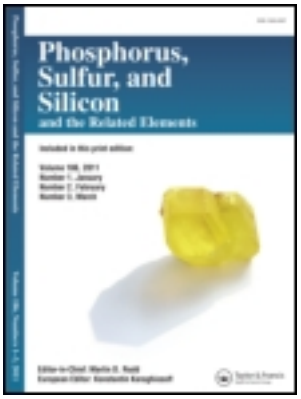

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Synthesis and Characterization of Some Novel Higher C,N-Diphenyl Nitrones, Isoxazolines, and Mercaptobenzimidazoles as Oleochemicals

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SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL HIGHER C,N-DIPHENYL NITRONES, ISOXAZOLINES, AND MERCAPTOBENZIMIDAZOLES AS OLEOCHEMICALS

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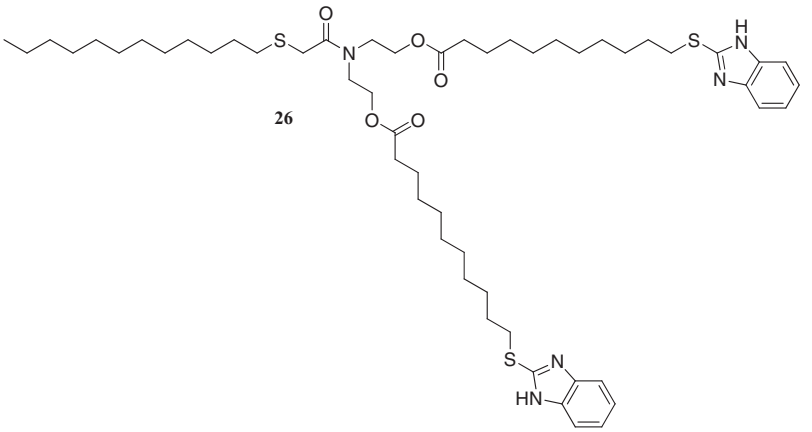
GRAPHICAL ABSTRACT



Abstract *Some novel long-chain nitrones, isoxazolines, and (1H-benzo[d]-imidazol-2-ylthio) derivatives were synthesized. Nitrones, N-{4-[2-(tetradecylthio)acetoxy]benzylidene}aniline oxide, and N-[4-(12-oxo-2,5,8,11-tetraoxadocosan-22-yloxy)benzylidene]aniline oxide were prepared via the reaction of β-phenylhydroxylamine with the corresponding aromatic aldehydes. The isoxazolines were prepared from undec-10-en-1-ol and benzonitrile-N-oxide which was generated in situ. The 1H-benzo[d]-imidazol-2-ylthio derivatives were synthesized via the replacement reaction of ω-bromo esters and 2-mercaptobenzimidazole.*

Keywords Benzimidazoles; fatty acids; isoxazolines; nitrones

INTRODUCTION

Synthetic fatty acids and their derivatives are widely used products, mainly as industrial raw materials. Examples for potential uses of these materials include oil field chemicals.[1] Long-chain compounds are widely used in the oil industry as corrosion inhibitors.[2–5] Industrial corrosion is a serious problem that causes severe economic losses

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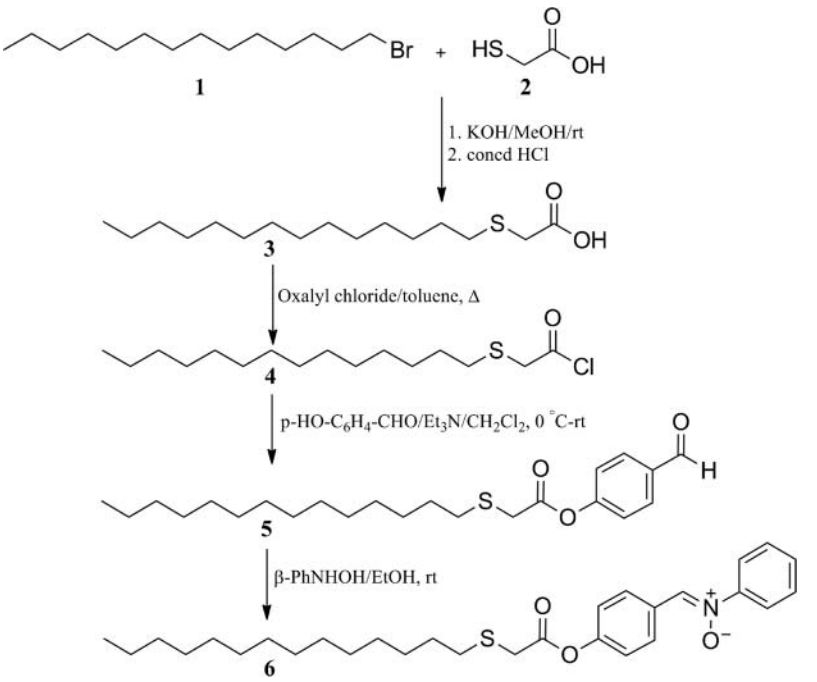
because of destruction-based process of metal and alloy equipments and devaluation of industrial products.

Long-chain *N*-alkyl-α-alkyl nitrones are exceptionally effective as process stabilizers for polyolefins.[6] Some homologous nitrones display mesomorphic properties.[7] There are many methods known in the literature for the synthesis of nitrones. For instance, nitrones can be obtained via the oxidation of secondary amines with oxone as the sole oxidant in a biphasic basic medium,[8] via the manganese dioxide oxidation of hydroxylamines,[9] and via the condensation reaction between aldehydes and hydroxylamine.[10]

There is a literature report describing the pharmacological properties of isoxazolines.[11] Isoxazolines are generally prepared by 1,3-dipolar cycloaddition between alkenes and nitrile oxides which are generated in situ.[3,12] Benzimidazole derivatives exhibit a wide range of pharmacological activities and industrial applications.[13–15]

RESULTS AND DISCUSSION

The starting 2-(tetradecylthio)acetic acid (**3**) was prepared according to a procedure given in a patent[16] with some modifications. Thereafter, this acid was reacted with two equivalents of oxalyl chloride to give the desired acyl chloride (**4**). 2-(Tetradecylthio)acetyl chloride (**4**) was treated with 4-hydroxybenzaldehyde to give a good yield of aldehyde (**5**) (Scheme 1). The IR spectrum of the compound showed peaks at 1760 cm^{-1} and 1720 cm^{-1} for the COO and CHO groups, respectively. The ^1H NMR spectrum of the compound showed singlets at δ 10.01 ppm and δ 3.45 ppm for the C<u>H</u>O and the $CH_2SC\underline{H}_2COO$ groups, respectively. Thereafter, the aldehyde **5** was treated with β-phenylhydroxylamine[17]

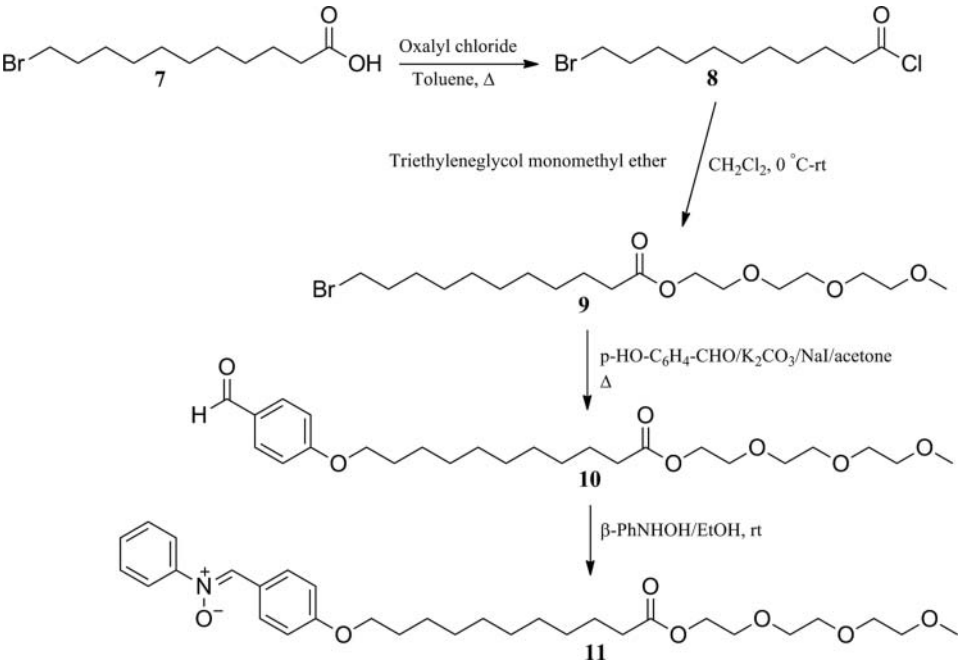


Scheme 1

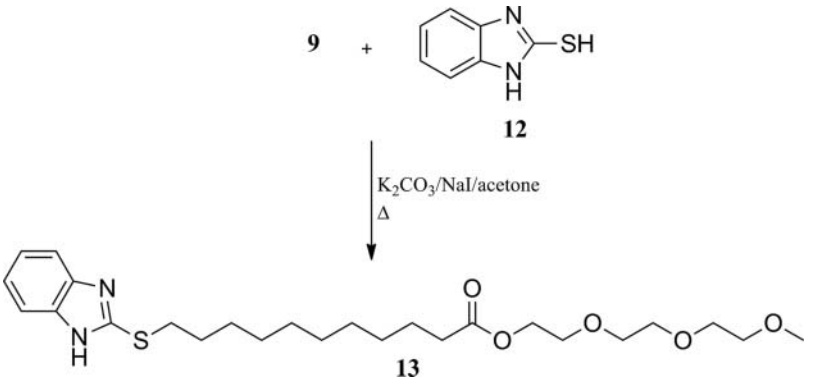
in a dark and closed vessel to afford the nitrone as a white crystalline compound with 61% yield after crystallization from THF. The absence of a peak for CHO in the IR and ^{1}H NMR spectra confirmed the structure of the condensation product. The characteristic IR peaks of **6** were observed at 1753 cm^{-1} for the COO group, at 1554 cm^{-1} for the C=N group, and at 1167 cm^{-1} for the N–O group. The ^{1}H NMR spectrum of **6** showed a singlet at δ 7.94 ppm for the ON=C<u>H</u> group.

Here we report also syntheses of compounds **11** and **13** with one-tailed hydrophobic groups (Schemes 2 and 3). To accomplish the synthesis of the **11**, first 11-bromoundecanoic acid (**7**) was converted to its acyl chloride (**8**) by treatment with oxalyl chloride which provided the desired ester **9** after reaction with triethylene glycol monomethyl ether. The isolated ester **9** exhibited acceptable purity for the IR analysis. Then, this compound was heated with 4-hydroxybenzaldehyde in the presence of potassium carbonate and catalytic amounts of sodium iodide in anhydrous acetone to afford the aromatic long-chain aldehyde **10** as a colorless oil with 72% yield. Characteristic IR peaks were obtained at 1732 cm^{-1} for the COO group and at 1688 cm^{-1} for the CHO group. The ^{1}H NMR spectrum showed two singlets at δ 9.87 ppm for the C<u>H</u>O group and at δ 3.38 ppm for the OC<u>H</u>$_3$ group. The amphiphilic nitrone *N*-[4-(12-oxo-2,5,8,11-tetraoxadocosan-22-yloxy)benzylidene]aniline oxide (**11**) was obtained with 57% yield upon reaction of **10** with β-phenylhydroxylamine in the dark (Scheme 2).

For the synthesis of the amphiphilic 2-[2-(2-methoxyethoxy)ethoxy]ethyl-11-(1*H*-benzo[*d*]imidazol-2-ylthio)undecanoate (**13**), the ester **9** obtained in Scheme 2 was heated with 2-mercaptobenzimidazole[18] **12** in the presence of potassium carbonate and a catalytic amount of sodium iodide.

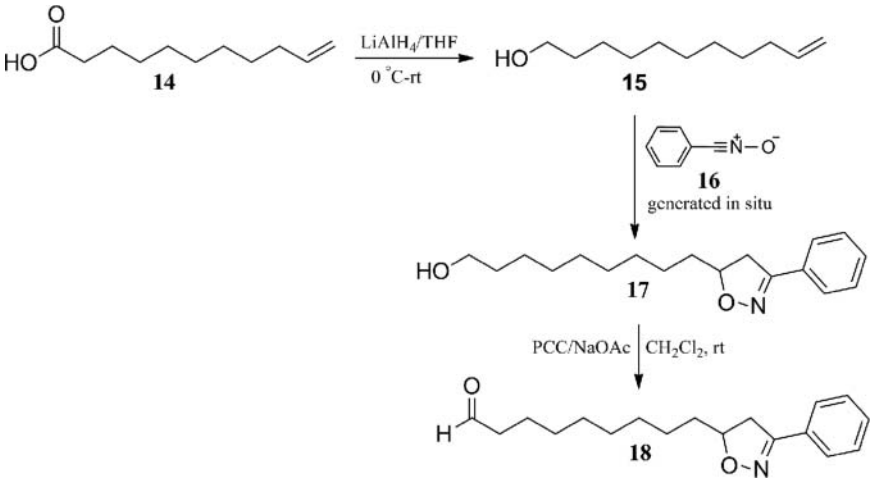


Scheme 2



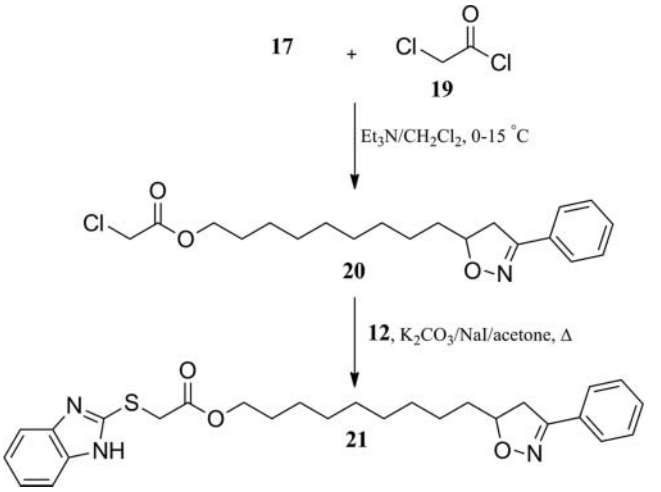
Scheme 3

Undec-10-en-1-ol (**15**) was synthesized by reduction of undec-10-enoic acid (**14**) with lithium alanate. Then, the unsaturated alcohol **15** and benzonitrile-*N*-oxide (**16**) were reacted to give isoxazoline **17** via cycloaddition reaction (Scheme 4). Benzonitrile-*N*-oxide (**16**) was generated in situ as described by Hassner and Lokanatha.[19] The cycloadduct **17** was oxidized with pyridinium chlorochromate to give the corresponding aldehyde **18**. The IR spectrum of **18** showed an absorption band at 1716 cm^{-1} due to the CHO stretching vibration. The adsorption band at 3279 cm^{-1} due to the OH group of **17** disappeared.



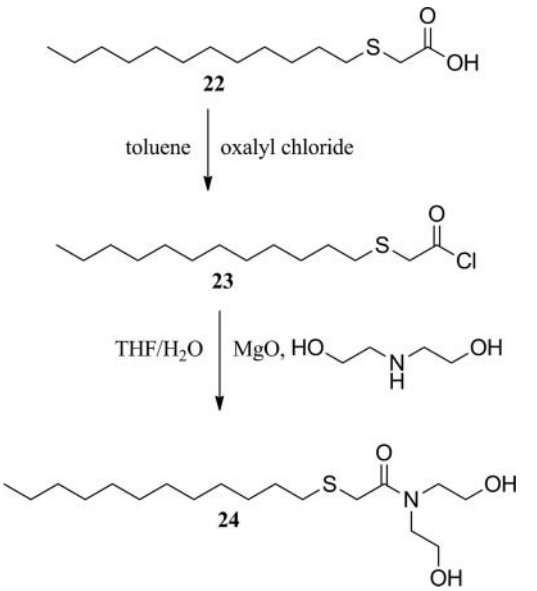
Scheme 4

The oxidized product also confirms the chemical structure of the prepared isoxazoline **17**. For the synthesis of **21**, first isoxazoline **17** was treated with chloroacetyl chloride (**19**) to give the chloroacetylated isoxazoline **20** in quantitative yield as a white waxy solid, which was used as obtained in the next step. Finally, **20** was heated with 2-mercaptobenzimidazole (**12**), in the presence of potassium carbonate and a catalytic amount of sodium iodide. Purification of the crude product on a short column packed with silica gel and petroleum ether-dichloromethane as eluent yielded 76% of pure **21** as a yellowish–orange solid (Scheme 5). In the ^1H NMR spectrum of the **21**, the protons of the methylene SCH_2COO group showed a singlet at δ 3.95 ppm.

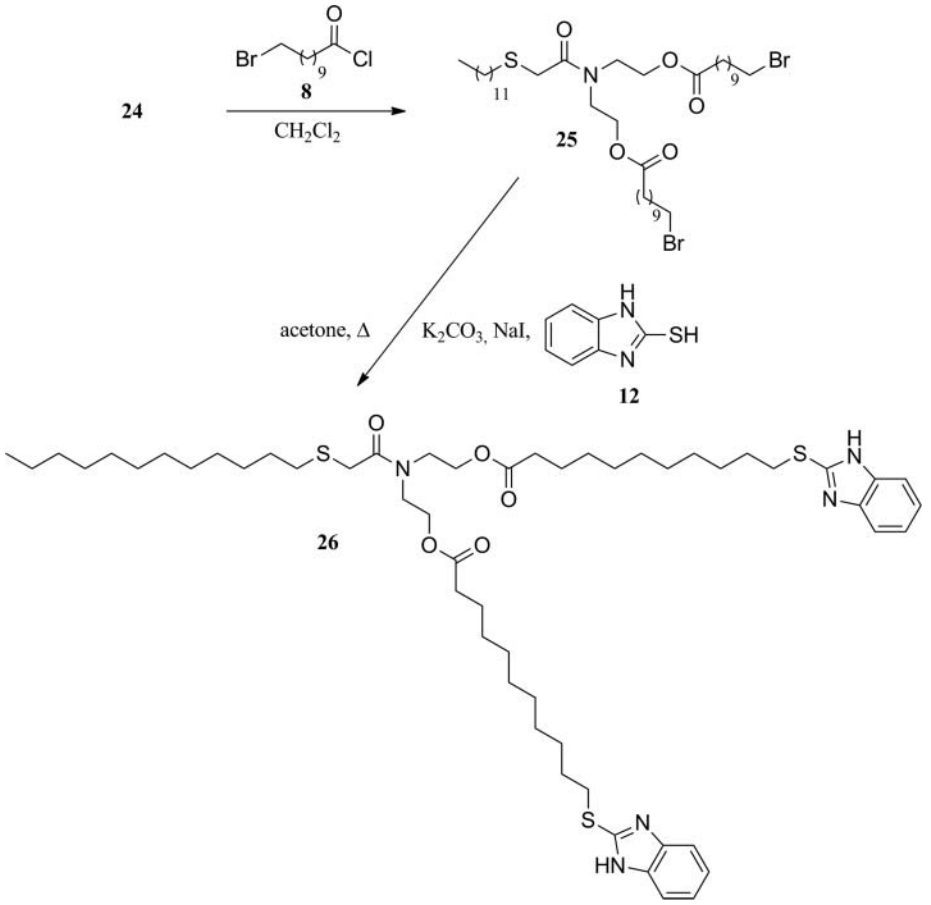


Scheme 5

2-(Dodecylthio)-*N*,*N*-bis(2-hydroxyethyl)acetamide (**24**) was prepared from the corresponding acyl chloride **23** via treatment with MgO as a basic reagent (Scheme 6). This reagent provides chemoselective acylation at the nitrogen atom of diethanolamine.[20] The characteristic IR peaks of the compound were obtained at 3379 cm^{-1} for the OH groups and at 1628 cm^{-1} for the C=O group. The ^1H NMR spectrum showed one doublet of triplets at δ 3.85 ppm for the $CH_2C\underline{H}_2OH$ protons, a singlet at δ 3.41 ppm for the two protons of the $CH_2S\underline{CH}_2C{=}O$ group, and a broad singlet at δ 3.31 ppm for the two OH protons. The synthesis of the three-armed **26** was accomplished by the reaction of 2-mercaptobenzimidazole[18] (**12**) with the ester **25** (Scheme 7). The characteristic IR peaks



Scheme 6



Scheme 7

of **26** were observed at 3244 cm^{-1} for the NH, at 1736 cm^{-1} for C=O of the ester groups, and at 1639 cm^{-1} for C=O of the amide group. The ^1H NMR spectrum showed one doublet at δ 10.37 ppm for the NH protons, a triplet at δ 4.25 ppm for the four protons of the two $C\underline{H}_2$–OC=O groups, a doublet of triplet at δ 3.67 ppm for the $N(C\underline{H}_2CH_2)_2$ protons, a singlet at δ 3.37 ppm for the $CH_2SC\underline{H}_2C$=O protons, and one triplet at δ 3.32 for the four protons of the two CH_2S-benzimidazole groups.

CONCLUSION

The synthesis and characterization of some novel long-chain 1,3-dipolar compounds, isoxazolines, and thio substituted benzimidazoles is described.

EXPERIMENTAL

All the reagents and solvents used were purchased from either Merck or Fluka Chemie and used without further purification. β-Phenylhydroxylamine and

2-mercaptobenzimidazole (**12**) were prepared according to the literature procedures.[17,18] Silica gel plates 60 F 254, Merck-1.05554 were used for thin layer chromatography (TLC). Column chromatography was performed using silica gel 60 (230–400 mesh). All moisture sensitive reactions were carried out under protection with $CaCl_2$. Air sensitive reactions were performed under N_2. Melting points were determined using a BÜCHI Melting Point B-540 apparatus in open capillary tubes and are uncorrected. IR spectra (KBr or neat, ν in cm^{-1}) were measured on a Nicolet FTIR 6700 spectrometer. ^1H NMR spectra (δ in ppm, J in Hz) were recorded on a Varian Mercury Plus spectrometer (400 MHz) in $CDCl_3$ using TMS as an internal standard. The elemental analyses were performed on a EuroEA 3000 CHNS analyzer.

***Supplemental Materials*:** IR data of all compounds can be found in "Supplemental Materials" files of the online version of this publication.

2-(Tetradecylthio)acetic Acid (3)[16]

In a 250 mL two-necked flask, KOH (7.8 g, 139 mmol) was dissolved in 100 mL of MeOH, and thioglycolic acid (**2**) (4.5 mL, 64.5 mmol) was dropped cautiously in over a 10-min period. Then, 1-bromotetradecane (**1**) (10 mL, 36.8 mmol) was dropped slowly into the reaction mixture with vigorous agitation. The observed slurry was stirred effectively under N_2 at room temperature (r.t.). for 1 day. The mixture was acidified with concentrated HCl, and H_2O was added. The precipitated white solid was filtered under vacuum and washed successively with H_2O. The crude product was dried at r.t. for 1 day and crystallized from 70% EtOH to afford 6.6 g (62%) of white crystalline **3**; mp 68–69 °C (lit.[16] 68 °C).

2-(Tetradecylthio)acetyl Chloride (4)

In a 50 mL two-necked flask fitted with a reflux condenser (protected by a $CaCl_2$ guard tube), **3** (2 g, 6.93 mmol) was dissolved in 15 mL of toluene. The flask was cooled to 0 °C in an ice bath, and oxalyl chloride (1.3 mL, 15.1 mmol) was added over a 30-min period. Then, the temperature was allowed to rise to r.t. and the mixture was stirred at this temperature for 1 h and for and additional 3 h at 70 °C. Thereafter, the solvent and the excess of oxalyl chloride were removed under vacuum. The residue was dissolved in 50 mL of petroleum ether and washed with 25 mL of ice-water. The organic phase was dried over anhydrous Na_2SO_4, the solvent was removed under vacuum and the brown–orange oily product (1.94 g, 91%) was obtained. The crude acyl chloride **4** was used in the next step without further purification.

4-Formylphenyl 2-(Tetradecylthio)acetate (5)

In a 50 mL two-necked flask fitted with a reflux condenser (protected by a $CaCl_2$ guard tube), 4-hydroxybenzaldehyde (0.77 g, 6.31 mmol) and NEt_3 (1 mL, 7.17 mmol, 1.1 equiv.) were successively dissolved in 20 mL CH_2Cl_2. The flask was cooled to 0 °C in an ice bath and acyl chloride **4** (1.94 g, 6.32 mmol) in 10 mL CH_2Cl_2 was added over a 30-min period. Then, the temperature was allowed to rise to r.t. and the mixture was stirred at this temperature for 2.5–3 h. After the aldehyde was consumed (checked by TLC), the organic phase was washed successively with 2 × 25 mL H_2O and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give a red–orange oily product which solidified upon standing. This was purified by column chromatography on silica gel (petroleum

ether-AcOEt) to afford **5** as a white crystalline solid. Yield (2.02 g, 82%); mp 49 °C; ^{1}H NMR: 0.88 (t, $J = 7.2$, 3H, C$\underline{H}_3$), 1.32–1.25 (m, 20 H, 10 C$\underline{H}_2$), 1.41 (quin, $J = 7.6$, 2 H, $CH_2C\underline{H}_2CH_2CH_2SCH_2$), 1.66 (quin, $J = 7.2$, 2 H, $CH_2C\underline{H}_2CH_2SCH_2$), 2.73 (t, $J = 7.6$ Hz, 2 H, $CH_2C\underline{H}_2SCH_2$), 3.45 (s, 2 H, $CH_2SC\underline{H}_2COO$), 7.31 (d, $J = 8.4$, 2 H, Ar-$\underline{H}$), 7.94 (d, $J = 9.2$, 2 H, Ar-$\underline{H}$), 10.01 (s, 1 H, C$\underline{H}$O). Anal. Calcd. for $C_{23}H_{36}O_3S$: C, 70.36; H, 9.24; O, 4.36; O, 12.23; S, 8.17. Found: C, 70.40; H, 9.23; O, 12.21; S, 8.16.

N-{4-[2-(Tetradecylthio)acetoxy]benzylidene}aniline Oxide (6)

In a 50 mL round-bottom flask aldehyde **5** (1.35 g, 3.44 mmol) and β-phenylhydroxylamine (0.37 g, 3.39 mmol) were dissolved in 4 mL EtOH. The flask was sealed and allowed to stand for 24 h in the dark. Thereafter, EtOH was evaporated cautiously under vacuum and the residue was purified by crystallization from MeOH to afford **6** as a white crystalline solid. Yield: 1.0 g, 61%; mp 92–95 °C; ^{1}H NMR: 0.88 (t, $J = 7.2$, 3 H, C$\underline{H}_3$), 1.32–1.26 (m, 20 H, 10 C$\underline{H}_2$), 1.42 (quin, $J = 8.0$, 2 H, $CH_2C\underline{H}_2CH_2CH_2SCH_2$), 1.67 (quin, $J = 7.6$, 2 H, $CH_2C\underline{H}_2CH_2SCH_2$), 2.74 (t, $J = 7.6$ Hz, 2 H, $CH_2C\underline{H}_2SCH_2$), 3.45 (s, 2 H, $CH_2SC\underline{H}_2COO$), 7.28–7.24 (m, 2 H, Ar-$\underline{H}$), 7.53–7.47 (m, 3 H, Ar-$\underline{H}$), 7.79–7.77 (m, 2 H, Ar-$\underline{H}$), 7.94 (s, 1H, ON=C$\underline{H}$), 8.47 (d, $J = 8.8$, 2 H, Ar-$\underline{H}$). Anal. Calcd. for $C_{29}H_{41}NO_3S$: C, 72.01; H, 8.54; N, 2.90; O, 9.92; S, 6.63. Found: C, 71.99; H, 8.50; N, 2.93; O, 9.97; S, 6.61.

11-Bromoundecanoyl Chloride (8)

In a 50 mL two-necked flask fitted with a reflux condenser (protected by a $CaCl_2$ guard tube) 11-bromoundecanoic acid (**7**) (9.78 g, 36.9 mmol) was dissolved in 20 mL of toluene. The flask was cooled to 0 °C in an ice bath and oxalyl chloride (6.3 mL, 73.4 mmol) was added over a 30-min period. Then, the temperature was allowed rise to r.t. and the mixture was stirred at this temperature for 1 h and for an additional 2 h at 70 °C. The residue was dissolved in 75 mL of petroleum ether and washed with 25 mL of ice-water. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to yield a yellowish oily product (9.52 g, 91%). The crude acyl chloride was used in the next step without further purification.

2-[2-(2-Methoxyethoxy)ethoxy]ethyl 11-Bromoundecanoate (9)

In a 100 mL two-necked flask fitted with a reflux condenser (protected by a $CaCl_2$ guard tube) triethylene glycol monomethyl ether (4.9 mL, 36.01 mmol) was dissolved in 20 mL CH_2Cl_2. The flask was cooled to 0 °C in an ice bath and **8** (8.9 g, 31.38 mmol) in 10 mL CH_2Cl_2 was added over a 30-min period. The temperature was allowed rise to r.t. and the mixture was stirred at this temperature for 3 h and additionally the flask was allowed to stand at 0–5 °C for 1 day. The reaction mixture was washed successively with 2×50 mL 10% $NaHCO_3$ and 50 mL of brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to yield a yellowish liquid product (12.05 g, 91%). The purity of the product was suitable for IR spectroscopy. IR: 2924, 2854, 1733, 1533, 1504, 1455, 1350, 1244, 1104, 1042, 949, 852, 732, 641.

2-{2-[2-(Methoxyethoxy)ethoxy]}ethyl 11-(4-Formylphenoxy)undecanoate (10)

In a 100 mL round-bottom flask ester **9** (7.6 g, 18.47 mmol), K_2CO_3 (2.56 g, 18.52 mmol) and NaI (0.3 g, 2 mmol) were dissolved in 50 mL of anhydrous acetone. The flask was heated in a water bath for 10–15 min under N_2, and 4-hydroxybenzaldehyde (2.26 g, 18.51 mmol) was added. The mixture was heated at 50–60 °C for 48 h under N_2. The salts were filtered under vacuum and the solids were washed with little acetone. The filtrate was concentrated under vacuum and the residue was dissolved in 50 mL CH_2Cl_2. Thereafter, the solution was dried over anhydrous Na_2SO_4 and the solvent was removed on a rotary evaporator. The obtained yellowish oily product was purified by column chromatography on silica gel (petroleum ether-AcOEt) to afford **10** as colorless liquid. Yield: 6.02 g, 72%; ^{1}H NMR: 1.34–1.29 (m, 10 H, 5 C$\underline{H}_2$), 1.46 (quin, $J = 7.6$, 2 H, ArOCH$_2$CH$_2$C$\underline{H}_2$CH$_2$CH$_2$), 1.61 (quin, $J = 7.2$, 2 H, CH$_2$C$\underline{H}_2$CH$_2$COO), 1.81 (quin, $J = 6.4$, 2 H, ArOCH$_2$C$\underline{H}_2$CH$_2$), 2.32 (t, $J = 7.2$, 2 H, C$\underline{H}_2$COO), 3.38 (s, 3 H, OC$\underline{H}_3$), 3.56–3.54 (m, 2 H, OCH$_2$C$\underline{H}_2$OCH$_3$), 3.71–3.63 (m, 8 H, C$\underline{H}_2$OC$\underline{H}_2$C$\underline{H}_2$OC$\underline{H}_2$), 4.03 (t, $J = 6.4$, 2 H, ArOC$\underline{H}_2$), 4.22 (t, $J = 5.2$, 2 H, COOC$\underline{H}_2$), 6.99 (d, $J = 8.4$, 2H, Ar-$\underline{H}$), 7.82 (d, $J = 8.8$, 2 H, Ar-$\underline{H}$), 9.87 (s, 1 H, C$\underline{H}$O). Anal. Calcd. for $C_{25}H_{40}O_7$: C, 66.35; H, 8.91; O, 24.75. Found: C, 66.41; H, 8.87; O, 24.72.

N-[4-(12-Oxo-2,5,8,11-tetraoxadocosan-22-yloxy)benzylidene]aniline Oxide (11)

In a 50 mL round-bottom flask **10** (0.64 g, 1.41 mmol) and β-phenylhydroxylamine (0.16 g, 1.47 mmol) were dissolved in 5 mL of EtOH. The flask was sealed and allowed to stand for 24 h in the dark. Thereafter, EtOH was evaporated cautiously under vacuum and the residue was purified by column chromatography on silica gel (petroleum ether-AcOEt) to afford **11** as a yellow solid. Yield: 0.45 g, 57%; mp 63–65 °C; ^{1}H NMR: 1.30 (m, 10 H, 5 C$\underline{H}_2$), 1.47 (quin, $J = 8.4$, 2 H, ArOCH$_2$CH$_2$C$\underline{H}_2$CH$_2$CH$_2$), 1.62 (quin, $J = 7.2$, 2 H, CH$_2$C$\underline{H}_2$CH$_2$COO), 1.82 (quin, $J = 7.2$, 2 H, ArOCH$_2$C$\underline{H}_2$CH$_2$), 2.33 (t, $J = 7.6$, 2 H, C$\underline{H}_2$COO), 3.38 (s, 3 H, OC$\underline{H}_3$), 3.56–3.54 (m, 2 H, OCH$_2$C$\underline{H}_2$OCH$_3$), 3.71–3.64 (m, 8 H, C$\underline{H}_2$OC$\underline{H}_2$C$\underline{H}_2$OC$\underline{H}_2$), 4.05 (t, $J = 6.4$, 2 H, ArOC$\underline{H}_2$), 4.22 (t, $J = 5.2$, 2 H, COOC$\underline{H}_2$), 7.00–6.98 (d, $J = 9.2$, 2 H, Ar-$\underline{H}$), 7.50–7.45 (m, 3 H, Ar-$\underline{H}$), 7.84–7.79 (m, 2 H, Ar-$\underline{H}$), 8.14 (s, 1 H, ON=C$\underline{H}$), 8.42–8.40 (d, $J = 8.8$, 2 H, Ar-$\underline{H}$). Anal. Calcd. for $C_{31}H_{45}NO_7$: C, 68.48; H, 8.34; N, 2.58; O, 20.60. Found: C, 68.54; H, 8.33; N, 2.52; O, 20.61.

2-[2-(2-Methoxyethoxy)ethoxy]ethyl 11-(1*H*-Benzo[d]imidazole-2-ylthio)undecanoate (13)

In a 50 mL round-bottom flask **9** (1.2 g, 2.92 mmol), K_2CO_3 (0.35 g, 2.53 mmol) and NaI (0.05 g, 0.3 mmol) were dissolved in 15 mL of anhydrous acetone. The flask was heated in a water bath for 10–15 min under N_2, and **12**[18] (0.4 g, 2.66 mmol) was added. The mixture was heated at 50–60 °C for 7 h and for an additional 1 day at r.t. under N_2. Acetone was removed under vacuum and the residue was dissolved in 25 mL $CHCl_3$. The organic phase was washed with 20 mL H_2O and the aqu. phase was extracted once with a small amount $CHCl_3$. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed on a rotary evaporator. The yellowish residue was purified by column chromatography on silica gel (petroleum ether-AcOEt-MeOH) to afford **13** as

a yellowish oily product. Yield: 1.26 g, 98%; ^{1}H NMR: 1.41–1.22 (m, 12 H, 6 C$\underline{H}_2$), 1.59 (quin, J = 7.2, 2 H, C$\underline{H}_2$CH$_2$C=O), 1.71 (quin, J = 7.2, 2 H, SCH$_2$C$\underline{H}_2$CH$_2$), 2.30 (t, J = 8, 2 H, C$\underline{H}_2$C=O), 3.37 (s, 3 H, OC$\underline{H}_3$), 3.42 (t, J = 5.2, 2 H, N$_2$CSC$\underline{H}_2$), 3.56–3.54 (m, 2 H, OCH$_2$C$\underline{H}_2$OCH$_3$), 3.70–3.64 (m, 8 H, C$\underline{H}_2$OC$\underline{H}_2$C$\underline{H}_2$OC$\underline{H}_2$), 4.22 (t, J = 5.2, 2 H, C$\underline{H}_2$OC=O), 7.28–7.23 (m, 2 H, Ar-$\underline{H}$), 7.63–7.58 (m, 2 H, Ar-$\underline{H}$). Anal. Calcd. for $C_{25}H_{40}N_2O_5S$: C, 62.47; H, 8.39; N, 5.83; O, 16.64; S, 6.67. Found: C, 62.51; H, 8.32; N, 5.85; O, 16.70; S, 6.62.

Undec-10-en-1-ol (15)

To an ice-cooled suspension of $LiAlH_4$ (2.5 g, 65.9 mmol) in 100 mL of THF, 10-undecenoic acid (**14**) (5 g, 27.1 mmol) in (50 mL) of THF was added dropwise over 30 min (protected by a $CaCl_2$ guard tube). Then, the mixture was stirred at 50 °C for 2 h and for another 1 day at r.t. After cooling in an ice bath, 50 mL of AcOEt and 200 mL H_2O were added cautiously. The mixture was acidified with 2M HCl and extracted with 3 × 50 mL of ether. The organic phase was washed successively with H_2O and brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The colorless residue was purified by column chromatography on silica gel (petroleum ether-AcOEt) to afford **15** as a colorless liquid. Yield: 4 g, 88%; ^{1}H NMR: 1.38–1.29 (m, 12 H, 6 C$\underline{H}_2$), 1.56 (quin, J = 6.4, 2 H, CH$_2$C$\underline{H}_2$CH$_2$OH), 1.70 (bs, 1 H, O$\underline{H}$), 2.07–2.01 (m, 2 H, CH$_2$=CHC$\underline{H}_2$), 3.64 (t, J = 7.2, 2 H, C$\underline{H}_2$OH), 5.02–4.91 (m, 2 H, C$\underline{H}_2$=CHCH$_2$), 5.86–5.76 (m, 1 H, CH$_2$=C$\underline{H}$CH$_2$). Anal. Calcd. for $C_{11}H_{22}O$: C, 77.58; H, 13.02; O, 9.40. Found: C, 77.64; H, 12.98; O, 9.38.

9-(3-Phenyl-4,5-dihydroisoxazol-5-yl)nonan-1-ol (17)

In a 50 mL two-necked flask fitted with a reflux condenser **15** (1 g, 5.87 mmol), 0.08 mL of NEt_3 and 7 mL solution of 6–14% NaOCl were mixed in 15 mL CH_2Cl_2. The flask was cooled to 1–2 °C, and benzaldoxime (0.76 g, 6.27 mmol) in 10 mL CH_2Cl_2 was dropped in over 30 min. The resulting two-phased mixture was stirred at 1–2 °C for 2 h and for an additional 3 h at r.t. The organic phase was separated and the aqu. phase was extracted with 3 × 10 mL CH_2Cl_2. The organic phases were combined and washed with 20 mL H_2O and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and a yellowish wax solid was obtained. The crude product was crystallized from MeOH and washed with cold petroleum ether to afford **17** as white leaf-like crystals. Yield: 1.5 g, 88%; mp 93–94 °C; ^{1}H NMR: 1.66–1.31 (m, 16 H, 8 C$\underline{H}_2$), 1.71 (bs, 1 H, O$\underline{H}$), 2.96 (dd, J_1 = 8.4, J_2 = 16.4, 1 H, C^{4}H), 3.39 (dd, J_1 = 10.4, J_2 = 16.4, 1 H, C^{4}H), 3.64–3.63 (m, 2 H, CH$_2$C$\underline{H}_2$OH), 4.77–4.69 (m, 1 H, C^{5}H), 7.41–7.38 (m, 3 H, Ar-$\underline{H}$), 7.69–7.65 (m, 2 H, Ar-$\underline{H}$),. Anal. Calcd. for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84; O, 11.06. Found: C, 74.76; H, 9.36; N, 4.85; O, 11.03.

9-(3-Phenyl-4,5-dihydroisoxazol-5-yl)nonanal (18)

In a 50 mL round-bottom flask isoxazoline **17** (0.37 g, 1.28 mmol) was dissolved in 30 mL CH_2Cl_2. Then, pyridinium chlorochromate (1.2 g, 5.57 mmol) and NaOAc (0.33 g, 4.02 mmol) were added. The resulting mixture was stirred at r.t. for 3 h and celite (2 g) was added. The suspension was filtered under vacuum and passed through a short silica gel packed column. The solvent was removed and the residue was purified by column

chromatography on silica gel (petroleum ether-AcOEt) to afford **18** as a white solid. Yield: 0.28 g, 76%; mp 66–68 °C; ^{1}H NMR: 1.82–1.32 (m, 14 H, 7 C$\underline{H}_2$), 2.45–2.40 (m, 2 H, C$\underline{H}_2$CHO), 2.97 (dd, $J_1 = 8.4$, $J_2 = 16.6$, 1 H, C^{4}H), 3.40 (dd, $J_1 = 10$, $J_2 = 16.4$, 1 H, C$^4\underline{H}$), 4.77–4.69 (m, 1 H, C^{5}H), 7.42–7.38 (m, 3 H, Ar-$\underline{H}$), 7.69–7.65 (m, 2 H, Ar-$\underline{H}$), 9.76 (t, $J = 2$, 1 H, C$\underline{H}$O). Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87; O, 11.13 Found: C, 75.23; H, 8.71; N, 4.91; O, 11.15.

9-(3-Phenyl-4,5-dihydroisoxazol-5-yl)nonyl 2-Chloroacetate (20)

In a 50 mL two-necked flask fitted with a reflux condenser (protected by a $CaCl_2$ guard tube), isoxazoline **17** (0.4 g, 1.38 mmol) and NEt_3 (0.2 mL, 1.44 mmol, 1 equiv.) were dissolved in 15 mL CH_2Cl_2 and cooled to 0 °C. Chloroacetyl chloride (0.11 mL, 1.42 mmol) in 5 mL CH_2Cl_2 was added dropwise over 15 min. The resulting mixture was stirred at 10–15 °C for 2 h. After the consumption of the isoxazoline (checked by TLC), the reaction mixture was washed successively with 2 × 15 mL of 5% Na_2CO_3 and 15 mL H_2O. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed on a rotary evaporator. A white wax solid product (0.5 g, 99%) was obtained. The crude chloroacetylated isoxazoline **20** was used in the next step without further purification.

9-(3-Phenyl-4,5-dihydroisoxazol-5-yl)nonyl 2-(1*H*-benzo[d]imidazol-2-ylthio)acetate (21)

In a 50 mL round-bottom flask, **20** (0.5 g, 1.37 mmol), K_2CO_3 (0.3 g, 2.17 mmol), and NaI (0.02 g, 0.13 mmol) were dissolved in 15 mL of anhydrous acetone. The flask was heated in water bath for 10–15 min under N_2 and **12** (0.21 g, 1.40 mmol) was added. Thereafter, the mixture was heated at 50–60 °C for 2 h. CH_2Cl_2 (10 mL) was added to the red–brown solution and the resulting salts were filtered. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (petroleum ether-CH_2Cl_2) to afford **21** as a yellowish–orange solid. Yield: 0.5 g, 76%; mp 101–102 °C; ^{1}H NMR: 1.35–1.28 (m, 10 H, 5C$\underline{H}_2$), 1.69–1.58 (m, 4 H, 2C$\underline{H}_2$), 2.97 (dd, $J_1 = 8.4$, $J_2 = 16.8$, 1 H, C^{4}H), 3.40 (dd, $J_1 = 10$, $J_2 = 16.4$, 1 H, C^{4}H), 3.95 (s, 2H, –SC$\underline{H}_2$COO–), 4.20 (t, $J = 6.8$ Hz, 2H, –COOC$\underline{H}_2$–), 4.78–4.70 (m, 1H, C^{5}H), 7.22 (sext, $J = 3.2$, 2 H, Ar-$\underline{H}$), 7.41–7.39 (m, 4 H, Ar-$\underline{H}$), 7.68–7.66 (m, 3 H, Ar-$\underline{H}$). Anal. Calcd. for $C_{27}H_{33}N_3O_3S$: C, 67.61; H, 6.93; N, 8.76; O, 10.01; S, 6.69. Found: C, 67.68; H, 6.90; N, 8.70; O, 9.97; S, 6.75.

2-(Dodecylthio)acetic Acid (22)

This compound was prepared according to procedure given for compound **3**. The crude product was dried at r.t. for 1 day and crystallized from 70% EtOH to afford **22** with 62% yield as a white crystalline compound; mp 57–59 °C (lit.[21] 61–62 °C).

2-(Dodecylthio)acetyl Chloride (23)

This compound was prepared according to procedure given for compound **4**. The solvent was removed under vacuum and a yellowish oily product was obtained (91% yield). The crude acyl chloride **23** was used in the next step without further purification.

2-(Dodecylthio)-*N*,*N*-bis(2-hydroxyethyl)acetamide (24)

This compound was synthesized according to procedure given by Kim et al.[20] from (3.64 g, 13.05 mmol) of **23**. After crystallization from 30 mL of petroleum ether/acetone (5/1), **24** was obtained as a colorless white product (yield: 3.85 g, 85%); mp 51–52.5 °C; ^{1}H NMR: 0.88 (t, $J = 7.2$, 3 H, CH_3), 1.38–1.26 (m, 18 H, 9 CH_2), 1.61 (quin, $J = 7.6$, $CH_2CH_2SCH_2C{=}O$), 2.64 (t, $J = 7.6$, 2 H, $CH_2SCH_2C{=}O$), 3.31 (bs, 2 H, 2 OH), 3.41 (s, 2 H, $CH_2SCH_2C{=}O$), 3.57 (q, $J = 4.8$, 4 H, 2 CH_2CH_2OH), 3.85 (dt, $J_1 = 20.4$, $J_2 = 5.2$, 4 H, 2 CH_2CH_2OH),. Anal. Calcd. for $C_{18}H_{37}NO_3S$: C, 62.20; H, 10.73; N, 4.03; O, 13.81; S, 9.23. Found: C, 62.24; H, 10.71; N, 3.96; O, 13.84; S, 9.25.

{[2-(Dodecylthio)acetyl]azanediyl}bis(ethane-2,1-diyl) bis(11-bromoundecanoate) (25)

In a 50 mL two-necked flask fitted with a reflux condenser (protected by a $CaCl_2$ guard tube), amide **24** (1.02 g, 2.93 mmol) and NEt3 (0.85 mL) were dissolved in 15 mL CH_2Cl_2 and cooled to 0 °C. 11-Bromoundecanoyl chloride (**8**) (1.68 g, 5.92 mmol) in 10 mL CH_2Cl_2 was added dropwise over 30 min. The mixture was stirred at r.t. for one night. The reaction mixture was washed successively with H_2O, dried over anhydrous Na_2SO_4 and the solvent was removed on a rotary evaporator. The residue was purified by column chromatography on silica gel (petroleum ether-AcOEt) to afford **25** as a white waxy solid. Yield: 1.55 g, 61%; ^{1}H NMR: 0.88 (t, $J = 7.6$, 3 H, CH_3), 1.44–1.26 (m, 42 H, 9 CH_2 and 12 CH_2), 1.60 (quin, $J = 7.2$, 6 H, $CH_2CH_2SCH_2C{=}O$ and $OC{=}OCH_2CH_2$), 1.85 (quin, $J = 7.6$, 4 H, 2 $CH_2CH_2CH_2Br$), 2.33–2.28 (m, 4 H, $OC{=}OCH_2CH_2$), 2.62 (t, $J = 7.6$, 2 H, $CH_2CH_2SCH_2C{=}O$), 3.35 (s, 2 H, $CH_2SCH_2C{=}O$), 3.41 (t, $J = 6.8$, 4 H, 2 CH_2Br), 3.65 (dt, $J_1 = 31.2$, $J_2 = 5.6$, 4 H, $N(CH_2CH_2)_2$), 4.23 (t, $J = 5.6$, 4 H, 2 $CH_2OC{=}O$). Anal. Calcd. for $C_{40}H_{75}Br_2NO_5S$: C, 57.06; H, 8.98; N, 1.66; S, 3.81. Found: C, 57.01; H, 9.00; N, 1.68; S, 3.84.

{[2-(Dodecylthio)acetyl]azanediyl}bis(ethane-2,1-diyl) bis-11-(benzimidazole-2-ylthio)undecanoate (26)

In a 50 mL round-bottom flask under N_2 atmosphere, 2-mercaptobenzimidazole (**12**) (0.54 g, 3.56 mmol) and K_2CO_3 (1 g, 7.24 mmol) were dissolved in 30 mL of anhydrous acetone and heated in a water bath for 15 min. Thereafter, NaI (0.03 g, 0.2 mmol) and 1.5 g, 1.78 mmol of amide **25** were added to the flask and heated for 20 h. The warm solution was filtered and the solvent was removed under vacuum. H_2O, EtOH, and a small amount of AcOEt were added to the oily residue. After storage at r.t. for a period of time, the precipitated white solid was filtered and dried at r.t. It was crystallized from EtOH to yield **26** (1.3 g, 74%); mp 75 °C; ^{1}H NMR: 0.88 (t, $J = 7.2$, 3 H, CH_3), 1.41–1.24 (m, 42 H, 9 CH_2 and 12 CH_2), 1.59 (quin, $J = 7.2$, 6 H, $CH_2CH_2SCH_2C{=}O$ and $OC{=}OCH_2CH_2$), 1.74 (quin, $J = 7.6$, 4 H, 2 CH_2CH_2S-benzimidazole), 2.33–2.28 (m, 4 H, $OC{=}OCH_2CH_2$), 2.62 (t, $J = 7.6$, 2 H, $CH_2CH_2SCH_2C{=}O$), 3.32 (t, $J = 7.2$, 4 H, 2 CH_2S-benzimidazole), 3.37 (s, 2 H, $CH_2SCH_2C{=}O$), 3.67 (dt, $J_1 = 23.2$, $J_2 = 5.6$, 4 H, $N(CH_2CH_2)_2$), 4.25 (t, $J = 5.2$, 4 H, 2 $CH_2OC{=}O$), 7.33 (d, $J = 7.6$, 4 H, Ar-H), 7.67 (d, $J = 6.8$, 4 H, Ar-H), 10.37 (d, $J = 14$, 2 H, NH). Anal. Calcd. for $C_{54}H_{87}N_5O_5S_3$: C, 66.01; H, 8.93; N, 7.13; S, 9.79. Found: C, 65.98; H, 8.95; N, 7.14; S, 9.75.

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