbohydrate ligands, and were the basis of detection biochips. Peptide microarrays were prepared using the Diels-Alder reaction between SAMs presenting benzoquinone groups and peptide-cyclopentadiene groups [67]. Finally, aldehyde terminated-thiols [68] were used to anchor amino-containing molecules, including enzymes and antibodies, to gold surfaces.

2.4.2. Non-Covalent Immobilization

Sigal *et al.* developed a SAM terminated with a nitrilotriacetic acid (NTA-SAM) chelating agent that binds Ni(II) and the His-Tag motif selectively and tightly [69]. SAMs presenting NTA ligands enabled the selective immobilization of His-tagged proteins (human TATA box binding protein, transcriptional activator Gal 4, two components of the yeast RNA polymerase II holoenzyme, and a single chain T-cell receptor construct) through

complexation of the Ni(II) atom by two histidines. Recently, Corn's group prepared maleimide-NTA SAMs for the study of protein-protein and protein-DNA interactions [70]. Biotinylated thiols were used in mixed SAMs to immobilize streptavidin [71]. Thiols terminated in imidazoles permitted selective immobilization of metalloporphyrins [72]. Whitesides' group studied the biospecific interaction between mixed SAMs presenting benzenesulfonamide ligands with bovine carbonic anhydrase (BCA) [73,74]. Mrksich and coworkers used SAMs terminated in phosphonate ligands for specific binding of fusion proteins [75,76]. The surfaces they prepared were subsequently used to guide the adhesion and spreading of cells. SAMs with amine and carboxy head groups were used to control the orientation of adsorbed antibodies [77].

DNA immobilization requires the use of thiols terminated in either charged or intercalating ligands. Mixed monolayers of methyl- and tetraalkylammonium(TMA)-terminated thiols on nanoparticles interacted with DNA via charge-charge interactions leading to complete inhibition of transcription by T7 RNA polymerase in vitro [78]. TMA-DNA interactions were recently used by Wang and Murray to prepare one-dimensional chains of gold nanoparticles coated along DNA molecules in solution [79]. Intercalation between DNA and anthryl head-groups of mixed-disulfide SAMs allowed immobilization and hybridization of nucleotides [80].

2.5. Molecular Electronics

Miniaturization of electronic devices has recently reached molecular dimensions [81, 82], and several model systems have been demonstrated whose electronic function is controlled be single molecules. Alkane thiols – and less frequently, alkane disulfides -- are important in molecular electronics research as components of SAMs through which electrons tunnel between two planar electrodes [83]. In the simplest gold-SAM-gold architecture used to study the electron transport through molecules, the thiols can be covalently linked to either one (alkane thiols, $SH\text{-}C_nH_{2n+1}$, usually n>~7) [84-86] or both electrodes (dithiols, $SH\text{-}C_nH_{2n}\text{-}SH$, usually n>~7) [87,88]; these molecules are also used to form contacts with other conductive surfaces (e.g., Ag, Hg, n-Si, p-Si, Pt/Ir) [83]. Functionalized thiols and disulfides are used in conductor-SAM-conductor or conductor-SAM1//SAM2-conductor junctions as current rectifiers [89,90]. The SAM1//SAM2 junctions using thiols terminated in carboxylic or amino groups have been used to probe electron migration through specific covalent or non-covalent chemical bonds [91].

2.6. Electrochemical Sensing

SAMs of appropriately functionalized alkane thiols have been used in either pH or chemical sensing [92]. In the former application, thiols bearing pH-sensitive groups are used in conjunction with a charged redox couple. As the pH of the solution changes, the head groups of the thiols change their ionization state and thus influence the electron transfer between the redox couple and the gold electrode. One of the most widely used couples is that of a SAM of COOH-terminated thiols groups, and $Fe(CN)_6^{3\text{-}/4\text{-}}$ ions in solution [93]. Electron transfer can also take place between different

head groups in mixed SAMs. In the now classic demonstration [94] of mixed-SAM pH sensors, ferrocenyl and quinone thiols were used to form a mixed monolayer on Au microelectrodes to give a two-terminal, voltammetric microsensor with reference and sensor functions on the same electrode. The detection was based on measurement of the potential difference of current peaks for oxidation and reduction of the reference (ferrocene) and indicator (quinone). Since the quinone has a half-wave potential that is pH-sensitive it was possible to use it as a pH indicator; the ferrocene was a pH-insensitive reference. Ferrocenyl thiols have been subsequently used in many electrochemical applications in mixed or one-components SAMs, in some cases in very adverse environments (e.g., in concentrated sulfuric acid [95]).

Electrochemical detection of analytes other than protons requires using thiols with highly selective head groups. Turyan and Mandler [96] used SAMs of -mercaptocarboxylic acids, $HS\text{-}(CH_2)_nCO_2H$ (n = 1,2,5, l0) on gold and mercury for ultrasensitive (~4*10-12M) detection of cadmium(II). The same authors developed a selective electrode for chromium-(VI) based on a self-assembled monolayer of 4-(mercaptoethyl)pyridinium; this electrode was capable of detecting Cr(VI) levels as low as 1 parts per trillion [97]. Selective detection of Cu^{2+} and Pb^{2+} cations usually requires the use of tetradentate ligands, such as 2,2'-thiobis(ethyl acetoacetate) [98]. We note that in all of these applications the sensitivity of the device was better for short than for longer alkyl chains. Longer chain alkane thiols (e.g., mercaptoundecanoic acid) were tried in electrochemical detection applications, but the reported sensitivities and selectivities were low.

Although voltammetric detection of ions is very sensitive, it is applicable only to electrochemically active ions. As it has recently been shown, binding of electrochemically inactive ions to SAMs can be monitored by impedance spectroscopy (IS). Using this technique, Reinhoudt's group studied the selective binding of different cations (Li^+, N^+, K^+ Cs^+) to thiols terminated with crown ethers [99]. Björefors *et al.* prepared SAMs from phosphate-terminated thiols; these monolayers showed discrimination in binding monovalent and divalent cations (notably, magnesium and calcium) [100]. Nahir and Bowden used IS to measure the rate of adsorption of cytochrome C onto mercaptohexanoic acid SAM [101].

2.7. Detection By Mass Sensitive Devices

The quantity of an analyte adsorbed onto a vibrating surface can be related to the change in vibration frequency upon adsorption. This property underlies the operation of quartz microbalance (QCM) and cantaliver-based sensors. Lang *et al.* used a microfabricated silicon cantilever coated with Au and supporting a SAM of mercaptoundecanoic acid to detect water vapor [102]. SAM of dodecanethiol was the essential element of a cantaliver used for selective detection of mercury ions [103]; calixarene-terminated dithiols were used to detect cesium ions [104].

Quartz microbalance was used for the detection of both small as well as macromolecules. The adsorption behavior and interaction mechanism of organic vapors on QCM sensors coated with SAMs composed of either $HS(CH_2)_6OH$

or HS(CH$_2$)$_6$OCH$_2$Ph were investigated [105]. The hydrogen bonding and dipole-induced/dipole interactions between the vapor molecules and the monolayer gave an excellent sensor response to organic vapors bearing strong electron attracting groups (e.g., acetic acid and alcohols). Hook *et al.* studied the adsorption of two structurally similar forms of hemoglobin (met-Hb and HbCO) to a hydrophobic, self-assembled methyl-terminated (octadecanethiol) monolayer on gold, and discovered significant differences in the viscoelastic properties of the two proteins [106]. SAMs made of *N*-Hydroxysulfosuccinimide (NHS) activated mercaptoundecanoic acid [107] were successfully tested for the specific adsorption of DNA. The QCM responses during the DNA hybridization were studied with high sensitivity using a mixed SAM of hexanethiol, mercaptopropionic acid and mercaptohexanol [108]. Finally, a QCM immunosensor was developed [109] for rapid detection of Escherichia coli O157:H7. It was based on the immobilization of affinity-purified antibodies onto a monolayer of NHS-activated 16-mercaptohexadecanoic acid. The binding of target bacteria onto the immobilized antibodies decreased the sensor's resonant frequency, and the frequency shift was correlated to the bacterial concentration.

2.8. Molecular Lubrication

Ultrathin organic layers have long been used as protective/lubrication organic coatings [110]. Chemisorbed self-assembled monolayers are especially interesting in this context [111] since their resistance to wear is much higher than that of physisorbed monolayers (e.g., LB films). SAMs composed of alkyl-thiols have been used to prepare SAMs of adjustable frictional coefficients. For example, Nelles *et al.* have shown that increasing the chain length from 2 to 18 carbons decreases friction forces by the factor of five [112]. In contrast, introduction of a small percentage of bulky CF$_3$ or CH$_2$(CH$_3$)$_2$ terminal groups dramatically increases friction [113]. Surface friction properties can also be varied by adjusting the surface composition of mixed SAMs [114]. Interesting behavior is expected of buckyball terminated thiols [4] – SAMs of similarly functionalized silanes on quartz gave surfaces with atypical, velocity-dependent frictional properties [115] (frictional forces showed a sharp maximum for intermediate velocities).

2.9. Corrosion Protection

Alkane thiols and disulfides can be used as coatings to prevent corrosion of an underlying metal surface. Copper is effectively protected against corrosion when covered by n-alkyl thiols; for chains having more that 16 carbons, the effectiveness of protection increases linearly with chain length [116]. Long-chain omega-alkoxy-n-alkanethiols (CH$_3$(CH$_2$)$_{m-1}$O(CH$_2$)$_n$SH; n = 11, 19, 22; m = 18, 22) are also effective for Cu protection. For SAMs where the ether substitution is farther from the copper surface, the initial coating resistances are similar to those of unsubstituted n-alkanethiolate SAMs of similar thickness. For SAMs where the ether substitution is nearer to the copper surface (n = 11), the resistances are significantly less than those for unsubstituted n-alkanethiolate SAMs of similar thickness [117].

Thiol-protection of silver is important for stabilizing colloidal metal particles. Burleigh *et al.* developed a family of SAMs based on perfluoroalkyl amideethanethiols, [118] CF$_3$(CF$_2$)$_m$CONH(CH$_2$)$_2$SH (m = 6, 7, or 8) that inhibit the corrosion of silver by hydrogen sulfide in air. Unlike conventional hydrocarbon thiols or disulfides [119,120], these amidethiols are almost odorless and impart fluorocarbon wettability properties to silver surfaces. Polymerization of 3-Mercaptopropyltrimethoxysilane gave an anti-corrosion, biocompatible layer for the protection of otherwise chemically unstable GaAs surface [121].

Repetitive deposition of 1,2-bis(trichlorosilyl)ethane and 1,8-octanediol on the hydroxy-terminated SAM gave a layer of mesh useful in corrosion protection of copper [122,123].

2.10. Definition of End Group(s) R

As seen from the discussion above, the properties of SAMs made of alkyl thiols and disulfides depend on and can be adjusted by changing the chemical nature of the terminal (end) groups, R. These groups range from simple alkyl, amino, or carboxyl functionalities to more elaborate ones like peptides, carbohydrates, calix[4]arenes, or crown ethers. (Tables **1** and **2**) give examples of terminal groups categorized by applications, in which the corresponding thiols and/or disulfides are used. The synthetic approaches to making these compounds are discussed in detail in Sections 4 and 5.

3. CHARACTERISTICS OF THE THIOL AND DISULFIDE GROUPS

3.1. Physical-Organic Properties

Sulfur is isovalent with oxygen and this fact makes thiols close analogues of alcohols. However, the decreased electronegativity of sulfur has several important consequences for the physical and chemical properties of thiols. Intermolecular hydrogen bonds are much weaker between thiol molecules and as a result thiols are more volatile than alcohols. For example, methanethiol is gaseous at room temperature, and the boiling point of 2-propanethiol is 30°C lower than that of the corresponding alcohol [124]. Boiling point of *n*-alkanethiols increases with increasing length of the alkyl chain and *n*-heptadecanethiol is a solid at room temperature [124].

Unlike alcohols, thiols can be deprotonated by aqueous base solutions and the resulting thiolate anions act as powerful nucleophilic agents. Examples illustrating their reactivity include nucleophilic substitution of alkyl halides to generate sulfides [125]. In acidic conditions and in the presence of a free-radical initiator, thiols easily undergo addition to double and triple carbon-carbon bonds [126]. Attack on electrophilic carbon of aldehydes and ketones is also possible to afford hemimercaptals [127] and dithioacetals [128], respectively.

Thiols also behave as excellent Michael donors. This reaction involves the addition of a thiol anion to an electrophilic multiple bond (Michaels addition). The electrophilic reaction partner is typically an , -unsaturated ketone, aldehyde, ester, or nitrile, but other electron-withdrawing substituents such as nitro or sulfonyl groups also activate carbon-carbon double and triple bonds towards nucleophilic attack. For example, reaction of a thiol with ethynyl-p-tolyl sulfon [155] or 3-(3-nitrophenyl)-1-phenyl-propenone [152] affords Z-2-(alkylthio)vinyl p-tolyl sulfone or 3 - (3 - nitrophenyl) - 3 - (arylthio) - 1 - phenylpropanone,

Table 1. Examples of applications of SAMs of alkyl thiols and/or disulfides. Procedures applicable to smaller values but this is what we suggest would work best. Abbreviations used: [a] EG – ethylene oxide, [b] Man – mannitol, [c] Mal -- maltose [Glc-R(1,4)-Glc-,(1)-O]. Stars denote that, although not recommended, chains of smaller values of *n* could be used.

Area	Application	End Group(s) R (HS-C_n-R)	n	Refs.
Soft Lithography	Etching	CH_3	>10	21
	Control of Surface	OH, COOH or $CONH_2$	15	24,26
	Wettability	CH_3, $OCH_2CF_2CF_3$ [5] or $O(CH_2)_mCH_3$ m=3,4	2,11,15,16	24,25,26
	"Sticky" surfaces	SH	8	27
Surface Reactions	Surface Activation	(NHSS) COO-NHS	> 7* > 7*	33 34
	Surface polymerization	$Si(OMe)_3$ AIBN-dithiol	2,4,6 10 3 10 10 10	40,41 42 43 44 45 46
	Photoswitchable Surfaces		10 6,10,12	47 48
Biocompatible Coatings	Protein-resistant surfaces	$(EG)_mOH^a$, m=2-6	11	55
		$(EG)_mOCH_3^a$, m>3	11	55
		$O(Man)^b$	11	58
		$O(Mal)^c$	10	52, 55
		$H(CH_3)N(Sar)_mN(CH_3)_2$, m=3-5, where Sar =	11	55
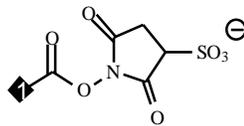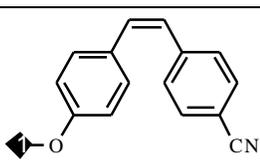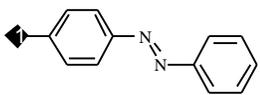
Immobilization of Biomolecules.	Covalent Immobilization	COO-NHS	2-11	59-62
		Cl, Br, -OSO$_2$CH$_3$	16	63
		X=O, NH	11	64,65
		EG3/EG5-maleimide disulfide	11	66
			11	67
		CHO	4	68
	Noncovalent Immobilization	X=maleimide or EG3CONH	11	69,70
			14	71
			10	72
			11	73,74
			11	75,76
		COOH and NH$_2$	11,16	77
		NMe$_3^+$	11	78,79
			8,11	80
		mixed disulfide		
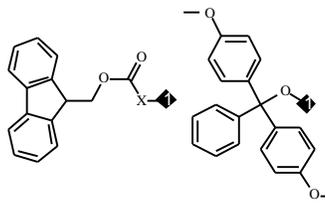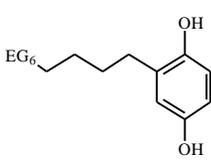
Molecular Electronics	Elecron Tunelling	CH₃ SH	7-11 8-12	84,85, 86 87,88
	Current Rectification		3 10*	89 90
	Probing Specific Chemical Bonds	COOH, NH₂	10	91
Electrochem. Sensing	pH Sensing	COOH	8 and 11 3 1,2,5,	94 93
	Voltammetric Sensing	COOH	10 2	96 97
	Impedance Spectroscopy	and also 15-crown-5 and 18-crown-6 COOH	1,6 2,15 5	99 100 101
Mass Detection	Cantilever sensors QCM	COOH CH₃ OH and OCH₂Ph CH₃	10 11 6 17 10	102 103 105 106 107
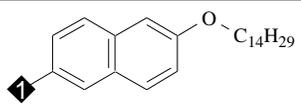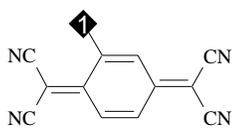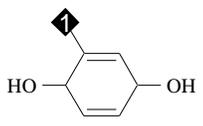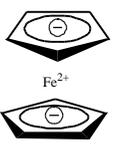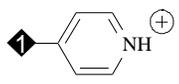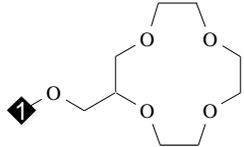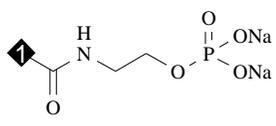
CH_3

SH

$O-C_{14}H_{29}$

NC ... CN, NC ... CN

Fe^{2+}

HO — OH

$COOH$

NH

$SO_3^{\ominus}$

H N P ONa ONa

		CH$_3$, OH, COOH	3,6	108
		COO-NHS	15	109
Molecular Lubricants	Tailoring Frictional Forces	CH$_3$	1-18	112
		CF$_3$, CH(CH$_3$)$_2$	10-12	113
		OH, CH$_3$	12	114
Corrosion Protection		CH$_3$	7, 11, 15, 17, 19, 21, and 28	116
		CH$_3$(CH$_2$)$_{m-1}$O m = 18, 22	11,19,22	117
		F(CF$_2$)$_m$CONH m = 6, 7, 8	2	118
		(CH$_3$O)$_3$Si	3	121
		OH	6	122, 123

respectively (cf. figure **1** section 3.2). These derivatives can be consequently converted into thiols. This type of reactivity has been used to reversibly block S–H bond and is discussed in that context in section 3.2.

$$2\ RSH \rightleftharpoons RS{-}SR + 2H^{+} + 2e^{-}$$

The primary need for the protection of S-H bond during synthesis comes from the fact that thiols are relatively unstable towards oxidation. Standard red-ox potential for the following half-reaction is relatively low (-1.0 0.5 with respect to SCE, strongly dependent on the structure, solvent and electrode material) and thiols are readily oxidized to corresponding disulfides with the use of a variety of oxidizing agents, e.g. H$_2$O$_2$ [130], Br$_2$ [131] and nitrogen oxides [132]. More violent conditions, e.g. boiling HNO$_3$, give sulfonic acids. Thiols can also be oxidized to sulfonyl chlorides with Cl$_2$ in water [133]. Thiol-disulfide equilibrium is very important in biochemistry, where the oxidation of cysteine side chains leads to the formation of disulfide bridges, a process crucial to the proper folding of proteins [129]. On the other hand, the thiol-disulfide often complicates the synthesis of pure thiols, uncontaminated with disulfide byproducts.

Dialkyl disulfides are typically oils only sparingly soluble in water [124]. Reduction of disulfides to thiols is straightforward and occurs in the presence of mild reducing agents such as triphenylphosphine in water [134] or potassium triisopropoxyborohydride in THF [135]. Further reduction to the corresponding alkanes and H$_2$S can be accomplished by catalytic hydrogenation of the C–S bond [136]. Disulfides can also be reductively cleaved by Grignard reagents to yield sulfides [137].

Unlike thiols, disulfides behave as electrophiles in the presence of strong nucleophilic agents. Enolates cleave S-S bond, with one thiolate moiety combining with the enolate to form a sulfide, and the other acting as a leaving group [138]. If the leaving thiolate anion is stabilized, this reaction occurs upon treatment with moderately weak nucleophiles. For example, di(2-pyridinyl) disulfide (Aldrithiol-2) [175] has

been used for the synthesis of unsymmetrical disulfides in a clever way (see Section 4.4).

3.2. Protective Groups

Because of their high reactivity, thiols need to be protected in multistep syntheses in which other functionalities are introduced and/or modified. A comprehensive survey of all available protection strategies is well beyond the scope of this review, and in the following we will focus on the most common and useful protection groups; more detailed discussion can be found in a recent monograph [139].

Historically, much of the research on thiol protection has been stimulated by the great importance of the S–H bond of cysteine in molecular biology and biochemistry. Thiols have been most commonly protected as thioethers, and, to a lesser extent, as thioesters and disulfides [140, 141]. The use of many common protecting groups is limited by the fact that strongly basic conditions are required for their introduction, and/or acidic, basic or reductive conditions are needed in the deprotection step. Formation of the corresponding disulfide is an expected and most often observed side reaction when the thiol group is protected under basic conditions. Also, presence of other functionalities in the molecule that are sensitive towards these conditions may create serious obstacles.

First successful examples of using protecting groups for thiols date back to 1930s, when, e.g., resolution of racemic D,L-homocysteine was achieved by conversion of the amino acid to its S-benzyl thioether, actual resolution and the subsequent removal of the protecting group [142]. Benzyl group used to be popular in peptide synthesis, even though its cleavage demands drastic conditions [143]. Introduction of a nitro group in the para position of the phenyl ring (4-nitrobenzyl group) makes the removal less troublesome [144]. Of other substituted benzyl groups, 4-methylbenzyl (MeBzl) group was shown to be practical [145].

Introduction of solid-phase peptide synthesis [146] greatly facilitated search for new, improved protecting groups. Acetamidomethyl (Acm) has been found to be

Fig. (1). Examples illustrating various approaches to the protection of S–H bond.

especially convenient [147] and it is one of the groups used routinely nowadays. The presence of more than one disulfide bridge in many natural peptides has been a challenge for chemical synthesis requiring introduction of orthogonal protecting groups for cysteine side chains. Tertiary alkyl groups, of which t-butyl (tBu) and trityl (Trt) thioethers have been the most popular reagents for selective protection [148-150]. In a recent synthesis of -conotoxin dimer, orthogonality of four cysteine protecting groups (MeBzl, tBu, Trt, Acm) has been demonstrated in an elegant way [151].

The fact that sulfur atom of the S–H moiety represents a powerful potential Michaels donor center, creates a possibility to selectively protect sulfhydryl group in the presence of an alcohol. 3-nitrobenzalacetophenone has been used as an acceptor in a reaction with thiophenol and the resulting thioether readily underwent Friedel-Crafts acylation, which has not been possible for the unprotected thiol [152]. Removal of the alkyl group to liberate free sulfhydryl group is, however, often troublesome [153]. p-Toluenesulfonylacetylene has been recently shown to act as a protecting agent for a variety of thiols, and reacts selectively in the presence of a hydroxyl group. The resulting Tosvinyl derivatives can easily be deprotected under relatively mild conditions [154,155].

All of the procedures for introduction and removal of protective groups presented in Fig. (**1**) are well established [156-158, 191, 198, 235]. It is, however, very convenient

when (i) the protected thiol group can be obtained in one step from the appropriate starting material or (ii) deprotection conditions are very mild. For these reasons, in the design of the retrosynthetic scheme described in Section 4, we have focused our attention on S-benzyl, S-acetyl, S-benzoyl derivatives (readily available from the corresponding alkyl halides and/or terminal alkenes) and symmetrical and unsymmetrical disulfides (very mild conditions for thiol group recovery). The uses of other, more "specific" protective groups are illustrated in the synthetic examples in Section 5.

3.3. Spectroscopic Characterization

NMR is the most convenient method for the analysis of thiols and disulfides. Features that are helpful in identifying primary thiols by NMR include the presence of the S–H proton signal in the spectrum and the chemical shift of the –CH_2–S protons (2.4-2.6 ppm). The chemical shift of the S–H proton signal is variable and depends on solvent, temperature, concentration, and the presence of other functional groups. Its precise position is not particularly significant in structure determination. The CH_2–S signals for thiols with a –CH_2–CH_2–SH fragment appear as a quartet. The assignment of a signal for –CH_2–SH protons is readily confirmed by adding D_2O - as a result, the observed quartet reduces to a triplet. The corresponding disulfide –CH_2–CH_2–S–S–CH_2–CH_2– is usually easy to distinguish as it always appears as a triplet. In practice, however, thiols and

disulfides are often confused. For instance, in a recently attempted synthesis of 11-aminoundecane-1-thiol [159] the authors identified the product (characterized by have observed ^{1}H NMR: (CDCl$_3$)   = 2.66 (t, *J*=7.2 Hz, 2H, –C$\underline{H}_2$–SH) and MS: *m/z* calculated 203.1708, found 203.1705) as a thiol. This identification is certainly incorrect, as, firstly, the triplet at 2.66 suggests a disulfide, and secondly, MS corresponds to (-S-(CH$_2$)$_{11}$-NH$_3^+$)$_2$ [disulfide + 2H]$^{2+}$, i.e. to observed 203.1708 (calculated). Application of the simple rules described above would have undoubtly allowed correct structural assignment. We note that we have recently synthesized 11-aminoundecane-1-thiol by a different method and the following results were obtained: ^{1}H NMR (CDCl$_3$)   = 2.52 (q, *J*=7.3 Hz, 2H, -C$\underline{H}_2$-SH) and MS *m/z* calculated for C$_{11}$H$_{26}$NS (protonated 11-aminoundecane-1-thiol) [M + H]$^+$ 204.1786, found 204.1790.

3.4. Propensities to form Monolayers

Both Au and S are "soft", and the strong interaction between these two species is a classic example illustrating the theory of hard and soft acids and bases [160]. Stability of a self-assembled monolayer (SAM) formed by alkyl thiols and dialkyl disulfides is the consequence of two orthogonal factors: interfacial linkage between sulfur and gold, and lateral van der Waals attractions between hydrocarbon chains. Therefore, the longer the hydrocarbon chains of the deposited thiol, the greater the stability of the resulting monolayer.

Although the most intensively studied SAMs were those derived from alkyl thiols, the concept was first demonstrated for dialkyl disulfides [161]. Disulfides can be delivered to a gold surface either from a solution [161] or in ultra high vacuum (UHV) conditions [162], and there is a general consensus that either case leads to the S–S bond cleavage. The resulting chemisorbed thiolate anions have a high value of activation energy of desorption (~28 kcal/mol) [162] and show remarkable thermal stability.

In the case of a gold surface immersed in a solution of an alkyl thiol, it is generally assumed that a hydrogen atom is abstracted from a thiol molecule and the resulting radical species undergoes precipitation onto the surface, forming a covalent Au–S bond therein. [4] The presence of the thiolate species has been detected by means of X-ray photoelectron spectroscopy (XPS) [163,164] and time-of-flight secondary ion mass spectrometry (TOF-SIMS) [165].

On the other hand, adsorption under UHV conditions gives thiols only weakly physisorbed on gold; it has been shown that S–H bond scission does not occur under these conditions [162,166]. The difference between these two experiments is not completely understood. Therefore, SAMs derived from thiols and corresponding disulfides are indistinguishable and observation has been confirmed by many criteria including XPS, [167] ellipsometry, [167] and transmission electron microscopy (TEM) [168].

Regarding the organization of thiols in SAMs, it has been originally proposed that sulfur atoms are arranged in a regular manner at the threefold hollow sites on Au(111) [169]. However, more recent studies using in-depth x-ray diffraction [170] and high-resolution electron-energy-loss spectroscopy (HREELS) [171] support the so-called associative mechanism of the adsorption of alkyl thiols. Here, it has been speculated that half of the sulfur atoms

remain at the hollow sites, while the rest occupy positions near the bridge sites. Because of the resulting close proximity of each two neighboring sulfur atoms on gold, it has been assumed that disulfide bonds are formed on the metal surface [170,171].

Additional evidence that adsorption of thiols and disulfides results in the same chemical composition of a SAM arises from kinetic studies of the film formation [160,172]. The rate of adsorption of hexadecanethiol is indistinguishable from that of the corresponding disulfide. This fact suggests that the overall rate-limiting step is very similar in both cases -- therefore, it can be neither disulfide dissociation (dissociatove mechanism), nor thiol association (associative mechanism) [167]. Most studies favor the two-regime model of SAM formation on, in which a very fast step (initial adsorption onto the surface) is followed by a slow orientational ordering of the chains [173]. Although the kinetics of both alkanethiol and disulfide assembly on Au surfaces is the same, adsorption of thiols is strongly preferred from a mixture of the two species [163]. Also, it has been shown that the interchange between components of a SAM and the species present in solution is equilibrated much slower in case of disulfides [167]. The likely explanation for these two observations is that adsorption of the disulfide is sterically disfavored due to the large value of the CSSC angle and the fact that a sulfur atom is more sterically hindered than that of a thiol.

In conclusion, both thiols and disulfides form chemically identical SAM on gold, although some concern remains over the nature of the species that actually bind to the metal surface.

4. SYNTHESIS OF FUNCTIONALIZED THIOL AND DISULFIDES

4.1. Synthesis of Functionalized n-Alkyl Thiols

Demonstration of the usefulness of SAMS in a range of applications has spurred an effort to synthesize new classes of constituent alkyl thiols terminated in a variety of functional groups. The most prominent examples of functionalities introduced in the omega position of the alkyl chain include: 2-imidazolyl [176], 1-pyrenyl [177], carboxyl [178], phosphonic acid [179], amino and ammonium [180], permethylated -cyclodextrin [159], 15-crown-5 [181], dibenzo-24-crown-8 [182], 2,6-diaminopyridin-4-gloxy [183], benzaldehyde [184], amino acid [185], peptides [186], calix[4]arene [187], phosphoric acid [188], fulleren [189], terthiophen [190], carbohydrates [191], cyano [192], benzoquinone and hydroquinone [193], bisphosphate [194], 4-aza-1-azonia-bicyclo[2.2.2]octane [195], methoxy [196], t-butyldimethylsiloxy [197], phosphocholine [198], benzoic acid [199], fluorinated hydrocarbons [200], azobenzene [201], nitrilotriacetic acid [202], biotin [203], (ethylene glycol)$_n$ n= 1-7 [65] etc. In the following, we will attempt to systematize the synthetic strategies that allow preparation of these and other functionalized alkyl thiols.

(i) Retrosynthetic Analysis

Based on published as well as on our own procedures, we have created a retrosynthetic scheme that rationalizes available synthetic approaches to the preparation of functionalized thiols. There are two major ways to prepare these compounds: in the first one, the end group(s) (denoted

R in the Scheme) is introduced *after* the protected thiol functionality (left part of the Table **2** and Scheme **1** below); in the second, functionalization is done *before* protection (right part of the Table **2** and Scheme **1** below). Based on the literature data collected in (Table **2**), the latter method seems

to be more common and versatile. This preference can be explained by the fact that the number of groups available for the protection of the thiol functionality is quite limited, and that their introduction requires very mild conditions (cf. methods A and B in Scheme **1**).

Y - functional group helpfull in the conversion, introduction, or attachment of End Group(s) R
X - in most cases halogen, tosyl or mesyl group
A1-A5 the most common methods of introduction of protected thiol group
B1 and B2 the methods of introduction of protected thiol group into the terminal alkene
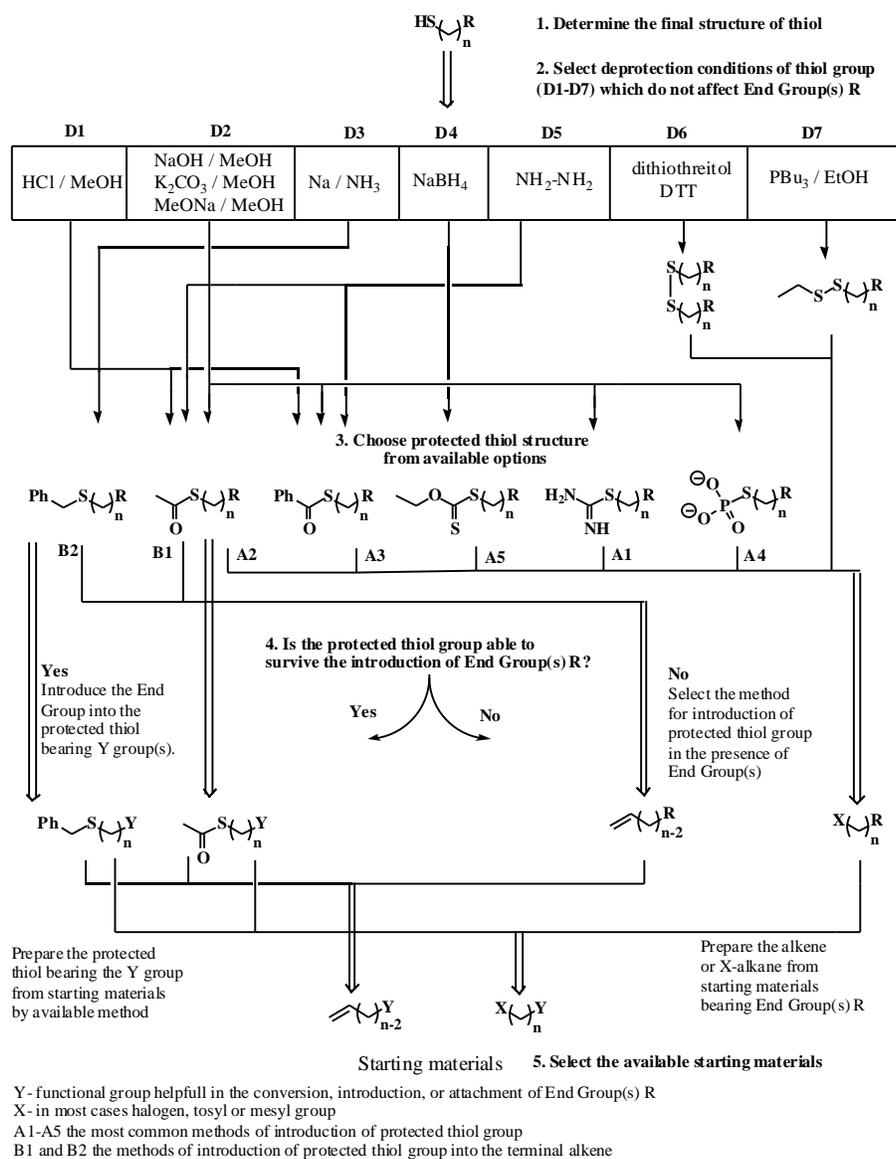
Scheme 1. Retrosynthesis of Functionalized Thiols. The synthetic planning should begin with writing out the structure of the desired thiol (Step **1**) and choosing appropriate conditions for the deprotection of the thiol group (Step **2**) from amongst the D1-D7 methods. These conditions should be such that they do not affect the end group(s) R. Since they are applied in the last step of synthesis, R must be already deprotected, or deprotection of R and the thiol groups must occur simultaneously. If the deprotection is performed stepwise then the protective group of thiol has to be stable towards conditions used for deprotection of end group(s) R. These requirements allow selection of one or more deprotection method (D1-D7) and the corresponding protective group (Step **3**). In Step **4**, it is determined whether the protected thiol group can survive the introduction of end group(s) R. If it can, then R is introduced into the structure *after* the protected thiol (left part of the Scheme); if it cannot, R is introduced *before* (right part of the Scheme after Step **4**). The latter procedure seems to be more common and versatile, since most end group(s) (protected or not) are able to survive mild conditions of the introduction of a protected thiol group into the structure (A1-A5, B1 and B2). Moreover, sulfur reagents can be used in excess to ensure better overall yields using this method. By the end of Step **4**, both the order and the methods of introduction of R and the thiol groups should be established in detail. Step **5**, selection of available starting materials, is the consequence of Step **4**. We note that if the retrosynthetic analysis fails at Steps **4** or **5**, it is necessary to return to Step **3** and chose another form of thiol protection. **Experimental details**: Nucleophilic substitution of alkyl halides by: A1. Thiourea, A2. Potassium thioacetate, A3. potassium thiobenzoate, A4 Na$_3$PO$_3$S, A5 potassium ethyl dithiocarbonate. Radical addition to terminal alkenes: B1. thioacetic acid, B2. PhCH$_2$SH, Experimental details for the deprotection of thiol group (see scheme **1** in the frame) by means of: D1.HCl in the methanol (or other alcohol), D2.NaOH (other hydroxides, MeONa, Na$_2$CO$_3$, or K$_2$CO$_3$) in MeOH (or EtOH), D3. Na in liquid NH$_3$, D4. NaBH$_4$, D5. NH$_2$-NH$_2$, D6. dithiothreitol HSCH$_2$CH(OH) CH(OH)CH$_2$SH (DTT), D7. PBu$_3$, EtOH.

To illustrate the proposed retrosynthetic scheme we apply it to design an efficient synthesis of an alkane thiol terminated in n = 1-6 units of ethylene glycol (**1**) (Fig. (**2**)) – this thiol is commonly used to prepare adsorption-resistant SAMs [54].

Step 1. The structure of the thiol is given below:
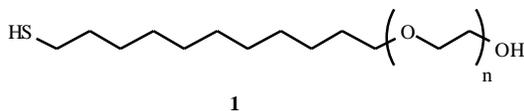
Fig. (2). Structure of an alkane thiol terminated in n = 1-6 units of ethylene glycol.

Step 2. In considering the choice of the deprotection method, it should be remembered that the (n)-ethylene glycol end group is unstable in strongly alkaline media. The penta or hexa ethylene glycol can be converted to the shorter tetra or penta ethylene glycol respectively, and some elimination
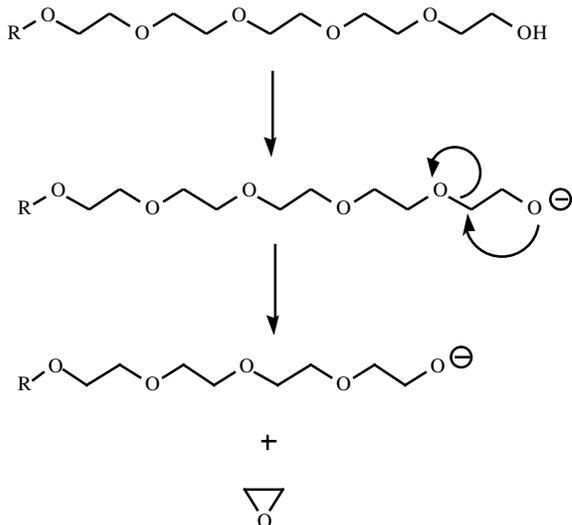
Fig. (3). The side reactions observed for penta and hexa etylene glycol terminated compounds.

of terminal hydroxyl group can occur (Fig. (**3**)); this elimination is less likely to occur for n=1-4 homologs [174].

Because of these side reactions, methods D2 (NaOH, MeONa)-D3 and D4 are not recommended. The suggested deprotection conditions are either mildly acidic (D1) or mildly basic (D2, D5), with a slight preference for the former, since D2 and D5 might promote formation of disulfides.

Step 3. All selected deprotection methods (D1, D2 and D5) can be applied to S-acetyl or S-benzoyl derivatives.

Step 4. It is now necessary to evaluate whether the S-acetyl or S-benzoyl groups would survive the conditions required for the introduction of ethylene glycol unit. The most convenient way do so is through the Williamson ether synthesis. Since the anion generated from the glycol will react with S-acyl derivatives, it must be introduced before the protection of the thiol group. This, in turn, restricts the

synthetic choices to the left part of (Scheme **1**) ("NO"); the available methods for the introduction of S-acetyl or S-benzoyl groups are based on either terminal alkenes (B1) or terminal haloalkanes (A1 and A3).

Based on these considerations, the following structures of the intermediates (**2**) and (**3**) can be proposed (Fig. (**4**)); where X is halogen and n = 1…6.
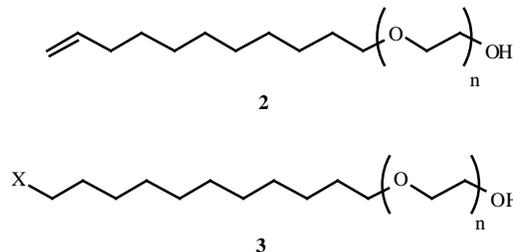
Fig. (4). The structure of the intermediates (2) and (3).
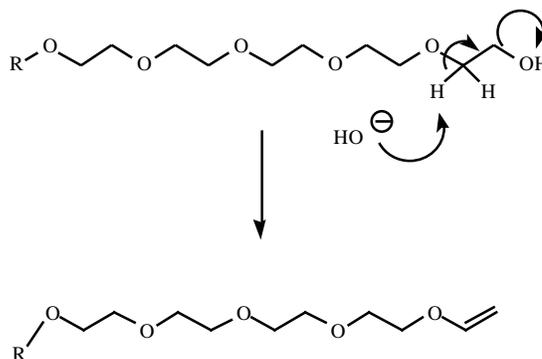
Step 5. These intermediates (**2**) and (**3**) can be made by the addition of n-ethylene glycol to either a dihaloalkane (**4**) or a terminal haloalkene (**5**) Fig. (**5**).

In the former method, an excess of dihaloalkane is required to replace one halogen; in the latter, excess of ethylene glycol is required to achieve monoalkylated product. We note that alkylation of ethylene glycol by means of haloalkene is usually more effective. Also, yields are optimal when (EG)$_n$ is applied in four- to fivefold excess.

With this selection of starting materials, a complete synthetic scheme can be outlined. In our practice, we use a procedure that starts with the alkylation of (n)-ethylene glycol with a haloalkene (usually, 11-haloundecene) followed by a radical addition of thioacetic acid to the terminal double bond (method B1, compound (**6**)) and deprotection of thiol group (methods D1, D2 or D5).
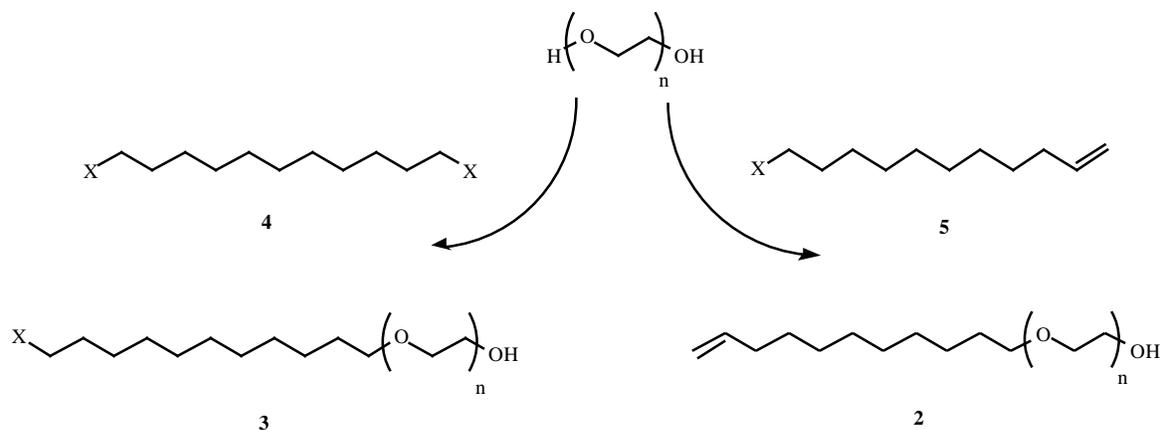
Fig. (5). The preparation of intermediates (2) and (3).
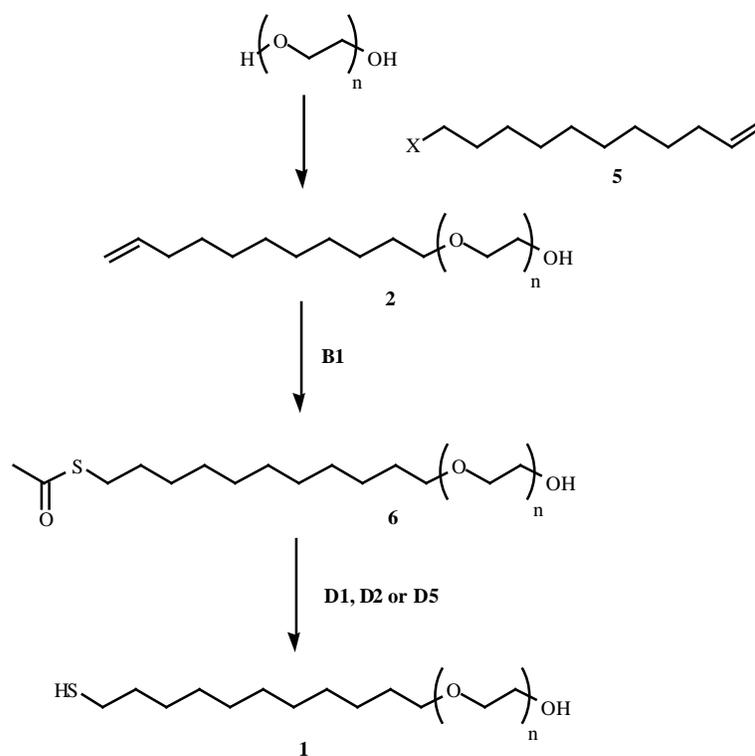
Fig. (6). The synthetic scheme for preparation of ethylene glycol terminated thiols.

Our synthetic solution based on the logic of Scheme 1 is very similar to – but not identical with - the reported synthesis [54]. First two steps of the synthesis are the same. While the deprotection of the thiol group for compound (**6**) reported in the literature was performed under acidic conditions (D1), our approach offers two additional options (methods D2 and D5). In general, the synthetic solutions obtained from (Scheme **1**) will lead to several alternative ways of synthesis of functionalized thiol. Although all of them will be viable, their efficiency will have to be verified experimentally.

The logic behind our retrosynthetic scheme can be used to categorize syntheses of various alkane thiols reported in the literature. This is done in (Table **2**), in which the major subdivision is done according to the sequence in which the R and thiol groups are introduced; the methods of introduction and deprotection as well as the literature sources are also provided. The combination of (Scheme **1** and Table **2**) can be a useful tool in planning the syntheses of new alkane thiols. In the following, we discuss the specific aspects of such retrosynthetic planning.

Table 2. Syntheses of various functionalized thiols categorized according to the logic of Scheme1. Left column: The end group(s) is introduced into the structure **after** the protected thiol group; right column: The end group(s) is introduced group into the structure **before** thiolprotection. Subcolumns give the methods of introduction and deprotection of thiol group, and the pertinent literature citations. Explanation of symbols corresponding to specific procedures is to be found in Scheme **1**.

The end group(s) R is introduced **after** protected thiol group into the structure.				The end group(s) R is introduced **before** protected thiol group into the structure.			
end group(s) R	Int.	Depr.	Refs.	end group(s) R	Int.	Depr.	Refs.
O(Man)[b]	B1	D1	58				
O(Mal)[c]	B1	D1	52,55	CH_3	A1	D2	21
$H(CH_3)N(Sar)_mN(CH_3)_2$, m=3-5, where Sar =	B1	D1	55	OH, COOH, $CONH_2$, $OCH_2CF_2CF_3$, $O(CH_2)_mCH_3$	A1 A1 A1 A4	D2 D2 D2	24,26 25 25 200
$Si(OMe)_3$	A2	D1	43	$(EG)_mOH^a$, m=2-6 $(EG)_mOCH_3^a$, m>3	B1 B1	D1 D1	55 55
X=O, NH	A2, B1	D1, D2	64,65		A1	D2	40,41
	B1	D1	67		A1	D2	42
	B2	D3	71, 203		A1	D2	44
Permethylated -cyclodextrins	B1	D5	159		A1	D2	45
					A1	D2	47
					A1	D2	48, 201
				X=maleimide or EG3CONH	B1	D1	69, 70, 202
					A1 A1	D2 D2	72 176
				COOH and NH_2	A1	D2	77, 180
				NMe_3^+	B1	D1	78,79
				NEt_3^+		D1	180
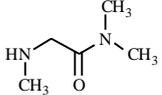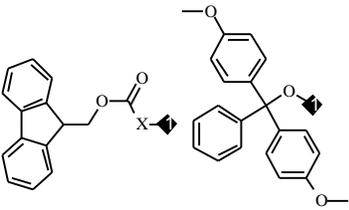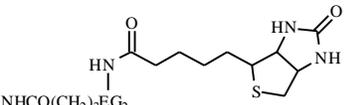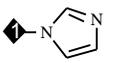
				Structure	Method A	Method D	Ref.
				and also 15-crown-5 and 18-crown-6	A1	D2	99 / 181
				1-pyrenyl	A2 or B1	D2	177
				COOH	A4 / A5	D4	178 / 178
				-P(O)(OH)$_2$ / -O-P(O)(OH)$_2$	A2 / B2	D2 / D3	179 / 188
				2,6-diaminopyridin-4-yloxy-	B1	D2	183
				CHO (aryl ether)	B1	D2	184
				HN—CH—C—OCH$_3$ (amino acid derivative)	A2	D2	185
				26,28-calix[4]crown-6	B1	D1	187
				Fullerenyl-		D1	189
				terthiophene	A1	D2	190
				Tetrapeptide-	B1	D1	186
				-CN	A1	D2	192
				hydroquinone and quinone	A2	D1	193
				phosphate diester	A3	D5	194
				Carbohydrates	A1	D6	191
				Phosphocholine derivatives		D7	198
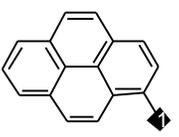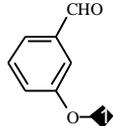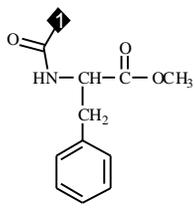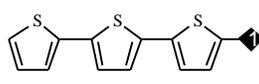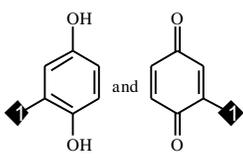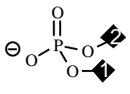
(ii) Introduction of the Thiol Group

Thiol functionality is always introduced in the protected form. When thiourea (method A1 Scheme **1**) or sodium thiophosphate (method A4 Scheme **1**) are used for formation of carbon-sulfur bond, the corresponding S-alkylated isothiourea and S-alkylthiophosphates are deprotected *in situ*. The one-pot procedure is the main advantage of these methods. Other syntheses of primary thiols begin with either (a) radical addition of thioacetic acid (method B1 Scheme **1**) or benzyl mercaptan (method B2 Scheme **1**) to terminal n-alkenes or (b) by nucleophilic substitution of sulfur nucleophiles (potassium thioacetate method A2, potassium

thiobenzoate method A3, and potassium ethyl dithiocarbonate method A5) at primary alkyl halides derivatives.

The removal of specific protective group (methods D1-D7, scheme **1**) affords thiols terminated in end group(s) –R. Although the synthetic routes starting from alkenes and alkyl halides seem to be very similar, there are quite a few substantial differences in the availability of starting materials and deprotection procedures. We have observed that preparation of thiols from alkenes usually gives better overall yields and higher purities. On the other hand, terminal-alkene substrates are harder to obtain and are more expensive than corresponding alkyl halides.

4.2. Synthesis of Thiols from Alkenes

Addition of thioacetic acid [159, 177, 179, 180, 183-186, 196, 201, 202, 204] (method B1, Scheme **1**), thiobenzoic acid [205, 206], and benzyl mercaptan [188, 203] (method B2, Scheme **1**) to terminal alkenes in the presence of benzoyl peroxide, AIBN or upon UV-irradiation follows the anti-Markovnikov rule and gives protected thiol derivatives in high yields (above 80-90%). The mild conditions for the

introduction and deprotection of resulting thiol derivatives are the main advantages of these methods. Moreover, the terminal double bond often does not require protection during the introduction of end group(s) into the structure. A wide range of functionalized terminal alkenes (CH_2=CH-$(CH_2)_n$-Y, scheme **1**) is known, and the Y groups (halogen, OH, NH_2, COOH, etc.) are very helpful in the attachment of appropriate end groups R (Scheme **1**).

This approach is well illustrated by the synthesis of nitrilotriacetic acid (NTA)-terminated alkanethiol (**7**) shown in Fig. (**7**) below [202] in which R was introduced before protected thiol functionality (right part of the Scheme **1** after Step **4** and right part of the Table **2**) and the thiol group was obtained from terminal carbon double bond.

The terminal double bond is inert toward nucleophilic substitution. This inertness is advantageous, for example, in the synthesis of ammonium terminated alkane thiol often used in noncovalent surface immobilization of DNA [78, 79]. Reaction of 11-bromoundecene with trimethylamine gives corresponding ammonium salt (**8**). Radical addition of thioacetic acid (method B1) and deprotection (method D2)

Fig. (7). The synthesis of nitrilotriacetic acid (NTA)-terminated alkanethiol (**7**).

Fig. (8). The synthesis of ammonium terminated alkane thiol (**9**).

afforded trimethylammonium thiol (**9**) in good yield (80%) Fig. (**8**).

(HSP(S)(CH$_3$)$_2$) and diphenylphosphinoditioic acid (HSP (S)Ph$_2$). Although they also give good yields [207], and the methods for their deprotection [208] are established, they often lead to undesired side reactions [209] and are relatively expensive.

The versatility of thioacetic acid is well illustrated in the example below, where its deprotection gave – depending on the conditions – two different and useful products Fig. (**9**).

Under acidic conditions (method D1), the (2-{2-[2-(2-{2-[2-(11-acetylsulfanyl-undecyloxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-acetic acid ethyl ester (**10**) precursor is converted to ethoxycarbonyl terminated thiol (**12**), while its basic hydrolysis gives carboxyl-terminated thiol (**11**). Both thiols are used in research on adsorption-resistant SAMs. We briefly mention that although both acidic (D1) and basic (D2) conversions are reported in the literature as efficient, we observed that basic conditions give a significant level of disulfide by-product. When the end group(s) cannot withstand conditions required for the deprotection of S-acetyl derivatives, protection with an S-benzyl group is a viable alternative; deprotection is then achieved with Na / liquid NH$_3$ (D3, Scheme **1**). The final step of the synthesis for phosphoric acid terminated thiol (**13**) [188] illustrates this method Fig. (**10**).

In this example, the acidic (D1) or basic (D2) conditions (most frequently used for deprotection of the S-acyl group) would have removed the phosphate end group - that is why the benzyl group was applied to protect sulfur instead of acetyl or benzoyl.

Because thiol group is rather sensitive and easily oxidizes to a disulfide, its deprotection is usually the final step in a synthesis. The best results are usually achieved by

Fig. (9). The versatility of S-acetyl protective group.

As seen from the above examples, double bond is a very convenient precursor to thiol group. Introduction of end group(s) via nucleophilic substitution can be used without risk of interaction with that bond. Thioacetic acid is the most common and versatile reagent for the free radical addition of thiol-precursors to terminal alkenes. It is inexpensive and straightforward to deprotect: acyl derivatives (benzoyl and acetyl) are deprotected in either acidic (HCl / MeOH, D1 Scheme **1**) or basic (NaOH, KOH, K$_2$CO$_3$, EtONa, MeONa, / MeOH, EtOH, butanol etc.; D2 Scheme **1**) conditions. Less common organosulfur compounds that can be used for a free radical addition include dimethylphosphinodithioic acid

Fig. (10). The synthesis for phosphoric acid terminated thiol (**13**).

performing the deprotection procedure under acidic conditions and under nitrogen or argon in a degassed protic solvent.

4.3. Synthesis of Thiols from Alkyl Halides

Preparation of thiols by this method begins with nucleophilic substitution of the halogen by means of the following reagents: thiourea [176, 178, 181, 190, 192, 201], potassium thioacetate [177-179, 210-212], potas-sium thiobenzoate [194, 213, 214], Na$_3$PO$_3$S (sodium thio-phosphate) [178, 200], potassium O-ethyl dithiocarbonate [178] as the source of sulfur nucleophiles. Although other sulfur nucleophiles can displace the halogen, they cannot be easily deprotected later on in the synthesis. The methods usually described in literature use alkyl halides but other derivatives like mesylates and tosylates should react similarly. Specific aspects of these methods are discussed below.

(i) Thiourea (Method A1, Scheme 1)

Reaction of an alkyl halide with thiourea gives a compound known as an isothiouronium salt that can subsequently be converted, by basic hydrolysis, into a desired thiol. Both steps can be carried out in the same reaction vessel without isolation of the intermediate isothiouronium salt. The main disadvantage of this method is the formation of disulfides and strong basic conditions it requires. Nevertheless, the yields of thiols are very often acceptable (above 60-70%). This approach is recommended when the end group(s) R in the starting, functionalized alkyl halide are not sensitive to strong basic conditions and increased temperature. Synthesis of 11-[2,2';5',2"] terthiophen-5-yl-undecane-1-thiol (**15**) [51] from 5-(11-bromoundecyl)-[2,2';5',2"] terthiophene (**14**) and thiourea
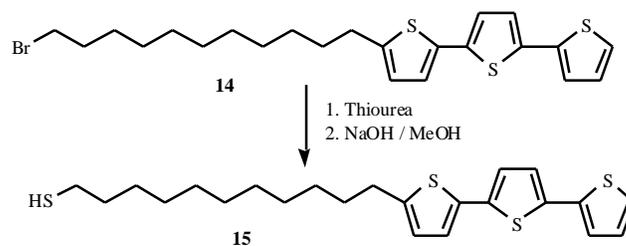
Fig. (11). The Synthesis of 11-[2,2';5',2"]terthiophen-5-yl-undecane-1-thiol (**15**).

provides an example of the method (for other examples, refer to Table **2**) Fig. (**11**):

(ii) Potassium Thioacetate. (Method A2, Scheme 1)

Substitution of a halogen by potassium thioacetate proceeds in mild conditions and very often excess of nucleophile can be applied. Most of the end group(s) R (protected or not) are insensitive towards this reagent, and mild conditions for deprotection of resulting S-acetyl thiols are very well established. These characteristics make this method one the most attractive ones for the introduction of a thiol group in the presence of end group(s) sensitive to strong basic conditions. In the Fig. (**12**) below, potassium thioacetate was used in the synthesis of N-(-thiol-heptadecanoyl)-phenylalanine methyl ester (**16**) - a reagent used in the study of ordering and hydrogen bonding within chiral and non-chiral SAMs on gold [185]. Under mild basic conditions, the acetyl group was efficiently removed from the thiol, leaving the ester and amide bonds intact.

Potassium thioacetate method allows milder conditions than thiourea method discussed previously. In addition,
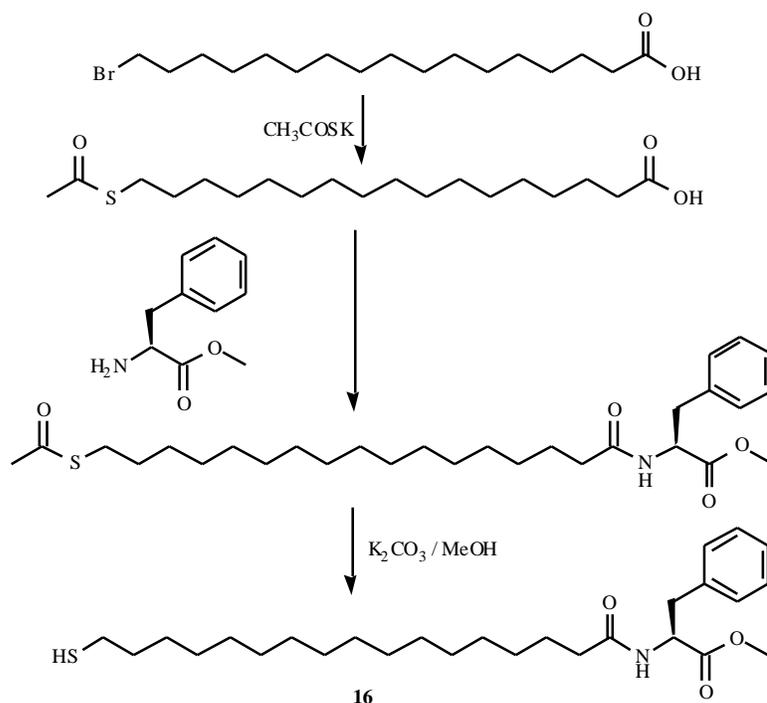
Fig. (12). The synthesis of N-(-thiol-heptadecanoyl)-phenylalanine methyl ester (**16**).

acidic conditions can sometimes be used to deprotect the S-acetyl group. This option facilitates the synthesis of 2-(11-mercaptoundecyl) hydroquinone (**17**) [193] (Fig. (**13**)) used in electrochemically modulated immobilization (through a Diels-Alder reaction) of cyclopentadiene-containing ligands [193c].

Deprotection of thiol and hydroxyl groups was performed stepwise in excellent yield (99%) [193].
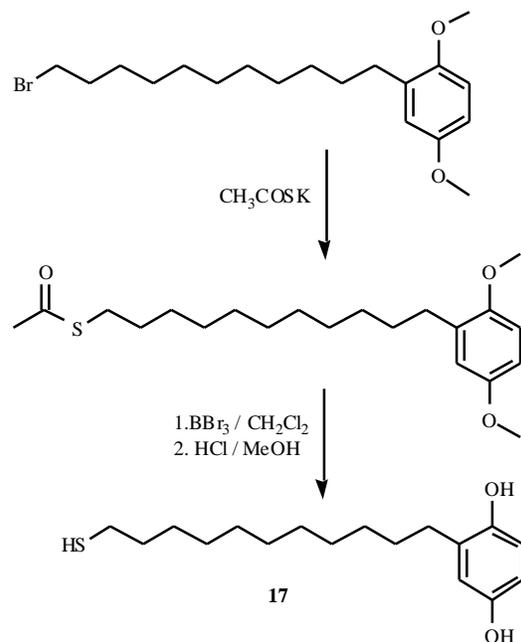
Fig. (13). The synthesis of 2-(11-mercaptoundecyl) hydroquinone (**17**).

(iii) Potassium Thiobenzoate. (Method A3 Scheme 1)

This method is less frequently used and is similar to the method based on potassium thioacetate (A2). The starting materials and conditions for substitution are almost the same. The commercially available thiobenzoic acid is, however, of lower quality than thioacetic acid. There is no particular reason to use this method, but its low cost and straightforward procedure (similar like for thioacetic acid) makes this method quite popular, especially when extreme purity is not a major concern. The following synthesis of bis(-mercaptoundecyl)phosphate (**18**) Fig. (**14**) (a reagent for the formation of monolayer ion-gating membranes) was reported by Nakashima and co-workers and uses potassium thiobenzoate [194].

(iv) Sodium Thiophosphate.(Method A4 Scheme 1)

Reactions of sodium thiophosphates with alkyl halides give alkyl thiophosphates, which can be hydrolyzed without separation. High cost and poor quality of sodium thiophosphate are major disadvantages of this method; they are partly offset by mild conditions and one-pot procedure. Although not highly recommended, this technique should nevertheless be present in a portfolio of available protection strategies. Literature examples of its use include alkane thiol described in reference [200] and 15-mercaptopentadecanoic acid [178b]. We remark that these compound could be done

be other methods we discussed (heptadecafluoronona-decanethiol- D2-A2, or D2-A1 [200]; 12-mercaptodo-decanoic acid- D4-A5 [178a and 178c], or D2-A2 [178e]; 16-mercaptohexadecanoic acid- D2-A1 [178d], or D2-A2 [178e]).
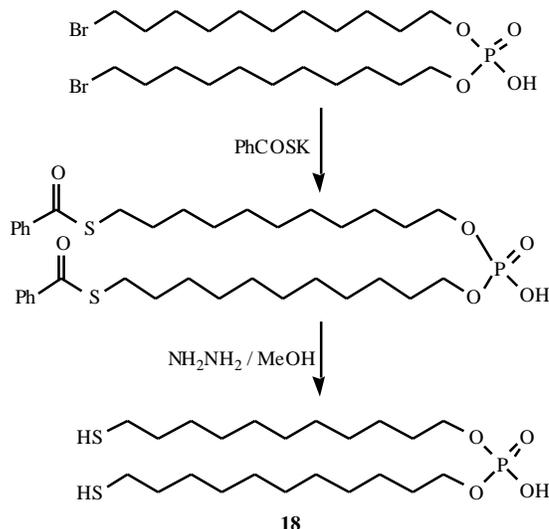
Fig. (14). The synthesis of bis(-mercaptoundecyl)phosphate (**18**).

(v) Potassium O-Ethyl Dithiocarbonate (Method A5 Scheme 1)

Although preparation of thiols from alkyl halides and potassium O-ethyl dithiocarbonate gives good yields of the corresponding S-alkyl O-ethyl dithiocarbonates, deprotection of these intermediates is less efficient than that of corresponding S-actetyl and S-benzoyl derivatives obtained from methods A2 and A3, respectively. Even vigorous reduction of the dithiocarbonates (**19**) by means of 67-fold excess sodium borohydride in the presence of ethylenediamine in ethanol gives a mixture of a desired thiol (**20**) (~90%) heavily contaminated by a product disulfide (**21**) (~10%) [178a] Fig. (**15**).

The corresponding disulfide (**21**) is the major product when a smaller or no sodium borohydride is present in the reaction mixture (the value of excess was not reported) [178a]. Formation of a disulfide is the main disadvantage of this procedure. 12-Mercaptododecanoic acid (**20**) shown in the Fig. (**15**) above can be prepared more efficiently by the potassium thioacetate method (A2, Scheme **1**) [178e] Fig. (**16**).

Although the formation of byproduct (disulfide (**21**)) was not reported in the original literature procedure [178e] we have found that basic deprotection of 12-acetylsulfanyl-dodecanoic acid (**22**) gives a mixture of a thiol (**20**) and a corresponding disulfide (**21**). Pure 12-mercaptodecanoic acid (**20**) was obtained when acidic conditions were applied (method D1, HCl, MeOH / H$_2$O).

(vi) Coda

Comparison of the described approaches (i) – (v) shows that methods based on the reaction of alkyl halides with thiourea (A1) and potassium thioacetate (A2) are the most common and versatile ones. Their success stems from the
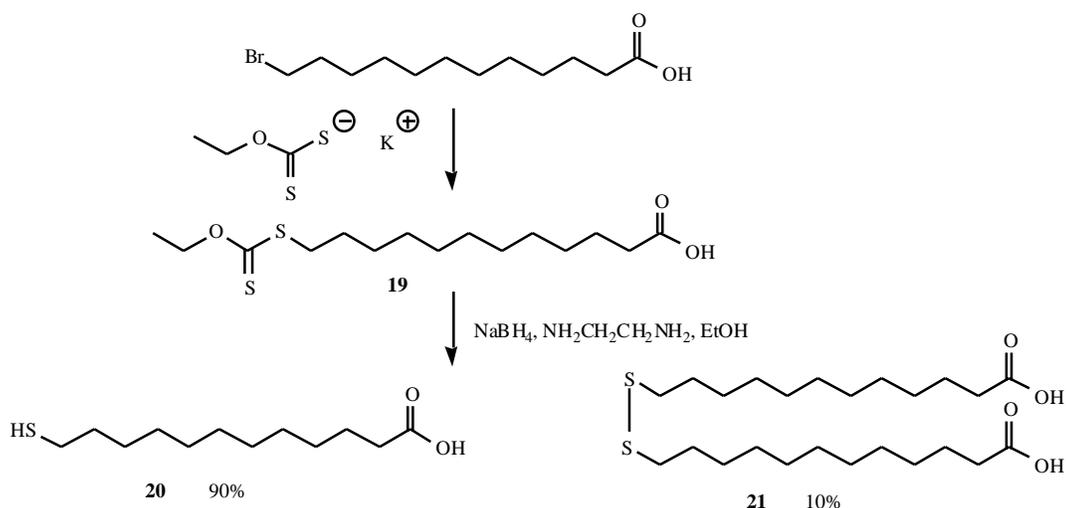
Fig. (15). Products distribution from the reduction of dithiocarbamate (**19**).
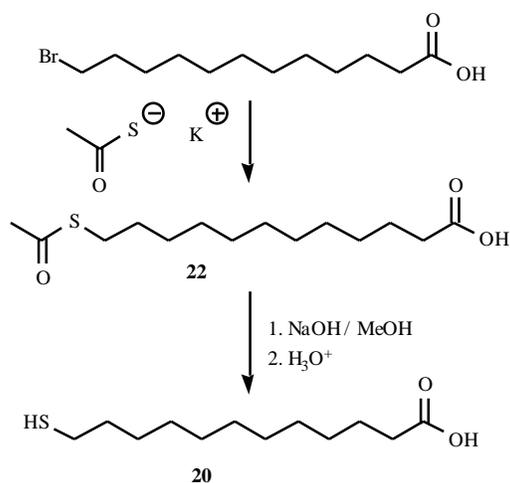
Fig. (16). The synthesis of 12-mercaptododecanoic acid (**20**) from potassium thioacetate.

availability of starting materials, straightforward procedures, and efficient deprotection of the thiol group. Other methods (A3-A5) are usually less attractive because of poor quality of available sulfur nucleophiles, low yields, and/or formation of disulfides upon deprotection.

4.4. Synthesis of Symmetrical and Unsymmetrical Disulfides

The synthesis of symmetrical disulfides is straightforwardly achieved by oxidation of corresponding thiols with: oxygen [215], $(NH_4)_2S_2O_8$ [216], iodine [175, 217], MnO_2 [218], $Bi(NO_3)_3$ [219] and other mild oxidants [220]. However, some of these reagents suffer from disadvantages such as long reaction times, limited availability, toxicity, difficult work-up, complicated preparation and instability. Oxidation with iodine is probably the most convenient method as it can be carried out in a wide range of solvents, always gives a good yields, and the reaction mixture is easy to work-up and purify.

Several thiol derivatives can also be converted to symmetrical disulfides. For example, sodium salt of thiosulfuric acid S-alkyl ester (**23**) (Bunte salt) gives dialkyldisulfides (**24**) upon treatment with samarium [221, 222] or iodine [223] Fig. (**17**).

Syntheses of unsymmetrical disulfides are performed starting from two different thiols. Literature gives two major approaches to such syntheses: The first one, less popular, is the oxidation of a mixture of two different thiols by means of iodine [224] or another mild oxidant [218]. Not surprisingly, the reaction mixture contains three disulfides in variable ratios. This method is not effective and can be performed
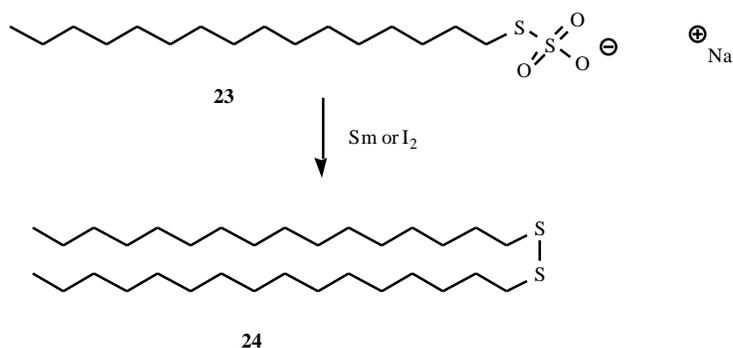
Fig. (17). The synthesis of dialkyldisulfides (24) from Bunte salt (**23**).

only in cases when structures of the thiols and disulfides allow facile separation. Oxidation of mixture benzenethiol (**25**) and dodecane-1-thiol (**26**) with MnO_2 in the presence molecular sieves in hexanes gave mixture of corresponding disulfides: dodecyldisylfanylbenzene (**27**) (57%), diphenyldisulfane (**28**) (20%) and didodecyldisulfane (**29**) (22%) [218] Fig. (**18**). The observed ratios are typical for oxidation of most thiols mixtures. This method is applied when reactant thiols are inexpensive (low conversion into the desired unsymmetrical disulfide) or when products can be easily separated – the latter is a seldom circumstance illustrated by the synthesis of hydroxy-iodo disulfide (**32**) shown in the Fig. (**19**) below:

A more effective class of methods is based on a reaction of one thiol with a derivative of the second one. The most common derivatives are symmetrical disulfides [225], methanethiosulfonic acid S-alkyl esters (ethyl, propyl or butyl) [226], alkyl thionitrite [227], sodium salt of thiosulfuric acid S-alkyl ester (Bunte salt) [228], and 2-(alkyldisulfamyl) pyridine [175,229]. All these derivatives bear electrophilic sulfur atom that is substituted in reaction with nucleophilic group of the reagent; all proceed in good yield.

An example of this approach is the synthesis of unsymmetrical disulfide (**35**) based on the disulfide exchange of N,N'-bis(tert-butoxycarbonyl)-L-cysteine (**33**) with octadecane-1-thiol (**34**) [225] Fig. (**20**).

Fig. (18). The products distribution from Oxidation of mixture benzenethiol (**25**) and dodecane-1-thiol (26) with MnO_2.
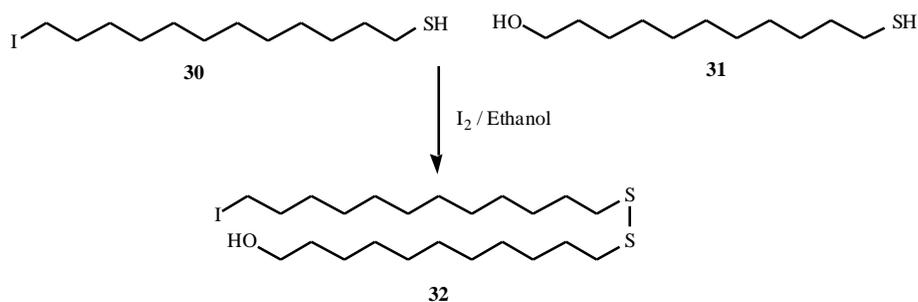
Fig. (19). The synthesis of 11-(12-iodododecyldisylfanyl)-undeca-1-ol (**32**).

When the mixture of 12-iodo-dodecane-1-thiol (**30**) and 11-mercapto-1-undecanol (**31**) was treated with iodine in ethanol the appropriate unsymmetrical disulfide (11-(12-iodododecyldisylfanyl)-undeca-1-ol (**32**)) was isolated by means of column chromatography [224] Fig. (**19**).

The success of this reaction was due to large differences in the values of R_f for symmetrical and unsymmetrical disulfides. Such behavior is not typical and separation cannot be accomplished in cases when difference in the R_f for starting materials is less than 0.2. When the differences in R_f's are sufficient and high-quality of the product is sought, at most ~75% of the main fraction should be collected.

In another procedure reported in the literature, 2'Deoxyuridin-2'-yl-dodecyl disulfide (**37**) was prepared using dodecyl thionitrite (**36**) for disufide bond formation Fig. (**21**). The progress of this reaction was, however, hampered by the formation of a symmetrical disulfide (**38**) (2,2'-disulfanediyl-bis-(2'-deoxyuridine)) [227].

Bunte salts can be used either for the preparation of symmetrical [221-223] or unsymmetrical disulfides [228]. The synthesis of 4-(12-(dodecyldithio)dodecyloxy)-azobenzene (**40**) is based on this method Fig. (**22**). Bunte salts (**39**) are readily available from the reaction of appropriate alkyl halide and sodium thiosulfate.
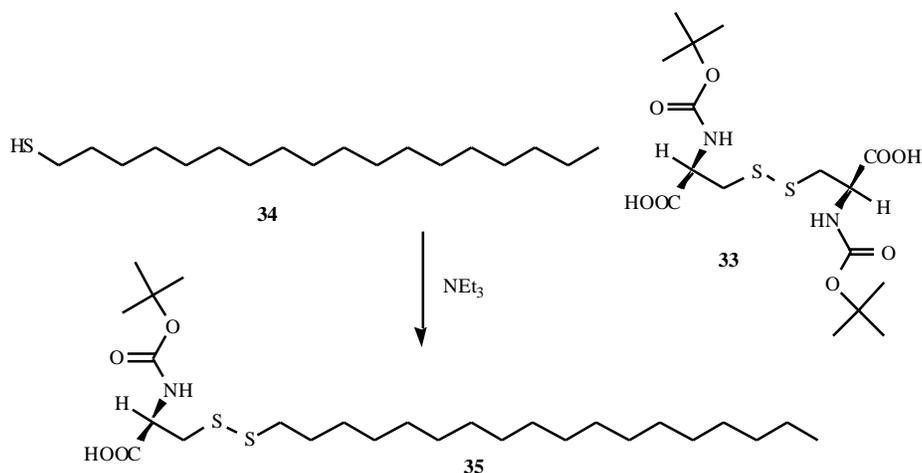
Fig. (20). An example of disulfide exchange for synthesis of unsymmetrical disulfide (**35**).
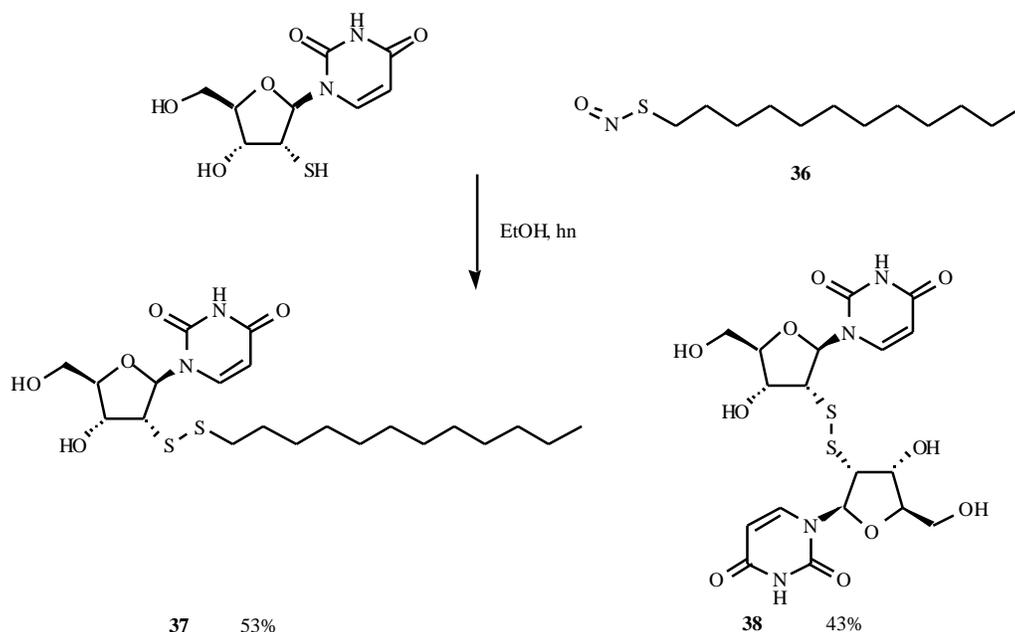
Fig. (21). The synthesis of 2'Deoxyuridin-2'-yl-dodecyl disulfide (**37**).

The method based on the disulfamyl pyridine derivatives seems to be one of the most attractive routes to unsymmetrical disulfides. These derivatives are readily available from the reaction of excess 2,2'-disulfanediyl-bis-pyridine (Aldrithiol-2) with a thiol of interest. These reactions proceed in good yields (above 60-70%), and the unsymmetrical disulfides can be isolated by column chromatography (usually, large difference in R_f for Aldrithiol-2 and the unsymmetrical disulfide is observed). The major advantage of this method is the stability of the isolated, pure disulfamyl pyridine derivatives. They can be stored below 0 °C for long times (3-4 weeks). In addition, the presence of most functional groups does not disturb this reaction, and it is thus suitable for more sophisticated disulfide synthesis. The S-acetyl and other thiol groups can disturb formation of these derivatives. This problem may,

however, be avoided by application of appropriate protective groups, as in the synthesis of an unsymmetrical disulfide (**41**) terminated with maleimide group and outlined in the Fig. (**23**) below (this disulfide was used as a building block of maleimide functionalized self-assembled monolayers for peptide and carbohydrate biochips [175]).

4.5. Synthesis of Thiols from Disulfides

A thiol can be protected by oxidation to the corresponding symmetrical disulfide, which subsequently can be cleaved by reduction using Sn /HCl, Zn/HCl or Zn /acetic acid [230]. Other reducing agents like Na or Li in Et_2O, xylene, and liquid NH_3, $LiAlH_4$, $NaBH_4$ [231] are also known to convert disulfides to thiols. The disulfide bond can be cleaved by other thiols such as dithiothreitol [191], $HOCH_2CH_2SH$ [232] or thiophenols [233]. Satisfactory
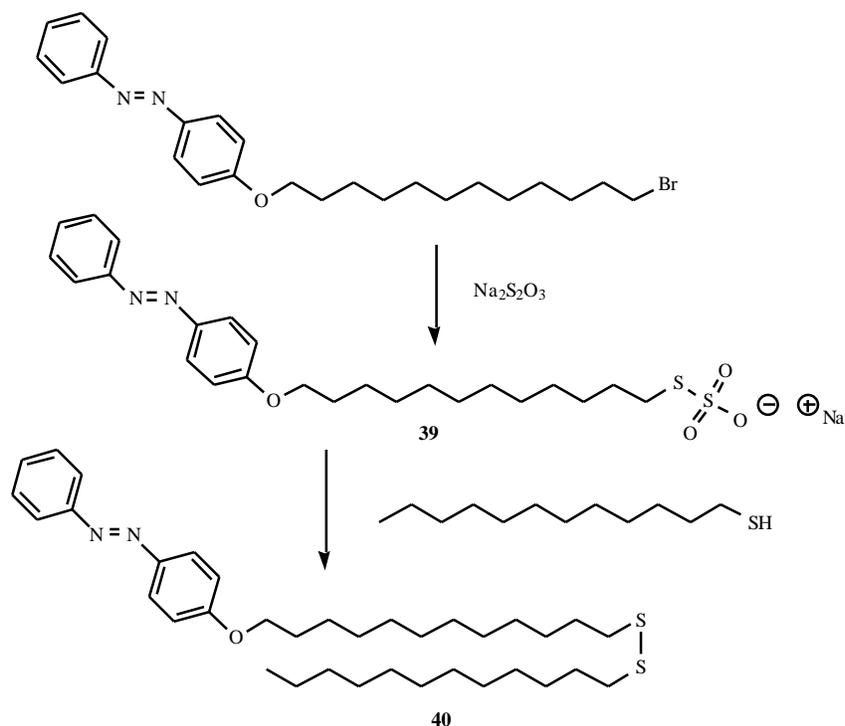
Fig. (22). The synthesis of unsymmetrical disulfide (**40**) from Bunte salt (**39**).
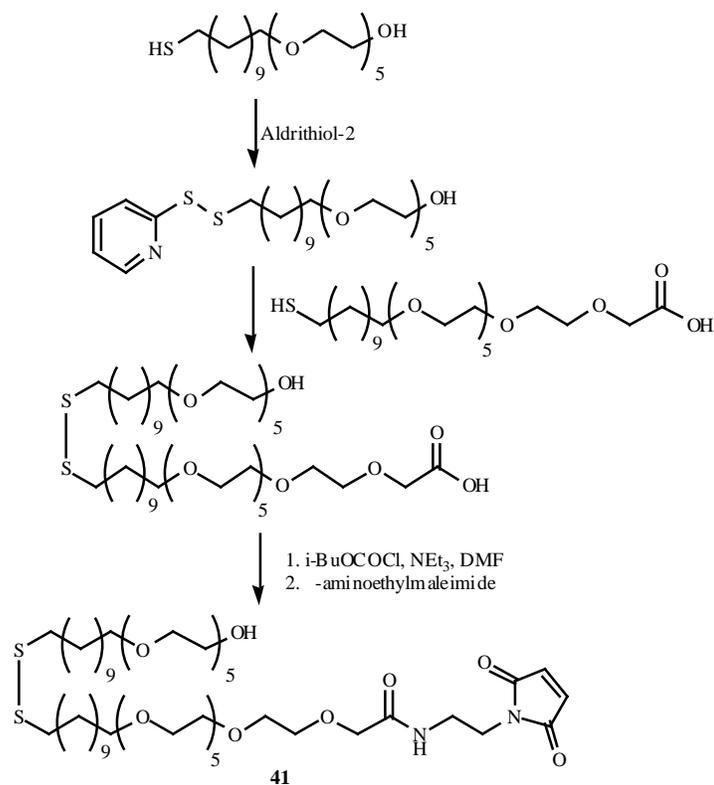
Fig. (23). The synthesis of an unsymmetrical disulfide (**41**).

cleavage of symmetrical disulfides is observed in some cases by means of tributylphosphine [234].

Conversion of thiols into corresponding disulfides is a very attractive method for protection of thiol functionality
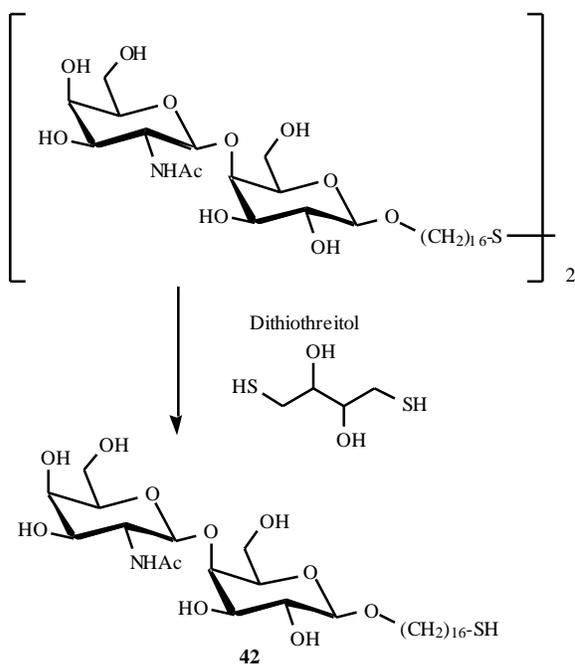
Fig. (24). The synthesis of carbohydrate terminated thiol (**42**).

until efficient and mild conditions can be applied for cleavage of disulfide bond. This approach is demonstrated by the synthesis of carbohydrate terminated thiol (**42**) [191]

Unsymmetrical disulfides as protected thiols have also been prepared. Mainly, synthesis and cleavage of S-ethyl- [198,235], S-propyl- [226], S-t-butyl- [236], and substituted S-phenyl- [237] derivatives of thiols were performed. This approach is recommended when reagents used for deprotection (D1-D5) of functionalized thiol derivatives can react with the end group(s) R or their protective groups respectively. Preparation and cleavage of unsymmetrical disulfides (D6 and D7) circumvents this problem. Synthesis of glycero-3-phosphocholine terminated thiol (**45**) Fig. (**26**) (used to construct vesicles that can be either oxidatively polymerized or reductively depolymerized [198]) required mild conditions for the deprotection of the thiol group. Most other procedures (e.g., D1-D5 in Scheme **1**) would lead to breaking of ester bonds (phosphate or carboxylate). The use of disulfide as the protective group allowed avoiding this complication [198].

Similar strategy for the protection of a thiol group was applied in the synthesis of dithio-phospholipids (**46**) Fig. (**27**) for oriented immobilization of proteins on gold. The disulfide bond was not cleaved under DCC conditions [226].

The major disadvantage of the synthesis of thiols via symmetrical or unsymmetrical disulfides lies in variable yields of the disulfide-to-thiol conversion. Although the examples described above were all accomplished with good (60%) [232] or excellent (above 90%) [198, 226, 230, 234] yields, there are many examples in the literature when the yields were poor (e.g. 32% in [191]). The origin of this variability is unclear. Development of new, more reliable
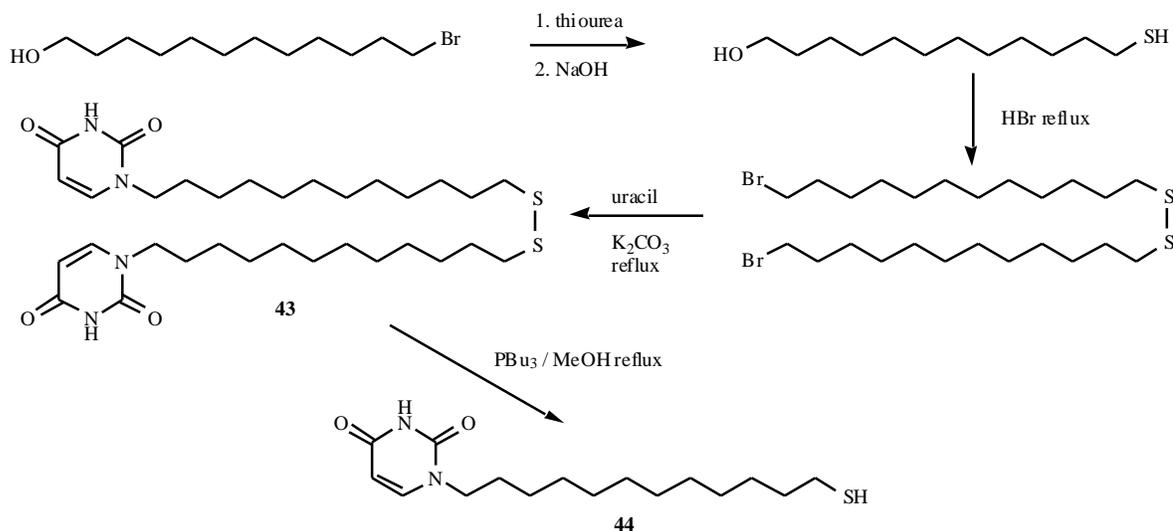
Fig. (25). The preparation of uracil terminated thiol (**44**).

developed by Mrksich and co-workers for adsorption-resistant SAMs [57] Fig. (**24**).

Similar solution for protection of thiol group was reported for the preparation of uracil terminated thiol (**44**) used to functionalize and stabilize gold nanocrystals that exhibited selective recognition and binding of a long-chain alkane incorporating a complementary substrate (*N,N'*-2,6-pyridinediylbis(undecamide)). Cleavage of the corresponding disulfide to the terminal thiol (**43**) was achieved using tributylphosphine [234] Fig. (**25**).

procedures for transforming disulfides to corresponding thiols would undoubtly expand the synthetic applicability of this method.

5. SYNTHESES OF SELECTED CLASSES OF THIOLS

Successful synthesis of functionalized thiols depends on a careful selection/planning of:

1. the method of introduction and protection of the thiol group.
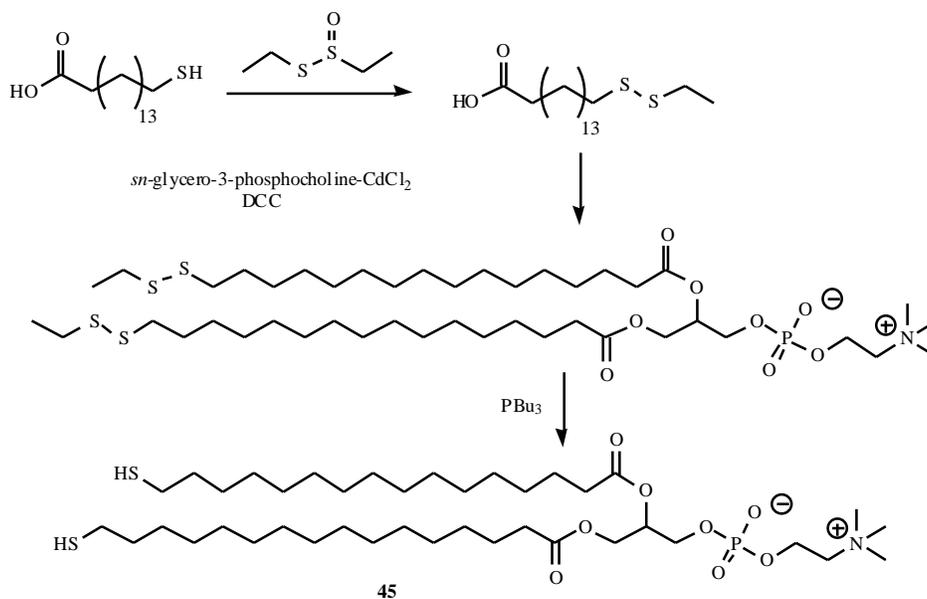
Fig. (26). The synthesis of glycero-3-phosphocholine terminated thiol (**45**).
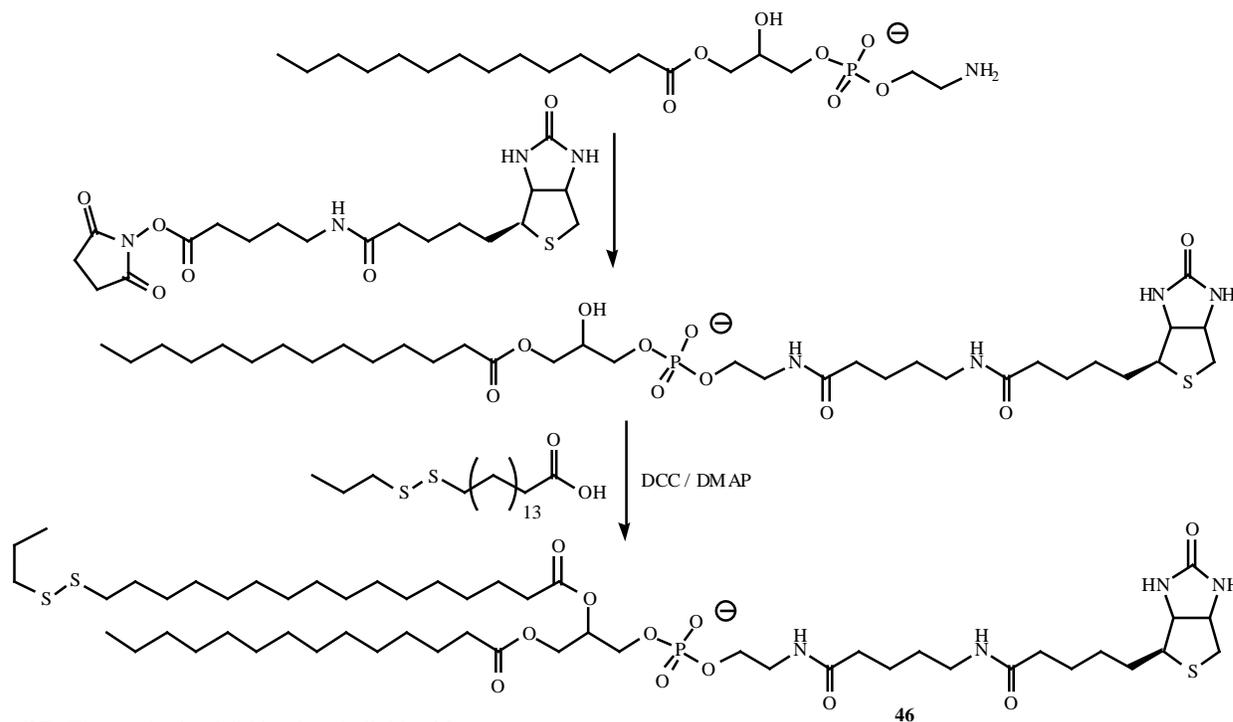
Fig. (27). The synthesis of dithio-phospholipids (**46**).

2. the method of introduction and protection of end group(s) R
3. functional group (see –Y group at the Scheme **1**) helpful in the conversion, introduction, or attachment of end group(s) (see –R group at the scheme **1**)
4. the order of steps 1 through 3.

This general strategy will now be illustrated in a series of advanced syntheses of relatively complex thiols and disulfides.

5.1. Synthesis of a Peptide-Substituted Alkanethiol

Self-assembled monolayers that present short peptide ligands are a versatile model system with which to study interactions of mammalian cells with artificial surfaces. The syntheses of peptide-terminated alkanethiols are, however, nontrivial. Houseman and Mrksich have reported a rapid and efficient method, based on solid-phase peptide synthesis, for the preparation of an alkanethiol terminated with a Gly-Arg-Gly-Asp-Ser peptide ligand [238]. Their strategy required a suitably S-protected alkanethiol (with Trityl group) that

could be coupled (carboxyl group is a helpful group Y for attachment of peptide, see Scheme **1**) to an appropriate peptide on solid support. The preparation of (2-{2-[2-(2-{2-[2-(11-tritylsulfanyl-undecyloxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-acetic acid (**51**) from undec-1-en-11-yl-hexa(ethylene glycol) (**47**) is shown in the Fig. (**28**) below.

The Fmoc-Gly-Arg-Gly-Asp-Ser pentapeptide (**52**) (Fig. (**29**)) moiety was prepared on Fmoc-Rink amide MHBA polystyrene resin as the solid support using routine protocols [239].

Removal of the terminal glycinyl Fmoc-carbamate with 20% piperidine / DMF, followed by coupling with acid (**51**) (described above) in the presence of DCC and 1-

47

N$_2$CHCOOEt, BF$_3$ Et$_2$O, CH$_2$Cl$_2$ 0° C, 62%

48

CH$_3$COSH, h , AIBN, THF, 93%

49

HCl / EtOH,

50

Ph$_3$CCl, THF, 71%

50

1N LiOH, THF/MeOH/H$_2$O, 85%

51

Fig. (28). The synthesis of (2-{2-[2-(2-{2-[2-(11-tritylsulfanyl-undecyloxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-acetic acid (**51**).

Alkylation of starting material with ethyl diazoacetate in the presence of 10 mol % BF$_3$ Et$_2$O afforded appropriate ester (**48**). Photochemical addition of thioacetic acid to the terminal olefin (method B1, Scheme **1**) gave corresponding thioacetate (**49**) in 93% yield. The thiol group was obtained in the protected form, but it would have to be removed under conditions required for the conversion of carboethoxy group into the carboxyl group. That is why the acetyl protective group was first replaced by the trityl group (deprotection conditions D1, Scheme **1**, then treatment with trityl chloride). This intermediate (**50**) was saponified with aqueous lithium hydroxide in THF / MeOH to afford (2-{2-[2-(2-{2-[2-(11-tritylsulfanyl-undecyloxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-acetic acid (**51**) with very good overall yield of 35%.

Fig. (29). The Fmoc-Gly-Arg-Gly-Asp-Ser pentapeptide (**52**) moiety on Fmoc-Rink amide MHBA polystyrene resin.

hydroxybenzotriazole (HOBT), provided the fully protected conjugate (**53**). Cleavage of the peptide from the resin,
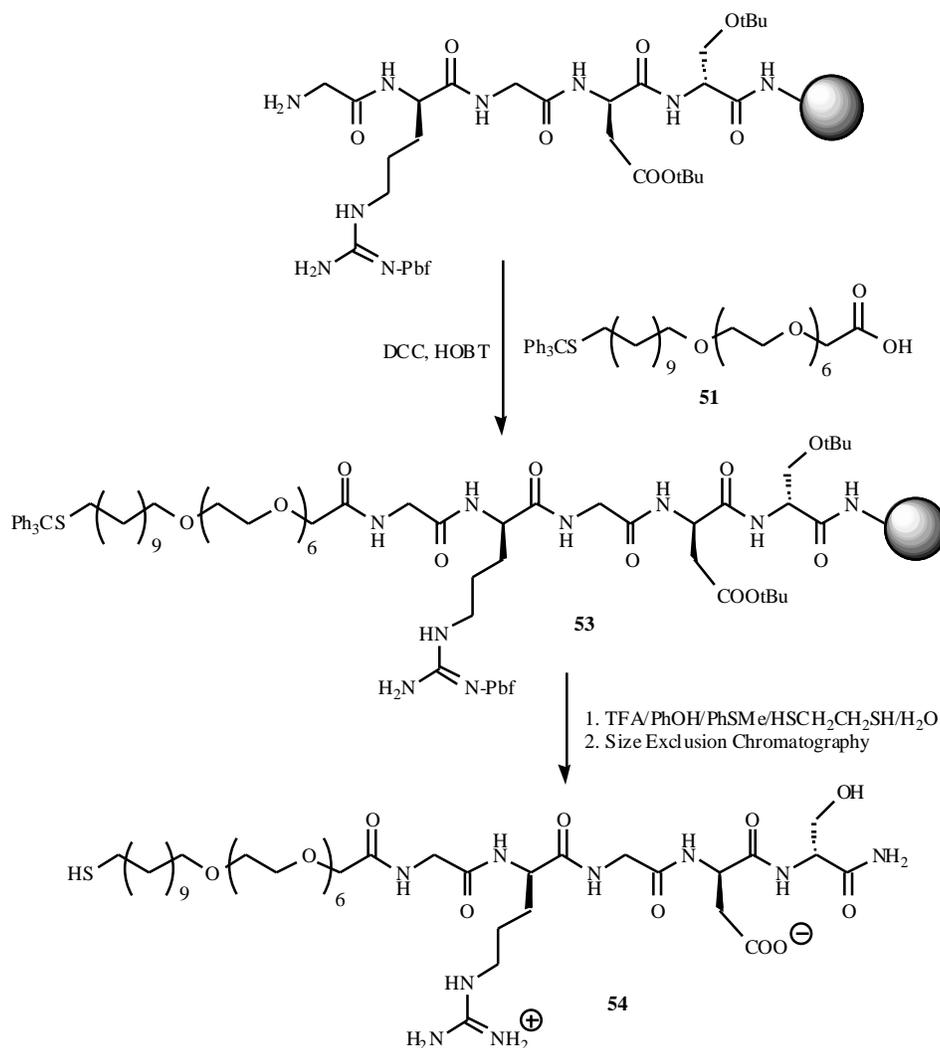
Fig. (30). The synthesis of pentapeptide terminated thiol (**54**).

followed by precipitation with diethyl ether and purification by gel permeation chromatography, afforded pentapeptide terminated thiol (**54**) in 51% overall yield based on initial loading of the resin Fig. (**30**). Note that terminal Ser was in the amide form.

The chemical shift of the methylene protons adjacent to the sulfur (t, 2.4 ppm, -C*H₂*-S; triplet was observed instead of a quartet because CD_3OD was used as solvent for ^1H NMR) demonstrated the presence of a sulfhydryl group; no disulfide (t, 2.7 ppm) was observed. Additionally, a thin layer chromatogram of the product turned bright yellow upon application of Ellman's reagent [240], confirming the presence of the sulfhydryl group.

The above example reminds us that although (Scheme **1**) is a useful synthetic aid, it does not provide complete synthetic procedures and leaves much room for creative planning. For instance, if the conditions required for the attachment, conversion or deprotection of end group(s) R interfere with the stability of the S-protective group, then it might be necessary to replace R with another protective moiety (cf. Section 3.2.). Here, the S-acetyl thiol (**49**) (from

method B1, Scheme **1**) was deprotected (D1, Scheme **1**) and masked with trityl group affording compound (**50**). This replacement permitted simultaneous cleavage of the peptide from the supporting resin and deprotection of the SH group for compound (**53**) in the last synthetic step.

5.2. Synthesis of an Amino-Terminated Semi-Fluorinated Long-Chain Alkanethiols

A family of SAMs based on perfluoroalkyl amideethanethiols, [118] $CF_3(CF_2)_mCONH(CH_2)_2SH$ (m = 6, 7, or 8) that inhibit the corrosion of silver by hydrogen sulfide in air were developed by Burleigh and co-workers. At the same time, Amato and Calas have designed and prepared amino-terminated, semi-fluorinated long-chain alkanethiols in order to form mixed SAMs that would constitute a new platform system for biosensors [241]. General strategy for the preparation of these compounds was based on the introduction of fluorinated carbon chain and protected amino group (phthaloyl protective group) before thiol functionality (right part of the Scheme **1**). The thiol group could then be introduced using either thiourea (method A1 and

deprotection D2, Scheme **1**) or thioacetic acid (method A2 and deprotection D5) methods. The reaction pathway and the obtained yields are shown in the Fig. (**31**) below.

The introduction of fluorinated carbon chain and protected amine group was performed and appropriate functionalized alcohol (**55**) was then converted into the

A mixture of the starting iodide (**57**), thiol (**58**) and undesired disulfide (**59**) (major disadvantage of this method, see section 4.3) was obtained Fig. (**32**). Separation of the thiol (**58**) could not be achieved, despite attempts of recrystallization and column chromatography. In order to overcome these difficulties, the Mitsunobu method was used
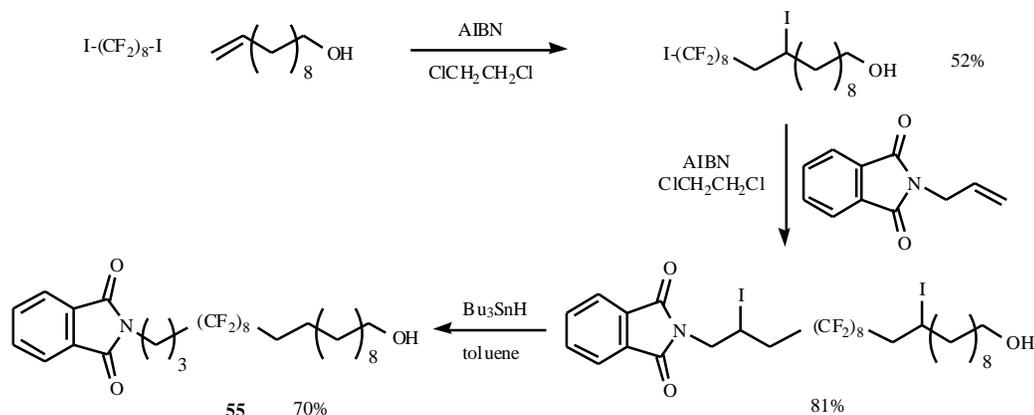
Fig. (31). The synthesis of N-protected semi-fluorinated alcohol (**55**).
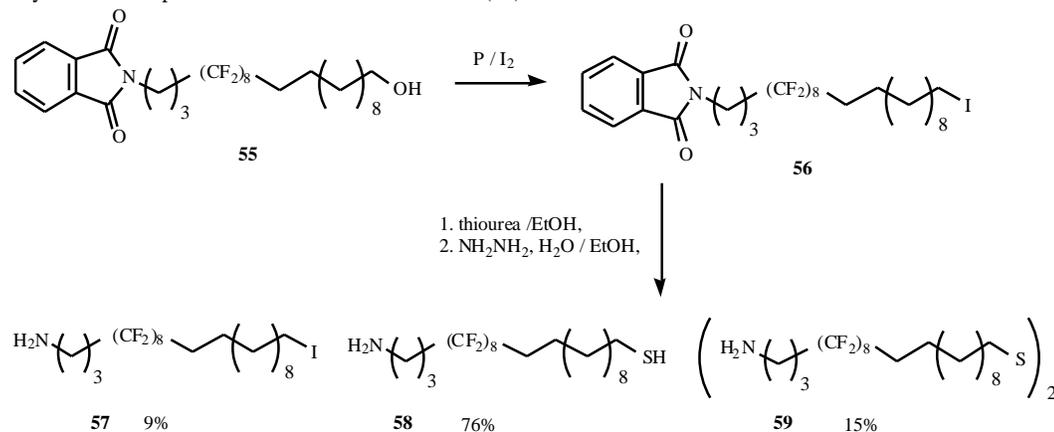
Fig. (32). The synthesis of alkanethiol (**58**) from iodide (**56**) and thiourea.
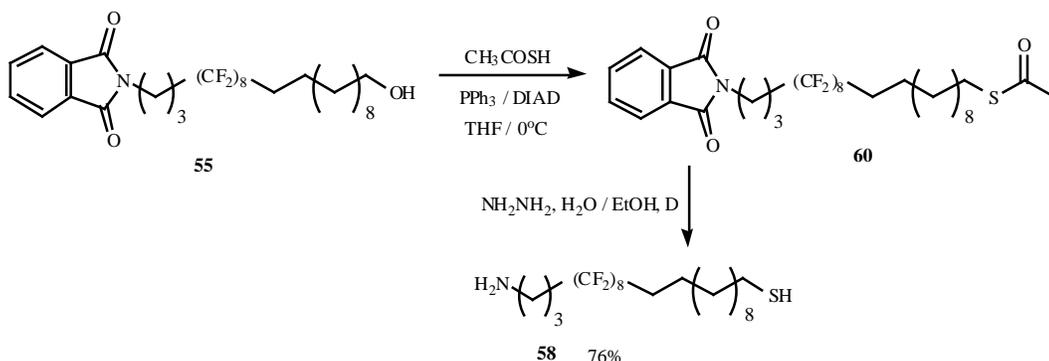
Fig. (33). The synthesis of amino-terminated semi-fluorinated long-chain alkanethiol (**58**).

amino-terminated semi-fluorinated long-chain alkanethiol (**58**) Fig. (**32**). The conversion of the alcohol (**55**) into the iodide (**56**), was followed by formation of the isothiouronium salt (A1 Scheme **1**). This salt was then converted into the thiol (**58**) and the amino group was deprotected with hydrazine.

to convert starting alcohol to corresponding thioacetate (**60**) Fig. (**33**).

The resulting thioacetate (**60**) was purified by recrystallization (a key step impossible to perform for the iodide intermediate in the preceding method, Fig. (**32**)) and

both the thiol and the amine functionalities were deprotected with hydrazine (method D5, Scheme **1**).

5.3. Synthesis of a Biotinylated Thiol

Streptavidin is an exceptionally stable tetrameric protein in which each of the four subunits binds biotin tightly with the free energy of binding comparable to that of a covalent bond. Biotin can be attached to proteins and saccharides as well to other compounds; streptavidin is then used as a molecular linker between the biotin-derivatized units. Among various biotinylated thiols reported in the literature, the 12-mercaptododecanoic-(8-biotinoylamido-3,6-dioxaoctyl) amide (**65**) has been widely used to attach streptavidin or avidin to SAMs of this biotinylated thiol. This compound was prepared as follows in the Fig. (**34**):

The benzyl protected thiol group was introduced in the first step before other end groups R (left part of Scheme **1**) in excellent yield (93%). 12-Benzylthiododecanoic *N*-hydroxy-

succinimide ester (**61**) was made using *N,N'*-disuccinimidyl carbonate (DSC). The ester was reacted with excess 2,2'-(ethylenedioxy)diethylamine to give monoamide (**62**) which reacted with biotin *N*-hydroxysuccinimide ester (**63**) to generate 12-benzylthiododecanoic-(8-biotinoylamido-3,6-dioxaoctyl) amide (**64**). The benzyl protecting group of this compound was readily removed using sodium in liquid ammonia (D3, Scheme **1**) to give the final product (**65**) [203].

5.4. Synthesis of a Metal-Chelating Thiol for Polymerizable SAMs

Binding of proteins to membranes is crucial for many aspects of biology and pharmacology. Interactions between SAMs and proteins mediated by transition metal ions can in many ways mimic biological systems [51]. A class of thiols has been designed and synthesized in which (i) various metal-chelating end-groups mediate specific binding of
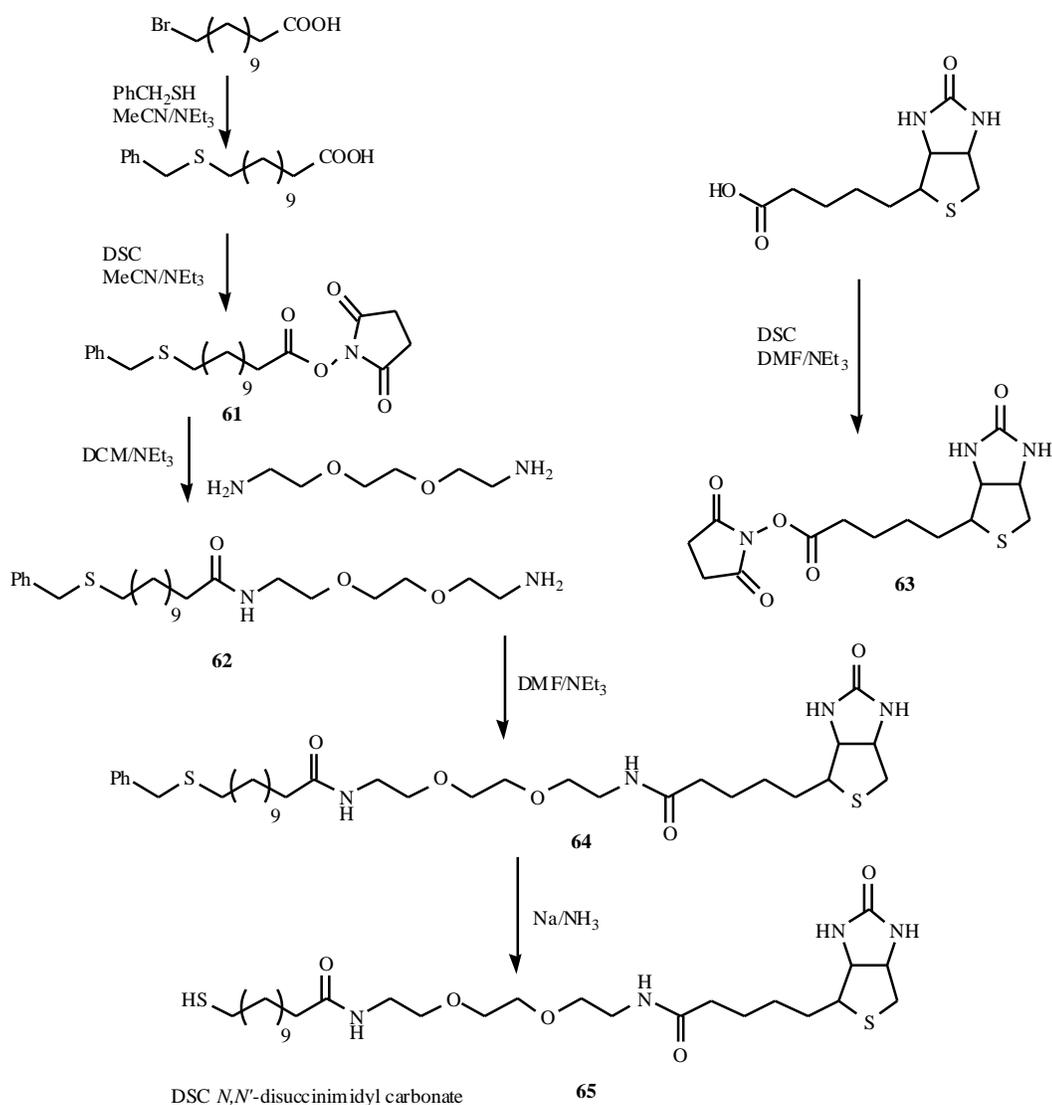
Fig. (34). The synthesis of biotinylated thiol (**65**).
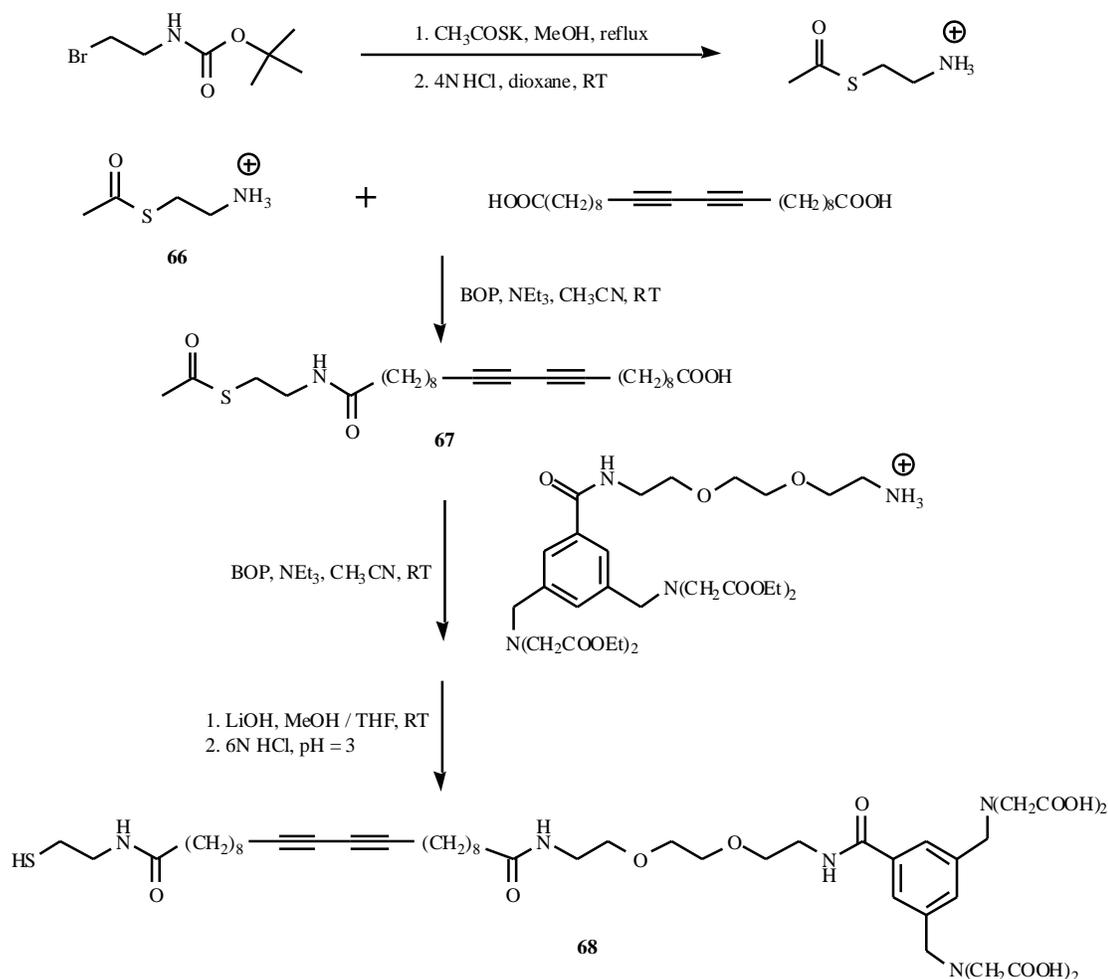
Fig. (35). The synthesis of a metal-chelating thiol (**68**).

proteins *via* metal ions, and (ii) diethylene glycol units prevent non-specific protein adsorption [242]. In SAMs formed from these compounds, metal cations act as "bridges" connecting the metal-chelating moiety at the surface of a monolayer to the histidine residues of a protein. Because some of the investigated proteins (notably, myoglobin and carbonic anhydrase) were found to penetrate the SAMs, it was necessary to introduce polymerizable diacetylene units into the alkyl chains of the thiols.

The reported synthesis of these multifunctional thiols was rather elegant and highly convergent [242]. Thiol group, masked as thioacetate (method A2, Scheme **1**), was reacted with N-Boc-protected 2-bromoethylamine and the subsequent deprotection of the amino group afforded protected thiol (**66**) in a good overall yield (90%). The product was then attached to only one side of the symmetric diacetylenic dicarboxylic acid according to the standard peptide chemistry and the amide (**67**) was obtained in 71% yield. The remaining free carboxylic group was then coupled to the previously reported iminodiacetate-derived primary amine [243], and the resulting product was hydrolyzed (method D2, Scheme **1**) to afford free thiol (**68**) Fig. (**35**).

5.5. Synthesis of a Thiol for Surface-Polymerizable SAMs

As discussed in Section 3.4., stability of organized monolayers of thiolates on gold arises from two orthogonal factors – strong Au-S interfacial linkage and lateral Van der Waals interactions between neighboring alkane chains. Conventional *n*-alkanethiolate SAMs on gold cannot withstand chronic exposure to organic solvents or air, limiting their usefulness. One way to enhance the stability of alkanethiolate SAMs is to incorporate a polymerizable group into the alkane backbone. Once intermolecular crosslinks have been made, they minimize desorption and delamination of the adsorbed thiolate molecules oxidized to the more weakly adhering sulfinates and sulfonates. Garrell and co-workers accomplished a convenient synthesis of epoxy-terminated dialkyl disulfides (**73**) Fig. (**36**) that spontaneously self-assembled onto gold surface, and which then underwent ring-opening polymerization (by cationic or anionic initiation) to form novel thin-film polymers [244].

The starting bromoalkene was dihydroxylated with t-butoxyperoxide and the resulting vicinal diol (**69**) was protected as acetonide (**70**). This protection was necessary for the next step, conversion of bromide to the thiol group
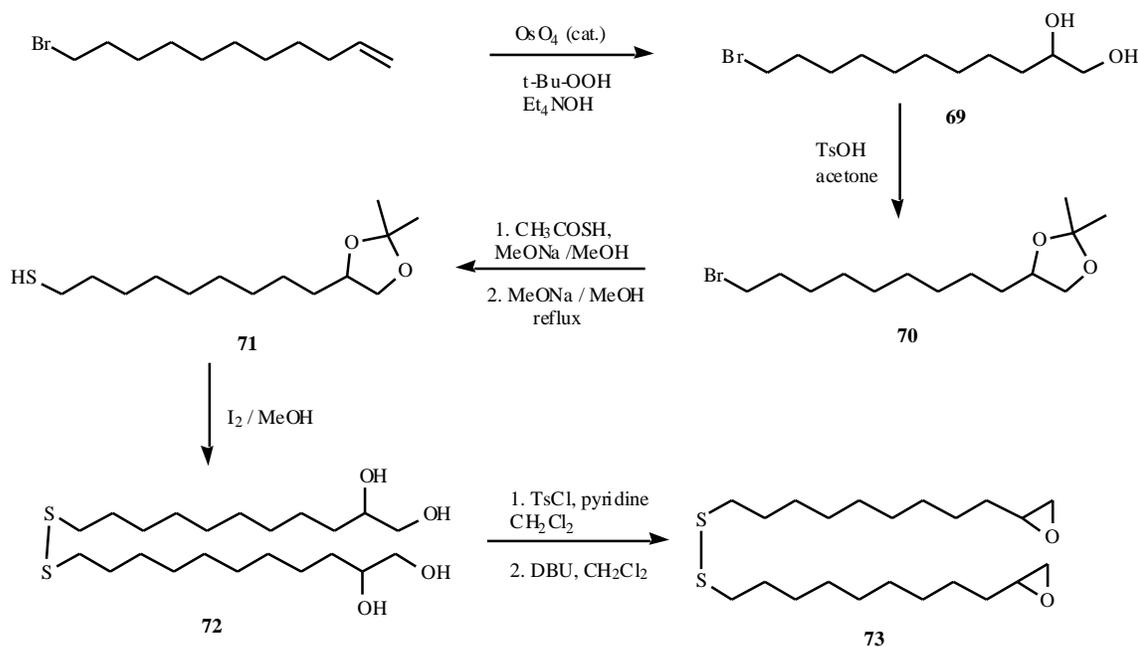
Fig. (36). The synthesis of epoxy-terminated dialkyl disulfides (**73**).

using thioacetic acid (introduction of protected thiol group method A2, deprotection conditions D2, Scheme **1**) in basic environment. Oxidation of the resulting thiol (**71**) and deprotection of the two hydroxyl groups was then achieved in one step with iodine solution in methanol. Vicinal diol (**72**) thus obtained in a high overall yield (69%) was converted to ditosylate and treatment with a strong base (DBU) afforded the final epoxy-terminated dialkyl disulfide (**73**).

This synthesis hinges on two key transformations. The first transformation is the formation of the epoxide ring in the last step by selective conversion of a primary hydroxyl group of terminal 1,2-diol to a tosylate group, followed by an intramolecular S_N2 reaction to close the three-membered ring. The problems of: (i) olefin oxidation in the presence of an electron-rich sulfur, and (ii) introduction of thiol group in the presence of the reactive epoxy ring are conveniently avoided by the indirect formation of epoxide ring in the last step of synthesis. The second transformation is the oxidation of the thiol to disulfide prior the tosylation step. This conversion (necessary to mask the nucleophilicity of the thiol) allows the tosylation of the alcohol to proceed without interference; it also minimizes any unwanted intra- or inter-molecular attack by the unprotected thiol on the epoxy ring once it has been formed.

CONCLUDING REMARKS

Functionalized thiols have become one of the most important classes of molecules in modern surface science. The self-assembled monolayers these molecules form have proven to be extremely useful systems for studying a variety of surface phenomena and reactions. Originally confined to basic research, SAMs are rapidly finding industrial applications, and the technologies of several companies rely on them (e.g., Biacore [SPR], SurfaceLogix [cellular assays], Platypus Technologies [DNA chips], BioScale [sensors]). As

the new methods of coupling biomolecules to SAMs are rapidly being developed, we envision further applications in bioanalytical techniques, especially in DNA and protein microarrays.

Despite their apparent structural simplicity, -substituted alkane thiols are often difficult to synthesize, mainly because of the high reactivity of unprotected thiol group. Manipulation of this group has to well-timed within the overall synthetic scheme – in this respect, the generic retrosynthetic strategy we described should be useful in identifying both the proper protection/deprotection groups/conditions, and the sequence of functionalization of the commonly used alkane or halo-alkane precursors.

ACKNOWLEDGEMENTS

REFERENCES

[1]   Ulman, A. *Chem. Rev.,* **1996**, *96*, 1533.
[2]   Nuzzo, R.G.; Allara, D.L. *J. Am. Chem. Soc.*, **1983**, *105*, 4481.
[3]   Bain, C.D.; Troughton, E.B.; Tao, Y.-T.; Evall, J.; Whitesides, G.M.; Nuzzo, R.G. *J. Am. Chem. Soc.*, **1989**, *111*, 321.
[4]   Bandyopadhyay, K.; Patil, V.; Vijayamohanan, K.; Sastry, M. *Langmuir*, **1997**, *13*, 5244.
[5]   Lang, P.; Mekhalif, Z.; Rat, B.; Garnier, F. *J. Electroanal. Chem.*, **1998**, *441*, 83.
[6]   Hagenstrom, H.; Schneeweiss, M.A.; Kolb, D.M. *Langmuir,* **1999**, *15*, 7802.
[7]   Love, J.C.; Wolfe, D.B.; Haasch, R.; Chabinyc, M.L.; Paul, K.E.; Whitesides, G.M.; R.G. Nuzzo, *J. Am. Chem. Soc.*, **2003**, *125*, 2597.
[8]   Muskal, N.; Mandler, D. *Electrochimica Acta,* **1999**, *45*, 537.
[9]   Allara, D. L. In *Nanoscale Structures Engineered by Molecular Self-Assembly of Functionalized Monolayer*s in *Nanofabrication and Biosystems*; H. C. Hoch, L. W. Jelinski, H. G. Craighead, Eds.; Cambridge University Press: Cambridge, UK., **1996**; pp. 180-200.

[10] Whitesides, G. M.; Gorman, C. B. In *The Handbook of Surface Imaging and Visualization*; Hubbard A. t. Ed.; CRC Press: Boca Raton, **1995**; pp. 713-732

[11] Crooks, R. M.; Ricco, A. J. *Acc. Chem. Res.,* **1998**, *31*, 219.

[12] a) Kumar, A.; Biebuyck, H.A.; Abbott, N.L.; Whitesides, G.M. *J. Am. Chem. Soc.,* **1992**, *114*, 9188.
b) Grzybowski, B.A.; Brittain S.T.; G.M. Whitesides, *Rev. Sci.Instrum*., **1999**, *70*, 2031.

[13] Piner, R.D.; Zhu, J.; Xu, F.; Hong, S.; Mirkin, C.A. *Science,* **1999**, *283*, 661.

[14] a) Lahiri, J.; Isaacs, L.; Grzybowski, B.A.; Carbeck J.; Whitesides, G.M., *Langmuir* **1999**, *15*, 7186.
b) Ostuni, E.; Grzybowski, B.A.; Mrksich, M.; Roberts C.S.; Whitesides, G.M., *Langmuir*, **2003**, *19*, 1861.
c) Singhvi, R.; Kumar, A.; Lopez, G.P.; Stephanopoulos, G.N.; Wang, D.I.C.; Whitesides, G.M.; Inber, D.E. *Science,* **1994**, *264*, 696.

[15] Gittins, D.I.; Bethell, D.; Schiffrin, D.J.; Nichols, R.J. *Nature,* **2000***, 408*, 67.

[16] Gobi, K.V.; Ohsaka, T. *J. Electroanal. Chem.,* **2000**, *485*, 61.

[17] McRipley, M.A.; Linsenmeier, R.A. *J. Electroanal. Chem.,* **1996,** *414*, 235.

[18] McDermott, M.T.; Green J.B.D.; Porter, M.D. *Langmuir*, **1997,** *13*, 2504.

[19] Jennings, G.K.; Laibinis P.E. *J. Am. Chem. Soc.,* **1997,** *119*, 5208.

[20] Aizenberg, J.; Black, A.J.; Whitesides, G.M. *Nature,* **1999**, *398*, 495.

[21] Xia, Y. N.; Whitesides, G.M. *Angew. Chem. Int. Ed.,* **1998**, *37*, 550.

[22] Xia, Y. N.; Whitesides, G.M. *Ann. Rev. Mat. Sci.,* **1998**, *28*,153.

[23] Whitesides, G.M.; Ostuni, E.; Takayama, S.; Jiang, X.Y.; Ingber, D.E. *Ann. Rev. Biomed. Eng.,* **2001**, *3*, 335.

[24] Dubois, L.H.; Zegarski, B.R.; Nuzzo, R.G. *J. Am. Chem. Soc.,* **1990**, *112*, 570.

[25] Laibinis, P.L.; Allara, D.L.; Tao, Y.-T.; Parikh, A.N.; Nuzzo, R.G. *J. Am. Chem. Soc.,* **1991**, *113*, 7152.

[26] Laibinis, P.E.; Bain, C.D.; Nuzzo, R.G.; Whitesides, G.M. *J. Phys. Chem.*, **1995**, *99*, 7663.

[27] Zaumseil J.; Meitl, M.A.; Hsu, J.W.P.; Acharya, B.R.; Baldwin, K.W.; Loo, Y.L.; Rogers, J.A. *Nanolett*., **2003**, *3*, 1223.

[28] Chechik, V.; Crooks, R.M.; Stirling, C.J.M. *Adv. Mater.*, **2000**, *12*, 1161.

[29] Duan, C. M.; Meyerhoff, M. E. *Mikrochim. Acta,* **1995**, *117*, 195.

[30] Wells, M.; Crooks, R. M. *J. Am. Chem. Soc.*, **1996**, *118*, 3988.

[31] Duevel, R. V.; Corn, R. M. *Anal. Chem.,* **1992**, *64*, 337.

[32] Baker, M. V.; Landau, J. *Aust. J. Chem.,* **1995**, 48, 1201.

[33] Frey, B. L.; Corn, R. M. *Anal. Chem.,* **1996**, *68*, 3187.

[34] Yang, M.X.; Chen, J.R. *Anal. Lett.,* **2002**, *35*, 1775.

[35] Mirkhalaf, F.; Schiffrin, D. J. *J. Chem. Soc., Faraday Trans.,* **1998**, 1321.

[36] Cline G. W.; Hanna, S. B. *J. Am. Chem. Soc.,* **1987**, *109*, 3087.

[37] Fox, M. A.; Whitesell, J. K.; McKerrow, A. J. *Langmuir,* **1998**, *14*, 816.

[38] He, Z.; Bhattacharyya, S.; Leavy, M.C.; Cleland, W. E.; Sabapathy, R. C.; Hussey, C. L. *J. Electroanal. Chem.,* **1998**, *458*, 7.

[39] Engquist, I.; Lestelius, M.; Liedberg, B. *Langmuir,* **1997**, *13*, 4003.

[40] Willicut, R. J.; McCarley, R. L. *Adv. Mater.,* **1995**, *7*, 759.

[41] Willicut, R. J.; McCarley, R. L. *J. Am. Chem. Soc.,* **1994**, *116*, 10823.

[42] Batchelder, D. N.; Evans, S. D.; Freeman, T. L.; Houssling, L.; Ringsdorf, H.; Wolf, H. *J. Am. Chem. Soc.* **1994**, *116*, 1050.

[43] Wang, J.; Pamidi, P. V. A.; Zanette, D. R. *J. Am. Chem. Soc.,* **1998**, *120*, 5852.

[44] Fox, M. A.; Wooten, M. D. *Langmuir,* **1997**, *13*, 7099.

[45] Li, W. J.; Lynch, V.; Thompson, H.; Fox, M. A. *J. Am. Chem. Soc.,* **1997**, *119*, 7211.

[46] Paul, R.; Schmidt, R.; Dyer, D.J. *Langmuir*, **2002**, *18*, 8719.

[47] Wolf, M. O.; Fox, M. A. *J. Am. Chem. Soc.,* **1995**, *117*, 1845.

[48] Evans, S. D.; Johnson, S. R.; Ringsdorf, H.; Williams, L. M.; Wolf, H. *Langmuir*, **1998**, *14*, 6436.

[49] Andrade, J.D.; Hlady, V. *Adv. Polym. Sci.,* **1986**, *79*, 1.

[50] Horbett, T.A.; Brash, J.L. In *Proteins at Interfaces: Physicochemical and Biochemical Studies;* Brash, J.L.; Horbett, T.A. (Eds.), American Chemical Society: Washington.

[51] Ostuni, E.; Yan, L.; Whitesides, G.M. *Coll. Surf. B,* **1999**,*15*, 3.

[52] Prime, K. L.; Whitesides, G. M. *Science,* **1991**, *252*, 1164.

[53] Chapman, R. G.; Ostuni, E.; Yan, L.; Whitesides, G. M. *Langmuir*, **2000**, *16*, 6927.

[54] Chapman, R. G.; Ostuni, E.; Takayama, S.; Holmlin, R. E.; Yan, L.; Whitesides, G. M. *J. Am. Chem. Soc.*, **2000**, *122*, 8303.

[55] Ostuni, E.; Chapman, R. G.; Holmlin, R. E.; Takayama, S.; Whitesides, G. M. *Langmuir*, **2001**, *17*, 5605.

[56] Ostuni, E.; Chapman, R. G.; Liang, M. N.; Meluleni, G.; Pier, G.; Ingber, D. E.; Whitesides, G. M. *Langmuir*, **2001**, *17*, 6336.

[57] Holmlin, R. E.; Chen, X.; Chapman, R. G.; Takayama, S.; Whitesides, G. M. *Langmuir*, **2001**, *17*; 2841.

[58] Luk, Y.Y.; Kato, M.; Mrksich, M. *Langmuir*, **2000**, *16*, 9604.

[59] Patel, N.; Davies, M.C.; Harshorne, M.; Heaton, R.J.; Roberts, C.J.; Tendler, S.J.B.; Williams, P.M. *Langmuir,* **1997**, *13*, 6485.

[60] Ball, J.C.; Puckett, L.G.; Bachas L.G. *Anal. Chem.,* **2003**, *75*, 6932.

[61] Zaugg, F.G.; Spencer, N.D.; Wagner, P.; Kernen, P.; Vinckier, A.; Groscurth, P.; Semenza, G. *J. Mat. Sci Mat. Med.*, **1999**, *10*, 255.

[62] Delamarche, E.; Bernard, A.; Schmid, H.; Bietsch, A.; Michel, B.; Biebuyck, H. *J. Am. Chem. Soc.*, **1998**, *120*, 500.

[63] Deckert, A.A.; Lesko, J.; Todaro, S.; Doyle M.; Delaney, C. *Langmuir*, **2002**, *18*, 8156.

[64] Brockman, J.M.; Frutos, A.G.; Corn, R.M. *J. Am. Chem. Soc.*, **1999**, *121*, 8044.

[65] Frutos, A.G.; Brockman, J.M.; Corn, R.M. *Langmuir*, **2000**, *16*, 2192.

[66] Houseman, B.T.; Gawalt, E.S.; Mrksich, M. *Langmuir*, **2003**, *19*, 1522.

[67] Houseman, B.T.; Huh, J.H.; Kron, S.J.; Mrksich, M. *Nat. Biotech*., **2002**, *20*, 270.

[68] Horton, R.C.; Herne, T.M.; Myles, D.C. *J. Am. Chem. Soc.,* **1997**, *119,* 12980.

[69] Sigal, G.B.; Bamdad, C.; Barberis, A.; Strominger, J.; Whitesides, G.M. *Anal. Chem.,* **1996**, *68*, 490–497.

[70] Wegner, G.J.; Lee, H.J.; Marriott, G.; Corn, R. M. *Anal. Chem.,* **2003**, *75*, 4740.

[71] Nelson, K.E.; Gamble, L.; Jung, L.S.; Boeckl, M.S.; Naeemi, E.; Golledge, S.L.; Sasaki, T.; Castner, D.G.; Campbell, C.T.; Stayton, P.S. *Langmuir*, **2001**, *17*, 2807.

[72] Offord, D.A.; Sachs, S.B.; Ennis, M.S.; Eberspacher, T.A.; Griffin, J.H.; Christopher E. D. Chidsey, C.E.D.; Collman, J.P. *J. Am. Chem. Soc.* **1998**, *120,* 4478.

[73] Mrksich, M.; Grunwell, J.R.; Whitesides, G.M. *J. Am. Chem. Soc.*, **1995**, *117*, 12009.

[74] Lahiri, J.; Isaacs L.; Grzybowski, B.A.; Carbeck J.; Whitesides, G.M. *Langmuir*, **1999**, *15*, 7186.

[75] Murphy, W. L.; Mercurius, K. O.; Koide, S.; Mrksich, M. *Langmuir*, **2004**, *20*, 1026.

[76] Hodneland, C.D.; Lee, Y.S.; Min, D.H.; Mrksich, M. *Proc. Nat. Acad. Sci.*, **2002**, *99*, 5048.

[77] Chen, S.; Liu, L.; Zhou, J.; Jiang, S. *Langmuir*, **2003,** *19*, 2859.

[78] McIntosh, C.M.; Esposito, E.A.; Boal, A.K.; Simard, J.M.; Martin, C.T.; Rotello, V.M. *J. Am. Chem. Soc.*, **2001**, *123***,** 7626.

[79] Wang, G.; Murray, R.W. *Nano Lett.*, **2004**, *4*, 95.

[80] Nakamura, F.; Mitsui, K.; Hara, M.; Kraemer, S.; Mittler, S.; Knoll, W. *Langmuir*, **2003**, *19*, 5823.

[81] Carroll, R.L.; Gorman, C.B. *Angew. Chem. Int. Ed.*, **2002**, *41*, 4379.

[82] Tour, J.M. *Acc. Chem. Res.,* **2000***, 33*, 791.

[83] Salomon, A; Cahen, D; Lindsay, S; Tomfohr, J; Engelkes, V.B.; Frisbie, C.D. *Adv. Mater.,* **2003**, *15*, 1881.

[84] Beebe, J.M.; Engelkes, V.B.; Miller, L.L.; Frisbie, C.D. *J. Am. Chem. Soc.*, **2002**, *124*, 11268.

[85]   Wang, W.Y.; Lee, T.; Reed, M.A. *Phys. Rev. B*, **2003**, *68*, 035416.
[86]   Cui, X.D.; Zarate, X.; Tomfohr, J.; Sankey, O.F.; Primak, A.; Moore, A.L.; Moore, T.A.; Gust, D.; Harris, G.; Lindsay, S.M. *Nanotechnology*, **2002**, *13*, 5.
[87]   Cui, X.D.; Primak, A.; Zarate, X.; Tomfohr, J.; Sankey, O.F.; Moore, A.L.; Moore, T.A.; Gust, D.; Nagahara, S.M.; Lindsay, S.M. *J. Phys. Chem. B*, **2002**, *106*, 8609.
[88]   Xu, B.; Tao, N.J. *Science*, **2003**, *301*, 1221.
[89]   Chang, S.C.; Li, Z.Y.; Lau, C.N.; Larade, B.; Williams, R.S. *Appl. Phys. Lett.*, **2003**, *83*, 3198.
[90]   Chabinyc, M.L.; Chen, X.X.; Holmlin, R.E.; Jacobs, H.; Skulason, H.; Frisbie, C.D.; Mujica, V.; Ratner, M.A.; Rampi, M.A.; Whitesides, G.M. *J. Am. Chem. Soc.*, **2002**, *124*, 11730.
[91]   Rampi, M.A.; Whitesides, G.M. *Chem. Phys.*, **2002**, *281*, 373.
[92]   Flink, S.; Van Veggel, F.C.; Reinhoudt, D.N. *Adv. Mater.*, **2000**, *12*, 1315.
[93]   Zhao, J.W.; Luo, L.Q.; Yang, X.R.; Wang, E.K.; Dong, S.J. *Electroanal.,* **1999**, *11*, 1108.
[94]   Hickman, J.J.; Ofer, D.; Laibinis, P.E.; Whitesides, G.M.; Wrighton, M.S. *Science*, **1991**, *252*, 688.
[95]   Issa, T.B.; Singh, P.; Baker, M**.** *ACS Sym. Ser.*, **1998**, *690*, 257.
[96]   Turyan, I.; Mandler, D. *Anal. Chem.*, **1994**, *66*, 58.
[97]   Turyan, I.; Mandler, D. *Anal. Chem.*, **1997**, *69*, 894.
[98]   Steinberg, S.; Rubinstein, I. *Langmuir*, **1992**, *8*, 1183.
[99]   Flink, S.; Van Veggel, F.C.; Reinhoudt, D.N. *J. Phys. Chem. B*, **1999**, *103*, 6515.
[100]   Ekeroth, J.; Konradsson, P.; Björefors, F.; Lundström, I.; Liedberg, B. *Anal. Chem.*, **2002**, *74*, 1979.
[101]   Nahir, T.M.; Bowden, E.F. *Langmuir*, **2002**,*18*, 5283.
[102]   Lang, H. P.; Baller, M. K.; Berger, R.; Gerber, Ch.; Gimzewski, J. K.; Battiston, F. M.; Fornaro, P.; Ramseyer, J. P.; Meyer, E.; Guntherodt, H. J. *Anal. Chim. Acta*, **1999**, *393*, 59.
[103]   Xu, X.; Thundat, T. G.; Brown, G. M.; Ji, H.-F. *Anal. Chem.*, **2002**, *74*, 3611.
[104]   Thundat, T.; Finot, E.; Ji, H.-F.; Dabestani, R.; Britt, P. F.; Bonnesen, P. V.; Brown, G. M.; Warmack, R. J. *Proc. Electrochem. Soc.*, **1999**, *99*, 314.
[105]   Zhou, X. C.; Zhong, L.; Li, S. F. Y.; Ng, S. C.; Chan, H. S. O. *Sens. & Actuators B*, **1997**, *42*, 59.
[106]   Hook, F.; Rodahl, M.; Kasemo, B.; Brzezinski, P. *Proc. Nat. Acad. Sci.,* **1998**, *95*, 12271.
[107]   Huang, E.; Zhou, F.; Deng, L. *Langmuir*, **2000**, *16*, 3272.
[108]   Satjapipat, M.; Sanedrin, R.; Zhou, F. *Langmuir*, **2001**, *17*, 7637.
[109]   Su, X.-L; Li, Y. *Biosens. Bioeletron.,* **2004***,19*, 563.
[110]   Muller, R. S. In *Micro/Nanotribology and ItsApplications*; Eds: B. Bhushan; Kluwer: Dordrecht, The Netherlands 1997, pp.579.
[111]   Maboudian, R.; Ashurst, W.R.; Carraro, C. *Sens. & Actuators A*, **2000**, *82*, 219.
[112]   Nelles, G.; Schönherr, H.; Vancso, G. J.; Butt, H.-J. *Appl. Phys. A*, **1998**, *66*, 1261.
[113]   Tsukruk, V.V. *Adv. Mater.*, **2001**, *13*, 95.
[114]   Li, L.Y.; Chen, S.F.; Jiang, S.Y. *Langmuir*, **2003**, *19*, 666.
[115]   Tsukruk, V.V.; Everson, M.P.; Lander L.M.; Brittain, W.J. *Langmuir*, **1996**, *12*, 3905.
[116]   Jennings, G.K.; Munro, J.C.; Yong, T.H.; Laibinis, P.E. *Langmuir*, **1998**, *14*, 6130.
[117]   Jennings, G.K.; Yong, T.H.; Munro, J.C.; Laibinis, P.E. *J. Am. Chem. Soc.,* **2003***, 125*, 2950.
[118]   Burleigh, T.D.; Shi, C.; Kilic, S.; Kovacik, S.; Thompson, T.; Enick, R.M. *Corrosion*, **2002**, *58*, 49.
[119]   Rao, C. N. R.; Kulkarni, G. U.; Thomas, P. J.; Edward, P. P. *Chem. Soc. Rev.,* **2000**, *29*, 27.
[120]   Rao, C. N. R.; Kulkarni, G. U.; Govindaraj, A.; Satishkumar, B. C.; Thomas, P. J. *Pure Appl. Chem.*, **2000**, *72*, 21.
[121]   Kirchner C.G.M.; Stein B.; Parak, W.J.; Gaub, H.E.; Seitz, M. *Adv. Funct. Mater.*, **2002**, *12*, 266.
[122]   Haneda, R.; Aramaki, K. *J. Electrochem. Soc.,* **1998**, *145*, 1856.
[123]   Haneda, R.; Aramaki, K. *J. Electrochem. Soc.,* **1998**, *145*, 2786.
[124]   *Handbook of Chemistry and Physics*, 84th ed.; CRC Press: Boca Raton, 2004.
[125]   Peach M. E. In *The Chemistry of the Thiol Group*, *part 2*; S. Patai, Ed.; Wiley: New York, 1974, pp. 721-735.
[126]   Wardell J. L. In S. Patai, *The Chemistry of the Thiol Group*, part 1; S. Patai, Ed.; Wiley: New York, 1974.
[127]   Fournier, L.; Lamaty, G.; Natat, A.; Roque, J. P. *Tetrahedron*, **1975**, *31*, 809.
[128]   Truce, W. E.; Roberts, F. E. *J. Org. Chem.*, **1963**, *28*, 961.
[129]   Erickson, H. K. *Biochemistry*, **2001**, *40*, 9631.
[130]   Evans, B.J.; Doi, J.T.; Musker, W.K. *J. Org. Chem.*, **1990**, *55*, 2337.
[131]   Drabowicz, J.; Mikolajczyk, M. *Synthesis*, **1980**, 32.
[132]   Pryor, W.A.; Church, D.F.; Govindan, C.K.; Crank, G. *J. Org. Chem.*, **1982**, *47*, 156.
[133]   Gilbert, E. E. *Sulfonation and Related Reactions*; Wiley: New York, **1965**, pp. 217-239.
[134]   Overman, L. E.; Smoot, J.; Overman J. D. *Synthesis*, **1974**, 59.
[135]   Brown, H. C.; Nazer, B.; Soon J. *Synthesis,* **1984**, 498.
[136]   Hauptmann, H.; Walter, W. F. *Chem. Rev.,***1962**, *62*, 347.
[137]   Negishi, E. *Organometallics in Organic Synthesis*; Wiley: New York, **1980**, pp. 243-247, 169-178.
[138]   Trost, B. M.; Salzmann, T. N. *J. Am. Chem. Soc.*, **1973**, *95*, 6840.
[139]   Kocienski, P.J. *Protecting Groups*, 3rd Ed.; Thieme: Stuttgart, **2003**.
[140]   Green, T.W.; Wuts P.G. In *Protective Groups In Organic Synthesis* 2nd ed.; John Wiley & Sons: New York, **1991**, pp. 277.
[141]   Wolman Y. In *Thiol Function*, S. Patai Ed.; John Wiley & Sons: London, **1974**, pp. 669
[142]   Sifferd, R.H.; du Vigneaud, V. *J. Biol. Chem.,* **1935**, *108*, 753.
[143]   White, J. *J. Biol. Chem.*, **1934**, *106*, 141.
[144]   Berse, C.; Boucher, R.; Piche, L. *J. Org. Chem.*, **1957**, *22*, 805.
[145]   Erickson, B.W.; Merrifield, R.B. *J. Am. Chem. Soc.*, **1973**, *95*, 3750.
[146]   Merrifield, R.B. *J. Am. Chem. Soc.*, **1963**, *85*, 2149.
[147]   Veber, D.F.; Milkowski, J.D.; Varga, S.L.; Denkewalter, R.G.; Hirschmann, R. *J. Am. Chem. Soc.*, **1972**, *94*, 5456.
[148]   Callahan, F.M.; Anderson, G.W.; Paul, R.; Zimmerman, J.E. *J. Am. Chem. Soc.*, **1963**, *85*, 201.
[149]   Pastuszak, J.J.; Chimiak, A. *J. Org. Chem.*, **1981**, *46*, 1868.
[150]   Zervas, L.; Theodoropoulos, D. M. *J. Am. Chem. Soc.*, **1956**, *78*, 1359.
[151]   Cuthbertson, A.; Indrevoll, B. *Org. Lett.*, **2003**, *5*, 2955.
[152]   Herz, A.H.; Tarbel, D.S. *J. Am. Chem. Soc.,* **1953**, *75*, 4657.
[153]   Tarbell, D.S.; Harnisch, D.P. *Chem. Rev.,* **1951**, *49*, 1.
[154]   Arjona, O.; Iradier, F.; Medel, R.; Plumet, J. *J. Org. Chem.,* **1999**, *64*, 6090.
[155]   Arjona, O.; Medel, R.; Rojas, J.; Costa, A. M.; Vilarrasa, J. *Tetrahedron Lett.,* **2003**, *44*, 6369.
[156]   Eritja, R.; Ziehler-Martin, J.P.; Walker, P.A.; Lee, T.D.; Legesse, K.; Albericio, F.; Kaplan, B.E. *Tetrahedron,* **1987**, *43*, 2675.
[157]   Albericio, F.; Nicolas, E.; Rizo, J.; Ruiz-Gayo, M.; Pedroso, E.; Giralt, E. *Synthesis*, **1990**, 119; Corey, E.J.; Gin, D.Y.; Kania, R.S. *J. Am. Chem. Soc.,* **1996**, *118*, 9202.
[158]   Sokolovsky, M.; Wilchek, M.; Patchornick, A. *J. Am. Chem. Soc.,* **1964**, *86*, 1202; Mairanovsky, V.G. *Angew. Chem., Int. Ed. Engl.,* **1976**, *15*, 281.
[159]   Ng, S. C.; Sun, T.; Chan, H. S. O. *Tetrahedron Lett.*, **2002**, *43*, 2863.
[160]   Pearson, R. G. *J. Am. Chem. Soc.,* **1963**, *85*, 3533.
[161]   Nuzzo, R. G.; Allara, D. L. *J. Am. Chem. Soc.,* **1983**, *105*, 4481.
[162]   Nuzzo, R.G.; Zegarski, B.R.; Dubois, L.H. *J. Am. Chem. Soc.,* **1987**, *109*, 733.
[163]   Bain, C.D.; Biebuyck, H.A.; Whitesides, G.M. *Langmuir*, **1989**, *5*, 723.
[164]   Castner, D.G.; Hinds, K.; Grainger, D.W. *Langmuir,* **1996**, *12*, 5083.

[165] Hagenhoff, B.; Benninghoven, A.; Spinke, J.; Liley, M.; Knoll, W. *Langmuir,* **1993***, 9*, 1622.

[166] Lee, J.-G.; Lee, J.; Yates, J.T. *J. Am. Chem. Soc.,* **2004**, *126*, 440.

[167] Biebuyck, H.A.; Bain, C.D.; Whitesides, G.M. *Langmuir,* **1994***, 10*, 1825.

[168] Strong, L.; Whitesides, G.M. *Langmuir*, **1988**, *4*, 546.

[169] Dubois, L.H.; Nuzzo, R.G. *Annu. Rev. Phys. Chem.,* **1992**, *43*, 437.

[170] Fenter, P.; Eberhardt, A.; Eisenberger, P. *Science,* **1994***, 266*, 1216.

[171] Kluth, G.J.; Carraro, C.; Maboudian, R. *Phys. Rev. B,* **1999**, *59*, 449.

[172] Dubois, L.H.; Zegarski, B.R.; Nuzzo, R.G. *J. Chem. Phys.*, **1993**, *98*, 678.

[173] Bain, C.D.; Troughton, E.B.; Tao, Y.-T.; Evall, J.; Whitesides, G.M.; Nuzzo, R.G. *J. Am. Chem. Soc.,* **1989**, *111*, 321.

[174] Boden, N.; Bushby, R.J.; Clarkson, S.; Evans, S.D.; Knowles, P.F.; Marsh, A. *Tetrahedron*, **1997**, *53*, 10939.

[175] Houseman, B.T.; Gawalt, E.S.; M. Mrksich, *Langmuir*, **2003**, *19*, 1522.

[176] Wei, J.; Liu, D.; Dick, R.A.; Yamamoto, H.; Ite, Y.; Waldeck D.H. *J. Am. Chem. Soc.*, **2002**, *124*, 9591.

[177] Nakamura, F.; Hara, M. *Mol. Cryst. Liq. Cryst. Sci. Technol. A.* **2002**, *377*, 57.

[178] a) Delfino, J.M.; Schreiber, S.L.; Richards F.M. *J. Am. Chem. Soc.*, **1993**, *115*, 3458.
b) Jung, M.Ch.; Kraus, W.; Leibnitz, P.; Pietzsch, H.J.; Kropp, J.; Spies, H. *Eur. J. Inorg. Chem.*, **2002**, 1219.
c) Delfino, J.M.; Stankociv, Ch.J.; Schreiber, S.L.; Richards *Tetrahedron Lett.*, **1987**, *28*, 2323.
d) Livni, E.; Davis, M.A.; Warner, V.D. *J. Med. Chem.,* **1979**, *22,* 580.
e) Finklea, H.O.; Liu, L.; Ravenscroft, M.S.; Punturi S. *J. Phys. Chem.,* **1996**, *100*, 18852.

[179] Skulason, H.; Frisbie, C.D. *J. Am. Chem. Soc.,* **2000**, *122*, 9750.

[180] a) Ji, A.F.; Thundat, T.; Dabestani, R.; Brown, G.M.; Britt, P.F.; Bonnesen, P.V. *Anal. Chem.*, **2001**, *73*, 1572.
b) Regen, S.L.; Samuel, N.K.P.; Khurana J.M. *J. Am. Chem. Soc.*, **1985**, *107*, 5804.

[181] Lin, S.Y.; Liu, S.W.; Lin, C.M.; Chen, C. *Anal. Chem*., **2002**, *74*, 330.

[182] Ryan, D.; Rav, S.N.; Rensmo, H.; Fitzmaurice, D.; Preece, J.A.; Wenger, S.; Stoddart, J.F.; Zaccheroni N. *J. Am. Chem. Soc.,* **2000**, *122*, 6252.

[183] Fullam, S.; Rao, S.N.; Fitzmaurice D. *J. Phys. Chem. B*, **2000**, *104*, 6164.

[184] Redman, J.E.; Sanders, J.K.M. *Org. Lett.,* **2000**, *2* , 4141.

[185] Nissink, J.W.M.; Maas J.H. *Appl. Spectrosc.,* **1999**, *53*, 33.

[186] Roberts, C.; Chen, C.S.; Mrksich, M.; Martichomok, V.; Donald, D.E.; Whitesides, G.M. *J. Am. Chem. Soc.*, **1998**, *120*, 6548.

[187] Ji, H.F.; Finot, E.; Dabestani, R.; Thundat, T.; Brown, G.M.; Britt P.F. *Chem. Commun*., **2000,** 457.

[188] Zhang, J.; Kirkham, J.; Robinson, C.; Wallwork, D.M.; Smith, D.A.; Marsh, A.; Wong, M. *Anal. Chem*., **2000**, *72*, 1973.

[189] Kim, S.H.; Lee, S.H.; Kang S.H. *Tetrahedron. Lett.*, **1998**, *39*, 9693.

[190] Liedberg, B.; Yang, Z.; Engquist, I.; Wirde, M.; Gelius, U. *J. Phys. Chem. B.,* **1997**, *101*, 5951.

[191] Kitov, I.P.; Railton, C.; Bundle, D.R. *Carbohydr. Res.*, **1998***, 307*, 361.

[192] a) Wei, J.; Liu, H.; Dick, A.R.; Yamamoto, H.; He, Y.; Waldeck D.H. *J. Am. Chem. Soc.*, **2002***, 124*, 9591.
b) Sigal, G.B.; Mrksich, M.; Whitesides, G.M. *J. Am. Chem. Soc.*, **1998***, 120*, 3464.
c) Kim, E.; Whitesides, G.M. *J. Phys. Chem. B.,* **1997***, 101*, 855.

[193] a) Ye, S.; Yashiro, A.; Sato, Y.; Kosaki, K. *J. Chem. Soc. Faraday Trans.*, **1996**, 3813. b) Kwon, Y.; Mrksich, M. *J. Am. Chem. Soc.*, **2002**, *124* , 806. c) Yousaf, M.N.; Houseman, B.T.; Mrksich, M. *Angew. Chem. Int. Ed.,* **2001**, *40*, 1093.

[194] Nakashima, N.; Taguchi, T.; Takada, Y.; Fujio, K.; Kunitake, M.; Manabe, O. *J. Chem. Soc. Chem. Commun.*, **1991**, 232.

[195] Garrott, P.J.; Ng, Y.E.; Steed, J.W. *Tetrahedron*, **2000**, *56*, 4501.

[196] Laibinis, P.E.; Bain, C.D.; Nuzzo, R.G.; Whitesides, G.M. *J. Phys. Chem.,* **1995**, *99*, 7663.

[197] Colin, C.D.; Troughton, E.B.; Tao, Y.T.; Evall, J.; Whitesides, G.M.; Nuzzo, R.G. *J. Am. Chem. Soc*., **1989**, *111*, 321.

[198] Samuel, N.K.P.; Singh, M.; Yamaguchi, K.; Regen, S.L. *J. Am. Chem. Soc.*, **1985**, *107*, 42.

[199] DeVries, V.G.; Moran, D.B; Allen, G.R.; Riggi S.J. *J. Med. Chem.*, **1976**, *19*, 946.

[200] Naud, C.; Calas, P.; Blancok, H.; Commeyres, A. *J. Fluor. Chem.*, **2000**, *104*, 173.

[201] a) Caldwell, W.B.; Campbell, D.J.; Chen, K.; Herr, B.R.; Mirkin, C.A. *J. Am. Chem. Soc.*, **1995**, *117*, 6071.
b) Jaschke, M.; Schoenherr, H.; Wolf, H.; Butt, H.J.; Bamberg, E. *J. Phys. Chem.,* **1996**, *100*, 2290.

[202] a) Sigal, G.B.; Bamdad, C.; Borberis, A.; Strominger, J.; Whitesides, G.M. *Anal. Chem.,* **1996**, *68*, 490.
b) Luk, Y.Y.; Tingey, M.L.; Hall, D.J.; Israel, B.A.; Murphy, C.J.; Berics, D.J.; Abbott, N.L., *Langmuir*, **2003**, *19*, 1671.

[203] a) Booth, C.; Bushby, R.J.; Cheng, Y.; Evans, S.D.; Liu, Q.; Zhang, H. *Tetrahedron*, **2001**, *57*, 9859.
b) Spinke, J.; Liley, M.; Schmitt, F.J.; Guder, H.J.; Angermaier, L.; Knou, W. *J. Chem. Phys*., **1993**, *99*, 7012.

[204] Pole-Grosdemange, C.; Simon, E.S.; Prime, K.L.; Whitesides, G.M. *J. Am. Chem. Soc.,* **1991**, *113*, 12.

[205] Kanagasabapathy, S.; Sudalai, A.; Benicewicz, B.C. *Tetrahedron Lett.*, **2001**, *42*, 3791.

[206] Lueoend, R. M.; Walker, J.; Neier, R. W. *J. Org. Chem*., **1992**, *57*, 5005.

[207] Knunyants, I.L. Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl.Transl.); **1977,** 26, 206; Izv. Akad. Nauk SSSR Ser. Khim., **1977**, 26, 231.

[208] a) Ueki, M.; Shinozaki, K. *Bull. Chem. Soc. Jpn*., **1983**, *56*, 1187.
b) Ueki, M.; Shinozaki, K.; *Bull. Chem. Soc. Jpn*., **1984**, *57*, 2156.
c) Horner, L.; Gehring, R.; Lindel, H. *Phosphorus Sulfur*, **1981**, *11*, 349.

[209] a) Chu, P.J.; Potrzebowski, M.J.; *Mag. Res. Chem*., **1990**, *28,* 477.
b) Dodin-Carnot, V.; Curci, M.; Wilhelm, J.C.; Mieloszynski, J.L.; Paquer, D. *Phosphorus, Sulfur Silicon Relat. Elem*., **1995**, *107*, 219.
c) Stoffey, D.G. *J. Org. Chem*., **1968**, 33, 1651.
d) Liakumovich, A.G.; Kadyrova, V.K.; Mukmeneva, N.A.; Bukharov, S.V. *J. Gen. Chem. USSR* (*Engl.Transl.),* **1991**, *61*, 237.
e) Michalski, J.; Potrzebowski, M.; Lopusinski, A. *Angew. Chem. Int. Ed*., **1982**, *94*, 134.

[210] Ferraboschi, P.; Fiecchi, A.; Grisenti, P.; Santaniello, E.; Trave, S.; *Synth. Commun*., **1987**, *17*, 1569.

[211] Miyauchi, H.; Kozuki, K.; Tanio, T.; Ohashi, N.; *Bioorg. Med. Chem*., **1996**, *4*, 263.

[212] Kim, S. H.; Lee, S. H.; Kang, S. H.; *Tetrahedron Lett*., **1998**, *39*, 9693.

[213] Nakashima, N.; Abe, K.; Hirohashi, T.; Hamada, K.; Kunitake, M.; Manabe, O.; *Chem. Lett.,* **1993**, *6*, 1021.

[214] Kumar, P.; Bhatia, D.; Rastogi, R. C.; Gupta, K. C.; *Bioorg. Med. Chem. Lett*., **1996**, *6*, 683.

[215] Rao, T. V.; Rao, K.N.; Jain, S.L.; Sain, B. *Synth. Commun.,* **2002**, *32*, 1151.

[216] Varma, R.S.; Meshram, H.M.; Dahiya, R. *Synth. Commun.,* **2000**, *30*, 1249.

[217] Ron, H.; Rubinstein, I. *J. Am. Chem. Soc.,* **1998**, *120*, 13444.

[218] Hirano, M.; Yakabe, S.; Chikamori, H.; Clark, J.H.; Morimito, T. *J. Chem. Res. Synop.,* **1998**, *6*, 310.

[219] Khodaei, M.M.; Mohammadpoor-Baltork, I.; Nikoofar, K. *Bull. Korean Chem. Soc.,* **2003**, *24*, 885.

[220] a) Christiansen, L.W.; Heacock, D.J. *Synthesis*, **1978**, 50,
b) Drabowicz, J.; Mikolajczyk, M. *Synthesis*, **1980**, 32.
c) Firouzabadi, H.; Mohammadpoor-Baltork, I. *Bull. Chem. Soc. Jpn.,* **1992**, *65*, 1485.
d) Iranpoor, N.; Firouzabadi, H.; Zolfigol, M.A. *Synth. Commun.,* **1998**, *28*, 367.

e) Iranpoor, N.; Zeynizadeh, B. *Synthesis*, **1999**, 49.

f) McKillop, A.; Koyuncu, D. *Tetrahedron Lett.,* **1990**, *31*, 5007.

g) Wu, X.; Rieke, R.D.; Zhu, L. *Synth. Commun.,* **1996**, *26*, 191.

h) Meshram, H.M.; Kache, R.; *Synth. Commun.,* **1997**, *27*, 2403.

i) Hirano, M.; Yakabe, S.; Ando, K.I.; Morimoto, T. *J. Chem. Res. (S),* **1998**, 816.

j) Hirano, M.; Yakabe, S.; Monobe, H.; Morimoto, T. *J. Chem. Res. (S),* **1998**, 472.

k) Sridhar, M.; Vadivel, S.K.; Bhalerao, U.T. *Synth. Commun.,* **1998**, *28*, 1499.

l) Rao, T.V.; Sain, B.; Murthy P.S.; Rao, T.S.; Jain, A.K.; Joshi, G.C. *J. Chem. Res. (S),* **1997**, 300.

m) Noureldine, M.C.; Hendry, J.; Lee, D.G. *Synthesis*, **1998**, 1587.

n) Kesavan, V.; Bonnet-Delpon, D.; Begue, J.P.; *Synthesis*, **2000**, 223.

o) Movassagh, B.; Lakouraj, M.M.; Ghodrati, K. *Synth. Commun.,* **1999**, *29*, 3597.

p) Hajipour, A.R.; Mallakpour, S.E.; *J. Chem. Res. (S),* **2000**, 32.

q) Raghavan, S.; Rajender, A.; Joseph, S.C.; Rasheed, M.A. *Synth. Commun.,* **2001**, *31*, 1477.

r) Salehi, P.; Farrokhi, A.; Gholizadeh, M. *Synth. Commun.,* **2001**, *31*, 2777.

s) Wang, J.X.; Gao, L.; Huang, D. *Synth. Commun.,* **2002**, *32*, 963.

t) Chen, F.E.; Lu, Y.W.; He, Y.P.; Luo, Y.F.; Yan, M.G. *Synth. Commun.,* **2002**, *32*, 3487.

[221] a) Wang, L.; Zhang, Y. *Tetrahedron,* **1999**, *55*, 10695.

b) Xu, X.; Lu, P.; Zhang, Y. *Synth. Commun.,* **2000**, *30*, 1917.

c) Wang, L.; Li, P.; Zhou, L. *Tetrahedron Lett.,* **2002**, *43*, 8141.

[222] Huang, Y.; Zhang, Y.; Wang, Y. *Synth. Commun.,* **1997**, *27*, 1043.

[223] Steinfatt, I.; Hoffmann, G.G.; Brouwer, L.; Menzel, F.; Brockner, W. *Phosphorus, Sulfur Silicon Relat. Elem.,* **1998**, *134*, 31.

[224] Cheng, J.; Miller, J. C. *J. Phys. Chem. B,* **1997**, *101*, 1058.

[225] Byk, G.; Wetzer, B.; Frederic, M.; Dubertret, C.; Pitard, B.; Jaslin, G.; Scherman, D. *J. Med. Chem.,* **2000**, *43*, 4377.

[226] Kada, G.; Reiner, C.K.; Gruber, H.J. *Tetrahedron Lett.,* **2001**, *42*, 2677.

[227] Fallois, L.L.H.; Decout, J.L.; Fontecave, M. *J. Chem. Soc. Perkin Trans.,* **1997**, 2587.

[228] Akiyama, H.; Tamada, K.; Nagasawa, J.; Abe, K.; Tamaki, T. *J. Phys. Chem. B,* **2003**, *107*, 130.

[229] Grosa, G.V.; Ceruti, M.B.; Delprino, L. *Eur. J. Med. Chem. Chim. Ther.,* **1994**, *29*, 17.

[230] Pfammatter, M.J.; Siljegovic, V.; Darbre, T.; Keese, R. *Helv. Chim. Acta,* **2001**, *84*, 678.

[231] a) Moses, R. *J. Am. Chem. Soc.,* **1926**, *48*, 776.

b) Chary, K. P.; Rajaram, S.; Iyengar, D.S. *Synth.Commun.*, **2000**, *30*, 3905.

c) Rajaram, S.; Chary, K.P.; Iyengar, D.S. *Ind. J.Chem. B*, **2001**, *40*, 622.

d) Ookawa, A.; Yokoyama, S.; Soai, K. *Synth.Commun.*, **1986**, *16*, 819.

e) Young, R.J.; Beams, R.M.; Carter, K.; Clark, H.A.R.; Coe, D.M.; Chambers, C.L.; Davies, P.I.; Dawson, J.; Drysdale, M.J.; Franzman, K.W.; French, C. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 597.

f) Batten, R.J.; Coyle, J.D.; Taylor, R.J.K. *Synthesis*, **1980**, 910.

g) Klein, L.L. *J. Org. Chem.*, **1985**, *50*, 1770.

h) Agami, C.; Couty, F.; Prince, B.; Venier, O. *Tetrahedron Lett.*, **1993**, *34*, 7061.

[232] Nuss, S.; Boettcher, H.; Wurm, H.; Hallensleben, M.L. *Angew. Chem. Int. Ed.,* **2001**, *40*, 4016.

[233] Gough, J.D.; Williams, R.H.; Donofrio, A.E.; Lees, W.J. *J. Am. Chem. Soc.,* **2002**, *124*, 3885.

[234] a) Aherne, D.; Rao, S.N.; Fitzmaurice, D. *J. Phys. Chem. B,* **1999**, *103*, 1821.

b) Ayers, J. T.; Anderson, S. R. *Synth.Commun.*,**1999**, *29*, 351.

[235] a) Armitage, D.A.; Clark, M.J.; Tso, C.C. *J. Chem. Soc. Perkin Trans.1,* **1972**, 680.

b) Inukai, N.; Nakano, K.; Murakami, M. *Bull. Chem. Soc. Jpn.,* **1967**, *40*, 2913.

[236] a) Field, L.; Ravichandran, R. *J. Org. Chem.,* **1979**, *44*, 2624.

b) Wunsch, E.; Moroder, L.; Romani, S. *Hoppe-Seyler's Z. Physiol. Chem.,* **1982**, *363*, 1461.

c) Wunsch, E.; Spangenberg, R. IN *Peptides*, Schoffone, E. Ed.; North Holland, Amsterdam, **1969**; pp.1971.

d) Ramage, R.; Steward, A.S.J. *J. Chem. Soc. Perkin Trans. 1,* **1993**, 1947.

[237] a) Fontana, A.; Scoffone, E.; Bennasi, C.A. *Biochemistry*, **1968**, *7*, 980.

b) Fontana, A. *J. Chem. Soc., Chem. Commun.,* **1975**, 976.

c) Fontana, A.; Veronese, F.M.; Scoffone, E. *Biochemistry*, **1968**, *7*, 3901.

d) Field, L.; Giles, P.M. *J. Org. Chem.,* **1971**, *36*, 309.

[238] Houseman, B.T.; Mrksich, M. *J. Org. Chem.,* **1998**, *63*, 7552.

[239] *Solid-Phase Peptide Synthesis: A Practical Approach*; E. Atherton, R.C. Sheppard, Eds.; IRL Press: New York, 1989.

[240] Ellman, G.L. *Arch. Biochem. Biophys.,* **1959**, *82*, 70.

[241] Amato, C.; Calas, P. *J. Fluor. Chem.,* **2003**, *124*, 169.

[242] Roy, B. C.; Mallik, S. *Org. Lett.*, **2001**, *12*, 1877.

[243] Roy, B. C.; Mallik, S. *J. Org. Chem.*, **1999**, *64*, 2969.

[244] Yeager, L. J.; Amirsakis, D. G.; Newman, E.; Garrell, R. L. *Tetrahedron*, **1998**, *39*, 8409.