Synthesis of 3,4-Disubstituted Pyrroline Nitroxides Containing Diphenylphosphane or Diphenylphosphane Oxide Substituents

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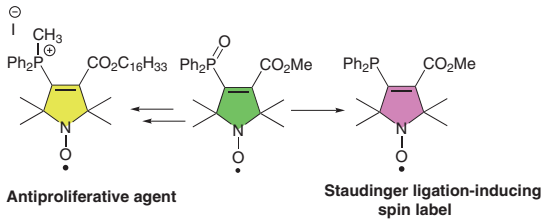
Dedicated to the memory of Prof. Ferenc Fülöp



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Abstract (Methyl 4-(diphenylphosphoryl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate-1-yl)oxydanyl was obtained as a key intermediate of the reaction starting from 3,4-dibromo-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxydanyl or (methyl 2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate-1-yl)oxidanyl. This key compound could be converted into an azido-specific Staudinger ligation-inducing spin label, amino- and thiol-specific spin label, or MITO-CP-like antiproliferative agent.

Key words free radicals, MITO-CP, lithiation, phosphane, Staudinger ligation, spin labeling

Nitroxides are the most common class of stable organic radicals bearing an unpaired electron on a non-bonding molecular orbital of the N–O bond. Nitroxides are extensively utilized in diverse science and technology, including spin labels,[1–3] spin traps,[4] magnetic resonance imaging reagents,[5] co-oxidants,[6] dynamic nuclear polarization agents,[7] and potential therapeutic agents.[8,9,] Among applications, cyclooctyne-attached nitroxide **I** facilitates azido-specific Cu(I)-free conjugation[10] and MITO-Carboxy Proxyl (Mito-CP) **II** is a potential therapeutic agent which accumulates in mitochondria[11] (Figure 1).

Organophosphorus compounds are a crucial molecular class in synthetic chemistry because of their applicability as building blocks in ligands of catalysts. In recent years, our laboratory successfully investigated reactions on stable free nitroxide radicals (Arbuzov,[12] Kabachnik–Fields,[13] McCormac,[14] and phospha–Brook rearrangement[15]), which yielded new paramagnetic organophosphorus compounds. In continuation of our research on pyrroline nitroxides diversely substituted with diphenylphosphane,[14] diphenylphosphane oxide,[14] or phosphonate ester,[12] we evaluated 3,4-disubstituted phosphorus-containing pyrroline nitroxide free radicals. The present study was focused on accessing and transforming these newly prepared compounds for realizing Staudinger ligation using azido-specific spin labels, thiol- and amino-specific spin labels, and an MITO-CP-like compound. Although the Staudinger reaction was reported a century ago,[16] it became one of the most significant bioconjugation techniques in the 1990s. Conjugation of fluorophores to biomacromolecules is well established in Bertozzi's works,[17–19] but, to the best of our knowledge, the Staudinger ligation[20] remains hither unexplored.

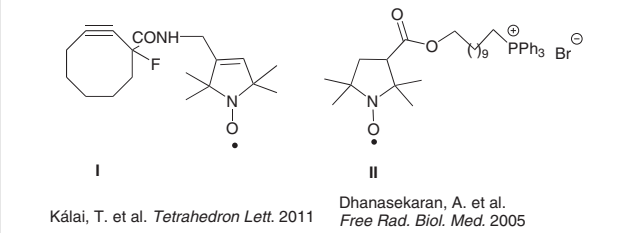
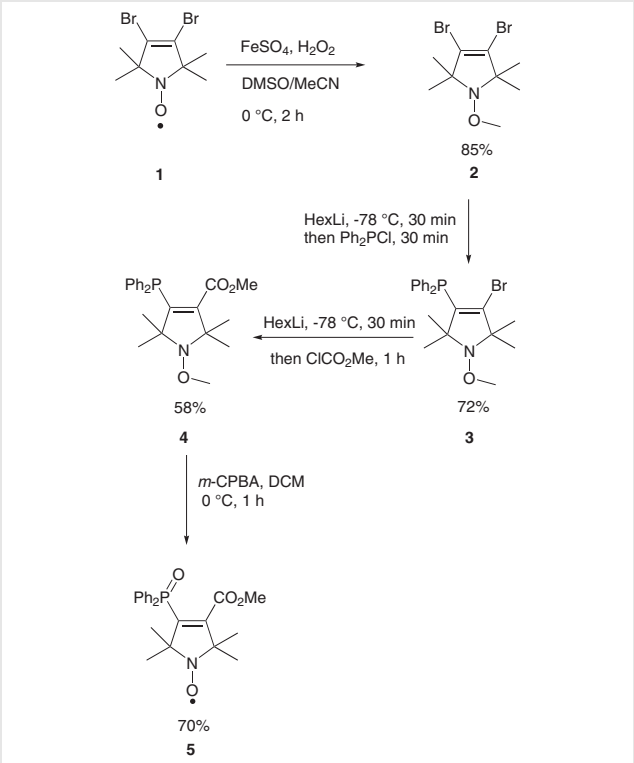


Figure 1 Pyrroline nitroxide containing orthogonal spin label (**I**) and pyrrolidine nitroxide containing mitochondria-directed potential therapeutic agent MITO-Carboxy Proxyl (**II**)

Herein, we report the synthesis of several 3,4-disubstituted nitroxides containing phosphorus substituents and their transformation to spin labels and potential therapeutic agents.

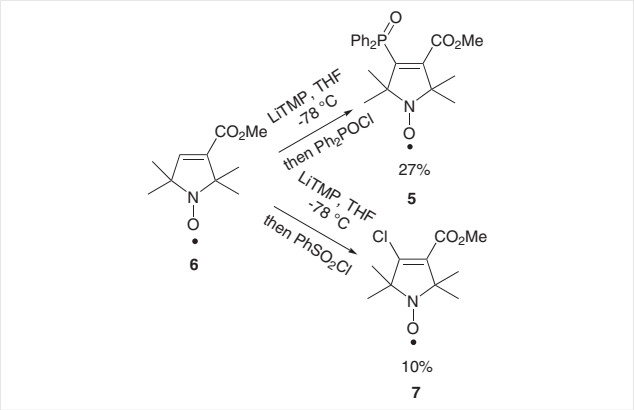
Starting from dibromo compound **1**,[21] the nitroxide function was protected as its *O*-methyl derivative. The methyl group was introduced with Fenton reaction[22] in dimethyl sulfoxide (DMSO)/acetonitrile solvent mixture in

the presence of Fe^{2+} ions; the solvent mixture was treated with H_2O_2. The resulting *O*-methyl derivative **2** was treated with hexyllithium to induce bromine/lithium exchange,[23] followed by treatment with chlorodiphenylphosphane to obtain compound **3**. Next, the purified compound **3** was reacted with hexyllithium and subjected to methyl chloroformate treatment to synthesize 3,4-disubstituted pyrroline nitroxide **4**. To restore the nitroxide function, compound **4** was treated with *meta*-chloroperbenzoic acid which removed the methyl group;[24] simultaneous oxidation of the phosphane function resulted in the formation of compound **5** (Scheme 1).



Scheme 1 Heterobifunctionalization of 3,4-dibromopyrroline nitroxide by lithiation

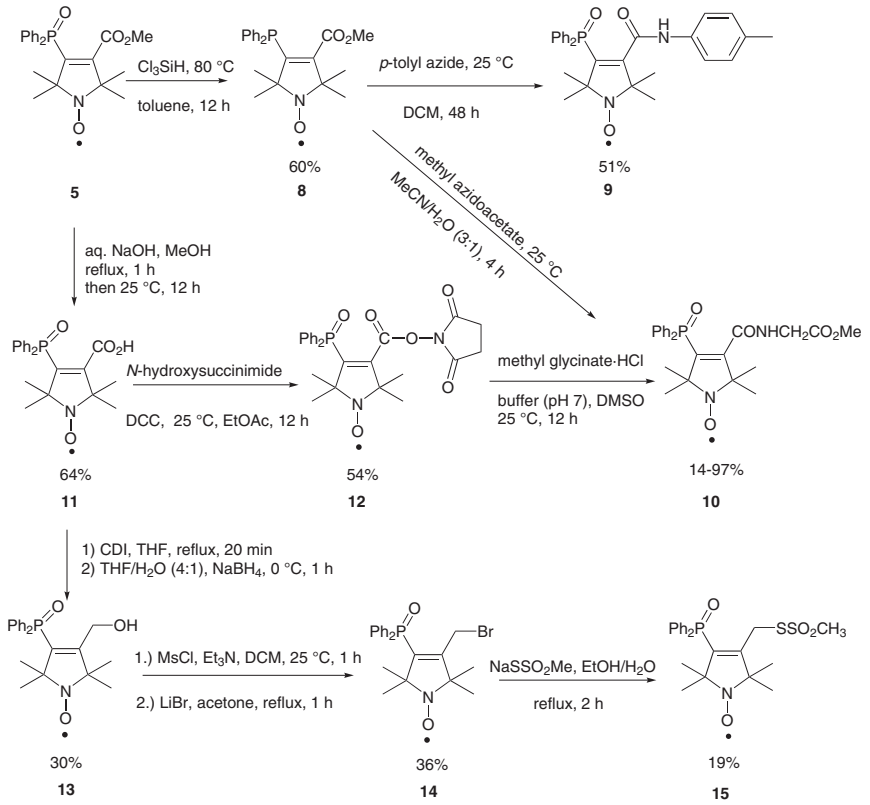
To expand the scope of the bifunctionalization process, we applied a proposed methodology to a more readily available starting material, ester **6**.[25] Previously, we described that deprotonation of this α,β-unsaturated ester with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) allows the incorporation of various functions at the β-position upon reacting with electrophiles.[26,27] Notably, after deprotonation in THF with LiTMP followed by treatment with diphenylphosphinoyl chloride, we also obtained compound **5** in a one-step reaction, although the yield (27%) was low. However, our attempts to use this methodology to achieve sulfones failed because, in an analogous reaction, benzenesulfonyl chloride unexpectedly led to the formation β-chloro-α,β-unsaturated ester **7** instead of an S–C bond formation (Scheme 2), as evidenced by NMR and MS measurements. To the best of our knowledge, this is the first report on the behavior of benzenesulfonyl chloride as a chlorinating agent for a nucleophilic center, although the yield of **7** compound was low (10%). However, its utilization as a chlorinating agent for alcohols was reported earlier.[28] Compound **5** was reduced with trichlorosilane[29] in toluene to obtain compound **8** as a Staudinger ligation inducing spin label compound (Scheme 3). To validate this result, **8** was treated with an aromatic azide, *p*-tolyl azide, and an amide derivative **9** was obtained.



Scheme 2 Reaction of the β-deprotonated α,β-unsaturated ester with diphenylphosphinoyl chloride and benzenesulfonyl chloride

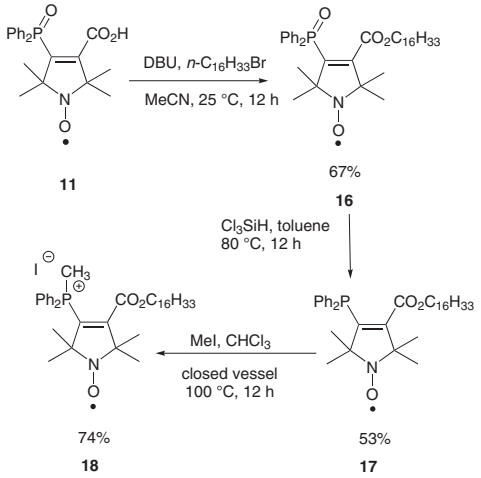
This label also functioned with aliphatic azide; treatment of **8** with methyl azidoacetate led to the formation of *N*-acylated glycine ester **10**.[17] Compound **5** was hydrolyzed with aq NaOH to a carboxylic acid **11**, which was a key compound that induced further transformations. Compound **11** could be transformed into an amino-specific *N*-hydroxysuccinimidate ester **12**. Acylation of methyl glycinate HCl salt in a neutral buffer in a DMSO solution[30] with succinate **12** led to the formation of compound **10**, which was previously prepared via Staudinger ligation from methyl azidoacetate. To access an SH-specific methanethiosulfonate, we selectively reduced carboxylic acid **11** to its corresponding alcohol **13** without reduction of the phosphane oxide function using the methodology of Sharma et al.[31] This reduction reaction proceeded from the non-isolated imidazolide of compound **11** followed by reduction with $NaBH_4$ in a THF/water 4:1 mixture and ultimately led to formation of alcohol **13** with an acceptable 32% yield. The alcohol **13** was converted into bromide **14** by first mesylation followed by treatment with LiBr in acetone. The paramagnetic bromo compound **14** was then treated with $NaSSO_2CH_3$ in aq ethanol to produce **15** with SH-specific methanethiosulfonate spin-label[32] with a bulky diphenylphosphane oxide substituent at position 4 in the pyrroline ring.

To construct the MITO-CP-like scaffold, compound **11** was esterified with hexadecyl bromide in the presence of DBU[33] to introduce a lipophilic chain. The hexadecyl ester



Scheme 3 Synthesis of azido-, amino- and SH-specific spin labels

16 was reduced to phosphane **17** in toluene with trichlorosilane. This phosphane **17** was treated with excess methyl iodide to synthesize phosphonium salt **18** with a yield of 74%. This yield was higher than that reported in our previous study[14] and was obtained with a smaller size of alkylating agent to generate a cationic center on the molecule (Scheme 4).



Scheme 4 Synthesis of new MITO-CP-like compounds

In summary, we demonstrated that both 3,4-dibromopyrroline nitroxide **1** and methyl 2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid nitroxide **6** were good starting substrates for constructing 3,4-disubstituted phosphorus substituent containing pyrroline nitroxides. These compounds were converted into orthogonal spin labels for Staudinger ligation and for developing amino- and SH-specific labels. The 3-carboxy-4-(diphenylphosphoryl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxydanyl (**11**) was the key to easily access to the cationic center, lipophilic moiety, and SOD-mimic (nitroxide) containing MITO-CP-like molecule. In addition, we developed a new synthetic route to chlorinate the (methyl 2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate-1-yl)oxydanyl (**6**) at position 4 in the pyrroline ring. Studies are ongoing to access the possible biological and biophysical applications of these derivatives.

Melting points were determined with a Boetius micro-melting point apparatus and are uncorrected. Elemental analyses (C, H, N, and S) were performed with a Fisons EA 1110 CHNS elemental analyzer. Mass spectra were recorded with a GCMS-2020 operated in EI mode (70 eV) and a ThermoScientific Q-Exactive HPLC/MS/MS with ESI(+) ionization. ^{1}H NMR spectra were recorded with a Bruker Avance 3 As-

cend 500 system operated at 500 MHz, and ^{13}C NMR spectra were obtained at 125 MHz, ^{31}P NMR 202 MHz in $CDCl_3$ or DMSO-d_6 at 298 K. The paramagnetic compounds were reduced to *N*-hydroxylamines with hydrazobenzene (DPPH, 5 equiv)/radicals in situ in the NMR tube. All monoradicals gave a triplet line at aN = 14.5 G. IR spectra were recorded with a Bruker Alpha FT-IR instrument with ATR support (diamond plate). Flash column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm). Compounds **1**,[21] **6**,[25] 4-azidotoluene,[34,] and methyl azidoacetate[35] were prepared as described previously; other reagents were purchased from Merck.

3,4-Dibromo-1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole (2)

To a stirred solution of **1** (2.98 g, 10.00 mmol) and $FeSO_4 \cdot 7H_2O$ (6.95 g, 25.00 mmol) in mixture of DMSO (30 mL) and CH_3CN (15 mL) was added 30% aq H_2O_2 (5 mL) at 0 °C over 2 h. Upon consumption of the starting material, the mixture was diluted with water (50 mL) and 10% aq Na_2SO_3 (25 mL). The aqueous solution was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated, and the crude product was purified by flash column chromatography (hexane/Et_2O, 9:1) to give **2**; yield: 2.65 g (85%); colorless oil; TLC (hexane/Et_2O, 9:1): R_f = 0.64.

IR: 2978, 1629 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 1.33 (s, 9 H), 1.29 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 126.4 (2 C), 71.9 (2 C), 65.3 (1 C), 29.7 (4 C).

MS (EI): *m*/*z* (%) = 315/313/311 ([M$^+$], 3/7/3), 300 (45), 298 (92), 296 (48), 219 (96), 217 (100), 138 (71).

Anal. Calcd for $C_9H_{15}Br_2NO$: C, 34.53; H, 4.83; N, 4.47. Found: C, 34.53; H, 4.92; N, 4.37.

3-Bromo-4-(diphenylphosphino)-1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole (3)

To a stirred solution of **2** (6.0 g, 19.00 mmol) in dry THF (30 mL) at –78 °C under N_2 was added dropwise hexyllithium (23.00 mmol, 10 mL in hexane (2.3 M)). After stirring for 30 min, Ph_2PCl (4.6 g, 20.90 mmol) in dry THF (15 mL) was added dropwise, and the mixture was continuously stirred for a further 30 min at –78 °C. The reaction was allowed to warm to 0 °C gradually. Sat. aq NH_4Cl solution (30 mL) was added to the mixture and it was extracted with Et_2O (3 × 20 mL); the combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified with flash chromatography (hexane/Et_2O, 95:5); yield: 5.76 g (72%); colorless oil; TLC (hexane): R_f = 0.42.

IR: 2975, 1582, 1480 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.37 (m, 10 H), 3.72 (s, 3 H), 1.41 (s, 3 H), 1.36, (s, 3 H), 1.29 (s, 3 H), 1.25 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.0 (d, *J* = 7 Hz, 1 C), 137.6 (d, *J* = 25 Hz, 1 C), 134.1 (d, *J* = 19.0 Hz, 2 C), 133.4 (4 C), 128.6 (2 C), 128.4 (d, *J* = 7.0 Hz, 4 C), 73.9 (d, *J* = 17 Hz, 1 C), 71.9 (d, *J* = 2.0 Hz, 1 C), 65.2 (1 C), 29.8 (2 C), 22.7 (2 C).

^{31}P NMR (202 MHz, $CDCl_3$): δ = –18.86.

MS (EI): *m*/*z* (%) = 419/417 ([M$^+$], 13/13), 404 (56), 402 (56), 373 (13), 371 (14), 292 (100), 185 (42).

Anal. Calcd for $C_{21}H_{25}BrNOP$: C, 60.30; H, 6.02; N, 3.35. Found: C, 60.45; H, 5.95; N, 3.38.

Methyl 4-(Diphenylphosphino)-1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4)

To a stirred solution of **3** (5.43 g, 13.00 mmol) in dry THF (15 mL) at –78 °C under N_2 was added dropwise hexyllithium (13.00 mmol, 5.6 mL in hexane (2.3 M)). After stirring for 30 min, methyl chloroformate (1.60 g, 17.00 mmol) in dry THF (5 mL) was added dropwise, and the mixture was stirred continuously for a further 30 min. The mixture was allowed to warm to 0 °C gradually, then aq sat. NH_4Cl solution (30 mL) was added to the mixture and it was extracted with Et_2O (3 × 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The crude product was purified with flash chromatography (hexane/EtOAc, 10:1); yield: 3.0 g (58%); white crystals; mp 127–129 °C; TLC (hexane/Et_2O, 2:1): R_f = 0.65.

IR: 2977, 1715, 1601, 1585 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73–7.28 (m, 10 H), 3.70 (d, *J* = 7.5 Hz, 3 H), 3.06 (d, *J* = 7.5 Hz, 3 H), 1.39 (s, 6 H), 1.28 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6 (1 C), 145.3 (d, *J* = 33 Hz, 1 C), 138.8 (d, *J* = 16 Hz, 2 C), 138.9 (1 C), 134.1 (4 C), 130.8 (2 C), 128.2 (d, *J* = 6.0 Hz, 4 C), 73.5 (d, *J* = 22 Hz, 1 C), 70.4 (1 C), 65.2 (1 C), 50.9 (1 C), 28.8 (2 C), 22.6 (2 C).

^{31}P NMR (125 MHz, $CDCl_3$): δ = –19.6.

MS (EI): *m*/*z* (%) = 397 ([M$^+$], 2), 382 (100), 336 (51), 242 (22), 183 (35).

Anal. Calcd for $C_{23}H_{28}NO_3P$: C, 69.51; H, 7.10; N, 3.52. Found: C, 69.53; H, 7.02; N, 3.57.

(Methyl 4-(Diphenylphosphoryl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate-1-yl)oxydanyl (5); Method A

To a stirred solution of **4** (2.6 g, 6.50 mmol) in DCM (20 mL) at 0 °C was added *m*-CPBA (4.7 g, 27.00 mmol) in 3–4 portions over 15 min. The solution was stirred for a further 30 min at 25 °C. The mixture was washed with 10% aq Na_2CO_3 solution (2 × 10 mL), and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by flash chromatography (hexane/EtOAc, 1:1, then $CHCl_3$/Et_2O, 2:1) to yield **5** (1.80 g, 70%) as yellow crystals; mp 194–196 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.34.

IR: 2975, 1728, 1618, 1590 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.97–7.93 (m, 4 H), 3.78 (s, 3 H), 1.55 (s, 3 H), 1.53 (s, 3 H), 1.39 (s, 3 H), 1.35 (s, 3 H); 6 H_{arom} are overlapped with diphenylhydrazine signals.

^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 165.3 (1 C), 149.6 (d, *J* = 5 Hz, 1 C), 139.0 (d, *J* = 108 Hz, 1 C), 132.2 (d, *J* = 10 Hz, 4 C), 132.0 (d, *J* = 8.5 Hz, 2 C), 131.1 (d, *J* = 70 Hz, 2 C), 128.3 (d, *J* = 12 Hz, 4 C), 73.4 (d, *J* = 10 Hz, 1 C), 70.9 (d, *J* = 10 Hz, 1 C), 51.6 (1 C), 25.1 (2 C), 24.4 (2 C).

^{31}P NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 33.95.

MS (EI): *m*/*z* (%) = 398 ([M], <1), 384 (27), 368 (3), 262 (5), 201 (45), 166 (100).

Anal. Calcd for $C_{22}H_{25}NO_4P$: C, 66.32; H, 6.32; N, 3.52. Found: C, 66.41; H, 6.50; N, 3.36.

(Methyl 4-(Diphenylphosphoryl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate-1-yl)oxydanyl (5); Method B

To a stirred solution of 2,2,6,6-tetramethylpiperidine (2.82 g, 20.00 mmol) in dry THF (10 mL) was added hexyllithium (10 mL in hexane 2.3 M) under N_2 at 0 °C and the mixture was continuously stirred for a further 15 min. The mixture was cooled to –78 °C, and **6** (3.96 g, 20.00 mmol) in dry THF (10 mL) was added dropwise and the mixture continuously stirred for 30 min at this temperature. A solution of diphen-

ylphosphinoyl chloride (4.73 g, 20.00 mmol) in THF (5 mL) was added dropwise, and the mixture was allowed to warm to 0 °C, sat. aq NH_4Cl solution (30 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The crude product was purified with flash chromatography (hexane/EtOAc) to give **5** (2.15 g, 27%) as yellow crystals; mp 194–195 °C. The spectroscopical data were identical with **5** obtained from Method A.

(Methyl 4-Chloro-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate-1-yl)oxydanyl (7)

To a stirred solution of 2,2,6,6-tetramethylpiperidine (705 mg, 5.00 mmol) in dry THF (10 mL) was added hexyllithium (3 mL in hexane 2.3 M) under N_2 at 0 °C and the mixture was continuously stirred for a further 15 min. The mixture was cooled to –78 °C, and **6** (990 mg, 5.00 mmol) in dry THF (10 mL) was added dropwise and the mixture was continuously stirred for 30 min. A solution of benzenesulfonyl chloride (883 mg, 5.00 mmol) in THF (5 mL) was added dropwise, and the mixture was allowed to warm to 0 °C, sat. aq NH_4Cl solution was added (30 mL), and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The crude product was purified with flash chromatography (hexane/Et_2O, 99:5) to yield **7** (120 mg, 10%) as yellow crystals, mp 108–110 °C; TLC (hexane/Et_2O, 4:1): R_f = 0.45.

IR: 2982, 1702, 1614 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 3.87 (s, 3 H), 1.50 (s, 6 H), 1.41 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 163.4 (1 C), 145.7 (1 C), 130.6 (1 C), 71.1 (1 C), 69.9 (1 C), 51.6 (1 C), 24.7 (2 C), 23.9 (2 C).

MS (EI): *m*/*z* (%) = 234/232 ([M^+], 9/28), 217 (36), 202 (52), 187 (29), 107 (100), 73 (56).

Anal. Calcd for $C_{10}H_{15}ClNO_3$: C, 51.62; H, 6.50; N, 6.02. Found: C, 51.46; H, 6.46; N, 5.84.

(Methyl 4-(Diphenylphosphino)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate-1-yl)oxydanyl (8)

Trichlorosilane (0.8 mL, 8.00 mmol) was added to a stirred solution of **5** (768 mg, 2.00 mmol) in anhyd toluene (10 mL) under argon at 0 °C. The resulting mixture was stirred at 80 °C for 12 h under argon, cooled to r.t. and then poured into a 250-mL beaker containing ice (40 g) and 10% aq Na_2CO_3 soln (10 mL). The mixture was extracted with EtOAc (2 × 15 mL) and the combined extracts were dried ($MgSO_4$), oxidized with PbO_2 (478 mg, 2.00 mmol) to convert hydroxylamine into nitroxide, filtered, and evaporated. The residue was purified by flash chromatography (hexane/Et_2O, 4:1); yield: 460 mg (60%); yellow crystals; mp 121–123 °C; TLC (hexane/Et_2O, 2:1): R_f = 0.42.

IR: 2977, 1707, 1583, 1557 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.42–7.38 (m, 6 H), 3.14 (s, 3 H), 1.45 (s, 6 H), 1.31 (s, 6 H), 4 H_{arom} are overlapped with diphenylhydrazine signals.

^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 165.7 (1 C), 146.1 (d, *J* = 30 Hz, 1 C), 144.5 (1 C), 134.5 (d, *J* = 8 Hz, 2 C), 134.0 (d, *J* = 20 Hz, 4 C), 128.8 (2 C), 128.4 (d, *J* = 7 Hz, 4 C), 73.4 (d, *J* = 20 Hz, 1 C), 70.3 (1 C), 51.0 (1 C), 25.4 (d, *J* = 5 Hz, 2 C), 24.6 (2 C).

^{31}P NMR (202 MHz, $CDCl_3$ + $(PhNH)_2$): δ = –18.66.

MS (EI): *m*/*z* (%) = 382 ([M^+], 2), 368 (12), 352 (15), 337 (100), 201 (30), 183 (27), 107 (22), 91 (17).

Anal. Calcd for $C_{22}H_{25}NO_3P$: C, 69.10; H, 6.59; N, 3.66. Found: C, 69.20; H, 6.67; N, 3.78.

(4-(Diphenylphosphoryl)-2,2,5,5-tetramethyl-*N*-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrole-3-carboxamide-1-yl)oxydanyl (9)

To a stirred solution of **8** (191 mg, 0.50 mmol) in CH_2Cl_2 (10 mL) was added 4-methylphenyl azide (70 mg, 0.50 mmol); the mixture was stirred for 2 d at r.t. and then concentrated. The crude product was purified by flash chromatography ($CHCl_3$/Et_2O, 9:1) to give **9** (120 mg, 51%) as yellow crystals; mp 231–233 °C; TLC ($CHCl_3$/Et_2O/MeOH, 4:1.5:0.5): R_f = 0.56.

IR: 3301, 2929, 1725, 1663, 1599, 1579 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 9.31 (s, 1 H), 7.85 (s, 4 H), 7.44 (s, 6 H), 7.29–7.24 (m, 4 H), 2.33 (s, 3 H), 1.59 (s, 6 H), 1.29 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 162.2 (d, *J* = 5 Hz, 1 C), 155.8 (d, *J* = 5 Hz, 1 C), 138.0 (d, *J* = 93 Hz, 1 C), 134.3 (d, *J* = 105 Hz, 2 C), 132.4 (2 C), 131.9 (d, *J* = 10 Hz, 4 C), 129.1 (2 C), 128.5 (d, *J* = 12.4 Hz, 4 C), 120.1 (2 C), 71.6 (d, *J* = 12 Hz, 1 C), 70.9 (d, *J* = 11 Hz, 1 C), 25.1 (2 C), 24.6 (2 C), 21.0 (1 C).

^{31}P NMR (202 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 23.98.

MS (EI): *m*/*z* (%) = 473 ([M^+], 7), 443 (44), 352 (15), 337 (89), 310 (40), 201 (100).

Anal. Calcd for $C_{28}H_{30}N_2O_3P$: C, 71.02; H, 6.39; N, 5.92. Found: C, 69.93; H, 6.15; N, 5.80.

(2-(4-(Diphenylphosphoryl)-*N*-(methoxycarbonylmethyl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxamide-1-yl)oxydanyl (10); Method A

To a stirred solution of **8** (95 mg, 0.25 mmol) in CH_3CN/water (3:1; 4 mL) was added methyl azidoacetate (60 mg, 0.52 mmol). The mixture was stirred for 4 h at r.t., then concentrated. The crude product was purified by flash chromatography ($CHCl_3$/Et_2O, 4:1) to give **10** (115 mg, 97%) as yellow crystals; mp 181–183 °C; TLC ($CHCl_3$/Et_2O/MeOH, 4:1.5:0.5): R_f = 0.50.

IR: 3251, 2930, 1748, 1656, 1647 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.87–7.83 (m, 4 H), 7.25 (d, *J* = 8.5 Hz, 1 H), 6.72 (1 H), 3.73 (s, 3 H), 3.34 (d, *J* = 4.5 Hz, 2 H), 1.47 (s, 6 H), 1.34 (s, 6 H); 5 H_{arom} are overlapped with diphenylhydrazine signals.

^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 169.4 (1 C), 164.6 (d, *J* = 5 Hz, 1 C), 153.6 (d, *J* = 6 Hz, 1 C), 137.1 (d, *J* = 100 Hz, 1 C), 132.2 (d, *J* = 10 Hz, 6 C), 131.1 (d, *J* = 97 Hz, 2 C), 128.4 (d, *J* = 12 Hz, 4 C), 72.6 (d, *J* = 11 Hz, 1 C), 70.8 (d, *J* = 10 Hz, 1 C), 52.3 (1 C), 40.8 (1 C), 25.2 (2 C), 24.5 (2 C).

^{31}P NMR (202 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 23.02.

MS (EI): *m*/*z* (%) = 455 ([M^+], 6), 441 (11), 425 (31), 352 (59), 336 (70), 321 (93), 201 (100).

Anal. Calcd for $C_{24}H_{28}N_2O_5P$: C, 63.29; H, 6.20; N, 6.15. Found: C, 63.09; H, 6.30; N, 5.99.

(2-(4-(Diphenylphosphoryl)-*N*-(methoxycarbonylmethyl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxamide-1-yl)oxydanyl (10); Method B

To a stirred solution of methyl glycinate hydrochloride (125 mg, 1.00 mmol) in a phosphate buffer (4 mL, pH = 7) was added **12** (240 mg, 0.50 mmol) dissolved in DMSO (4 mL); the mixture was stirred at 25 °C for 12 h. Then the mixture was diluted with water (15 mL) and extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with sat. aq $NaHCO_3$ (5 mL), dried ($MgSO_4$), filtered, and evaporated. The crude product was purified with flash chromatography

($CHCl_3/Et_2O$, 2:1) to give **10** (31 mg, 14%) as yellow crystals; mp 192–194 °C; TLC ($CHCl_3/Et_2O$, 2:1): R_f = 0.34. The spectroscopical data were identical with compound **10** achieved with Method A.

(3-Carboxy-4-(diphenylphosphoryl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yl)oxydanyl (11)

To a solution of **5** (2.15 g, 5.40 mmol) in MeOH (30 mL) was added 10% aq NaOH solution (10 mL) and the mixture was refluxed for 1 h. The MeOH was evaporated and the resulting mixture was acidified with 5% aq H_2SO_4 solution. After standing at 25 °C for 12 h the precipitated crystals were filtered and air-dried to give **11**; yield: 1.32 g (64%); pale yellow crystals; mp 221–223 °C; TLC ($CHCl_3$/MeOH, 9:1): R_f = 0.39.

IR: 3437, 1918, 1694, 1623, 1590, 1488 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6 + $(PhNH)_2$): δ = 7.77–7.69 (m, 6 H), 6.63 (s 1 H), 1.32 (s, 6 H), 1.29 (s, 6 H), 4 H_{arom} are overlapped with diphenylhydrazine signals.

^{13}C NMR (125 MHz, DMSO-d_6 + $(PhNH)_2$): δ = 166.5 (d, *J* = 4 Hz, 1 C), 151.6 (d, *J* = 5.5 Hz, 1 C), 137.5 (d, *J* = 98 Hz, 1 C), 132.8 (d, *J* = 104 Hz, 2 C), 132.1 (d, *J* = 10 Hz, 4 C), 131 (d, *J* = 10 Hz, 2 C), 128.7 (d, *J* = 12 Hz, 4 C), 72.4 (d, *J* = 10 Hz, 1 C), 70.3 (d, *J* = 10 Hz, 1 C), 25.5 (2 C), 24.8 (2 C).

^{31}P NMR (202 MHz, DMSO-d_6 + $(PhNH)_2$): δ = 23.27.

MS (EI): *m*/*z* (%) = 384 ([M⁺], 8), 354 (23), 336 (38), 321 (65), 295 (48), 201 (100), 108 (29), 77 (44).

Anal. Calcd for $C_{21}H_{23}NO_4P$: C, 65.62; H, 6.03; N, 3.64. Found: C, 65.51; H, 5.92; N, 3.45.

((3-((2,5-Dioxo-1-pyrrolidinyl)oxy)carbonyl)-4-(diphenylphosphoryl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yl)oxydanyl (12)

To a solution of **11** (384 mg, 1.00 mmol) and *N*-hydroxysuccinimide (115 mg, 1.00 mmol) in anhyd EtOAc (20 mL) at 0 °C was added dropwise DCC (227 mg, 1.10 mmol) dissolved in anhyd EtOAc (5 mL). The mixture was stirred for 1 h at 25 °C and then the precipitated dicyclohexylurea was filtered, the EtOAc phase was washed with water (10 mL), the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the crude product was purified by flash column chromatography (hexane/EtOAc, 2:1 then $CHCl_3/Et_2O$, 1:1) to give **12**; yield: 260 mg (54%); yellow crystals; mp 75–77 °C; TLC ($CHCl_3$/ Et_2O/MeOH, 4:1.5:0.5): R_f = 0.52.

IR: 2978, 1809, 1778, 1740, 1626, 1590 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.84–7.80 (m, 4 H), 2.65 (s, 4 H), 1.61 (s, 6 H), 1.56 (s, 6 H); 6 H_{arom} are overlapped with diphenylhydrazine signals.

^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 167.8 (2 C), 159.2 (d, *J* = 4 Hz, 1 C), 150.0 (d, *J* = 2 Hz, 1 C), 134.4 (d, *J* = 78 Hz, 1 C), 132.3 (2 C), 132.1 (d, *J* = 10 Hz, 4 C), 130.9 (d, *J* = 107 Hz, 2 C), 12.6 (d, *J* = 13 Hz, 4 C), 74.3 (d, *J* = 9 Hz, 1 C), 71.2 (d, *J* = 9 Hz, 1 C), 25.5 (2 C), 24.8 (2 C), 24.4 (2 C).

^{31}P NMR (202 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 24.03.

MS (EI): *m*/*z* (%) = 481 ([M⁺], 6), 467 (7), 451 (18), 353 (34), 336 (82), 321 (72), 201 (100).

Anal. Calcd for $C_{25}H_{26}N_2O_6P$: C, 62.37; H, 5.44; N, 5.82. Found: C, 62.23; H, 5.24; N, 5.70.

(3-(Hydroxymethyl)-4-(diphenylphosphoryl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yl)oxydanyl (13)

To a solution of **11** (546 mg, 1.40 mmol) in anhyd THF (20 mL) was added CDI (320 mg, 2.00 mmol) and the mixture was refluxed for 20 min. The solvent was evaporated, and the resulting product was dissolved in THF/water (4:1; 15 mL). $NaBH_4$ (200 mg, 5.30 mmol) was added to the solution at 0 °C and the mixture was stirred for 1 h at r.t. The solvent was evaporated, brine was added, and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated and the crude product was purified by flash column chromatography ($CHCl_3/Et_2O$, 2:1) to give **13** (155 mg, 30%) as yellow crystals; mp 187–189 °C; TLC ($CHCl_3$/ Et_2O/MeOH, 4:1.5:0.5), R_f = 0.6.

IR: 3288, 2974, 1603, 1467, 1437 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.81–7.62 (m, 8 H), 4.17 (s, 2 H), 1.41 (s, 6 H), 1.00 (s, 6 H); 2 H_{arom} are overlapped with diphenylhydrazine signals.

^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 164.5 (d, *J* = 5 Hz, 1 C), 134.1 (d, *J* = 94 Hz, 1 C), 132.7 (2 C), 132.5 (d, *J* = 10 Hz, 4 C), 132.3 (d, *J* = 105 Hz, 2 C), 131.9 (1 C), 128.6 (d, *J* = 12 Hz, 4 C), 70.5 (1 C), 70.4 (d, *J* = 11 Hz, 1 C), 56.6 (d, *J* = 5 Hz, 1 C), 25.2 (2 C), 24.2 (2 C).

^{31}P NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 27.42.

MS (EI): *m*/*z* (%) = 370 ([M⁺], 17), 340 (31), 325 (72), 307 (34), 201 (100).

Anal. Calcd for $C_{21}H_{25}NO_3P$: C, 68.09; H, 6.80; N, 3.78. Found: C, 68.25; H, 6.73; N, 3..94.

(3-(Bromomethyl)-4-(diphenylphosphoryl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yl)oxydanyl (14)

To a stirred solution of **13** (120 mg, 0.30 mmol) in DCM (5 mL) was added Et_3N (50 mg, 0.50 mmol) and MsCl (57 mg, 0.50 mmol) and the mixture was stirred at 25 °C for 1 h. The mixture was diluted with DCM (10 mL) and washed with water (5 mL); the organic layer was dried ($MgSO_4$), filtered, and evaporated. The crude product was dissolved in anhyd acetone (15 mL), LiBr (86 mg, 1.00 mmol) was added, and the mixture was stirred at reflux temperature for 1 h. The solvent was evaporated, and the mixture was partitioned in water (5 mL) and $CHCl_3$ (10 mL). The aqueous phase was extracted with $CHCl_3$ (10 mL), the combined organic phases were dried ($MgSO_4$) and evaporated, and the crude product was purified by flash column chromatography (hexane/EtOAc, 2:1)to afford **14**; yield: 50 mg (36%); yellow crystals; mp 176–178 °C; TLC ($CHCl_3/Et_2O$, 2:1): R_f = 0.41.

IR: 2972, 1605, 1589 cm^{-1}.

MS (EI): *m*/*z* (%) = 434/432 ([M⁺], 1/1), 420/418 (2/2), 404/402 (3/3), 358 (6), 323 (90), 307 (54), 201 (71), 57 (100).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{25}BrNO_2P$: 433.0806; found: 433.0802.

Anal. Calcd for $C_{21}H_{24}BrNO_2P$: C, 58.21; H, 5.58; N, 3.23. Found: C, 58.04; H, 5.70; N, 3.40.

(3-(((Methylsulfonyl)thio)methyl)-4-(diphenylphosphoryl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yl)oxydanyl (15)

A solution of **14** (100 mg, 0.23 mmol) and sodium methanethiosulfonate (37 mg, 0.28 mmol) in EtOH (20 mL) and water (2 mL) was heated at reflux temperature until consumption of the starting material (~2 h). After cooling, the solution was diluted with brine (10 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated and the crude product

was purified by flash column chromatography (hexane/EtOAc, 1:1) to give **15** (20 mg, 19%) as a pale yellow amorphous solid; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.33.

IR: 2920, 1718, 1662, 1604, 1590 cm^{-1}.

MS (EI): *m*/*z* (%) = 464 ([M⁺], 2), 434 (1), 385 (27), 355 (44), 339 (100), 201 (90).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{28}NO_4PS_2$: 465.1197; found: 465.1192.

Anal. Calcd for $C_{22}H_{27}NO_4PS_2$: C, 56.88; H, 5.86; N, 3.02; S, 13.80. Found: C, 57.02; H, 5.92; N, 2.91; S, 13.66.

(Hexadecyl 4-(Diphenylphosphoryl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate-1-yl)oxydanyl (16)

A solution of **11** (768 mg, 2.00 mmol), DBU (310 mg, 2.20 mmol), and hexadecyl bromide (1.83 g, 6.00 mmol) in CH_3CN (10 mL) was stirred overnight. The solvent was evaporated, the residue was partitioned in 5% aq H_2SO_4 solution (10 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, evaporated, and the crude product was purified by flash column chromatography (hexane/Et_2O, 4:1); yield: 810 mg (67%); yellow crystals; mp 83–85 °C; TLC (hexane/EtOAc, 2:1): R_f = 0.32.

IR: 2954, 1714, 1591, 1468, 1438 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$+ $(PhNH)_2$): δ = 7.86–7.82 (m, 4 H), 3.36 (t, *J* = 6.5 Hz, 2 H), 1.53 (s, 6 H), 1.43 (s, 6 H), 1.34 (s, 28 H), 0.96 (t, *J* = 6.5 Hz, 3 H); 6 H_{arom} are overlapped with diphenylhydrazine signals.

^{13}C NMR (125 MHz, $CDCl_3$+ $(PhNH)_2$): δ = 165.0 (d, *J* = 5 Hz, 1 C), 150.0 (d, *J* = 4 Hz, 1 C), 138.6 (d, *J* = 97 Hz, 1 C), 132.3 (d, *J* = 10 Hz, 4 C), 132.0 (2 C), 131.7 (d, *J* = 74 Hz, 2 C), 128.3 (d, *J* = 12.5 Hz, 4 C), 73.4 (d, *J* = 10.0 Hz, 1 C), 71.0 (d, *J* = 10 Hz, 1 C), 65.3 (1 C), 32.1 (1 C), 29.79 (3 C), 29.76 (2 C), 29.72 (1 C), 29.64 (1 C), 29.55 (1 C), 29.45 (1 C), 29.20 (1 C), 28.1 (1 C), 25.9 (1 C), 25.2 (2 C), 24.5 (2 C), 22.8 (1 C), 14.2 (1 C).

^{31}P NMR (202 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 24.50.

MS (EI): *m*/*z* (%) = 608 ([M⁺], 4), 594 (5), 578 (55), 336 (100), 321 (78), 201 (94), 136 (94), 108 (37).

Anal. Calcd for $C_{37}H_{55}NO_4P$: C, 72.99; H, 9.11; N, 2.30. Found: C, 72.95; H, 9.30; N, 2.34.

(Hexadecyl 4-(Diphenylphosphino)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate)-1-yl)oxydanyl (17)

Trichlorosilane (0.5 mL, 0.50 mmol) was added to a stirred solution of **16** (700 mg, 1.15 mmol) in anhyd toluene (10 mL) at 0 °C under argon. The resulting mixture was stirred at 80 °C for 12 h under argon, cooled to r.t. and then poured into a 250-mL beaker containing ice (40 g) and 10% aq Na_2CO_3 (10 mL) solution. The mixture was extracted with EtOAc (2 × 15 mL) and the combined organic extracts were dried ($MgSO_4$), then the hydroxylamine was oxidized by stirring with PbO_2 (478 mg, 2.00 mmol) for 30 min. The mixture was filtered and the solvent was evaporated. The residue was purified by flash chromatography (hexane/Et_2O) to obtain **17** (360 mg, 53%) as yellow crystals; mp 61–63 °C; TLC (hexane/Et_2O, 4:1): R_f = 0.32.

IR: 2919, 1703, 1586, 1563 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.41–7.40 (m, 7 H,), 3.51 (t, *J* = 6.5 Hz, 2 H), 1.49 (s, 6 H), 1.37–1.30 (m, 34 H), 0.99 (t, *J* = 6.5 Hz, 3 H); 3 H_{arom} are overlapped with diphenylhydrazine signals.

^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 165.4 (1 C), 145. 5 (d, *J* = 30.13 Hz, 1 C), 145.3 (d, 1 C), 134.5 (d, *J* = 9 Hz, 2 C), 134.0 (d, *J* = 20 Hz, 4 C), 128.8 (2 C), 128.3 (d, *J* = 7 Hz, 4 C), 73.4 (d, *J* = 17.0 Hz, 1 C), 70.3 (1 C), 64.6 (1 C), 32.1 (1 C), 29.83 (1 C), 29.81 (1 C), 29.79 (1 C), 29.70 (4 C), 29.61 (1 C), 29.49 (1 C), 29.30 (1 C), 28.29 (1 C), 26.06 (1 C), 25.40 (2 C), 24.6 (2 C), 22.8 (1 C), 14.3 (1 C).

^{31}P NMR (202 MHz, $CDCl_3$ + $(PhNH)_2$): δ = –18.87.

MS (EI): *m*/*z* (%) = 592 ([M⁺], 0.3), 561 (2), 376 (7), 352 (73), 336 (100), 201 (65).

Anal. Calcd for $C_{37}H_{55}NO_3P$: C, 74.96; H, 9.35; N, 2.36. Found: C, 75.05; H, 9.42; N, 2.18.

(3-((Hexadecyloxy)carbonyl)-2,2,5,5-tetramethyl-4-(methyldiphenylphosphonio)-2,5-dihydro-1*H*-pyrrol-1-yl)oxydanyl Iodide (18)

A mixture of **17** (330 mg, 0.54 mmol) and CH_3I (300 mg, 2.17 mmol) in $CHCl_3$ (10 mL) in a pressure-proof closed vial was stirred and heated at 100 °C overnight. After cooling to r.t., the solvent was evaporated, Et_2O was added, and the precipitated crystals were filtered to yield **18** (300 mg, 74%) as brown crystals; mp 85–87 °C; TLC ($CHCl_3$/MeOH, 9:1): R_f = 0.48.

IR: 2921, 1719, 1607, 1586 cm^{-1}.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{38}H_{58}NO_3P$: 607.4154; found: 607.4150.

Anal. Calcd for $C_{38}H_{58}INO_3P$: C, 62.12; H, 7.96; N, 1.91; Found: C, 62.20; H, 7.93; N, 1.88.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References

(1) Miao, Q.; Nitsche, C.; Orton, H.; Overhand, M.; Otting, G.; Ubbink, M. *Chem. Rev.* **2022**, *122*, 9571.
(2) Trakhinina, S. Y.; Taratayko, A. I.; Glatzachev, Y. I.; Kirylyuk, A. I. *Russ. Chem. Bull.* **2023**, *72*, 1569.
(3) *Nitroxides: Synthesis, Properties, and Applications*; Ouari, O.; Gigmes, D., Ed.; The Royal Society of Chemistry: Cambridge, **2021**.
(4) Kamran, M.; Morsy, M. A.; Kandiel, T. A.; Iali, W. *Photochem. Photobiol. Sci.* **2022**, *21*, 2071.

(5) Hilt, S.; Tang, T.; Walton, J. H.; Budamagunta, M.; Maezewa, I.; Kálai, T.; Hideg, K.; Singh, V.; Wulff, H.; Gong, Q.; Jin, L.-W.; Louise, A.; Voss, J. C. *J. Alzheimer's Dis.* **2017**, *55*, 1667.
(6) Leifert, D.; Studer, A. *Chem. Rev.* **2023**, *123*, 10302.
(7) Matsuki, Y.; Maly, T.; Ouari, O.; Karoui, H.; Mogne, L. F.; Rizzato, E.; Lyubenova, S.; Herzfeld, J.; Prisner, T.; Tordo, P.; Griffin, R. G. *Angew. Chem. Int. Ed.* **2009**, *48*, 4996.
(8) Zsidó, B.; Balog, M.; Erős, N.; Poór, M.; Mohos, V.; Fliszár-Nyúl, E.; Hetényi, Cs.; Nagane, M.; Hideg, K.; Kálai, T.; Bognár, B. *Int. J. Mol. Sci.* **2020**, *21*, 508.
(9) Rayner, C. L.; Bottle, S. E.; Martyn, A. P.; Barnett, N. L. *Neurochem. Res.* **2023**, *48*, 3402.
(10) Kálai, T.; Fleissner, M. R.; Jekő, J.; Hubbell, W. L.; Hideg, K. *Tetrahedron Lett.* **2011**, *52*, 2747.
(11) Dhanasekaran, A.; Kotamraju, S.; Karunakaran, C.; Kalivendi, S. V.; Thomas, S.; Joseph, J.; Kalyanaraman, B. *Free Rad. Biol. Med.* **2005**, *39*, 567.
(12) Isbera, M.; Bognár, B.; Jekő, J.; Sár, C.; Hideg, K.; Kálai, T. *Molecules* **2020**, *25*, 2430.
(13) Isbera, M.; Bognár, B.; Sár, C.; Jekő, J.; Kálai, T. *ARKIVOC* **2022**, *(iii)*, 186.
(14) Isbera, M.; Bognár, B.; Gallyas, F.; Bényei, A.; Jekő, J.; Kálai, T. *Molecules* **2021**, *26*, 4366.
(15) Isbera, M.; Bognár, B.; Sár, C.; Jekő, J.; Kálai, T. *Synth. Commun.* **2021**, *51*, 1353.
(16) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
(17) Lemieux, G. A.; De Graffenried, C. L.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 4708.
(18) Lin, F. L.; Hoyt, H. M.; van Halbeek, H.; Bergman, R. G.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2005**, *127*, 2686.
(19) Sletten, E. M.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6974.
(20) Bednarek, C.; Wehl, I.; Jung, N.; Schepers, U.; Bräse, S. *Chem. Rev.* **2020**, *120*, 4301.
(21) Zhdanov, R. I. *Nitroxyl Radicals and Non-Radical Reactions of Free Radicals*, In *Bioactive Spin Labels*; Zhdanov, R. I., Ed.; Springer: Berlin, **1992**, 24.
(22) Keddie, D. J.; Johnson, T. E.; Arnold, D. P.; Bottle, S. E. *Org. Biomol. Chem.* **2005**, *3*, 2593.
(23) Gassman, P. G.; Gennic, I. *J. Am. Chem. Soc.* **1980**, *102*, 6863.
(24) Chalmers, B. A.; Morris, J. C.; Fairfull-Smith, K. E.; Grainger, R. S.; Bottle, S. E. *Chem. Commun.* **2013**, *49*, 10382.
(25) Rozantsev, E. G. In *Free Nitroxide Radicals*; Plenum Press: New York, **1970**, 207.
(26) Úr, G.; Kálai, T.; Hideg, K. *Tetrahedron Lett.* **2016**, *57*, 778.
(27) Chen, M.; Kálai, T.; Cascio, D.; Bridges, M. D.; Whitelegge, J. P.; Elgeti, M.; Hubbell, W. L. *Appl. Magn. Reson.* **2024**, *55*, 251.
(28) Zheng, D.; Zhu, X.; Zhou, A.; Luo, N.; Peng, L.; Zeng, X. CN 106187674, **2017**.
(29) Kovács, T.; Keglevich, G. *Curr. Org. Chem.* **2017**, *21*, 569.
(30) Zhang, R.; Sioma, C. S.; Wang, S.; Regnier, F. E. *Anal. Chem.* **2001**, *73*, 5142.
(31) Sharma, R.; Voynov, G. H.; Ovaska, T. V.; Marquez, V. E. *Synlett* **1995**, 839.
(32) Berliner, L. J.; Grunvald, J.; Hankovszky, H. O.; Hideg, K. *Anal. Biochem.* **1982**, *119*, 450.
(33) Rao, C. G. *Org. Prep. Proced. Int.* **1980**, *12*, 225.
(34) Awolade, P.; Cele, N.; Kerru, N.; Singh, P. *Mol. Diversity* **2021**, *25*, 2201.
(35) Margetic, D.; Warrener, R. N.; Butler, D. N.; Holland, C. M. *J. Heterocycl. Chem.* **2015**, *52*, 1447.