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Solution- and Solid-Phase Synthesis of Components for Tethered Bilayer Membranes

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The synthesis of the novel compound $PhCH_2SS(C_{24}H_{44}N_4O_{10})(C_{20}H_{41})$ (**5**) for the preparation of tethered bilayer membranes is described. The compound is the all-amide analogue of the previously reported ester-containing membrane-forming material $PhCH_2SS(C_{24}H_{40}O_{14})(C_{20}H_{41})$ (**1**). The advanced intermediate $(C_{20}H_{41})\ C_{16}H_{28}N_3O_8$ (**17**) was prepared from the same starting materials using both solution-phase (13% yield) and solid-phase (81% yield) techniques. Monolayers on gold derived from **5** have been analyzed by ellipsometry and FTIR. The monolayers exhibit thicknesses similar to monolayers derived from **1** and possess H-bonded amide functionality.

Introduction

The formation of self-assembled monolayers (SAMs) through the chemisorption of organosulfur species to gold surfaces is now well-known.[1] A variety of sulfur moieties (e.g., thiols, disulfides, thioethers, thiophenols, thiophenes, thiocarbamates)[2] have been shown to adsorb to gold, and through such interactions varied classes of sulfur-containing organic compounds, ranging from unsubstituted alkyl chains to complex organic molecules (such as porphyrins,[3] cavitands,[4] and cyclodextrins[5]), have been immobilized onto gold surfaces. The adsorption of sulfur-containing species and the formation of SAMs occurs rapidly upon exposure of a clean gold surface to a dilute solution (nM → μM) of the organosulfur compound.[6] The SAMs formed through this simple procedure are generally stable to a variety of conditions including atmospheric and aqueous environments,[7] while polymeric SAMs have demonstrated remarkable stability at elevated temperatures and to corrosive environments.[8] The wide variety of materials which can be adsorbed to gold, the relatively straightforward preparation of SAMs and their robustness in many environments have stimulated numerous publications exploring the use of SAMs for various technological applications including surface protection,[9] lithographic patterning,[10] molecular recognition,[11] photoresponsive structures,[12] and biosensing.[13]

SAMs have also found use in the construction of synthetic bilayer membranes where the SAM constitutes the inner leaflet of the bilayer membrane.[14] Such systems, known as tethered bilayer membranes (t-BLMs), have great potential as stable and robust cellular membrane mimetics into which membrane proteins can be inserted.[15] Particularly useful classes of compounds

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(1) Dubois, L. H.; Nuzzo, R. G. *Annu. Rev. Phys. Chem.* **1992**, *43*, 437.

(2) Ulman, A. *Chem. Rev.* **1996**, *96*, 1533.

(3) Gryko, D. T.; Clausen, C.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 8635, and references therein.

(4) Thoden van Velzen, E. U.; Engbersen, J. F. J.; de Lange, P. J.; Mahy, J. W. G.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 6853.

(5) Rojas, M. T.; Königer, R.; Stoddart, J. F.; Kaifer, A. E. *J. Am. Chem. Soc.* **1995**, *117*, 336.

(6) Poirier, G. E.; Pylant, E. D. *Science* **1996**, *272*, 1145, and references therein.

(7) Schlenoff, J. B.; Li, M.; Ly, H. *J. Am. Chem. Soc.* **1995**, *117*, 12528.

(8) Kim, T.; Chan, K. C.; Crooks, R. M. *J. Am. Chem. Soc.* **1997**, *119*, 189.

(9) Laibinis, P. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1992**, *114*, 9022.

(10) (a) Lewis, M.; Tarlow, M.; Carron, K. *J. Am. Chem. Soc.* **1995**, *117*, 9574. (b) Kumar, A.; Abbott, N. L.; Kim, E.; Biebuyck, H. A.; Whitesides, G. M. *Acc. Chem. Res.* **1995**, *28*, 219.

(11) (a) Thoden van Velzen, E. U.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 3597. (b) Rubinstein, I.; Steinberg, S.; Tor, Y.; Shanzer, A.; Sagiv, J. *Nature* **1998**, *332*, 426.

(12) (a) Willner, I.; Rubin, S.; Riklin, A. *J. Am. Chem. Soc.* **1991**, *113*, 3321. (b) Zahavy, E.; Rubin, S.; Willner, I. *J. Chem. Soc., Chem. Commun.* **1993**, 1753. (c) Willner, I.; Rubin, S.; Cohen, Y. *J. Am. Chem. Soc.* **1993**, *115*, 4937.

(13) (a) Lopez, G. P.; Biebuyck, H. A.; Harter, R.; Kumar, A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 10774. (b) Bhatia, S. K.; Teixeira, J. L.; Anderson, M.; Shriverlake, L. C.; Calvert, J. M.; Georger, J. H.; Hickman, J. J.; Dulcey, C. S.; Schoen, P. E.; Ligler, F. S. *Anal. Biochem.* **1993**, *208*, 197. (c) Spinke, J.; Liley, M.; Guder, H.-J.; Angermaier, L.; Knoll, W. *Langmuir* **1993**, *9*, 1821.

(14) (a) Raguse, B.; Braach-Maksvytis, V.; Cornell, B. A.; King, L. G.; Osman, P. D. J.; Pace, R. J.; Wieczorek, L. *Langmuir* **1998**, *14*, 648. (b) Heyse, S.; Ernst, O. P.; Dienes, Z.; Hofmann, K. P.; Vogel, H. *Biochemistry* **1998**, *37*, 507. (c) Gizeli, E.; Liley, M.; Lowe, C. R.; Vogel, H. *Anal. Chem.* **1997**, *69*, 4808. (d) Charych, D.; Cheng, Q.; Reichert, A.; Kuziemko, G.; Stroh, M.; Nagy, J. O.; Spevak, W.; Stevens, R. C. *Chem. Biol.* **1996**, *3*, 113. (e) Lang, H.; Duschl, C.; Vogel, H. *Langmuir* **1994**, *10*, 197. (f) Plant, A. L.; Gueguetchgeri, M.; Yap, W. *Biophys. J.* **1994**, *67*, 1126.

(15) (a) Naumann, R.; Schmidt, E. K.; Jonczyk, A.; Fendler, K.; Kadenbach, B.; Liebermann, T.; Offenhäusser, A.; Knoll, W. *Biosens. Bioelec.* **1999**, *14*, 651. (b) Stora, T.; Lakey, J. H.; Vogel, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 389. (c) Cornell, B. A.; Braach-Maksvytis, V. L. B.; King, L. G.; Osman, P. D. J.; Raguse, B.; Wieczorek, L.; Pace, R. J. *Nature* **1997**, *387*, 580. (d). Plant, A. L.; Gueguetchkeri, M.; Yap, W. *Biophys. J.* **1994**, *67*, 1126.

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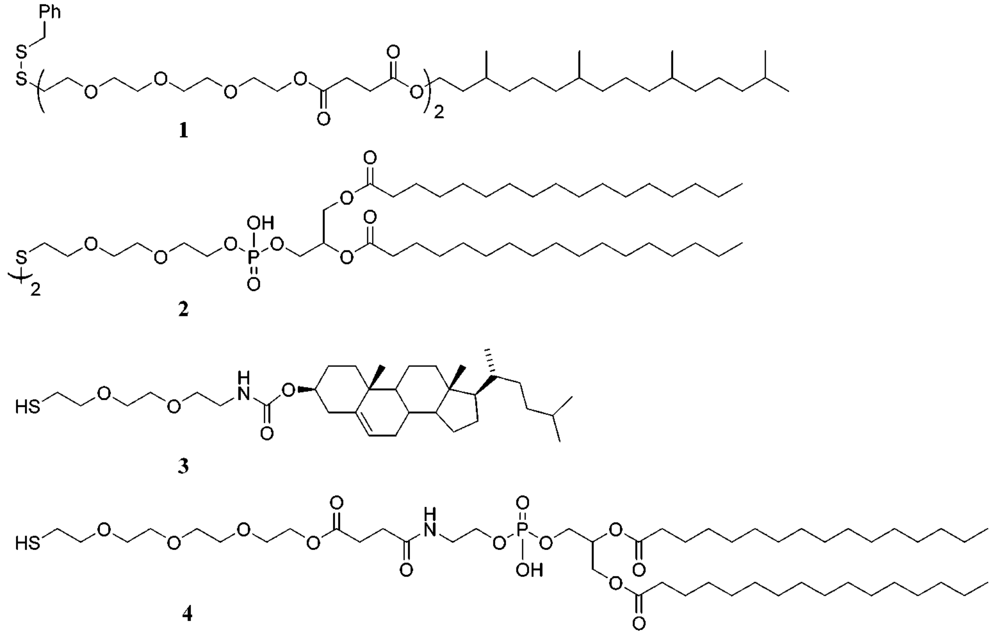
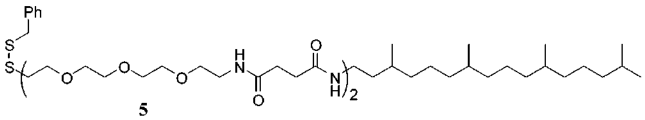


Figure 1. Representative examples of compounds used in the preparation of t-BLM's.

which form t-BLMs possess hydrophilic functionality between the sulfur anchoring moiety and the membrane-forming hydrocarbon, e.g., **1**,[14a] **2**,[14e] **3**,[16] **4**[17] (Figure 1), thus allowing for the formation of an ultrathin aqueous compartment between the gold surface and the membrane. This aqueous compartment can act as a reservoir into which ions can flow, thereby permitting the study of ion channel function in the synthetic bilayer membrane.[15]

We have recently reported that the bacterial ion channel gramicidin A can be inserted into such a t-BLM, and that the conduction of ions through the channel dimers can be monitored by impedance spectroscopy.[15c,18] This system has been employed as a highly sensitive sensing device by using the binding of an analyte (such as the biologically important species ferritin, TSH, digoxin, and thyroxin) to affect conductivity across the bilayer membrane. Thus, antibodies to the analyte of interest are attached to the membrane surface, and analyte binding either leads to disruption, or allows the formation, of conductive gramicidin dimers. A molecular binding event (e.g., antigen to antibody; receptor to ligand) is thereby detected in real time as a change in the electrical conductivity across the membrane.

The principal material of the inner leaflet of the t-BLM reported by our group is the compound **1** which consists of a polyether component (derived from two tetraethylene glycol units linked via a succinate bridge) attached to a phytanyl chain. As part of ongoing studies examining the effect of molecular changes on biosensor function,[19] the length of the hydrophilic component has been shown to correlate with the conductivity of the t-BLM, with longer linkers leading to greater membrane conductivity presumably as a result of an increased capacity for ions.[14a] In this work we report the preparation of **5** which is a tetraamide analogue of **1** possessing the same atom-count length. Compound **5** possesses a more polar hydrophilic tether compared to **1** as well as being more resistant to hydrolytic cleavage. Furthermore, compound **5** should also improve overall membrane stability through the formation of an intermolecular network of hydrogen bonds which has been shown in SAMs to increase monolayer stability.[20] The synthesis of compound **5** was achieved by conventional solution-phase synthesis and also through the use of solid-phase techniques. We also report preliminary surface analysis of SAMs formed from this compound.



5

Results and Discussion

Solution-Phase Approach. The synthetic route to **5** began with the formation of phytanylamine (**6**) followed by stepwise introduction of the required hydrophilic functionality, with final introduction of the unsymmetrical disulfide moiety. The presence of the C20 phytanyl chain aided in handling the intermediate materials, particularly rendering them soluble in organic

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(16) Boden, N.; Bushby, R. J.; Clarkson, S.; Evans, S. D.; Knowles, P. F.; Marsh, A. *Tetrahedron* **1997**, *53*, 10939.

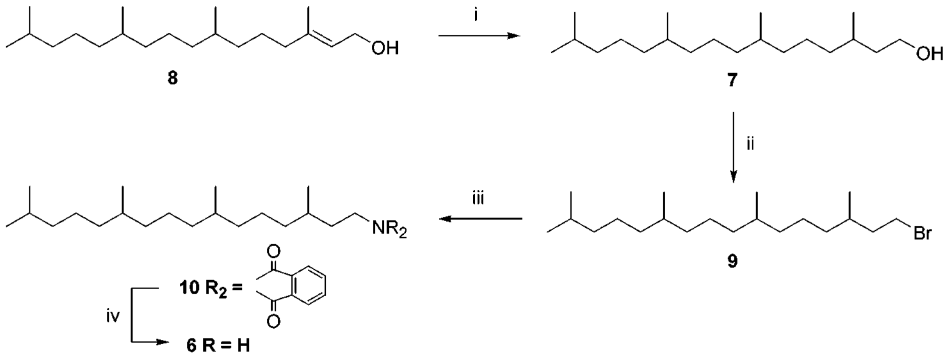
(17) Steinem, C.; Janshoff, A.; von dem Bruch, K.; Reihs, K.; Goossens, J.; Galla, H.-J. *Bioelectrochem. Bioenerg.* **1998**, *45*, 17.

(18) (a) Burns, C. J.; Braach-Maksvytis, V. L. B.; King, L. G.; Osman, P. D. J.; Pace, R. J.; Raguse, B.; Wieczorek, L.; Cornell, B. A. *Proceedings of SPIE* **1999**, *3858*, 17. (b) Pace, R. J.; Braach-Maksvytis, V. L. B.; King, L. G.; Osman, P. D. J.; Raguse, B.; Wieczorek, L.; Cornell, B. A. *Proceedings of SPIE* **1998**, *3270*, 50. (c) Cornell, B. A.; Braach-Maksvytis, V. L. B.; King, L. G.; Osman, P. D. J.; Raguse, B.; Wieczorek, L.; Pace, R. J. The Gramicidin-based biosensor: a functioning nano-machine. In *Gramicidin and Related Ion Channel Forming Peptides*; Chadwick, D. J., Cardew, G., Eds.; Wiley: London, 1999; p 231. (d) Woodhouse, G. E.; King, L. G.; Wieczorek, L.; Cornell, B. A. *Faraday Discuss.* **1998**, *111*, 247. (e) Woodhouse, G. E.; King, L. G.; Wieczorek, L.; Osman. P. D. J.; Cornell, B. A. *J. Mol. Recog.* **1999**, *12*, 1.

(19) Burns, C. J.; Culshaw, P.; Field, L. D.; Islam, M.; Morgan, J.; Raguse, B.; Ridley, D. D.; Wieczorek, L.; Wilkinson, M.; Vignevich, V. *Aust. J. Chem.* **1999**, *52*, 1071.

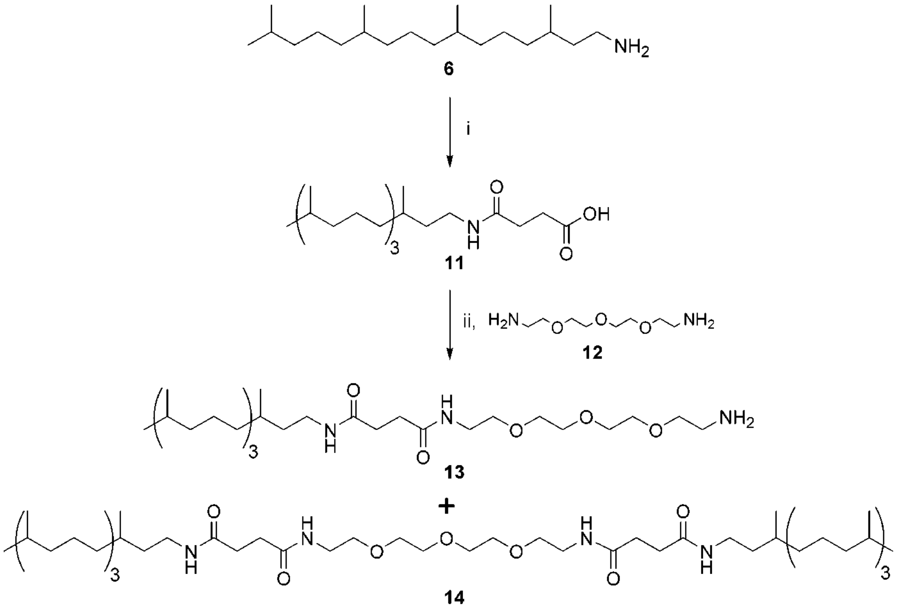
(20) (a) Clegg, R. S.; Reed, S. M.; Hutchison, J. E. *J. Am. Chem. Soc.* **1998**, *120*, 2486. (b) Tam-Chang, S.-K.; Biebuyck, H. A.; Whitesides, G. M.; Jeon, N.; Nuzzo, R. G. *Langmuir* **1995**, *11*, 4371.

Scheme 1[a]



[a] i. H_2, RaNi, EtOH. ii. HBr, H_2SO_4, H_2O. iii. Potassium phthalimide, DMF. iv. $H_2NNH_2{\cdot}H_2O$, EtOH.

Scheme 2[a]



[a] i. Succinic anhydride, pyridine. ii. DCC, DMAP, CH_2Cl_2.

solvents and amenable to conventional chromatographic purification.

Hydrogenation of phytol (**8**) over Raney nickel[21] furnished phytanol (**7**),[22] which was subsequently exposed to HBr in water[23] to give phytanyl bromide **9**. Reaction with potassium phthalimide in DMF furnished the phthalimide **10**, which was converted to the primary amine **6** upon exposure to hydrazine hydrate in ethanol. The conversion of **8** to **6** (Scheme 1) was accomplished in 76% yield.

Phytanylamine (**6**) was reacted with excess succinic anhydride in pyridine to generate the hemisuccinamide **11** (Scheme 2). The reaction proceeded smoothly and in near quantitative yield; however, isolation of the product, and separation from excess succinic anhydride (and succinic acid formed in workup), required repeated chromatography. The coupling of **11** with diamine **12**,[24] using DCC and DMAP, was attempted in the presence of excess amine to generate the monofunctionalized amino derivative **13**; however, the bis-substituted product **14** was formed almost exclusively. The use of alternative coupling agents (e.g., 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-*p*-toluenesulfonate (morpho-CDI)) had little impact on the product ratios which presumably is a result of greater solubility of **13** over **12** in the reaction medium; however, alternative solvents (CH_2Cl_2 and DMF) had minimal effect on the product ratio. Isolation of a pure sample of **13** was further complicated through difficulty in removing the urea byproduct (derived from the coupling agent employed) by a variety of chromatographic procedures.

To improve the yield of **13**, monoprotection of the diamine **12** was examined (Scheme 3). Thus, following an analogous procedure for the monoprotection of tris-(ethylene glycol)-1,8-diamine,[25] excess diamine **12** was

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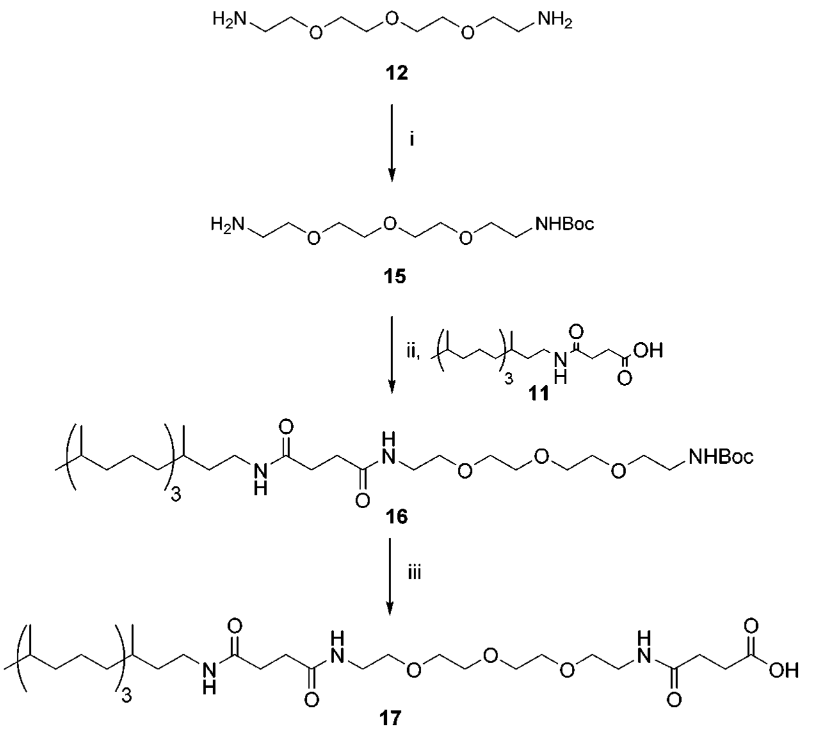
(21) Jellum, E.; Eldjarn, L.; Try, K. *Acta Chem. Scand.* **1966**, *20*, 2535.

(22) All materials prepared in this work are derived from phytanol synthesised by this method. Phytol is commercially available as a 66:34 mixture of *E*:Z isomers, with the stereochemistry at C7 and C11 fixed (both *R*). Hydrogenation of phytol under the conditions stated generates a mixture of diastereoisomers which in our hands is inseparable by conventional chromatography. For routes to chirally pure phytanol see Burns, C. J.; Field, L. D.; Hashimoto, K.; Petteys, B. J.; Ridley, D. D.; Rose, M. *Aust. J. Chem.* **1999**, *52*, 387 and references therein.

(23) Joo, C. N.; Shier, T.; Kates, M. *J. Lipid Res.* **1968**, *9*, 782

(24) Dietrich, B.; Lehn, J. M.; Sauvage, J. P.; Blanzat, J. *Tetrahedron* **1973**, *29*, 1629.

Scheme 3[a]



[a] i. BOC−ON, NEt_3, H_2O, dioxane. ii. DCC, DMAP, CH_2Cl_2. iii. TFA; CH_2Cl_2; succinic anhydride, pyridine.

reacted with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON) to give the monoprotected diamine **15**. This reaction proceeded in low yield (26% based on diamine), and the product could only be isolated after repeated extractions with dichloromethane. The monoamine **15** was coupled with the hemisuccinamide **11** using DCC and DMAP, to afford the BOC-protected amine derivative **16** in 71% yield. The BOC group was removed by treatment with TFA and the liberated amine converted to the corresponding hemisuccinamide **17**, using identical procedures to that reported above, furnishing **17** in 80% yield from **16**.

With the hemisuccinamide **17** in hand, attention turned to the synthesis of the unsymmetrical disulfide **18**, starting from the known disulfide alcohol **19**.[14a] As an unsymmetrical disulfide, this material is susceptible to disproportionation at elevated temperatures and also under basic conditions,[26] and so conversion of **19** to the amine was potentially problematic. Reaction of **19** with phthalimide under Mitsunobu reaction conditions[27] generated the phthalimide derivative **20** in good yield (66%) (Scheme 4). Attempted removal of the phthalimide function by reaction of **20** with hydrazine hydrate led to the formation of multiple products (as assessed by TLC analysis); however, exposure of **20** to an excess of ethanolic methylamine[28] at room temperature generated the primary amine **18** in fair yield (26%). The primary amine **18** was unstable on storage, presumably due to the presence of the basic amino moiety, and hence the crude product obtained upon evaporation of excess methylamine and ethanol was used immediately after brief passage through silica. The final condensation of amine **18** and succinate **17** was performed using morpho-CDI as coupling agent. The final product was purified by chromatography as a low melting solid with analytically pure material being obtained by reverse phase HPLC.

Solid-Phase Approach. In view of the difficulties met in the synthesis and handling of the materials generated in the preparation of **5**, the synthesis of these compounds on a solid support was investigated. An additional advantage in employing solid-phase techniques is that it is well-known that α,ω-diamines react with a solid-supported substrate at only one terminus, thereby circumventing the necessity for monoprotection of the diamine **12**.[29]

The total synthesis of **5** on solid phase was initially examined starting from commercially available thiol resin; however, we opted not to persevere with this route due to the expense of the resin and its apparent degradation on storage. As an alternative, the synthesis of the advanced intermediate, the hemisuccinamide **17**, on Wang resin was explored (Scheme 5). There are several literature reports of attachment of succinate functionality to Wang Resin as well as methods for detachment of succinate derivatives from a polymer support.[30] Wang Resin was functionalized as the hemisuccinate according to the literature procedure by reaction with succinic anhydride in pyridine at 80 °C for 24 h. Reaction of the free carboxylic acid residue of the hemisuccinate **22** with excess diamine **12** was effected using bromo-tris-pyrrolidino-phosphonium hexafluoprophosphate (PyBroP) as the coupling agent.[31] Alternative coupling agents including DCC or morpho-CDI did not give a clean product as

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[25] Sigal, G. B.; Mammen, M.; Dahmann, G.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 3789.

[26] Koval, I. V. *Russ. Chem. Rev.* **1994**, *63*, 735.

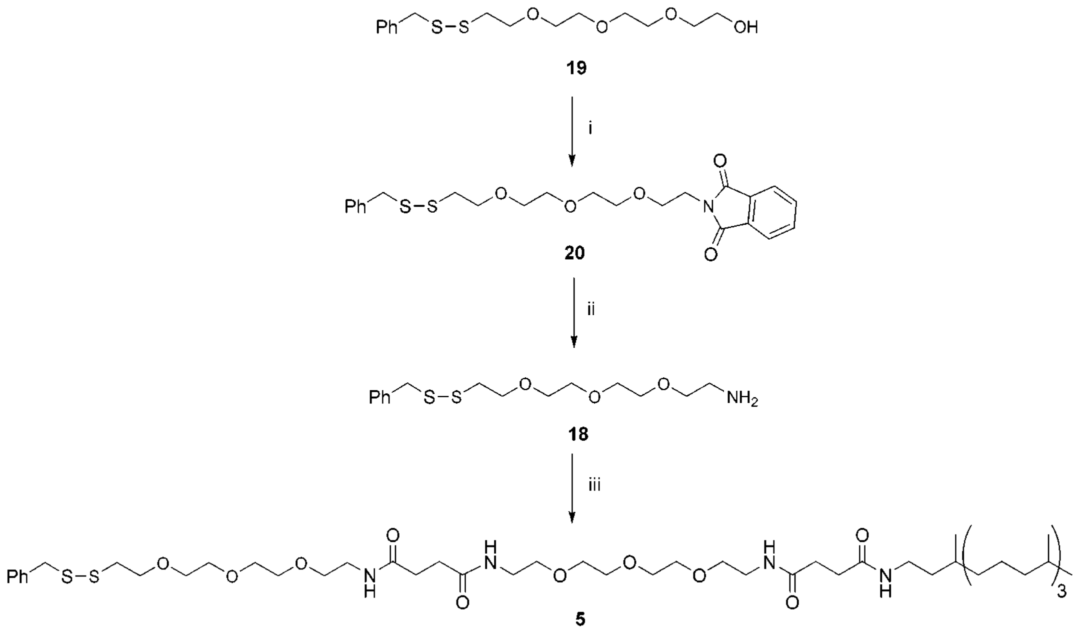
[27] Mitsunobu, O. *Synthesis* **1981**, 1.

[28] Motawia, M. S.; Wengel, J.; Abdel-Megid, A. E. S.; Pedersen, E. B.; *Synthesis* **1989**, 384.

[29] See for example, Swali, V.; Wells, N. J.; Langley, G. J.; Bradley, M. *J. Org. Chem.* **1997**, *62*, 4902.

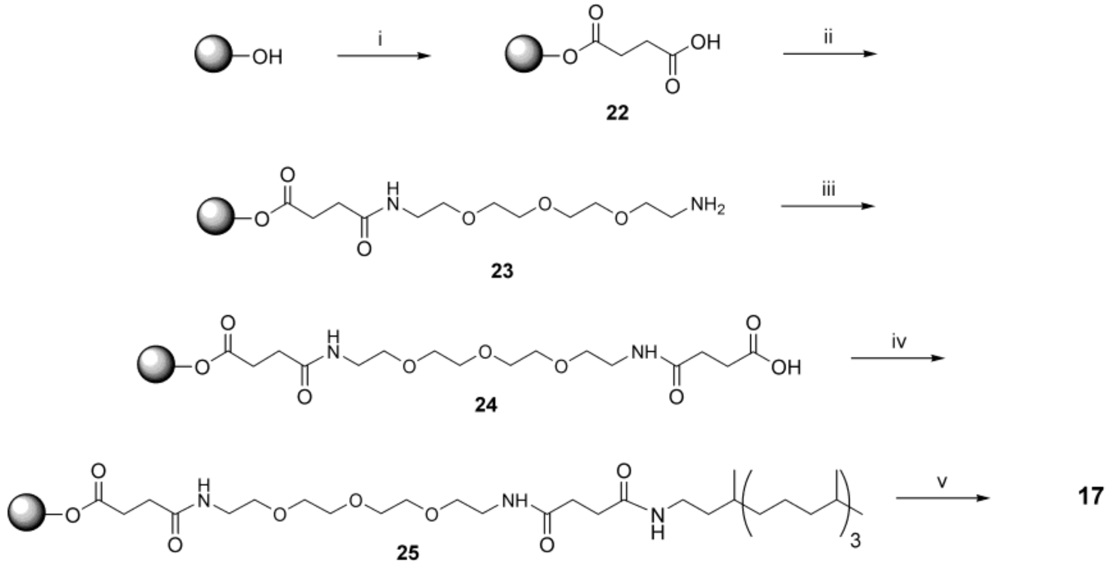
[30] (a) Apsimon, J. W.; Dixit, D. M. *Synth. Commun.* **1982**, *12*, 113. (b) Strocker, A. M.; Keating, T. A.; Tempest, P. A.; Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1149.

Scheme 4[a]



[a] i. Phthalimide, DEAD, PPh_3, THF. ii. $MeNH_2$, EtOH. iii. **17**, Morpho-CDI, DMAP, CH_2Cl_2.

Scheme 5[a]



[a] i. Succinic anhydride, pyridine. ii. **12**, PyBroP, DMAP, DMF. iii. Succinic anhydride, pyridine, DMF. iv. **6**, PyBroP, DMAP, DMF. v. TFA, CH_2Cl_2.

monitored by IR spectroscopy, with a number of peaks in the carbonyl region apparent. Further succinate functionality was introduced by reaction of the resin-bound amine **23** with succinic anhydride in pyridine to give the bound acid **24**. Coupling of the acid **24** with phytanylamine **6** was performed using PyBroP in DMF, and the resulting polymer-bound product **25** exhibited a broad amide stretch at 1660 cm^{-1} in the IR spectrum. The required material was cleaved from the resin with TFA at room temperature over 1 h, following conditions reported in the literature for similar reactions.[30] The material cleaved from the resin was identical in all respects to the hemisuccinamide **17** prepared via solution-phase techniques. Assuming a resin loading of 0.47 mmol/g, based on the manufacturer's specifications, **17** was obtained in 81% overall yield.

Surface Analysis. Monolayers formed from **5** by immersion of a freshly prepared gold surface in a dilute (1 mM) ethanolic solution of **5** for 1 h were examined by ellipsometry and FTIR and the results obtained compared with data for monolayers formed from **1** under identical conditions.

The ellipsometric film thickness of the monolayer formed from **5** is measured as 25 (±2) Å which is similar (within experimental error) to the thickness of monolayers of **1** (28 (±2) Å[19]). Further, FTIR spectra of monolayers formed from **1** and **5** both show a strong band at 1120 cm^{-1}, assigned as an ether (C−O) stretch. In addition,

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(31) Frerot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259.

the spectrum for the monolayer derived from **5** exhibits three bands at 1660, 1550, and 1262 cm^{-1} assigned as an amide I band (predominantly C═O stretch), an amide II band (NH and OCN vibration), and an amide III band (CN stretch), respectively. The position of these amide bands is fully consistent with a hydrogen-bonded trans secondary amide.[20b,32] By contrast, the monolayer derived from **1** exhibits a single carbonyl peak at 1740 cm^{-1} in the FTIR spectrum, consistent with an ester (C═O) stretch.

Conclusion

Tethered bilayer membrane systems have great potential in biotechnological applications such as biosensing and drug discovery;[33] however, the synthesis of new molecular components to further study and develop these systems is challenging. In particular, those components that lead to the formation of t-BLM's possessing an aqueous reservoir between the gold surface and the membrane present a significant synthetic challenge due to the size of the compounds, the hydrophilicity of the tether and the hydrophobicity of the membrane-forming section. Combined, these structural features lead to compounds that are difficult to isolate, handle, and purify.

While we,[14a,15c,19] and others,[14e,16,17] have synthesized these materials by conventional solution-phase techniques, solid-phase techniques have not been employed in the preparation of such compounds, despite the suitability of the methodology to this class of materials. Other groups have employed solid-phase techniques in the synthesis of structurally similar molecules though for different uses—the synthesis of hydrophilic linkers for bioconjugation studies,[34] and the synthesis of amphiphilic glycopyranosides for formation of stable liposomes,[35] being two recent examples. A hydrophilic *thiopeptide*, for attachment of lipid layers to gold surfaces, is the only example we are aware of where solid-phase synthetic techniques have been employed in the preparation of components for tethered bilayer membranes; however, in this instance the final membrane-forming material was prepared in situ on the gold surface.[36]

The all-amide material **17** prepared in this work by solid-phase techniques is identical in all respects to the material prepared by solution-phase synthesis, though notably the solid-phase synthesis was achieved with simpler purification procedures and in significantly higher yield.

The disulfide species **5**, prepared from **17**, has been shown to form monolayers on gold of similar thickness to those formed from the previously described compound **1**, and possessing hydrogen bonded amide functionality in the hydrophilic region of the SAM. While the adsorption of unsymmetrical disulfides on gold has been reported by a number of groups,[37] deviations from a 1:1 composition of the derived monolayers have been reported recently.[38] The preliminary surface analysis of SAM's derived from both **1** and **5** presented here does not address this issue, and further work in this area, and the study of **5** and related species in t-BLM's, will be reported elsewhere.

Experimental Section

General. All anhydrous reactions were carried out under an atmosphere of dry nitrogen. All solvents were distilled prior to use. THF was dried by distillation from sodium benzophenone ketyl, and dichloromethane by distillation from calcium hydride. All other commercially available materials were used without further purification. Wang resin (200−400 mesh) was purchased from Novabiochem (Läufelfingen, Switzerland). Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plastic-backed plates and materials visualized under UV (254 nm) followed by staining with phosphomolybdic acid (5% in ethanol). Flash chromatography was performed using Merck silica gel 60 (0.015−0.040 mm).

^1H NMR spectra were recorded on Bruker AC-200 (200 MHz) and AMX-400 (400 MHz) spectrometers with samples dissolved in $CDCl_3$, CD_2Cl_2, or CD_3OD. ^1H NMR spectra were referenced to solvent residuals ($CDCl_3$ 7.26; CD_2Cl_2 5.31; CD_3-OD 3.35 ppm). Electron ionization (EI) mass spectra were recorded on a modified Kratos Mass Spectrometer calibrated using perfluorokerosene (PFK). High-resolution EI spectra were recorded on a VG Autospec. Chemical ionization (CI) mass spectra were recorded on a AEI Ms30 spectrometer with methane as the ionizing gas. Electrospray mass spectra were recorded on a Finnigan LCQ MS detector. FAB mass spectra were recorded on a VG ZAB-2SEQ instrument using a cesium ion gun at ca. 25 kV to produce a beam of fast Cs^+ ions, using a matrix of *p*-nitrobenzyl alcohol. Microanalyses were performed by the Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, Dunedin, New Zealand.

Gold substrates were prepared using a DC sputtering system (Dynavac, Australia) operating at 0.5 Pa Ar pressure and 500 eV ion energy. Silicon wafers were coated with a 25 Å adhesion layer of titanium followed by 1000 Å of gold. The freshly prepared gold slides were immersed in ethanolic solutions (1 mM) of the compounds **1** or **5** for 1 h. The slides were rinsed with ethanol and dried under a stream of nitrogen before analysis.

Infrared reflection absorption spectroscopy was performed using a BIORAD FTS-65A Infrared Spectrometer. Ellipsometric thicknesses were determined using a custom-built spectroscopic ellipsometer[39] with a rotating analyzer scanning from 350 to 800 nm at 5 nm intervals at an angle of 70° with respect to the surface normal. The ellipsometric parameters δ and ψ were measured before and after monolayer adsorption. The thickness of the monolayers was estimated using VASE software (J. A. Woollam Co. Inc., Lincoln, NE), assuming an isotropic layer with a real refractive index of $n = 1.45$. The imaginary refractive index was assumed to be $k = 0$.

Synthesis of Phytanyl Bromide 9 (1-Bromo-3*RS*,7*R*,11*R*,15-tetramethylhexadecane). A solution of phytol **8** (49.3 g, 166 mmol) in ethanol (250 mL) was reduced with hydrogen gas at atmospheric pressure over Raney nickel (10 g) for 3 days. The catalyst was removed by filtration through Celite and the filtrate concentrated under reduced pressure to give phytanol (**7**) (49.3 g, 100%). ^1H NMR ($CDCl_3$) δ 0.8−0.95 (m, 15H), 1.0−1.75 (m, 24H), 3.65−3.75 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 19.67 (3 × Me), 22.60 (Me), 22.69 (Me), 24.36 (CH_2), 24.45 (CH_2), 24.78 (CH_2), 27.95 (CH), 29.50 (CH), 32.76 (2 × CH), 37.28−37.43 (m, 5 × CH_2), 39.35 (CH_2), 39.73 and 40.05

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[32] Bellamy, L. J. *The Infra-Red Spectra of Complex Molecules*; Methuen: New York, 1959.

[33] Sackmann, E. *Science* **1996**, *271*, 43.

[34] Rose, K.; Vizzavona, J. *J. Am. Chem. Soc.* **1999**, *121*, 7034.

[35] Reichel, F.; Roelofsen, A. M.; Geurts, H. P. M.; van der Gaast, S. J.; Feiters, M. C.; Boons, G.-J. *J. Org. Chem.* **2000**, *65*, 3357.

[36] Bunjes, N.; Schmidt, E. K.; Jonczyk, A.; Rippmann, F.; Beyer, D.; Ringsdorf, H.; Gräber, P.; Knoll, W.; Naumann, R. *Langmuir* **1997**, *13*, 6188.

[37] (a) Schönherr, H.; Ringsdorf, H. *Langmuir* **1996**, *12*, 3891. (b) Biebuyck, H. A.; Whitesides, G. M. *Langmuir* **1993**, *9*, 1766. (c) Schönherr, H.; Ringsdorf, H.; Jaschke, M.; Butt, H.-J.; Bamberg, E.; Allinson, H.; Evans, S. D. *Langmuir* **1996**, *12*, 3898.

[38] Heister, K.; Allara, D. L.; Bahnck, K.; Frey, S.; Zharnikov, M.; Grunze, M. *Langmuir* **1999**, *15*, 5440.

[39] Bendavid, A.; Martin, P. J.; Wieczorek, L. *Thin Solid Films* **1999**, *354*, 169.

(together CH$_2$), 61.18 (CH$_2$). Concentrated sulfuric acid (80 mL) was added slowly over a 15−20 min. period to a stirred solution of 48% hydrobromic acid (800 mL). To this mixture was added phytanol (**7**) (80 g; 0.27 mol), and the reaction mixture was heated at reflux for 6 h. After cooling to room temperature, the mixture was extracted with diethyl ether (2 × 500 mL), and the combined ether layers were washed (10% aqueous NaHCO$_3$; 3 × 300 mL). The combined aqueous layers were extracted with ether (2 × 300 mL), and the combined ether layers washed with saturated aqueous NaCl (3 × 300 mL). The organic layer was dried (MgSO$_4$) and concentrated in vacuo. The crude bromide was distilled under vacuum (160−170 °C/10 mmHg) to give pure phytanyl bromide (**9**) (87.5 g, 90%). ^{1}H NMR (CDCl$_3$) δ 0.80−0.94 (15H, m, phytanyl CH$_3$'s); 0.94−1.65 (24H, m, phytanyl CH$_2$'s and CH's); 3.41 (2H, m, C*H*$_2$Br)

Synthesis of Phytanylamine 6 (1-Amino-3*RS*,7*R*,11*R*,-15-tetramethylhexadecane). Phytanyl bromide (**9**) (12.34 g, 34.1 mmol), potassium phthalimide (6.95 g, 37.5 mmol), and DMF (50 mL) were heated at 130 °C for 4 h. The DMF was removed under reduced pressure and the crude product dissolved in dichloromethane (100 mL), washed with water (2 × 50 mL), and dried (MgSO$_4$). The crude product was chromatographed on flash silica (ethyl acetate−hexane, 10:90 as eluant) to yield pure phthalimide **10** (11.89 g, 81%). ^{1}H NMR (CDCl$_3$) δ 0.82−1.8 (m, 39H), 3.73 (t, 2H, CH$_2$N), 7.73 (m, 2H, Ar*H*), 7.88 (m, 2H, Ar*H*); *m*/*z* 431 (M$^+$). The phthalimide **10** (1.7 g, 4.5 mmol) was dissolved in ethanol (100 mL), hydrazine hydrate (2 mL) was added, and the mixture was heated at reflux for 2.5 h. The reaction mixture was cooled and concentrated hydrochloric acid (1 mL) added. The white precipitate formed was filtered, the filtrate neutralized with 20% sodium hydroxide and then extracted with dichloromethane and dried (MgSO$_4$), and the solvent removed under reduced pressure to furnish the amine **6** as a colorless oil (1.9 g, 85%). ^{1}H NMR (CDCl$_3$) δ 0.82−1.8 (m, 39H), 3.65 (t, 2H, NCH$_2$); *m*/*z* (CI) 297 (M + H).

Synthesis of Hemisuccinimide 11 (N-(3*RS*,7*R*,11*R*,15-Tetramethylhexadecyl)succinamic acid). A solution of phytanylamine (**6**) (2.32 g, 7.8 mmol) and succinic anhydride (1.16 g, 11.6 mmol) in pyridine (10 mL) was stirred at room temperature for 48 h. The solution was concentrated under reduced pressure and the crude product dissolved in dichloromethane (100 mL) and washed with 2 M HCl (2 × 100 mL). The organic layers were combined, dried (MgSO$_4$), and concentrated to dryness. The crude material was purified by chromatography (ethyl acetate as eluant) to give pure **11** as a thick liquid, which solidified on standing (1.23 g, 91%). (Found: C, 71.3; H, 12.1; N, 3.6. C$_{24}$H$_{47}$NO$_3$·0.5H$_2$O requires C, 70.89; H, 11.90; N, 3.44%.). ^{1}H NMR (CDCl$_3$) δ 0.8−0.89 (m, 15H, CH$_3$'s of phytanyl), 0.89−1.6 (m, 24H, CH and CH$_2$ of phytanyl), 2.5 (m, 2H, C*H*$_2$CONH), 2.6 (m, 2H, C*H*$_2$COOH), 3.2 (m, 2H, CH$_2$N), 5.79 (br t, 1H, NH); *m*/*z* (CI) 398 (M$^+$).

Synthesis of Mono-Boc Diamine 15 ((2-{2-[2-(2-Aminoethoxy)ethoxy]ethoxy}ethyl)carbamic acid *tert*-butyl ester). 3,6,9-Trioxa-1,11-diaminoundecane (**12**) (1.03 g, 5.4 mmol), BOC-ON (1.38 g, 5.62 mmol), and triethylamine (0.81 g) were dissolved in water−dioxane (40 mL, 1:1). The reaction mixture was stirred at room temperature for 24 h and concentrated under reduced pressure. The crude product was dissolved in water (100 mL) and extracted with dichloromethane (4 × 100 mL). The combined organic extracts were dried (MgSO$_4$), and the solvent was removed under reduced pressure to give the crude product as a thick liquid. This was chromotographed on flash silica (20% methanol in dichloromethane as eluant) to give mono-*N*-(*tert*-butyloxycarbonyl)-3,6,9-trioxa-1,11-diaminoundecane (**15**) as a colorless thick liquid (0.16 g, 26%). ^{1}H NMR (CDCl$_3$) δ 1.44 (s, 9H, ^{t}Bu), 2.85 (br s, 2H, C*H*$_2$NH$_2$), 3.31 (m, 2H, C*H*$_2$NHCOO^{t}Bu), 3.30−3.70 (m, 8H, OCH$_2$), 5.4 (br s, 1H, CH$_2$N*H*COOtBu); *m*/*z* (CI) 293 (M$^+$), 265, 237, 193.

Synthesis of 16 ({2-[2-(2-{2-[3-(3*RS*,7*R*,11*R*,15-Tetramethylhexadecylcarbamoyl)propionylamino]ethoxy}-ethoxy)ethoxy]ethyl}carbamic acid *tert*-butyl ester). A solution of phytanyl hemisuccinimide **11** (626 mg, 1.57 mmol), monoamine **15** (390 mg, 1.57 mmol), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (morpho-CDI) (733 mg, 1.9 mmol), and DMAP (192 mg, 1.57 mmol) in dichloromethane (10 mL) was stirred at room temperature for 24 h. The white precipitate formed was removed by filtration and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane−methanol, 95:5 → 90:10) to give **16** as a thick, light yellow liquid (403 mg, 71%). (Found: C, 65.3; H, 11.2; N, 6.3. C$_{37}$H$_{93}$N$_3$O$_7$·0.5H$_2$O requires C, 65.26; H, 10.95; N, 6.17%.). ^{1}H NMR (CDCl$_3$) δ 0.8−0.89 (m, 15H, CH$_3$'s of phytanyl), 0.89−1.6 (m, 24H, CH and CH$_2$'s of phytanyl), 1.44 (s, 9H, ^{t}Bu), 2.52 (m, 4H, NCOC*H*$_2$C*H*$_2$CON), 3.22−3.64 (m, 18H, NC*H*$_2$C*H*$_2$O + OC*H*$_2$C*H*$_2$O + phytanyl C*H*$_2$NH), 5.15 (br s, 1H, NH), 6.0 (br s, 1H, NH), 6.4 (br s, 1H, NH); *m*/*z* (CI) 673 (M + H), 599 (M − ^{t}BuO), 573 (M − BOC).

Synthesis of 17 (*N*-{2-[2-(2-{2-[3-(3*RS*,7*R*,11*R*,15-Tetramethylhexadecylcarbamoyl)propionylamino]ethoxy}-ethoxy)ethoxy]ethyl}succinamic acid). The BOC-protected amine **16**, (1.5 g, 2.23 mmol) was dissolved in trifluoroacetic acid (10 mL) and allowed to stand at room temperature for two h. Excess trifluoroacetic acid was removed under reduced pressure and the crude product purified by chromatography (dichloromethane−methanol, 80:20) as the trifluoroacetate salt. The salt was dissolved in dichloromethane and stirred with potassium carbonate to give the free amine as a colorless liquid (1.33 g, 100%). ^{1}H NMR (CDCl$_3$) δ 0.62−1.4 (m, 39H, phytanyl CH$_2$'s and CH$_3$'s), 2.23 (s, 4H, NCOCH$_2$CH$_2$CON), 2.6 (m, 2H, C*H*$_2$NH$_2$), 2.9−3.4 (m, 16H, C*H*$_2$NH + NHC*H*$_2$C*H*$_2$O + OC*H*$_2$C*H*$_2$O); *m*/*z* (CI) 572 (M$^+$). The free amine **(**1.3 g, 2.3 mmol) was dissolved in pyridine (25 mL) and succinic anhydride (340 mg, 3.4 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and the solvent removed under reduced pressure. The crude product was purified by chromatography (dichloromethane−methanol, 97:3 → 90:10) to give pure **17** as a low melting solid (1.22 g, 80%). (Found: C, 64.1; H, 10.5; N, 6.3. C$_{36}$H$_{69}$N$_3$O$_8$ requires C, 64.35; H, 10.35; N, 6.25%.). ^{1}H NMR (CDCl$_3$) δ 0.8−0.89 (m, 15H, phytanyl CH$_3$'s), 0.89−1.6 (m, 24H, phytanyl CH's and CH$_2$'s), 2.5−2.7 (m, 8H, NCOC*H*$_2$C*H*$_2$CON), 3.22 (m, 2H, C*H*$_2$NH), 3.43 (m, 4H, OCH$_2$C*H*$_2$NH), 3.56 (OC*H*$_2$CH$_2$NH), 3.65 (s, 8H, OC*H*$_2$C*H*$_2$O), 6.29 (m, 1H, NH), 6.90 (br s, 1H, NH), 7.11 (br s,1H, NH); *m*/*z* (CI) 655 (M − H$_2$O).

Synthesis of 20 (1-(3*RS*,7*R*,11*R*,15-Tetramethylhexadecyl)pyrrolidine-2,5-dione). Diethyl diazodicarboxylate (0.06 mL, 0.39 mmol) was added into a solution of alcohol **19** (120 mg, 0.36 mmol), phthalimide (58 mg, 0.39 mmol), and triphenylphosphine (104 mg, 0.39 mmol) in THF (5 mL), and the mixture was stirred at RT for 30 min. The crude material obtained after removal of the solvent was partially purified by flash chromatography (dichloromethane−methanol, 99:1) and further purified by reverse phase HPLC (SORBAX, 30% methanol in water) to give the phthalimide **20** as a low melting solid (110 mg, 66%). (Found: C, 59.7; H, 6.2; N, 3.2. C$_{23}$H$_{27}$NO$_5$S$_2$ requires C, 59.84; H, 5.90; N, 3.03%.). ^{1}H NMR (CD$_2$Cl$_2$) δ 2.61 (t, 2H, S−S−CH$_2$), 3.5−3.65 (m, 10H, OC*H*$_2$C*H*$_2$O), 3.74 (t, 2H, C*H*$_2$CH$_2$-phthalimide), 3.9 (t, 2H, CH$_2$C*H*$_2$-phthalimide), 3.90 (s, 2H, C*H*$_2$Ph), 7.2−7.4 (m, 5H, CH$_2$Ar*H*), 7.6−7.9 (m, 4H, phthalimide-Ar*H*); MS *m*/*z* (EI) 461.1(M$^+$).

Synthesis of 18 (2-{2-[2-(2-Benzyldisulfanylethoxy)-ethoxy]ethoxy}ethylamine). The phthalimide **20** (70 mg, 0.15 mmol) was dissolved in a solution of methylamine in ethanol (2 M, 2.5 mL) and was allowed to stand at 0 °C for 24 h. The crude material obtained upon removal of the solvent and methylamine under reduced pressure was purified by flash chromatography (dichloromethane−methanol, 97:3 + 0.05% NH$_4$OH) to afford the product as an oil (13 mg, 26%). The product **18** was unstable on standing and was used immediately after purification. ^{1}H NMR (CD$_3$OD) δ 2.58 (t, 2H, S−S−CH$_2$), 2.82 (t, 2H, NH$_2$C*H*$_2$CH$_2$), 3.4−3.7 (m, 12H, CH$_2$C*H*$_2$O), 3.92 (s, 2H, C*H*$_2$Ph), 7.3 (m, 5H, ArH).

Synthesis of 5 (*N*-{2-[2-(2-{2-[3-(2-{2-[2-(2-Benzyldisulfanylethoxy)ethoxy]ethoxy}ethylcarbamoyl)propionylamino]ethoxy}ethoxy)ethoxy]ethyl}-*N*′-(3,7,11,15-tetramethylhexadecyl)succinamide). A solution of the carboxylic acid **17** (138 mg, 0.205 mmol), amine **18** (60 mg, 0.181 mmol), morpho-CDI (96 mg, 0.225 mmol), and DMAP (30 mg, 0.225 mmol) in dichloromethane (10 mL) was stirred under nitrogen for 24 h. The solution was filtered and the filtrate concentrated in vacuo to give a thick oil which was purified by flash chromatography (dichloromethane−methanol, 95:5). Analytically pure material was obtained by normal phase HPLC (Whatman particil B, dichloromethane−methanol, 95:5) (32 mg, 18%). ^{1}H NMR (CD_2Cl_2) δ 0.8−0.89 (m, 15H, phytanyl CH_3's), 0.89−1.6 (m, 24H, phytanyl CH's and CH_2's), 2.4−2.5 (m, 8H, CH_2CO), 2.63 (t, 2H, SCH_2CH_2), 2.15 (m, 2H, $CH(CH_3)$-CH_2CH_2NH), 3.36 (m, 6H, OCH_2CH_2NHCO), 3.4−3.6 (m, 24H, CH_2CH_2O), 3.90 (s, 2H, CH_2Ph), 6.2 (br s, 1H, NH), 6.4 (br s, 1H, NH), 6.7 (br s, 2H, NH), 7.3 (m, 5H, ArH); MS (FAB positive) m/z 1007.6 $(M + Na)^+$, 985.6 $(M + H)^+$ exact MS FAB positive required (for $C_{51}H_{93}N_4O_{10}S_2$) 985.6304. Found 985.6333.

Solid-Phase Synthesis of 17. Wang Resin (1.0 g) was suspended in DMF (5 mL) and pyridine (0.4 mL). Succinic anhydride (500 mg) was added and the mixture heated at 80 °C for 16 h. The resin was separated by filtration, washed successively with ethanol, water, ethanol, and ether, and dried under high vacuum for 3 h. υ_{max} (KBr) 1732, 1706 cm^{-1}. The resin was suspended in DMF (5 mL), and bromo-tris-pyrrolidino-phosphonium hexafluoprophosphate (PyBroP) (280 mg), diamine **12** (250 mg), and DMAP (60 mg) were added. The mixture was stirred gently for 16 h at room temperature and then was filtered. The filtered solid was washed successively with ethanol, water, and ethanol and finally was dried under high vacuum for 3 h. υ_{max} (KBr) 1734.1, 1686.6 cm^{-1}. To a suspension of this resin in a mixture of DMF and pyridine (3 mL, 1:1) was added succinic anhydride (100 mg), and the resulting mixture was stirred slowly at room temperature for 16 h. The resin was separated by filtration, washed with ethanol, water, and ethanol, and then dried under high vacuum for 3 h. υ_{max} (KBr) 1733.8 (b), 1686.1 cm^{-1}. To a suspension of this resin in DMF (5 mL) and PyBroP (225 mg) were added DMAP (60 mg) and phytanylamine **6** (200 mg). The reaction mixture was stirred slowly at room temperature for 16 h and the reaction worked up as before. υ_{max} (KBr) 1732.4, 1693.3 cm^{-1}. The resin (207 mg) was suspended in dichloromethane (2.5 mL) and TFA (2.5 mL) and the mixture stirred slowly under nitrogen at room temperature for 1 h. The resin was separated by filtration and washed several times with dichloromethane. The filtrate and combined washings were concentrated under reduced pressure and the desired product isolated by chromatography to furnish the acid **17 (**50 mg, 81%) with identical physical properties and spectroscopic data as that reported above.

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