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Volume 54, 2001

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Aust. J. Chem. **2001**, *54*, 431–438

Components for Tethered Bilayer Membranes: Synthesis of Hydrophilically Substituted Phytanol Derivatives

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In order to optimize the performance of the AMBRI™ biosensor (*Nature* **1997**, *387*, 580), a variety of hydrophilic linkers between the hydrophobic bilayer membrane and the gold surface have been synthesized. The principal components are prepared from phytanyl hemisuccinate, which is linked by repeating ethylene glycol or propylene glycol units to a second succinic acid unit. The syntheses of analogous substances in which the ester links are replaced by amide and by ether links are also described.

Manuscript received: 30 August 2001.
Final version: 21 September 2001.

Introduction

The fabrication, study, and use of synthetic bilayer membranes tethered to a solid support (known as tethered bilayer membranes or t-BLMs) has been reported by a number of research groups over the last decade. Such systems have great potential as stable and robust cellular membrane mimetics for use in the study of membrane bound proteins[1–3] and in biosensing.[4–9] t-BLMs are generally prepared in two steps: formation of a well ordered monolayer on a solid support such as silicon or gold, and deposition of a lipid layer from either a lipid solution or from lipid vesicles.[4–12]

The preparation of a novel t-BLM, as part of the fabrication of a highly sensitive biosensor, was first reported by our group in 1997,[6] and since that time a number of reports on the utility of this technology have been published.[13–15] The biosensor technology is based on a t-BLM attached to a gold surface (through a hydrophilic linker terminating in a disulfide group) with the small ion-channel gramicidin embedded in both leaflets of the bilayer. Attachment of receptors to the gramicidin channels in the outer leaflet of the membrane, and to a stationary lipid species attached to gold, generates the sensing surface (Fig. 1). Binding of the analyte to the receptors renders the upper leaflet gramicidin immobile and, therefore, limits ion-flow across the membrane, which is measured through the technique of impedance spectroscopy.

Part of the t-BLM in this sensor is the hydrophilic linker between the membrane-forming hydrocarbon and the sulfur moiety that binds to the gold surface. The hydrophilic region is required to provide an aqueous compartment into which ions can flow, and other results[16] indicate the length of the tether is important. The major component of the t-BLM is the disulfide species (1), which constitutes about 99% of the lipid material of the lower membrane leaflet. As part of ongoing studies to examine the effect of changes to the molecular components on bilayer properties and sensor function,[16–18] it was necessary to synthesize a variety of hydrophilic linkers attached to phytanol.

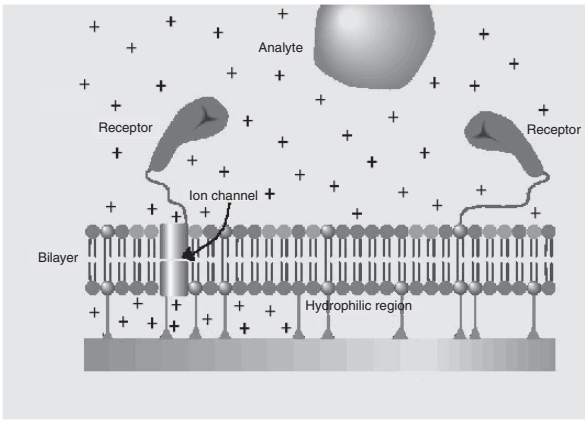

Fig. 1. Schematic of the AMBRI™ biosensor.

One requirement was that the various hydrophilic linkers be of approximately equal length in order for the effect of different types of linkers to be assessed. We wished to

 10.1071/CH01111 0004-9425/01/030431

explore combinations of ether/ester and ether/amide linkers, but since their conformations in the hydrophilic region could not be predicted at the outset, we set initial goals to prepare linkers in which the numbers of atoms in the chains were at least similar. We report here on the syntheses of a number of such hydrophilic linkers.

Results and Discussion

Ester Derivatives of Succinic Acid

The major component (1) of the inner leaflet of the biosensor's bilayer membrane has previously been prepared from the disulfide alcohol (2) through successive reaction with succinic anhydride, tetraethylene glycol, and succinic anhydride, prior to coupling with phytanol.[16] To prepare a series of congeners of this compound, phytanol was reacted with excess succinic anhydride in pyridine to generate the hemisuccinate (3) in 56% yield. Significantly higher yields (> 90%) were obtained for this compound when the reaction was performed in dichloromethane in the presence of excess triethylamine (Fig. 2).

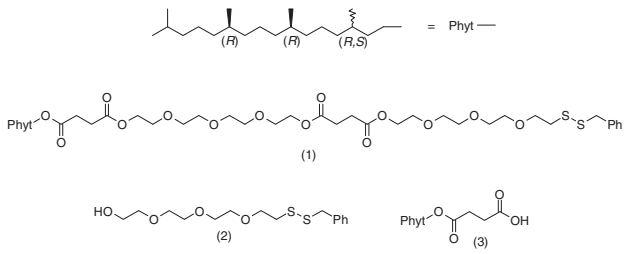

Fig. 2. Schematic representation of the phytanyl group and compounds (1)–(3).

The unsymmetrical succinic acid diester (4) was generated by coupling the hemisuccinate (3) with excess (> 5 molar equiv.) tetraethylene glycol in the presence of DMAP (4-dimethylaminopyridine) using either DCC (1,3-dicyclohexylcarbodiimide) or morpho-CDI (1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate) as coupling agent. Use of an excess of diol minimized the formation of bis-substituted products, while removal of excess diol from the reaction mixture was easily accomplished by washing with water.

In a similar way, the unsymmetrical diester (5) was prepared from the hemisuccinate (3) and hexaethylene glycol. However, because of the relative lack of availability of heptaethylene glycol, the heptaethylene glycol analogue (7) needed to be prepared by a multi-step process involving protecting group chemistry.[19] Thus reaction of the anion of the monobenzyl ether of tetraethylene glycol (8) with the tosylate (9)[20] afforded the protected ether (10) which, on treatment with acid, gave the monobenzyl ether of heptaethylene glycol (11). The alcohol (11) was then coupled with the hemisuccinate (3) to yield the benzyl ether (6). Hydrogenolysis of this ether then afforded the desired heptaethylene glycol derivative (7), and the overall yield from tetraethylene glycol was satisfactory (Fig. 3).

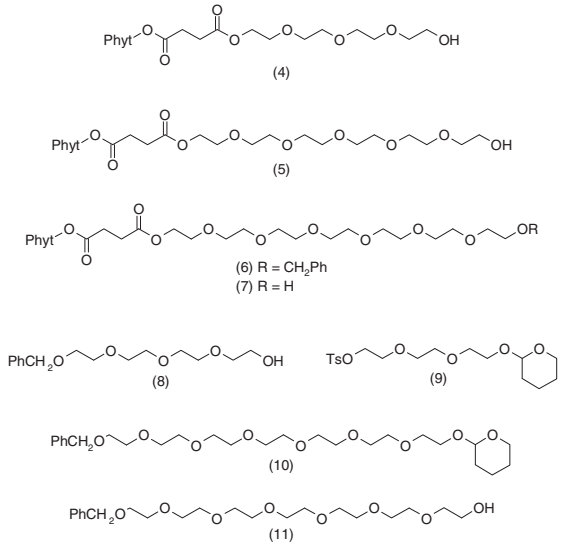

Fig. 3. Schematic representation of compounds (4)–(11).

To date only ethylene glycol derivatives have been used in the hydrophilic component in the biosensor, but we required modified hydrophilic components in order to explore the precise function of this region in the system. Accordingly, tripropylene glycol (12),[21] which like tetraethylene glycol contains a 13-atom chain, was treated with the hemisuccinate (3) in the presence of morpho-CDI/DMAP to give the unsymmetrical diester (13) (Fig. 4).

The other major components of the hydrophilic region in the biosensor are derived from glycerol diphytanyl ether (14),[16] so to complete the series we required the unsymmetrical

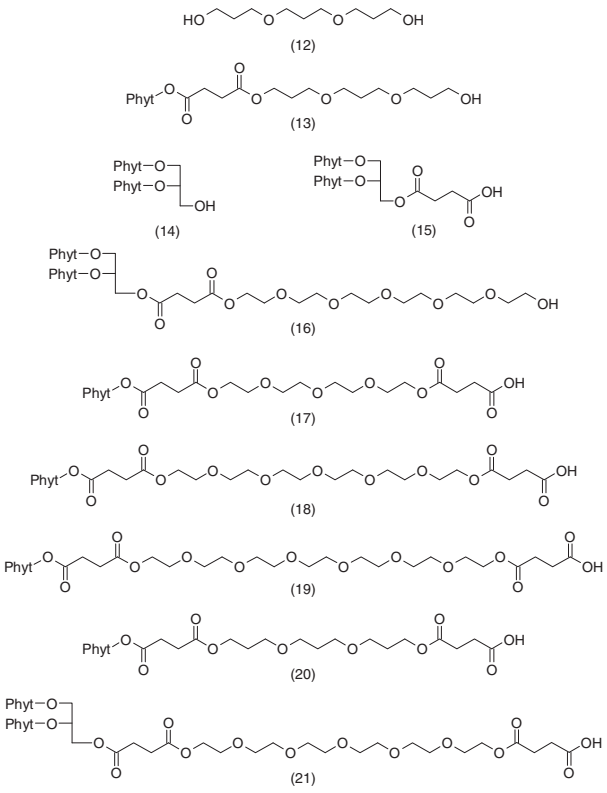

Fig. 4. Schematic representation of compounds (12)–(21).

succinate (16). Accordingly, the hemisuccinate (15) was prepared by reaction of the diphytanyl ether (14) with succinic anhydride in pyridine. Subsequent reaction of the acid with excess hexaethylene glycol in the presence of DMAP using morpho-CDI as coupling agent furnished the alcohol (16) in good yield (Fig. 4).

Coupling of the alcohols (4), (5), (7), (13) and (16) with succinic anhydride was performed in pyridine and gave excellent yields of the corresponding hemisuccinates (17), (18), (19), (20) and (21) respectively (Fig. 4).

All Ether and Succinamide/Ether Derivatives

One of the issues with use of the hydrophilic component (1) was the stability of the ester functional group, and to minimize the likelihood of component degradation through ester hydrolysis, we set out to replace ester functionality with either ether or amide functionality.

The preparation of the all-ether analogue of disulfide (1) began with reaction of phytanyl bromide with excess of the alkoxide formed from reaction of triethylene glycol and sodium hydride, to afford the alcohol (22). Conversion of this alcohol (22) into the tosylate (23), followed by reaction of the tosylate with excess of the alkoxide generated from tetraethylene glycol and sodium hydride, furnished the heptaethylene glycol derivative (24). On further reaction with the anion from triethylene glycol, the tosylate (25) of this alcohol generated the decaethylene glycol derivative (26), while reaction of the tosylate (25) with the anion from tetraethylene glycol gave the undecaethylene glycol derivative (27). This last product (27) has 33 atoms attached to the phytanol oxygen and this compares with the 34 atoms in the oxygen precursor to the disulfide (1) (Fig. 5).

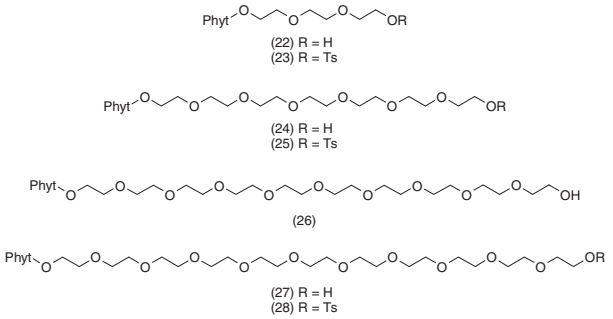

Fig. 5. Schematic representation of compounds (22)–(28).

The preparation of amide analogues of disulfide (1) commenced with phytanoic acid (29).[22] Conversion into the *N*-methyl amide (30) was accomplished in 70% yield by treatment of the acid (29) with thionyl chloride and then with methylamine. Subsequent reduction of the amide (30) with lithium aluminium hydride afforded methylphytanylamine (31), which on treatment with succinic anhydride gave the hemisuccinamide (32). Chain extension was effected by reaction of this acid amide (32) with the diamine (33)[23] and DCC to give the amide derivative (34), which on heating with succinic anhydride gave the acid amide (35). This derivative (35) was the amide analogue of the ester derivative (17) (Fig. 6).

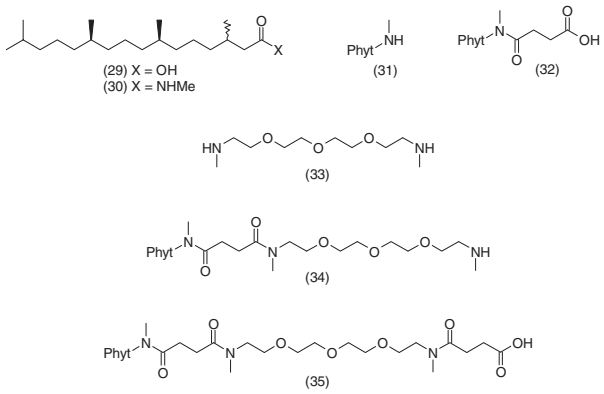

Fig. 6. Schematic representation of compounds (29)–(35).

In order to test their effectiveness in the biosensor, these hydrophilically substituted phytanol derivatives now need to be attached to sulfur-containing end groups for attachment to the gold surface. We shall report separately on the syntheses of a variety of sulfur-containing end groups, on the attachment of the hydrophilically substituted phytanol derivatives, and on the performance of the modified biosensors.

Experimental

All reactions were performed under an atmosphere of dry nitrogen, unless stated otherwise. Anhydrous benzene, diethyl ether, tetrahydrofuran (THF) and toluene were obtained by distillation from sodium benzophenone ketyl immediately prior to use. Anhydrous dichloromethane was obtained by distillation from calcium hydride or P_2O_5 immediately prior to use. Anhydrous *N*,*N*-dimethylformamide (DMF) was obtained by stirring over calcium hydride for 24 h and distilling under reduced pressure immediately prior to use. Anhydrous pyridine was obtained by storing analytical-grade pyridine (Merck) over KOH pellets.

Purifications were achieved by flash chromatography on silica gel (0.040–0.063 mm) unless stated otherwise. Thin-layer chromatography was performed using Merck 60 F_{254} plates with samples visualized by means of iodine vapour, phosphomolybdic acid (5% in ethanol) with heating, or under ultraviolet (254 nm) light. Purifications by preparative high-pressure liquid chromatography (HPLC) were performed using a Waters Model 510 chromatography pump incorporating a Waters Differential Refractometer and an ISCO Model 226 Absorbance detector (λ 254 nm).

^{1}H Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AC-200F (200 MHz) and AMX-400 (400 MHz) spectrometers. All samples were dissolved in $CDCl_3$ and referenced to residual solvent ($CHCl_3$, 7.26 ppm). ^{13}C NMR spectra were recorded on Bruker AC-200F (50 MHz) and AMX-400 (100 MHz) spectrometers. All samples were dissolved in $CDCl_3$ and referenced on residual solvent ($CHCl_3$, 77.00 ppm). Infrared (IR) spectra were acquired on a Perkin–Elmer 1600 series spectrometer and the spectra for oils were recorded on the neat compounds between NaCl plates. Electron-ionization (EI) mass spectra were recorded on a modified Kratos mass spectrometer calibrated with perfluorokerosene (PFK). Chemical-ionization (CI) mass spectra were recorded on an Hewlett Packard 5989A spectrometer with methane as the ionizing gas. Matrix-assisted laser desorption ionization (MALDI) mass spectra were recorded on a Fisons VG TofSpec spectrometer. Electrospray ionization (ESI) mass spectra were recorded on a Finnigan LCQ mass spectrometer. Molecular ion peaks and other significant peaks are quoted in parentheses with their assignment (where applicable) and intensity (as a percentage of the base peak). Microanalyses were performed by the Campbell Microanalytical Laboratory, Department of Chemistry,

University of Otago, Dunedin, New Zealand. Note that some of the hydrophilic derivatives retained moisture very strongly, and that in these cases analytical data for partially hydrated derivatives resulted.

1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (morpho-CDI), dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP) and its hydrochloride (DMAP·HCl), tetraethylene glycol, and hexaethylene glycol were purchased from Sigma–Aldrich. Other reagents were prepared by literature methods as described below. Phytanol was prepared as described previously as a mixture of the 3*R*,7*R*,11*R*- and 3*S*,7*R*,11*R*-diastereomers.[22]

Phytanyl Hemisuccinate (3)

(i) Using triethylamine. Triethylamine (194 mg, 1.91 mmol) was added to a solution of phytanol (952 mg, 3.19 mmol) and succinic anhydride (415 mg, 4.14 mmol) in dichloromethane (20 mL). The mixture was heated at reflux for 3 h and then was cooled to room temperature. The solvent was removed under reduced pressure and diethyl ether was added (50 mL). The organic layer was washed with 1M HCl (50 mL), water (50 mL), brine (50 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give the hemisuccinate (3) as a colourless *oil* (1.23 g, 97%) (Found: C, 72.0; H, 11.9. $C_{24}H_{46}O_4$ requires C, 72.3; H, 11.6%). IR ν_{max} 3200–2900, 1738 cm^{-1}. ^1H NMR δ 0.82–0.90, m, 15H, phytanyl CH_3s; 0.94–1.68, m, 24H, phytanyl CHs and CH_2s; 2.57–2.73, m, 4H, succinyl CH_2s; 4.10–4.17, m, 2H, CH(Me)$CH_2C\mathbf{H}_2O$. ^{13}C NMR δ 19.4–19.7, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.4, CH_2; 24.8, CH_2; 27.9, CH; 28.9, succinyl CH_2; 29.0, succinyl CH_2; 29.8, CH; 32.7, CH; 35.4, CH_2; 35.5, CH_2; 37.2, CH_2; 37.4, CH_2; 39.3, CH_2; 63.5, CH_2; 172.2, C(O); 177.7, C(O)OH. Mass spectrum (CI) *m/z* 399 ($[M+H]^+$, 100%), 101 (41).

(ii) Using pyridine. Succinic anhydride (10.0 g, 10.0 mmol) was added portionwise to a solution of phytanol (10.0 g, 33.5 mmol) in pyridine (150 mL), and the mixture was stirred at room temperature for 3 days. The solvent was removed under vacuum, and 3 M HCl (250 mL) was then added to the residue. The aqueous solution was extracted with dichloromethane (3×120 mL). The combined organic extracts were washed with water (2×100 mL), brine (150 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford the hemisuccinate (3) (7.50 g, 56%) as a pale yellow oil. The data acquired were identical to those obtained for the preparation of the hemisuccinate using triethylamine.

Phytanyl Tetraethylene Glycol Succinate (4)

A mixture of the hemisuccinate (3) (190 mg, 0.48 mmol), tetraethylene glycol (463 mg, 2.4 mmol), DCC (120 mg, 0.58 mmol), DMAP (19 mg, 0.16 mmol) and DMAP·HCl (25 mg, 0.16 mmol) in dichloromethane (2 mL) was stirred for 70 h at room temperature. The suspension was filtered through Celite®, the precipitate was washed with dichloromethane, and the combined filtrates were concentrated to dryness under reduced pressure. The resulting pale yellow oil was chromatographed using ethyl acetate as eluent and provided the ester (4) (186 mg, 68%) as a colourless viscous *oil* (Found: $[M+H]^+$ 575.4504. $C_{32}H_{62}O_8$ requires $[M+H]^+$ 575.4523). IR ν_{max} 3500–2500, 1734 cm^{-1}. ^1H NMR δ 0.84–0.95, m, 15H, phytanyl CH_3s; 0.90–1.75, m, 24H, phytanyl CHs and CH_2s; 2.63, m, 4H, succinyl CH_2s; 3.55–3.75, m, 14H, OCH_2CH_2O; 4.09, m, 2H, CH(Me)$CH_2C\mathbf{H}_2O$; 4.28, m, 2H, $OCH_2C\mathbf{H}_2OC(O)$. ^{13}C NMR δ 19.4–19.7, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.2, CH_2; 24.4, CH_2; 24.7, CH_2; 27.9, CH; 29.0, succinyl CH_2; 29.05, succinyl CH_2; 29.8, CH; 32.7, CH; 35.4, CH_2; 35.5, CH_2; 37.2, CH_2; 37.3, CH_2; 39.3, CH_2; 61.5, CH_2; 61.7, CH_2; 63.4, CH_2; 63.7, CH_2; 69.0, CH_2; 70.3, CH_2; 70.5, CH_2; 72.5, CH_2; 172.3, C(O). Mass spectrum (EI) *m/z* 575 (2%), 425 (15), 399 (12), 277 (33), 195 (10), 189 (15), 145 (100).

Phytanyl Hexaethylene Glycol Succinate (5)

Hexaethylene glycol (2.91 g, 10.3 mmol), morpho-CDI (1.07 g, 2.5 mmol), DMAP (86 mg, 0.7 mmol) and DMAP·HCl (112 mg, 0.7 mmol) were dissolved in anhydrous dichloromethane (9 mL) at room temperature. Phytanyl hemisuccinate (3) (0.840 g, 2.1 mmol) was added dropwise over 10 min to the stirred solution, and the mixture was stirred for 4 days. The suspension was filtered and the solid urea washed with dichloromethane. The filtrate was washed with water (20 mL), 1 M HCl (20 mL) and brine (20 mL), and was then dried (Na_2SO_4). The solvent was evaporated to give a colourless oil. Purification by chromatography using ethyl acetate as eluent yielded the diester (5) as a colourless *oil* (0.90 g, 64%) (Found: C, 65.7; H, 10.8. $C_{36}H_{70}O_{10}$ requires C, 65.7; H, 10.6%). IR ν_{max} 3463(br), 2873, 1737 cm^{-1}. ^1H NMR δ 0.75–0.91, m, 15H, phytanyl CH_3s; 0.91–1.72, m, 24H, phytanyl CHs and CH_2s; 2.62, m, 4H, succinyl CH_2s; 3.04, s, 1H, OH; 3.56–3.73, m, 22H, OCH_2CH_2O; 4.10, m, 2H, CH(Me)$CH_2C\mathbf{H}_2O$; 4.23, m, 2H, $OCH_2C\mathbf{H}_2OC(O)$. ^{13}C NMR δ 19.4–19.7, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_3; 24.4, CH_2; 24.75, CH_2; 27.9, CH; 29.0, succinyl CH_2; 29.1, succinyl CH_2; 29.8, CH; 32.7, CH; 35.4, CH_2; 35.5, CH_2; 37.2, CH_2; 37.3, CH_2; 39.3, CH_2; 61.7, CH_2; 63.35, CH_2; 63.8, CH_2; 69.1, CH_2; 70.3, CH_2; 70.5, CH_2; 72.5, CH_2; 172.3, C(O). Mass spectrum (CI) *m/z* 663 ($[M+1]^+$, 100%).

Monobenzyl Tetraethylene Glycol (8)

A mixture of tetraethylene glycol (30 g, 205 mmol), benzyl chloride (6.5 g, 51.3 mmol) and 40% (w/w) aqueous sodium hydroxide (15 mL) was heated at 100°C with stirring for 24 h. The cooled reaction mixture was diluted with water (20 mL) and extracted with ether (3×200 mL). The combined organic extracts were washed with brine (100 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give the crude material as a pale orange oil. Purification by chromatography using ethyl acetate provided the monobenzyl ether (8) (10.5 g, 72%) as a pale yellow oil. ^1H NMR δ 2.82, br s, 1H, OH; 3.57–3.73, m, 16H, OCH_2CH_2O; 4.57, s, 2H, $C\mathbf{H}_2Ar$; 7.27–7.36, m, 5H, ArH. Mass spectrum (ESI) *m/z* 307 ($[M+Na]^+$). These data were consistent with those previously reported.[24]

1-Benzyl-22-(tetrahydropyranyl) Heptaethylene Glycol (10)

(i) Using sodium hydride. A 60% dispersion of sodium hydride (217 mg, 5.42 mmol) was added to the benzyl-protected polyether (8) (1.03 g, 3.62 mmol) in THF (15 mL), and the mixture was stirred at room temperature for 30 min. A solution of the tosylate (9)[20] (1.10 g, 4.34 mmol) in THF (10 mL) was added to the reaction mixture, which was stirred for a further 24 h. The solvent was removed under reduced pressure, and the residue was diluted with saturated aqueous NH_4Cl (5 mL) and water (75 mL). The aqueous solution was extracted with dichloromethane (3×50 mL), the combined organic extracts were washed with brine (75 mL), dried (Na_2SO_4) and the solvent was removed under vacuum to give the crude material as a dark brown oil. Purification by chromatography using 98:2 CH_2Cl_2/MeOH as eluent gave the heptaethylene glycol derivative (10) as an *oil* (1.29 g, 71%) (Found: C, 61.6; H, 9.2. $C_{26}H_{44}O_9 \cdot H_2O$ requires C, 61.6; H, 8.9%). ^1H NMR δ 1.46–1.84, m, 6H, THP CH_2s; 3.44–3.75, m, 28H, OCH_2CH_2O; 3.81–3.92, m, 2H, THP CH_2O; 4.56, s, 2H, $C\mathbf{H}_2Ar$; 4.62, br t, *J* 3.4 Hz, 1H, $OC\mathbf{H}(CH_2)O$; 7.27–7.35, m, 5H, ArH. ^{13}C NMR (50 MHz) δ ($CDCl_3$) 19.4, CH_2; 25.4, CH_2; 30.5, CH_2; 62.2, CH_2; 66.6, CH_2; 69.4, CH_2; 70.6, CH_2; 73.2, CH_2Ar; 98.9, CH; 127.5, Ar; 127.7, Ar; 128.3, Ar; 138.2, Ar quat. Mass spectrum (CI) *m/z* 417 ([M−THP], 100%), 219 (18), 175 (25), 133 (20), 85 (65).

(ii) Using phase transfer catalysis. A solution of 40% (w/w) aqueous sodium hydroxide (10 mL, 20 equiv.) was added to a mixture of monobenzyl ether (8) (2.41 g, 8.48 mmol), the tosylate (9) (2.57 g, 10.17 mmol) and tetrabutylammonium hydrogen sulfate (288 mg, 0.85 mmol). The mixture was stirred vigorously for 3 days at 65°C, then was cooled to room temperature. Dichloromethane (100 mL) was added and the organic phase was washed with water (3×75 mL), brine (75 mL), dried (Na_2SO_4) and filtered through a plug of silica gel using ethyl acetate as eluent. After removing the solvent under reduced pressure, the resultant yellow liquid was purified by flash chromatography using 98:2 to 96:4 CH_2Cl_2/MeOH as eluent, to give the heptaethylene glycol derivative (10) (2.90 g, 68%) as a yellow oil. The data acquired were identical to those obtained for the preparation described above using sodium hydride.

Monobenzyl Heptaethylene Glycol (11)

10 M HCl (0.05 mL) was added to a stirred solution of the heptaethylene glycol derivative (10) (500 mg, 1.0 mmol) in a 1:1 mixture of CH_2Cl_2/MeOH (5 mL) at room temperature. After 6 h the solvent was removed under reduced pressure. The crude material was dissolved in ethyl acetate and the solution was filtered through Celite®. The solvent was removed under vacuum to give the monoprotected diol (11) as a pale yellow *oil* (416 mg, 100%) (Found: C, 57.7; H, 8.4. $C_{21}H_{36}O_8 \cdot 1¼H_2O$ requires C, 57.5; H, 8.8%). IR ν_{max} 3600–3200 cm^{-1}. ^1H NMR δ 2.10 (br) s, 1H, OH; 3.57–3.72, m, 28H, OCH_2CH_2O; 4.56, s, 2H, C**H**$_2$Ar; 7.29–7.35, m, 5H, ArH. ^{13}C NMR δ 61.6, CH_2; 69.4, CH_2; 70.2, CH_2; 70.5, CH_2; 72.6, CH_2; 73.2, CH_2; 127.6, Ar; 127.7, Ar; 128.3, Ar; 138.2, Ar quat. Mass spectrum (CI) *m/z* 417 ($[M+H]^+$, 100%), 327 (14), 219 (11), 175 (13), 133 (11), 91 (11).

Phytanyl 1-Benzyl Heptaethylene Glycol Succinate (6)

DMAP (11 mg, 0.09 mmol) was added to a solution of benzyl-protected heptaethylene glycol (11) (151 mg, 0.36 mmol), the hemisuccinate (3) (105 mg, 0.26 mmol) and morpho-CDI (134 mg, 0.32 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 16 h, and then was filtered through Celite®. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (75 mL). The organic phase was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and the solvent was removed under vacuum to give the crude product as a pale yellow oil. Purification by chromatography using ethyl acetate as eluent provided the succinic acid diester (6) (76 mg, 36%) as a colourless *oil* (Found: C, 67.5; H, 10.4. $C_{45}H_{80}O_{11}$ requires C, 67.8; H, 10.1%). IR ν_{max} 1738 cm^{-1}. ^1H NMR δ 0.81–0.90, m, 15H, phytanyl CH_3s; 1.01–1.67, m, 24H, phytanyl CHs and CH_2s; 2.59–2.67, m, 4H, succinyl CH_2s; 3.62–3.70, m, 26H, OCH_2CH_2O; 4.09–4.13, m, 2H, C**H**$_2$OH; 4.24, br t, *J* 4.9 Hz, 2H, C**H**$_2$$OCH_2$Ph; 4.56, s, 2H, CH_2Ph; 7.28–7.34, m, 5H, ArH. ^{13}C NMR δ 19.44–19.74, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.5, CH_2; 24.8, CH_2; 28.0, CH; 29.0, succinyl CH_2; 29.1, succinyl CH_2; 29.9, CH; 32.8, CH; 35.4, CH_2; 35.5, CH_2; 37.27, CH_2; 37.34, CH_2; 37.4, CH_2; 39.4, CH_2; 63.4, CH_2; 63.8, CH_2; 69.1, CH_2; 69.4, CH_2; 70.6, CH_2; 73.2, **C**H_2Ar; 127.6, Ar; 127.7, Ar; 128.3, Ar; 138.3, Ar quat.; 172.3, C(O). Mass spectrum (MALDI) *m/z* 822 ($[M+H+Na]^+$, 100%).

Phytanyl Heptaethylene Glycol Succinate (7)

A catalytic amount of 10% Pd/C was added to a solution of the benzyl ether (6) (856 mg, 1.07 mmol) in ethanol (25 mL), and the mixture stirred under an atmosphere of hydrogen for 60 h. The solution was filtered through Celite® and the filtrate was concentrated under reduced pressure to give the succinate (7) (759 mg, 100%) as a colourless oil. An analytically pure sample was obtained by HPLC purification (Whatman Partisil 10 column, 13.5 mL/min flow rate) using dichloromethane/methanol (97:3) as eluent (Found: C, 64.0; H, 10.6. $C_{38}H_{74}O_{11} \cdot {}^1/_3H_2O$ requires C, 64.0; H, 10.6%). IR ν_{max} 3600–3300, 1738 cm^{-1}. ^1H NMR δ 0.81–0.89, m, 15H, phytanyl CH_3s; 1.06–1.68, m, 24H, phytanyl CHs and CH_2s; 2.63, br t, *J* 3.6 Hz, 4H, succinyl CH_2s; 3.10, br s, 1H, OH; 3.57–3.74, m, 26H, OCH_2CH_2O; 4.10, br t, *J* 6.8 Hz, 2H, C**H**$_2$OH; 4.21–4.26, m, 2H, $CH(Me)CH_2CH_2O$. ^{13}C NMR δ 19.39–19.70, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.4, CH_2; 24.8, CH_2; 27.9, CH; 28.96, succinyl CH_2; 29.02, succinyl CH_2; 29.8, CH; 32.7, CH; 37.2, CH_2; 37.3, CH_2; 39.3, CH_2; 61.6, CH_2OH; 63.3, CH_2; 63.8, CH_2; 69.0, CH_2; 70.2, CH_2; 70.5, CH_2; 72.5, CH_2; 172.3, C(O). Mass spectrum (CI) *m/z* 708 ($[M+H]^+$, 14%), 487 (27), 425 (23), 327 (75), 133 (73), 89 (100).

Phytanyl Tripropylene Glycol Succinate (13)

To a solution of tripropyleneglycol[21] (12) (2.05 g, 10.6 mmol) and phytanyl hemisuccinate (3) (850 mg, 2.1 mmol) in dry dichloromethane (10 mL), was added morpho-CDI (1.08 g, 2.5 mmol), DMAP·HCl (113 mg, 0.71 mmol) and DMAP (86 mg, 0.71 mmol), and the mixture was stirred at room temperature for 48 h. The suspension was filtered and the residue was washed with dichloromethane (50 mL). The combined filtrates were evaporated and the residue was chromatographed (ethyl acetate/light petroleum, 1:1) to give the *succinate* (13) (980 mg, 80%) (Found: C, 69.2; H, 11.4. $C_{33}H_{64}O_7$ requires C, 69.2; H, 11.3%). IR ν_{max} ($CHCl_3$) 1731 cm^{-1}. ^1H NMR δ 0.81–0.91, m, 15H, phytanyl CH_3s; 1.0–1.7, m, 24H, phytanyl CHs and CH_2s; 1.79–1.91, m, 6H, CH_2C**H**$_2$$CH_2$; 2.61, s, 4H, succinyl CH_2s; 3.44–3.54, m, 4H, CH_2O; 3.61, t, 2H, CH_2O; 3.76, t, 2H, CH_2O; 4.11, t, 2H, $CH_2OC(O)$; 4.17, t, 2H, $CH_2OC(O)$. ^{13}C NMR δ 19.4–19.7, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.5, CH_2; 24.8, CH_2; 28.0, CH; 29.0, CH_2; 29.2, CH_2; 29.9, CH; 30.0, CH_2; 32.0, CH_2; 32.8, CH; 35.4, CH_2; 35.5, CH_2; 37.2–37.4, overlapping signals, CH_2; 39.4, CH_2; 61.9–62.2, overlapping signals, CH_2; 67.2, CH_2; 67.8, CH_2; 68.2, CH_2; 70.4, CH_2; 172.3, C(O). Mass spectrum (CI) *m/z* 573 ($[M+H]^+$, 100%).

(Diphytanyl)glyceryl Hemisuccinate (15)

Glycerol diphytanyl ether (14) (2.0 g, 3.06 mmol)[16] and succinic anhydride (0.919 g, 9.19 mmol) were stirred in dry pyridine (6 mL) for 3 days at room temperature. The mixture was diluted with chloroform (40 mL), and the solution was washed with water (2×25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed at high vacuum. The hemisuccinate (15) was obtained as a colourless *oil* (2.2 g, 97%) (Found $[M+H]^+$, 753.6997. $C_{47}H_{92}O_6$ requires $[M+H]^+$, 753.6972). IR ν_{max} 2923, 2867, 1744, 1715 cm^{-1}. ^1H NMR δ 0.73–0.93, m, 30H, phytanyl CH_3s; 0.93–1.74, m, 48H, phytanyl CHs and CH_2s; 2.67, br s, 4H, succinyl CH_2s; 3.41–3.72, 7H, m, CH_2 and CHO; 4.06–4.30, 2H, m, $CH_2OC(O)$. ^{13}C NMR δ 19.7, br s, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.4, CH_2; 24.5, CH_2; 24.8, CH_2; 28.0, CH_2; 28.8, succinyl CH_2; 29.7–29.9, overlapping signals, CH; 32.8, CH; 36.6, CH_2; 36.7, CH_2; 37.0, CH_2; 37.1, CH_2; 37.3–37.6, overlapping signals, CH_2; 39.4, CH_2; 64.4, CH_2; 69.0, CH_2; 70.1, CH_2: 70.3, CH_2; 76.5, CH; 172.0, C(O); 177.5, C(O). Mass spectrum (ESI, negative ion) *m/z* 1505.3 (2M, 100%); 752.8 (M). This compound hydrolysed readily and was converted immediately into the succinate (16).

(Diphytanyl)glyceryl Hexaethylene Glycol Succinate (16)

The hemisuccinate (15) (2.0 g, 2.66 mmol) and hexaethylene glycol (3.75 g, 13.3 mmol) were dissolved in dry dichloromethane (10 mL). Morpho-CDI (1.35 g, 3.2 mmol), DMAP (107 mg, 0.88 mmol) and DMAP·HCl (141 mg, 0.88 mmol) were added and the solution was stirred at room temperature for 3 days. The suspension was diluted with dichloromethane (40 mL), washed with water (2×25 mL), dried (Na_2SO_4) and the solvent was removed to give a colourless oil. Chromatography with ethyl acetate as eluent gave the succinate (16) as a colourless *oil* (1.97 g, 74%) (Found: C, 69.6; H, 11.6. $C_{59}H_{116}O_{12}$ requires C, 69.6; H, 11.5%). IR ν_{max} 3466, 2925, 2868, 1739 cm^{-1}. ^1H NMR δ 0.73–0.93, 30H, m, phytanyl CH_3s; 0.93–1.72, 48H, m, phytanyl CHs and CH_2s; 2.65, 4H, s, succinyl CH_2s; 3.40–3.71, 29H, m, OCH_2CH_2O and OCH_2C**H**(CH_2O); 4.07–4.32, 4H, m, $CH_2OC(O)$. ^{13}C NMR δ 19.4–19.8, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.4, CH_2; 24.7, CH_2; 27.9, CH; 28.9, succinyl CH_2; 29.6–29.8, overlapping signals, CH; 32.7, CH; 36.5, CH_2; 36.6, CH_2; 36.9–37.4, overlapping signals, CH_2; 39.3, CH_2; 61.6, CH_2; 63.8, CH_2; 64.3, CH_2; 69.0, CH_2; 70.0–70.5, overlapping signals, CH_2; 72.6, CH_2; 76.4, CH; 172.1, C(O); 172.2, C(O). Mass spectrum (FAB) *m/z* 1040 ($[M+H+Na]^+$, 100%), 780 (10).

(Phytanol Tetraethylene Glycol Succinate) Hemisuccinate (17)

Succinic anhydride (1.7 g, 16.7 mmol) was added portionwise to a solution of alcohol (4) (3.2 g, 5.6 mmol) in pyridine (20 mL), and the mixture was stirred at room temperature for 3 days. Chilled 2 M HCl (150 mL) was added and the aqueous solution was extracted with dichloromethane (3×300 mL). The combined organic extracts were washed with 1M HCl (300 mL), water (300 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by chromatography using 1:1 ethyl acetate/hexane to ethyl acetate to 95:5 ethyl acetate/ethanol as eluent provided the acid (17) (3.1 g, 83%) as a pale yellow *oil* (Found: C, 64.0; H, 9.7. $C_{36}H_{66}O_{11}$ requires C, 64.1; H,

9.9%). IR ν_{max} 3500–2500, 1734 cm^{-1}. ^1H NMR δ 0.83–0.90, m, 15H, phytanyl CH_3s; 1.03–1.68, m, 24H, phytanyl CHs and CH_2s; 2.62–2.67, m, 8H, succinyl CH_2s; 3.63–3.71, m, 12H, OCH_2CH_2O; 4.07–4.14, m, 2H, $CH(Me)CH_2CH_2O$; 4.23–4.27, m, 4H, $CH_2OC(O)$. ^{13}C NMR δ 19.4–19.7, m, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.5, CH_2; 24.8, CH_2; 28.0, CH; 29.0–29.3, m, CH_2s; 29.8, CH; 32.8, CH; 35.4, CH_2; 35.5, CH_2; 37.3, CH_2; 37.4, CH_2; 39.3, CH_2; 63.4, CH_2; 63.7, CH_2; 63.8, CH_2; 69.0, CH_2; 70.5, CH_2; 70.7, CH_2; 172.0, C(O); 172.4, C(O); 175.6, C(O)OH. Mass spectrum (MALDI) *m/z* 697 ($[M+Na]^+$, 100%).

(Phytanyl Hexaethylene Glycol Succinate) Hemisuccinate (18)

The hexaethylene glycol derivative (5) (0.80 g, 1.21 mmol) and succinic anhydride (361 mg, 3.6 mmol) were stirred in dry pyridine (4.5 mL) at room temperature under nitrogen for 45 h. The mixture was poured into cold 2 M HCl (20 mL) and was extracted with dichloromethane (3×130 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), filtered and the solvent was removed to give the *acid* (18) (0.84 g, 91%) (Found: C, 62.4; H, 10.15. $C_{40}H_{74}O_{13}\cdot{}^1/_2H_2O$ requires C, 62.2; H, 9.8%). IR ν_{max} 3474, 2931, 1734 cm^{-1}. ^1H NMR δ 0.75–0.94, m, 15H, phytanyl CH_3s; 0.94–1.75, m, 24H, phytanyl CHs and CH_2s; 2.62, m, 8H, succinyl CH_2s; 3.55–3.75, m, 20H, OCH_2CH_2O; 4.12, m, 2H, $CH(Me)CH_2C\mathbf{H}_2O$; 4.25, m, 4H, $OCH_2C\mathbf{H}_2OC(O)$.

(Phytanyl Heptaethylene Glycol Succinate) Hemisuccinate (19)

Succinic anhydride (84 mg, 0.84 mmol) was added to a solution of alcohol (7) (149 mg, 0.21 mmol) in pyridine (1 mL). The mixture was stirred for 40 h at room temperature and 1M HCl (30 mL) was added. The aqueous solution was extracted with dichloromethane (3×25 mL), and the combined organic extracts were washed with water (2×50 mL) and brine (50 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the acid (19) (163 mg, 96%) as a colourless viscous *oil* (Found: C, 62.1; H, 9.9. $C_{42}H_{78}O_{14}$ requires C, 62.5; H, 9.7%). IR ν_{max} 3500–2500, 1732 cm^{-1}. ^1H NMR δ 0.82–0.90, m, 15H, phytanyl CH_3s; 1.01–1.69, m, 24H, phytanyl CHs and CH_2s; 2.62–2.67, m, 8H, succinyl CH_2s; 3.61–3.75, m, 24H, OCH_2CH_2O; 4.07–4.14, m, 2H, $CH(Me)CH_2C\mathbf{H}_2O$; 4.22–4.29, m, 4H, $OCH_2C\mathbf{H}_2OCO$. ^{13}C NMR δ 19.39–19.70, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.4, CH_2; 24.8, CH_2; 27.9, CH; 28.96, succinyl CH_2; 29.01, succinyl CH_2; 29.4, succinyl CH_2; 29.8, CH; 32.7, CH; 35.35, CH_2; 35.44, CH_2; 37.2, CH_2; 37.3, CH_2; 39.3, CH_2; 63.4, CH_2; 63.8, CH_2; 68.9, CH_2; 69.0, CH_2; 70.4, CH_2; 70.6, CH_2; 172.0, C(O); 172.4, C(O); 175.0, C(O)OH. Mass spectrum (MALDI) *m/z* 846 ($[M+K]^+$, 46%), 829 ($[M+Na]^+$, 100).

Phytanyl Tripropylene Glycol Bissuccinate (20)

A solution of phytanyl tripropylene glycol succinate (13) (350 mg, 0.61 mmol) and succinic anhydride (120 mg, 1.2 mmol) in pyridine (5 mL) was stirred for 24 h at room temperature under nitrogen. The reaction mixture was poured into 3 M sulfuric acid (50 mL), and the suspension was extracted with chloroform (3×30 mL). The organic layer was washed with water (3×30 mL), then dried ($MgSO_4$) and evaporated. Purification by chromatography using ethyl acetate/hexane (1:1) as eluent provided the *succinate* (20) (340 mg, 82%) as a pale yellow oil (Found $[M+H]^+$, 673.4868. $C_{37}H_{68}O_{10}$ requires $[M+H]^+$, 673.4891; Found $[M+Na]^+$, 695.4715. $C_{37}H_{68}O_{10}$ requires $[M+Na]^+$, 695.4710). IR ν_{max} ($CHCl_3$) 1731 cm^{-1}. ^1H NMR δ 0.7–0.9, m, 15H, phytanyl CH_3s; 0.9–1.7, m, 24H, phytanyl CHs and CH_2s; 1.7–1.95, m, 6H, $CH_2CH_2CH_2$; 2.60, m, 8H, succinyl CH_2s; 3.40–3.55, m, 8H, CH_2O; 4.10–4.25, m, 6H, CH_2OCO; 5.4, (br)s, 1H, COOH. ^{13}C NMR δ 19.4–19.7, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.4, CH_2; 24.7, CH_2; 27.9, CH; 28.8–29.1, overlapping signals, succinyl CH_2s; 29.8, CH_2; 32.7, CH; 35.4, CH_2; 35.5, CH_2; 37.2, CH_2; 37.3, CH_2; 39.3, CH_2; 62.0, m, CH_2; 63.4, CH_2; 66.9–67.1, overlapping signals, CH_2; 67.6–67.8, overlapping signals, CH_2; 172.4, overlapping signals, C(O); 176.2, COOH. Mass spectrum (ESI, positive ion) *m/z* 695.3 ($[M+Na]^+$, 100%), 673.4 ($[M+H]^+$, 30).

((Diphytanyl)glyceryl Hexaethylene Glycol Succinate) Hemisuccinate (21)

Compound (16) (1.83 g, 1.80 mmol) and succinic anhydride (504 mg, 5.40 mmol) were stirred in dry pyridine (4 mL) under nitrogen at room temperature for 3 days. The mixture was diluted with chloroform (50 mL) and washed with water (4×25 mL), dried (Na_2SO_4), filtered and the solvent removed. The residue was chromatographed using ethyl acetate/hexane (50:50 to 100:0) to give the title compound (1.62 g, 81%) as a colourless *oil* (Found $[M+Na]^+$, 1139.8509, $C_{63}H_{120}O_{15}$ requires $[M+Na]^+$, 1139.8525). ^1H NMR δ 0.75–0.92, m, 30H, phytanyl CH_3s; 0.92–1.72, m, 48H, phytanyl CHs and CH_2s; 2.65, broad s, 8H, succinyl CH_2s; 3.40–3.72, m, 27H, CH_2O and CHO; 4.06–4.32, m, 6H, CH_2OCO. ^{13}C NMR δ 19.5–19.8, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.4, CH_2; 24.7, CH_2; 27.9, CH; 28.9, CH_2; 29.7, CH_2; 29.8, CH; 32.7, CH; 36.6, CH_2; 36.7, CH_2; 37.0, CH_2; 37.1, CH_2; 37.2–37.5, overlapping signals, CH_2; 39.3, CH_2; 63.8, CH_2; 64.3, CH_2; 69.0, broad, CH_2; 70.1, CH_2; 70.5, CH_2; 70.7, CH_2; 76.5, CH; 172.0–172.3, overlapping signals, CO. Mass spectrum (ESI, positive ion) *m/z* 1139.6 ($[M+Na]^+$, 100%), 1140.6 ($[M+Na+H]^+$, 70%), 1117.6 ($[M+H]^+$, 19%), 1155.4 ($[M+K]^+$, 18%).

Monophytanyl Triethylene Glycol (22)

A 60% dispersion of sodium hydride (1.56 g, 39.0 mmol) was added portionwise to a solution of triethylene glycol (5.86 g, 39.0 mmol) in THF (120 mL). The mixture was heated at reflux for 20 min, and was allowed to cool to room temperature. A solution of phytanyl bromide[25] (2.82 g, 7.80 mmol) in THF (5 mL) was added and the mixture heated at reflux for 30 min, cooled to room temperature and water (10 mL) was added. The solvent was removed under vacuum and the residue was diluted with 3 M HCl (50 mL). The aqueous phase was extracted with ethyl acetate (3×40 mL), and the combined organic extracts were washed with water (50 mL), brine (50 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product as a dark brown oil. Purification by chromatography using ethyl acetate as eluent afforded the alcohol (22) (1.9 g, 57%) as a colourless *oil* (Found: C, 67.0; H, 11.8. $C_{26}H_{54}O_4$ requires C, 67.3; H, 11.6%). IR ν_{max} 3500–3200 cm^{-1}. ^1H NMR δ 0.80–0.89, m, 15H, phytanyl CH_3s; 1.00–1.68, m, 24H, phytanyl CHs and CH_2s; 2.39, br s, 1H, OH; 3.45–3.52, m, 2H, $CH(Me)CH_2C\mathbf{H}_2O$; 3.57–3.75, m, 12H, OCH_2CH_2O. ^{13}C NMR δ 19.63–19.70, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.5, CH_2; 24.8, CH_2; 28.0, CH; 29.9, CH; 32.8, CH; 36.5, CH_2; 36.6, CH_2; 37.25–37.48, overlapping signals, CH_2s; 39.4, CH_2; 61.8, CH_2OH; 69.9, CH_2; 70.0, CH_2; 70.4, CH_2; 70.6, CH_2; 72.5, CH_2CH_2OH. Mass spectrum (ESI, positive ion) *m/z* 884 ($[2M+Na]^+$, 56%), 453 ($[M+Na]^+$, 65), 448 ($[M+H_2O]^+$, 100), 431 ($[M+H]^+$, 30).

Monophytanyl Tri(ethylene Glycol) Tosylate (23)

Triethylamine (3.74 g, 37.0 mmol) was added to a mixture of alcohol (22) (3.19 g, 7.40 mmol) and *p*-toluenesulfonyl chloride (1.69 g, 8.88 mmol) in dichloromethane (20 mL), and the solution was stirred for 12 h at room temperature. Dichloromethane (40 mL) was added and the organic layer was washed with 3 M HCl (50 mL), water (50 mL), brine (50 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude product was obtained as a yellow oil. Purification by chromatography using dichloromethane as eluent afforded the tosylate (23) as a pale yellow viscous oil (4.05 g, 94%) (Found: C, 67.9; H, 10.3. $C_{33}H_{60}O_6S$ requires C, 67.8; H, 10.3%). ^1H NMR δ 0.80–0.88, m, 15H, phytanyl CH_3s; 1.00–1.65, m, 24H, phytanyl CHs and CH_2s; 2.44, s, 3H, $ArC\mathbf{H}_3$; 3.43–3.51, m, 2H, $CH(Me)CH_2C\mathbf{H}_2O$; 3.55–3.62, m, 8H, OCH_2CH_2O; 3.66–3.71, m, 2H, $C\mathbf{H}_2CH_2OTs$; 4.16, m, 2H, $C\mathbf{H}_2OTs$; 7.34 and 7.80, AA´XX´, 4H, Ar**H**. ^{13}C NMR δ 19.63–19.70, overlapping signals, non-terminal CH_3s; 21.6, $ArCH_3$; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.5, CH_2; 24.8, CH_2; 28.0, CH; 29.9, CH; 32.8, CH; 36.6, CH_2; 36.7, CH_2; 37.3, CH_2; 37.38, CH_2; 37.43, CH_2; 37.5, CH_2; 39.4, CH_2; 68.7, CH_2; 69.2, CH_2; 69.9, CH_2; 70.1, CH_2; 70.5, CH_2; 70.7, CH_2; 70.8, CH_2; 128.0, Ar; 129.8, Ar;

132.9, Ar quat.; 144.7, Ar. Mass spectrum (ESI) *m/z* 1191 ([2M+Na]$^+$, 25%), 608 ([M+Na]$^+$, 91), 585 ([M+H]$^+$, 100).

Monophytanyl Heptaethylene Glycol (24)

A 60% dispersion of sodium hydride (243 mg, 6.07 mmol) was added to a solution of tetraethylene glycol (1.18 g, 6.07 mmol) in THF (25 mL). The mixture was heated at reflux for 10 min and cooled to room temperature. A solution of the tosylate (23) (710 mg, 1.21 mmol) in THF (25 mL) was added and the mixture heated at reflux for 30 min The solvent was removed under vacuum and the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with water (30 mL). The aqueous phase was extracted with dichloromethane (3×25 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford the crude product as a dark yellow oil. Purification by chromatography using 9:1 ethyl acetate/MeOH as eluent gave the alcohol (24) as a pale yellow *oil* (611 mg, 83%) (Found: C, 67.0; H, 11.8. $C_{34}H_{70}O_8$ requires C, 67.3; H, 11.6%). IR ν_{max} 3600–3100 cm^{-1}. ^{1}H NMR δ 0.81–0.87, m, 15H, phytanyl CH_3s; 1.06–1.64, m, 24H, phytanyl CHs and CH_2s; 2.73, br s, 1H, OH; 3.43–3.51, m, 2H, CH(Me)CH_2C**H**$_2$O; 3.56–3.74, m, 28H, OCH_2CH_2O. ^{13}C NMR δ 19.71, br s, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.4, CH_2; 24.5, CH_2; 24.8, CH_2; 28.0, CH; 29.9, CH; 32.8, CH; 36.6, CH_2; 36.7, CH_2; 37.29–37.53, overlapping signals, CH_2s; 39.4, CH_2; 61.8, CH_2OH; 69.9, CH_2; 70.1, CH_2; 70.4, CH_2; 70.6, CH_2; 72.6, CH_2CH_2OH. Mass spectrum (ESI) *m/z* 631 ([M+H+Na]$^+$, 38%), 630 ([M+Na]$^+$, 100).

Monophytanyl Hepta(ethylene Glycol) Tosylate (25)

Triethylamine (2.34 g, 23.2 mmol) was added to a mixture of alcohol (24) (2.81 g, 4.63 mmol) and *p*-toluenesulfonyl chloride (1.32 g, 6.94 mmol) in dichloromethane (20 mL) and the solution was stirred for 12 h at room temperature. Dichloromethane (40 mL) was added and the organic layer was washed with 3 M HCl (50 mL), water (50 mL), brine (50 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude product was obtained as a dark yellow oil. Chromatography using ethyl acetate as eluent afforded the tosylate (25) as a pale yellow viscous *oil* (3.25 g, 92%) (Found: C, 64.8; H, 9.8. $C_{41}H_{76}O_{10}S$ requires C, 64.7; H, 10.1%). ^{1}H NMR δ 0.82–0.88, m, 15H, phytanyl CH_3s; 1.00–1.64, m, 24H, phytanyl CHs and CH_2s; 2.44, s, 3H, ArC**H**$_3$; 3.44–3.51, m, 2H, CH(Me)CH_2C**H**$_2$O; 3.53–3.70, m, 26H, OCH_2CH_2O; 4.13–4.18, m, 2H, C**H**$_2$OTs; 7.33 and 7.80 (AA′XX′), 4H, ArH. ^{13}C NMR δ 19.64–19.73, overlapping signals, non-terminal CH_3s; 21.6, $ArCH_3$; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.5, CH_2; 24.8, CH_2; 27.9, CH; 29.9, CH; 32.8, CH; 36.6, CH_2; 36.7, CH_2; 37.28–37.51, overlapping signals, CH_2s; 39.4, CH_2; 68.7, CH_2; 69.2, CH_2; 69.9, CH_2; 70.1, CH_2; 70.57, CH_2; 70.59, CH_2; 70.8, CH_2; 128.0, Ar; 129.8, Ar; 133.1, Ar quat.; 144.7, Ar. Mass spectrum (ESI) *m/z* 785 ([M+H+Na]$^+$, 12%), 784 ([M+Na]$^+$, 100).

Monophytanyl Decaethylene Glycol (26)

A 60% dispersion of sodium hydride (166 mg, 4.16 mmol) was added to a solution of triethylene glycol (625 mg, 4.16 mmol) in THF (30 mL). The mixture was heated at reflux for 10 min and cooled to room temperature. A solution of the tosylate (25) (633 mg, 0.83 mmol) in THF (10 mL) was added, and the mixture heated at reflux for 20 min. The solvent was removed under vacuum and the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and diluted further with water (30 mL). The aqueous phase was extracted with dichloromethane (3×25 mL), the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford the crude product as a yellow oil. Chromatography using 9:1 to 8:2 ethyl acetate/MeOH as eluent afforded the decaethylene glycol derivative (26) as a pale yellow viscous *oil* (536 mg, 87%) (Found: C, 64.0; H, 11.1. $C_{40}H_{82}O_{11}\cdot\frac{1}{2}H_2O$ requires C, 64.2; H, 11.2%). IR ν_{max} 3600–3200 cm^{-1}. ^{1}H NMR δ 0.80–0.90, m, 15H, phytanyl CH_3s; 1.01–1.66, m, 24H, phytanyl CHs and CH_2s; 1.91, br s, 1H, OH; 3.44–3.51, m, 2H, CH(Me)CH_2C**H**$_2$O; 3.54–3.76, m, 40H, OCH_2CH_2O. ^{13}C NMR δ 19.68, br s, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.5, CH_2; 24.8, CH_2; 28.0, CH; 29.9, CH; 32.8, CH; 36.6, CH_2; 36.7, CH_2; 37.3, CH_2; 37.38, CH_2; 37.43, CH_2; 37.5, CH_2; 39.4, CH_2; 61.7, CH_2; 69.9, CH_2; 70.1, CH_2; 70.3, CH_2; 70.6, CH_2; 72.6, CH_2. Mass spectrum (ESI) *m/z* 778 ([M+K]$^+$, 12%), 762 ([M+Na]$^+$, 100), 759 (25).

Monophytanyl Undecaethylene Glycol (27)

To a stirred solution of tetraethylene glycol (6.7 g, 34 mmol) in THF (50 mL) was added sodium (0.53 g) in small pieces, and the mixture was stirred until all the sodium had been consumed. A solution of the tosylate (25) (3.5 g, 4.6 mmol) in THF (25 mL) was added and the mixture was heated at reflux for 90 min. Water (150 mL) was added to the reaction mixture which was extracted with dichloromethane (1×100 mL, 1×60 mL). The combined organic layers were washed with water (100 mL), brine (50 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product (27) as a pale yellow *oil* (3.18 g, 88%) (Found: C, 64.6; H, 10.8. $C_{42}H_{86}O_{12}$ requires C, 64.4; H, 11.0%). ^{1}H NMR δ 0.82–0.89, m, 15H, phytanyl CH_3s; 1.0–1.7, m, 24H, phytanyl CHs and CH_2s; 2.17, br s, 1H, OH; 3.47, m, 2H, and 3.59–3.80, m, 44H, CH_2O. Mass spectrum (ES) *m/z* 822 ([M+K]$^+$, 17%), 806 ([M+Na+H]$^+$, 100). The alcohol (27) was further characterized as its tosylate (28). Thus a mixture of the alcohol (27) (2.2 g, 2.8 mmol) and *p*-toluenesulfonyl chloride (1.07 g, 5.63 mmol) in dry dichloromethane (7 mL) was stirred at room temperature under nitrogen. Triethylamine (1.42 g, 14.1 mmol) was added and the solution continued stirring for 24 h. The reaction mixture was diluted with dichloromethane (80 mL), and the organic layer was washed with 3 M HCl (50 mL), water (2×50 mL), and brine (50 mL). The solution was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by chromatography (CH_2Cl_2/MeOH, 96:4) on silica to afford the tosylate (28) (2.14 g, 81%) as a colourless *oil* (Found: C, 62.4; H, 10.0. $C_{49}H_{92}O_{14}S$ requires C, 62.8; H, 9.9%). ^{1}H NMR δ 0.82–0.89, m, 15H, phytanyl CH_3s; 1.0–1.7, m, 24H, phytanyl CHs and CH_2s; 2.45, s, 3H, C**H**$_3$Ar; 3.47, m, 2H, and 3.59–3.80, m, 44H, CH_2O; 4.15, t, 3H, *J* 6.8Hz, CH_2OTs; 7.32 and 7.77 (AA′XX′), 4H, ArH. *m/z* (ESI) 961 ([M+H+Na]$^+$, 54%), 960 ([M+Na]$^+$, 100).

N-*Methylphytanamide (30)*

Phytanoic acid (29)[22] (6.4 g, 20.5 mmol) was dissolved in thionyl chloride (10 mL) and the mixture was heated under reflux for 1.5 h. Excess thionyl chloride was removed by distillation and the product was dried under reduced pressure for 1 h. The resultant pale yellow oil was added dropwise into a solution of methylamine in tetrahydrofuran (2 M solution in THF, 50 mL), and the mixture was stirred for 18 h. The solution was concentrated under reduced pressure and the product partitioned between water (150 mL) and dichloromethane (100 mL). The organic layer was collected and was washed with 1 M HCl (2×50 mL), then with brine (50 mL) and dried ($MgSO_4$). The solvent was removed and the crude product purified by chromatography (CH_2Cl_2/MeOH, 96:4–90:10) to give the amide (30) as a colourless *oil* (4.77 g, 70%) (Found: C, 77.7; H, 13.5; N, 4.4. $C_{21}H_{43}NO$ requires C, 77.5; H, 13.3; N, 4.3%). IR ν_{max} 3292, 3092, 1644, 1556 cm^{-1}. ^{1}H NMR δ 0.81–1.64, m, 37H, phytanyl CHs, CH_2s and CH_3s; 1.93, m, and 2.19, m, 2H, C**H**$_2$CONHCH$_3$; 2.79 and 2.81, s, 3H, NCH_3; 5.30, br s, 1H, NH. ^{13}C NMR δ 19.6, non-terminal CH_3s; 22.5, CH_3; 22.6, CH_3; 24.4, CH_2; 24.7, CH_2; 26.1, NCH_3; 27.9, CH; 30.7, CH; 32.7, CH; 37.0–37.4, overlapping signals, CH_2; 39.3, CH_2; 44.35, CH_2; 44.42, CH_2; 173.4, C(O). Mass spectrum (CI) *m/z* 326 (M^+), 270.

Methyl Phytanyl Amine (31)

A mixture of *N*-methylphytanamide (29) (4.0 g, 12.3 mmol) and lithium aluminium hydride (pellets 95%, 2.0 g) in THF (100 mL) was heated under reflux for 2 h. The reaction mixture was cooled, excess lithium aluminium hydride was destroyed, and solid salts were filtered off. The filtrate was evaporated, the residue was dissolved in dichloromethane (100 mL) and the solution was washed with water (50 mL), dried ($MgSO_4$) and the solvent was removed. The crude product was chromatographed (CH_2Cl_2/MeOH/aq-NH_3, 90:10:1–80:20:1) to give methylphytanylamine (31) (2.08 g, 54%) as a colourless *oil* (Found: C, 79.3;

H, 14.5; N, 4.5. $C_{21}H_{45}N\cdot{}^1/_3H_2O$ requires C, 79.4; H, 14.5; N, 4.4%). IR ν_{max} (film) 3392 cm^{-1}. ^1H NMR δ 0.82–1.5, m, 39H, phytanyl CHs, CH_2s and CH_3s; 2.44, s, 3H, NCH_3; 2.54, m, 2H, C**H**$_2$NH. ^{13}C NMR δ 19.7, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.4, CH_2; 24.5, CH_2; 24.8, CH_2; 28.0, CH; 31.0, CH; 32.8, CH; 36.2, NCH_3; 36.8, overlapping signals, CH_2; 37.4, overlapping signals, CH_2; 39.4, CH_2; 49.9, CH_2N. Mass spectrum (ES) *m/z* 419 (M^+, 100%).

N-*Methylphytanylamine Hemisuccinamide (32)*

Methylphytanylamine (31) (1.0 g, 3.2 mmol) and succinic anhydride (1.0 g, 10 mmol) were dissolved in pyridine (5 mL) and the solution was stirred at room temperature for 18 h. The solvent was removed, and the crude product was dissolved in dichloromethane (50 mL). The organic solution was washed with 2 M HCl (20 mL), then with water (20 mL) and finally dried ($MgSO_4$). The crude product was obtained after removal of the solvent and was chromatographed (CH_2Cl_2/MeOH, 98:2–95:5) to give *N*-methylphytanylamine hemisuccinamide (32) (1.3 g, 100%) as a colourless *oil* (Found $[M+H]^+$, 412.3789. $C_{25}H_{49}NO_3$ requires $[M+H]^+$, 412.3790). IR ν_{max} 3300–2500(br), 1746, 1716, 1634, 1597. ^1H NMR δ 0.82–1.55, m, 39H, phytanyl CHs, CH_2s and CH_3s; 2.69, m, 4H, succinyl CH_2s; 2.95 and 3.01, s, 3H, NCH_3; 3.25–3.5, m, 2H, CH_2N. ^{13}C NMR δ 19.4–19.7, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.4, CH_2; 24.8, CH_2; 27.9, CH; 28.6, CH_2; 30.0–30.3, overlapping signals, CH_2; 30.8, CH; 32.7, CH; 33.8, NCH_3; 34.1, CH_2; 34.2, CH_2; 35.2, NCH_3; 37.4, overlapping signals, CH_2; 39.3, CH_2; 46.6, CH_2N; 48.4, CH_2N; 171.9, C(O); 176.5, COOH. Mass spectrum (ESI, negative ion) *m/z* 822 (dimer, 100%), 412 (1).

N-*Methylphytanamine (*N-*Methyl*-N´*-methyl-3,6,9-trioxa-1,11-diaminoundecane) Succinamide (34)*

N-Methylphytanylamine hemisuccinamide (32) (447 mg, 1.1 mmol), the diamine (33)[23] (1.2 g, 5.5 mmol) and DCC (270 mg, 1.3 mmol) were dissolved in dry dichloromethane (50 mL), and the mixture was stirred for 96 h at room temperature under nitrogen. The white precipitate formed was removed by filtration, and the crude product obtained from the filtrate was chromatographed (CH_2Cl_2/MeOH, 85:5) to give the succinamide (34) as a colourless *oil* (313 mg, 69%). ^1H NMR δ 0.82–1.55, m, 39H, phytanyl CHs, CH_2s and CH_3s; 2.45, (br) s, NH; 2.64, m, 4H, succinyl CH_2s; 2.76, m, 2H, C**H**$_2$NH; 2.91, 2.96, 3.01, 3.11, singlets, 6H, C(O)NCH_3; 3.36, m, 2H, C**H**$_2$NC(O); 3.59, m, 14H, CH_2s. This compound was used immediately in the next step.

*(*N-*Methylphytanamine (*N *-Methyl*-N´*-methyl-3,6,9-trioxa-1,11-diaminoundecane) Succinamide) Hemisuccinamide (35)*

From reaction with succinic anhydride. The succinamide (34) (461 mg, 0.75 mmol) and succinic anhydride (200 mg, 2 mmol) were dissolved in pyridine (10 mL), and the solution was stirred at room temperature for 48 h. The solvent was removed and the crude product was purified by chromatography (CH_2Cl_2/MeOH/AcOH, 84:15:1 as eluent) to give the acid (35) (530 mg, 100%) as a colourless *oil* (Found: C, 62.8; H, 10.2; N, 5.7. $C_{39}H_{75}N_3O_8\cdot1½H_2O$ requires C, 63.2; H, 10.6; N, 5.7%). IR ν_{max} ($CHCl_3$) 1731, 1632 cm^{-1}. ^1H NMR δ 0.82–1.55, m, 39H, phytanyl CHs, CH_2s and CH_3s; 2.68, m, 8H, succinyl CH_2s; 2.91, 2.96, 3.01, 3.09, 3.11, singlets, 9H, NCH_3; 3.36, m, 2H, $CH(Me)CH_2C$**H**$_2$N; 3.60, m, 16H, $N(Me)C$**H**$_2C$**H**$_2$O and OC**H**$_2C$**H**$_2$O. ^{13}C NMR (signals from the different conformational isomers are recorded as observed) δ 19.4–19.7, overlapping signals, non-terminal CH_3s; 22.6, CH_3; 22.7, CH_3; 24.3, CH_2; 24.4, CH_2; 24.7, CH_2; 27.9, CH; 28.0, CH_2; 28.4, CH_2; 29.6, CH_2; 29.8, CH_2; 30.8, CH; 32.7, CH; 33.6, NCH_3; 33.9, NCH_3; 34.1, CH_2; 34.3, NCH_3; 35.1, NCH_3; 35.3, CH_2; 36.8, NCH_3; 36.9, NCH_3; 37.3, overlapping signals, CH_2; 39.3, CH_2; 46.3, CH_2N; 47.8, CH_2N; 48.0, CH_2N; 48.3, CH_2N; 49.4, CH_2N; 49.8, CH_2N; 68.4, CH_2; 69.1, overlapping signals, CH_2; 70.2–71.0, overlapping signals, CH_2; 171.9–172.7, overlapping signals, C(O); 175.0, COOH. Mass spectrum (MALDI) *m/z* 715, 714; (ESI) *m/z* 736.4 ($[M+Na]^+$, 100%).

Acknowledgments

We acknowledge financial support from the Australian Government through the Cooperative Research Centre for Molecular Engineering and Technology, and Pacific Dunlop Ltd for the award of a Pacific Dunlop Scholarship (B.J.P.).

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