Synthesis of Lipophilic 3,4-Disubstituted 2,5-Dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxyl Radicals

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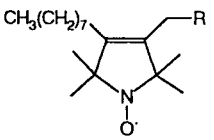
The Grignard reaction of the esters **2a, b** with octylmagnesium bromide proceeds through an allylic rearrangement to give the 3-methylene-4-octyl radical **3**. Bromination of its *O*-acetyl derivative **5** gives allylic bromides **6** and **7** as key intermediates toward lipophilic spin labels.

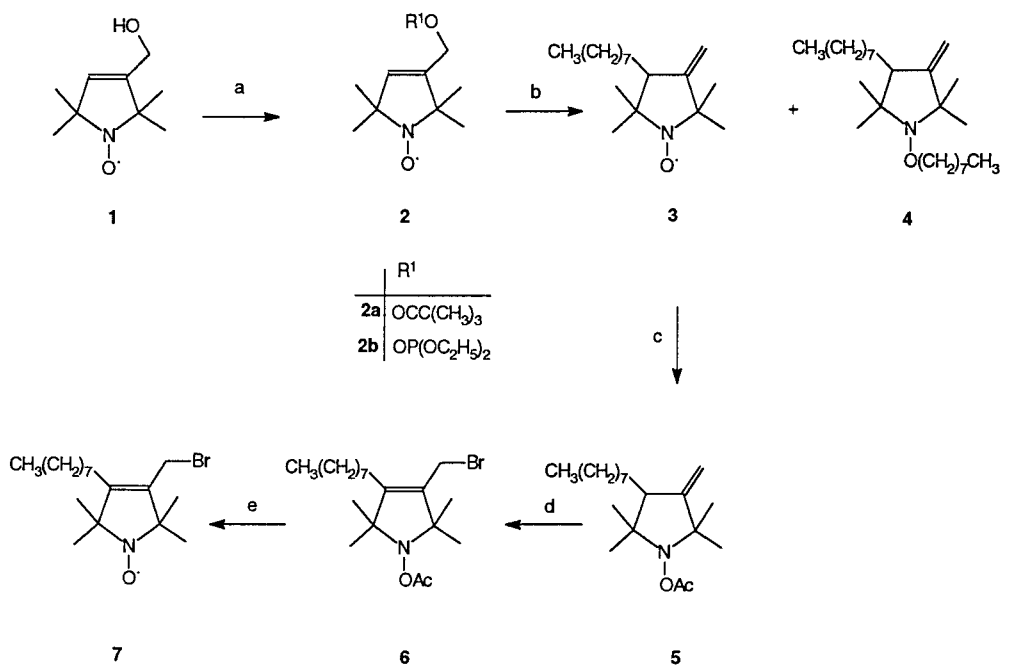
Thiol-reactive spin labels are important tools for the investigations of structure and function in proteins.[1-3] The most useful compounds so far appear to be the thiosulfonate derivatives obtained from the allylic alcohol **1**, although the disulfide, diseleno, thiouronium and selenouronium derivatives are expected to be equally useful.[4-9] The *endo* double bond in these compounds ensures planarity of the ring and increases the reactivity of substituents at the allylic position.[10,11]

To extend the range of potential applications of this important class of spin labels, we report here general routes for the synthesis of 3,4-disubstituted 2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxyl nitroxide radicals. These routes permit the introduction of a reactive function at the 3-position and a second substitutent at the 4-position. The latter may be chemically inert, and selected to confer unique properties to the reagent.



For example, a bulky group may be chosen to constrain the motion of the nitroxide in the protein. Such a reagent would be useful in exploring local steric features in the protein environment. Alternatively, a highly hydrophobic group may be chosen to direct the reagent to liphopilic domains in the system under study. For example, a sufficiently hydrophobic reagent would selectively modify sulfhydryl groups on the nonpolar surface of membrane proteins. A set of topo-selective reagents could be based on this strategy. To illustrate the synthetic routes, we describe the preparation of a number of new hydrophobic sulfhydryl reactive and phosphonium spin-labels bearing an octyl substituent at the 4-position of the five-membered nitroxide ring.

Our strategy was to introduce a medium length alkyl chain into pyrrol-1-yloxyl radical. The octyl chain was



Scheme 1

(a) $ClCO(CH_3)_3$ or $ClPO(OC_2H_5)_2$ / CH_2Cl_2, pyridine or Et_3N / 0°C → r.t. / 3-5 h / 58-78 %. (b) 1. $C_8H_{17}MgBr$ / CuCN / Et_2O / -30°C → 0°C / 4 h, 2. NH_4Cl / MnO_2 / $CHCl_3$ / O_2 / r.t. / 20 min. / **3** (33) %, **4** (30 %). (c) 1. ascorbic acid / dioxane / H_2O / 40°C / 15 min., 2. AcCl / Et_3N /$CHCl_3$ / 0°C → r.t./ 1h / 65 %. (d) NBS / AIBN / CCl_4 / 76 °C / 16 h / 55 %. (e) 1. $NaOCH_3$ / THF / r.t. / 40 min, 2. MnO_2 / $CHCl_3$ / O_2 / r.t. / 20 min. / 40 %.

introduced at low temperatures (−30–0 °C) by Grignard reaction in the presence of copper(I) cyanide to the γ-position of esters **2a, b** bearing the bulky pivaloyloxymethyl and diethylphosphonatomethyl groups, respectively, to avoid α-alkylation.[12,13] However, during alkylation the esters **2a, b** produced the rearranged paramagnetic compound **3**; in a parallel reaction the alkylation of *N*-oxyl function had also occurred resulting in the diamagnetic compound **4**.[14] To introduce a functionalizable arm on paramagnetic alkene **3** we utilized our experience on allylic bromination with 1,3-dibromo-5,5-dimethylhydantoin (DDH) or *N*-bromosuccinimide (NBS) of bridgehead *exo* methylenic pyrrolidine radicals.[8,9] The *N*-oxyl function was protected by reduction to hydroxylamine followed by acetylation with acetyl chloride yielding the diamagnetic protected compound **5**. The allylic bromination which took place with migration of the *exo* double bond into the ring gave the diamagnetic allylic bromine **6**, which could be deprotected to labile *N*-hydroxy compound with a catalytic amount of freshly made sodium methoxide in tetrahydrofuran. After oxidation with activated manganese(IV) oxide, the key intermediate paramagnetic allylic bromide **7** was obtained (Scheme 1).

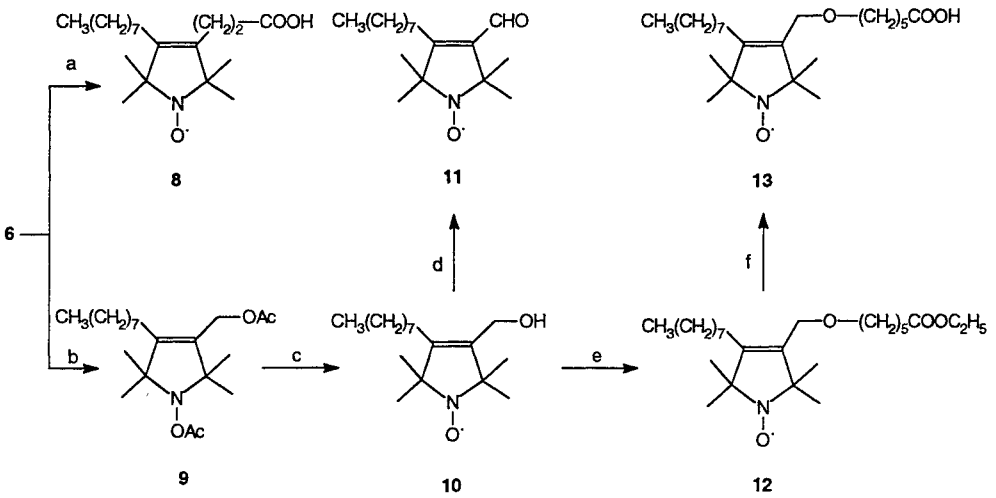
The alkylation of diethyl malonate with allylic bromide **6** under phase-transfer conditions gave the alkyl diethyl malonate derivative which was not isolated but hydrolysed directly to the unsaturated carboxylic acid derivative **8**. The reaction of **6** with sodium acetate gave the diacetate **9**, which after mild hydrolysis and aeration in the presence of lead(IV) oxide gave the allylic alcohol **10**. The oxidation of allylic alcohol **10** with activated manganese(IV) oxide gave the α,β-unsaturated aldehyde **11**, a potential substrate for a Wittig reaction toward diene fatty acids. Compound **10** was converted to ethyl (*Z*)-7-oxaoctadec-9-enoic acid derivative **12** by reaction with ethyl 6-bromohexanoate. The hydrolysis of ester **12** gave acid **13** which with the chosen octyl chain mimics the natural oleic acid (Scheme 2). The allylic bromide **7** with triarylphosphines gave spin labelled phosphonium ions **14a, b** which are important in investigation of membrane potentials.[15] Previously, we reported the synthesis of 2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxyl radicals bearing a triarylphosphonium substituent at the 3-position.[16] This class of spin labels, in principle, are able to modify the physical properties with an additional substituent at the 4-position. For example, a hydrophobic substituent could be selected to achieve any desired association constant with the membrane surface.[17,18]

To obtain the thiol specific spin labels, the allylic bromide **7** was reacted with $NaSSO_2Me$, thiourea and selenourea to give the thiosulfonate **15** and the more water soluble thiouronium **16a** and selenouronium **16b** salts, respectively (Scheme 3). The spin-labelling experiments with

Table. Compounds **2–16** Prepared

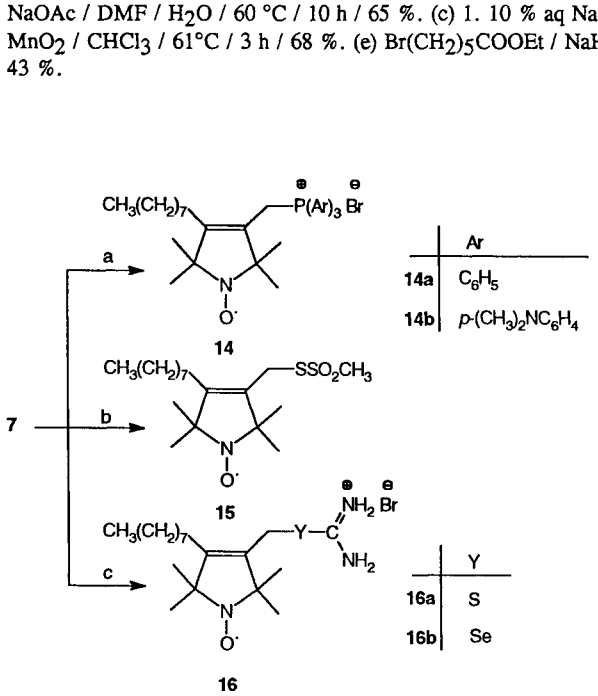
Product[a]	Yield (%)	mp (°C)	IR (neat or Nujol) ν (cm⁻¹)	MS (EI) *m/z* (%)
2a	58	97–98	1740 (C=O)	254 (M^+, 21), 239 ($M^+ - CH_3$, 7), 122 (239 − HOCOBu-*t*, 60), 107 (122 − CH_3, 100)
2b	78	oil	1270 (P=O)	306 (M^+, 25), 155 [$M^+ - CH_3 - PO(OEt)_2$, 100], 122 ($C_9H_{14}^+$, 52), 107 (122 − CH_3, 77)
3	33	oil	1660 (C=C)	266 (M^+, 100), 236 ($M^+ - NO$, 59), 109 ($M^+ - NO - CH_3 - C_8H_{16}$, 74), 41 ($C_3H_5^+$, 72)
4	30	oil	1650 (C=C)	379 (M^+, 6), 364 ($M^+ - CH_3$, 100), 252 ($M^+ - CH_3 - C_8H_{16}$, 20)
5	65	oil	1760 (C=O), 1640 (C=C)	309 (M^+, 1), 294 ($M^+ - CH_3$, 14), 267 ($M^+ - CH_2CO$, 12), 252 (267 − CH_3, 100)
6	55	oil	1760 (C=O), 1640 (C=C)	387/389 (M^+, 1/1), 372/374 ($M^+ - CH_3$, 31/31), 330/332 ($M^+ - CH_3 - CH_2CO$, 99/100), 308 (M^+ − Br, 21), 266 (308 − CH_2CO, 36), 250 (330/332 − HBr, 26)
7	40	oil	1640 (C=C)	344/346 (M^+, 36/36), 329/331 ($M^+ - CH_3$, 11/11), 250 ($M^+ - CH_3$ − Br, 100), 152 (M^+ − Br − C_8H_{17}, 39)
8	37	oil	1720 (C=O)	324 (M^+, 65), 310 ($[M + H]^+ - CH_3$, 100), 309 ($M^+ - CH_3$, 87), 294 ($M^+ - NO$, 75), 197 ($M^+ - CH_3 - C_8H_{16}$, 19)
9	65	oil	1760, 1740 (C=O), 1660 (C=C)	367 (M^+, 1), 352 ($M^+ - CH_3$, 46), 310 ($M^+ - CH_3 - CH_2CO$, 100), 43 (44)
10	60	oil	3400 (OH)	282 (M^+, 70), 267 ($M^+ - CH_3$, 100), 250 ($M^+ - CH_3$ − OH, 28), 155 ($M^+ - CH_3 - C_8H_{16}$, 63)
11	68	oil	1670 (C=O), 1640 (C=C)	280 (M^+, 100), 265 ($M^+ - CH_3$, 64), 250 ($M^+ - NO$, 45), 207 ($M^+ - C_3H_7NO$, 60), 152 ($M^+ - CH_3 - C_8H_{17}$, 87)
12	27	oil	1730 (C=O)	425 ($[M + H]^+$, 5), 379 ($[M + H]^+ - C_2H_5OH$, 8), 310 ($[M + H]^+ - (H_2)_3CO_2Et$, 20), 143 [$C_2H_5O_2C(CH_2)_5^+$, 44], 88 [$C_2H_5O_2HC(CH_2)^+$, 100]
13	43	oil	1700 (C=O)	398 ($[M + 2H]^+$, 4), 397 ($[M + H]^+$, 8), 396 (M^+, 5), 284 ($[M + 2H - C_5H_9CO_2H]^+$, 100)[b]
14a	65	81–83		528 ($[M + H]^+$, 100), 527 (M^+, 85), 262 (PPh_3^+, 58)[b]
14b	42	118–120		657 ($[M + H]^+$, 87), 656 ($[M^+$, 68), 391 (PAr_3^+, 100), 271 (PAr_2^+, 96)[b]
15	76	oil	1640 (C=C)	378 ($[M + 2H]^+$, 48), 266 ($[M + 2H - HSSO_2CH_3]^+$, 100)[b]
16a	39	63–65	1680, 1660 (C=N)	342 ($[M + 2H]^+$, 9), 308 ($[M + 2H - H_2S]^+$, 9), 266 ($[M + 2H - S{=}C(NH)_2]^+$, 100), 152 ($[M + H - S{=}C(NH)_2 - C_8H_{17}]^+$, 43)[b]
16b	44	68–70	1680, 1630 (C=N)	386/387/388/389/390 ($[M + 2H]^+$, 2.8/3.9/3.0/3.7/3.1), 266 ($[M + 2H - Se{=}C(NH)_2]^+$, 100), 152 ($[M + H - Se{=}C(NH)_2 - C_8H_{17}]^+$, 61)

[a] Satisfactory microanalyses obtained: C ± 0.13, H ± 0.17, N ± 0.12.
[b] FAB mass spectrum.



Scheme 2

(a)1. $CH_2(COOEt)_2$ / K_2CO_3 / 18-crown-6 / dioxane / 100 °C / 3 h, 2. 10 % aq NaOH / EtOH / r.t. / 1 h / 5 % H_2SO_4 / 37 %. (b) NaOAc / DMF / H_2O / 60 °C / 10 h / 65 %. (c) 1. 10 % aq NaOH / EtOH / r.t. / 1 h, 2. PbO_2 / $CHCl_3$ / O_2 / r.t. / 15 min./ 60 %. (d) MnO_2 / $CHCl_3$ / 61°C / 3 h / 68 %. (e) $Br(CH_2)_5COOEt$ / NaH / THF / DMF / 0°C → 67 °C / 1 h / 27 %. (f) KOH / EtOH / r.t. / 3 h / 43 %.



Scheme 3

(a) $P(Ar)_3$ / $CHCl_3$ / 61 °C / 2 h / 42-65 %. (b) $NaSSO_2CH_3$ / EtOH / H_2O / 78 °C / 30 min. / 76 %. (c) $(NH_2)_2CS$ or $(NH_2)_2CSe$ / EtOH / 78 °C / 1 h / 39-44 %.

these novel lipophilic SH specific reagents are part of an ongoing collaboration.[5,6]

In conclusion, the synthetic route described herein enables us to introduce alkyl chains into a spin label molecule which could be transformed further to several new lipophilic spin label reagents.

Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were performed on Heraeus Micro U/E apparatus or (Hal) were carried out titrimetrically by Schöniger's method. The IR (Specord 75) spectra of the compounds were in each case consistent with the assigned structures. Mass spectra were taken on a Finnigan MAT 8430 mass spectrometer/SS300 data acquisition system. Operating conditions: U_{acc} = 3 kV, R = 1250, EI: E_{el} = 70 eV, I_{el} = 0.5 mA, $T_{ion\ source}$ = 250 °C. FAB: Iontech FAB gun (Xe), in *m*-nitrobenzyl alcohol matrix. Samples were introduced via the direct insertion probe. Assignments were corroborated by high-resolution mass measurements made at R = 10000 by the peak matching technique, with perfluorokerosene as the reference material. Flash column chromatography on silica gel was performed with Merck Kieselgel 60 (0.040–0.063 mm). Qualitative TLC was carried out on commercially prepared plates (20 × 20 × 0.2 cm) coated with Merck Kieselgel GF_{254}. Compound **1**[3] was prepared according to published procedures. Physical and spectral data of all new compounds are listed in the Table.

2,5-Dihydro-2,2,5,5-tetramethyl-3-pivaloyloxymethyl-1*H*-pyrrol-1-yloxyl Radical (2a):

To a stirred solution of allylic alcohol **1** (8.51 g, 50 mmol) in anhydr. pyridine (50 mL) was added dropwise pivaloyl chloride (6.03 g, 50 mmol) at 0 °C. After stirring for 3 h at r.t., the mixture was poured onto crushed ice (300 g), stirred for 30 min, filtered, dried at r.t. and recrystallised from hexane/Et_2O to give **2a** as pure yellow crystalls; yield: 7.40 g (58 %); R_f 0.44 (hexane/Et_2O, 2:1); mp 97–98 °C.

3-Diethylphosphonatomethyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxyl Radical (2b):

To a stirred solution of **1** (1.70 g, 10 mmol) and Et_3N (1.21 g, 12 mmol) in anhydr. CH_2Cl_2 (70 mL) was added diethyl chlorophosphate (1.72 g, 10 mmol) at 0 °C and the stirring was continued for 5 h at r.t. The mixture was washed with 5 % H_2SO_4 (20 mL), then with brine (20 mL), dried ($MgSO_4$) and evaporated to dryness to give **2b** as a yellow thick oil, yield: 2.38 g (78 %); R_f 0.38 (Et_2O/$CHCl_3$, 1:1).

2,2,5,5-Tetramethyl-3-methylene-4-octylpyrrolidin-1-yloxyl Radical (3) and 2,2,5,5-Tetramethyl-3-methylene-4-octyl-1-octyloxypyrrolidine (4):

Under N_2 atmosphere, a catalytic amount of CuCN (500 mg, 5.5 mmol) was added to a stirred solution of octylmagnesium bro-

mide, freshly prepared from octyl bromide (11.58 g, 60.0 mmol) and Mg turnings (1.46 g, 60.0 mmol) in anhydr. Et_2O (80 mL) at −30 °C. The mixture was stirred at −30 °C for 30 min after which a solution of allyl ester **2a** (7.63 g, 30.0 mmol) or **2b** (9.19 g, 30.0 mmol) in anhydr. THF (20 mL) was added during 20 min. The mixture was stirred at 0 °C for 4 h, then quenched with aq NH_4Cl solution (20 mL). The organic phase was separated, the aqueous phase was washed with Et_2O (2 × 50 mL), the combined organic phase was dried ($MgSO_4$) and evaporated in vacuo to give a pale yellow oil. The residue was taken up in $CHCl_3$ (80 mL), catalytic amount of active MnO_2 was added and O_2 was bubbled through it for 20 min. The deep orange solution was filtered, evaporated again to dryness and flash chromatographed on silica gel with hexane/Et_2O as eluent. The first colorless band was the diamagnetic byproduct **4**; yield: 3.41 g (30%); oil; R_f 0.44 (hexane); the second yellow band was the paramagnetic compound **3**; yield: 2.67 g (33%); oil; R_f 0.53 (hexane/Et_2O, 2:1).

1-Acetoxy-2,2,5,5-tetramethyl-3-methylene-4-octylpyrrolidine (5):
To a solution of radical **3** (3.0 g, 11.2 mmol) in dioxane (20 mL) was added a solution of ascorbic acid (8.80 g, 50.0 mmol) in water (10 mL) and the mixture was stirred at 40 °C under N_2 for 15 min. The colorless solution was extracted with $CHCl_3$ (2 × 25 mL) and dried ($MgSO_4$) under N_2. First Et_3N (1.21 g, 12.0 mmol) and then AcCl (0.942 g, 12.0 mmol) were added at 0 °C. The stirring was continued for 1 h at r.t., the mixture was filtered and evaporated to dryness. The residue was dissolved in brine and extracted with Et_2O (3 × 20 mL). The organic layer was dried ($MgSO_4$), evaporated and the residue was purified by flash chromatography (hexane/Et_2O) giving the diamagnetic title compound **5** as a colorless oil, yield: 2.25 g (65%); R_f 0.6 (hexane/Et_2O, 2:1).

1-Acetoxy-3-bromomethyl-2,5-dihydro-2,2,5,5-tetramethyl-4-octyl-1*H*-pyrrole (6):
To a solution of *O*-acetate **5** (2.20 g, 7.1 mmol) was added the brominating reagent NBS (1.28 g, 7.2 mmol) or DDH (1.03 g, 3.6 mmol) and α,α′-azoisobutyronitrile (AIBN) (32.8 mg, 0.2 mmol) in anhydr. CCl_4 (40 mL) and the mixture was refluxed for 16 h. The reaction was monitored by TLC (hexane/Et_2O). The succinimide or 5,5-dimethylhydantoin was filtered and washed with CCl_4 (10 mL). The filtrate was evaporated, the residue was taken up in Et_2O, washed with brine, dried ($MgSO_4$), filtered and evaporated again. The residue was flash chromatographed (hexane/Et_2O) to give the diamagnetic allyl bromide **6** as a yellow oil; yield: 1.50 g (55%). R_f 0.52 (hexane/Et_2O, 2:1).

3-Bromomethyl-2,5-dihydro-2,2,5,5-tetramethyl-4-octyl-1*H*-pyrrol-1-yloxyl Radical (7):
The acetate **6** (1.50 g, 3.8 mmol) was dissolved in THF (15 mL) and NaOMe solution, freshly prepared from anhydr. MeOH (5 mL) and Na (23 mg, 1 mmol), was added. The mixture was kept at r.t. for 40 min, then the solvents were evaporated, and the residue was dissolved in Et_2O, the Et_2O phase was washed with brine and dried ($MgSO_4$). The residue was taken up in $CHCl_3$ (25 mL), MnO_2 (87 mg, 1 mmol) was added and O_2 was bubbled through the solution for 20 min. The orange solution was filtered, evaporated and purified by flash chromatography on silica gel, giving the paramagnetic allylic bromide **7** as an orange oil, yield: 520 mg (40%); R_f 0.46 (hexane/Et_2O, 2:1).

3-Carboxyethyl-2,5-dihydro-2,2,5,5-tetramethyl-4-octyl-1*H*-pyrrol-1-yloxyl Radical (8):
To a solution of the diamagnetic allylic bromide **6** (700 mg, 1.8 mmol) in dioxane (15 mL), were added K_2CO_3 (552 mg, 4.0 mmol), diethyl malonate (641 mg, 4.0 mmol) and 18-crown-6 (100 mg, 0.38 mmol) and the mixture was refluxed and stirred vigorously for 3 h. The reaction was monitored by TLC. After cooling, the mixture was diluted with THF (15 mL), filtered and the filtrate was evaporated. To the residue brine (10 mL) was added and acidified with 5% H_2SO_4 to pH 2, and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ layers were dried ($MgSO_4$) and evaporated to give the red-brown crude alkyl diethyl malonate. The crude malonic ester was dissolved in EtOH (15 mL) and 10% aq NaOH (5 mL) was added and the mixture allowed to stand at r.t. for 1 h. The mixture was acidified with 5% aq H_2SO_4 to pH 2, extracted with $CHCl_3$ (2 × 10 mL), the combined $CHCl_3$ layers were dried ($MgSO_4$) and evaporated. The product **8** was obtained by flash column chromatography ($CHCl_3$/Et_2O); yield: 220 mg (37%); R_f 0.57 ($CHCl_3$/MeOH, 9:1); yellow oil.

1-Acetoxy-3-acetoxymethyl-2,5-dihydro-2,2,5,5-tetramethyl-4-octyl-1*H*-pyrrole (9):
A solution of acetate **6** (4.0 g, 10.3 mmol) and NaOAc (1.64 g, 20 mmol) in DMF (15 mL) and water (2 mL) was heated at 60 °C for 10 h. The DMF was evaporated in vacuo, the residue was taken up in Et_2O (50 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$), evaporated and purified by flash chromatography (hexane/Et_2O) on silica gel to give diacetate **9** as a colorless oil; yield: 2.46 g (65%); R_f 0.38 (hexane/Et_2O, 2:1).

2,5-Dihydro-3-hydroxymethyl-2,2,5,5-tetramethyl-4-oxo-1*H*-pyrrol-1-yloxyl Radical (10):
The diacetate **9** (2.50 g, 6.8 mmol) was dissolved in EtOH (30 mL), then 10% aq NaOH solution was added (10 mL) and the mixture was kept at r.t. for 1 h. The reaction was monitored by TLC. After hydrolysis, the mixture was neutralised with 5% aq H_2SO_4, extracted with $CHCl_3$ (2 × 20 mL), dried ($MgSO_4$), filtered, evaporated to dryness. The residue was taken up in $CHCl_3$ (20 mL), PbO_2 (100 mg, 0.4 mmol) was added to the solution and aerated for 15 min, filtered, evaporated and purified by flash chromatography (hexane/EtOAc) to give allylic alcohol **10**; yield: 1.15 g (60%) as a red oil. R_f 0.37 (hexane/EtOAc, 2:1).

3-Formyl-2,5-dihydro-2,2,5,5-tetramethyl-4-octyl-1*H*-pyrrol-1-yloxyl Radical (11):
To a solution of allylic alcohol **10** (500 mg, 1.77 mmol) in anhydr. $CHCl_3$ (30 mL) was added activated MnO_2 (869 mg, 10 mmol) and the mixture was refluxed and stirred for 3 h. The MnO_2 was filtered, the filtrate was evaporated in vacuo, and flash chromatographed (hexane/Et_2O) to give title compound **11** as a red oil; yield: 340 mg (68%); R_f 0.41 (hexane/Et_2O, 2:1).

3-(8-Ethoxycarbonyl-7-oxaoctyl)-2,5-dihydro-2,2,5,5-tetramethyl-4-octyl-1*H*-pyrrol-1-yloxyl Radical (12):
A solution of the allylic alcohol **10** (1.13 g, 4.0 mmol) in anhydr. DMF (3 mL) was added dropwise to the stirred suspension of NaH (96 mg, 4 mmol) in anhydr. THF (5 mL) at 0 °C. The mixture was stirred for further 30 min at r.t. and ethyl 6-bromohexanoate (1.33 g, 6 mmol) dissolved in anhydr. THF (5 mL) was added dropwise. The mixture was stirred and refluxed for 1 h. After cooling a few drops of EtOH (0.3 mL) were added, then the mixture was diluted with Et_2O (20 mL) and washed with water (10 mL), dried ($MgSO_4$), flash chromatographed (hexane/Et_2O) on silica gel to give ester **12** as an orange oil; yield: 458 mg (27%); R_f 0.32 (hexane/Et_2O).

3-(8-Carboxy-7-oxaoctyl)-2,5-dihydro-2,2,5,5-tetramethyl-4-octyl-1*H*-pyrrol-1-yloxyl Radical (13):
To a solution of KOH (112 mg, 2 mmol) in EtOH (15 mL) was added the ester **12** (424 mg, 1 mmol) and the mixture was kept at r.t. for 3 h. The EtOH was evaporated, brine (10 mL) was added to the residue and extracted with Et_2O (5 mL). The aqueous phase was carefully acidified with 5% H_2SO_4 to pH 2, extracted with $CHCl_3$ (2 × 10 mL) and the combined $CHCl_3$ layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was flash chromatographed (hexane/EtOAc) to give the title carboxylic acid **13** as a yellow oil; yield: 170 mg (43%); R_f 0.33 (hexane/EtOAc, 2:1).

Phosphonium Salts 14a–b; General Procedure:
A mixture of allylic bromide **7** (500 mg, 1.44 mmol) and Ph_3P (377.69 mg, 1.44 mmol) or tris-(4-dimethylaminophenyl)phosphine (563 mg, 1.44 mmol) was refluxed in anhydr. $CHCl_3$ (5 mL) for 2 h. After cooling, the mixture was diluted with Et_2O (2 mL) upon which the phosphonium salt precipitated. The precipitate was filtered and washed with Et_2O.

2,5-Dihydro-2,2,5,5-tetramethyl-4-octyl-3-triphenylphosponiummethyl-1H-pyrrol-1-yloxyl Bromide Radical (**14a**); yield: 568 mg (65%); R_f 0.38 ($CHCl_3$/MeOH, 9:1); yellow crystalline solid, mp 81–83 °C.

2,5-Dihydro-3-[tris-(4-dimethylaminophenyl)phosphoniummethyl]-2,2,5,5-tetramethyl-4-octyl-1H-pyrrol-1-yloxyl Bromide Radical **(14b)**; yield: 445 mg (42%); R_f 0.40 ($CHCl_3$/MeOH, 9:1); yellow crystalline solid, mp 118–120°C.

2,5-Dihydro-3-methanethiosulfonylmethyl-2,2,5,5-tetramethyl-4-octyl-1*H*-pyrrol-1-yloxyl Radical (15):
To a solution of the allylic bromide **7** (500 mg, 1.44 mmol) in EtOH (10 mL) was added $NaSSO_2Me$ (402 mg, 3 mmol) in water (2 mL) and the mixture was refluxed for 30 min. EtOH was evaporated, the residue was taken up in $CHCl_3$ (15 mL), washed with brine, dried ($MgSO_4$), evaporated and purified by flash column chromatography on silica gel ($Et_2O/CHCl_3$) to give **15** as a reddish-brown oil; yield: 414 mg (76%); R_f 0.38 (hexane/EtOAc, 2:1).

Thiouronium and Selenouronium Salts 16a–b; General Procedure:
A mixture of the allyl bromide **7** (250 mg, 0.72 mmol) and thiourea (54 mg, 0.72 mmol) or selenourea (88 mg, 0.72 mmol) was refluxed in anhydr. EtOH (10 mL) for 30 min. After cooling, the EtOH was evaporated, the residue was taken up in $CHCl_3$ and purified by preparative TLC ($CHCl_3$/MeOH, 9:1).

2,5-Dihydro-2,2,5,5-tetramethyl-3-thiouroniummethyl-4-octyl-1H-pyrrol-1-yloxyl Bromide Radical **(16a)**: yield: 120 mg (39%); R_f 0.35 ($CHCl_3$/MeOH, 9:1); mp 63–65°C.

2,5-Dihydro-2,2,5,5-tetramethyl-3-selenouroniummethyl-4-octyl-1H-pyrrol-1-yloxyl Bromide Radical **(16b)**: yield: 150 mg (44%); yellow solid; R_f 0.28 ($CHCl_3$/MeOH, 9:1); mp 68–70°C.

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