Synthesis of Pyrroline Nitroxide Annulated Carbocycles and Heterocycles

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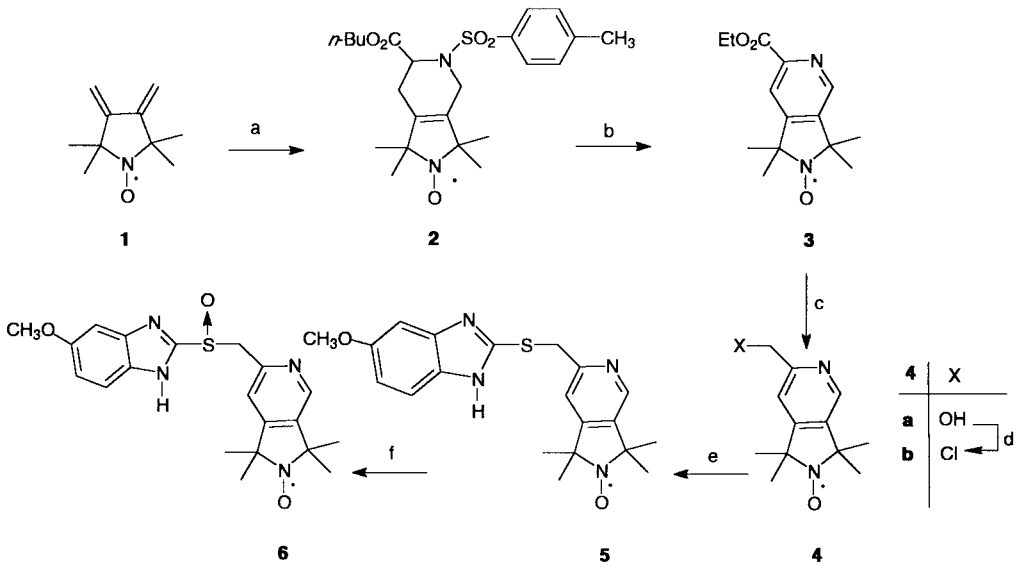
Dedicated to Prof. G. Sosnovsky on the occasion of his 80th birthday

Abstract: Starting from symmetric paramagnetic diene **1**, pyrroline nitroxide fused pyridine derivatives such as the paramagnetic omeprazole derivative **6**, paramagnetic quinones **7b**, **8b**, **11**, nitroxide fused pyrrole **14b** and furan **18** were synthesized.

Key words: free radicals, furans, pyridines, pyrroles, quinones, heterocycles

The synthesis of stable nitroxide radicals has witnessed considerable attention due to their application as spin labels,[1-3] spin traps,[4] MRI reagents[5] and co-oxidants.[6] For spin labelling studies compounds are required which do not alter significantly the structure and function of the biomolecule. A great variety of spin labelled biomolecules such as nucleic acids,[7] drugs,[8–12] lipids,[13] amino acids[1] and proteins[14] have been synthesized. To achieve this aim more conveniently, we have synthesized in recent years two useful intermediates: symmetric paramagnetic diene **1** and the paramagnetic 1,4-dibromomethyl derivative **12.**[15] In this paper we report the synthesis of further spin labelled biomolecules containing nitroxide annulated heterocycles and carbocycles from intermediates **1, 12**. Heterocycles and functionalized carbocycles were coupled mainly with nitronyl nitroxides for study of their magnetic properties and crystal structure[16,17] although heterocycle and carbocycle annulated nitroxides have been reported.[2, 18]

Synthesis of stable pyrroline nitroxide annulated thiophene,[19] thiazepine,[19] fullerene,[15] substituted benzene,[15] pyridazine,[15] 1,2-thiazine,[15] 1,2-dithianes[15] and 1,2-diselenanes[15] have been reported recently from our laboratory. Further examples of the usefulness of diene **1** in the Diels–Alder reaction are now reported. Diels–Alder reaction of *N*-(butoxycarbonylmethylene)-*p*-toluenesulfonamide[20] with **1** gave 6-butoxycarbonyl-1,3,4,5,6,7-hexahydro-1,1,3,3-tetramethyl-5-(*p*-toluenesulfonyl)-2*H*-pyrrolo[3,4-*c*]pyridin-2-yloxyl radical (**2**). This was hydrolyzed with NaOH in ethanol to paramagnetic picolinic acid[21] which was not isolated. To get a more conveniently isolable product, the acid was converted to its ethyl ester **3** in a one-pot reaction, followed by HNO_2 treatment[22] for recovering of the radical. The ester



Reagents and conditions: (a) *N*-(butoxycarbonylmethylene)-*p*-toluenesulfonamide (1.2 equiv)/toluene, 110 °C, 10 h, 67%; (b) KOH (11.5 equiv)/EtOH, 78 °C, 3 h, then EtOH/HCl, 78 °C, 1 h, then, r. t., 12 h, then evaporation of volatiles, $NaNO_2$ (3.2 equiv), r. t., 10 min, 73%; (c) $NaBH_4$ (2.5 equiv)/EtOH, r.t., 30 min, 90%; (d) $SOCl_2$ (1.5 equiv)/CH_2Cl_2, r.t., 30 min, 30–90%; (e) **4b**•HCl/5-methoxy-2-mercaptobenzimidazole/NaOH (2.1 equiv)/EtOH/H_2O, 78 °C, 2 h, 18%; (f) MCPBA (2 equiv)/CH_2Cl_2, 0 °C, 20 min, 48%

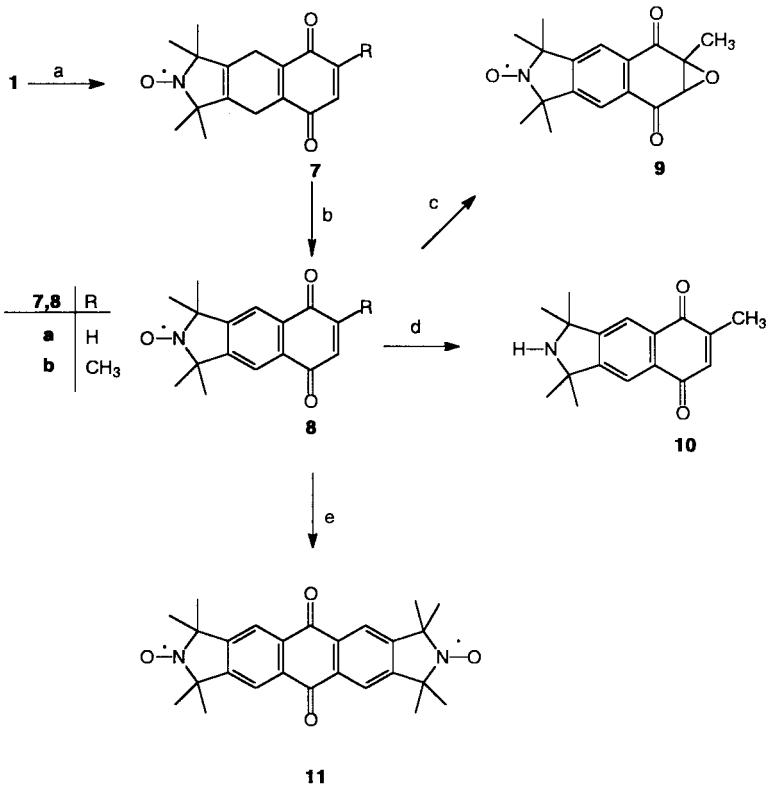
Scheme 1

was reduced to alcohol **4a** which could be converted to the picolyl chloride derivative **4b** with $SOCl_2$. The *S*-alkylation of 5-methoxy-2-mercaptobenzimidazole with paramagnetic picolyl chloride derivative **4b** gave 5-methoxy-2{[(2-oxyl-1,1,3,3-tetramethyl-2*H*-pyrrolo[3,4-*c*]pyridin-5-yl)methyl]thio}-1*H*-benzimidazole (**5**).[23] This compound was oxidized with 3-chloroperoxybenzoic acid (MCPBA) to the sulfoxide **6**, which can be regarded as a paramagnetic derivative of omeprazole, which is an inhibitor of gastric acid secretion[24] and a widespread[25] antiulcer agent (Scheme 1).

To synthesize further biologically active molecules, diene **1** was reacted with 1,4-benzoquinone and methyl-1,4-benzoquinone in 2 M ethereal $LiClO_4$ solution.[26] Fortunately, under these conditions the Diels–Alder reaction of symmetric paramagnetic diene took place relatively quickly compared to the reactions of asymmetric paramagnetic dienes with benzoquinone described earlier.[8,27] After workup of the reaction, a mixture of three different compounds was observed by TLC. Oxidation of this mixture with activated MnO_2 gave mainly compound **7a**, with traces of **8a**, and **7b** with traces of **8b**, respectively.[28] The oxidation of dihydro derivatives **7a, 7b** could be completed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to yield 1,3-dihydro-1,1,3,3-tetramethyl-2*H*-benz[*f*]isoindol-5,8-dione-2-yloxyl radical (**8a**), and 1,3-dihydro-1,1,3,3,7-pentamethyl-2*H*-benz[*f*]isoindol-5,8-dione-2-yloxyl radical (**8b**) respectively.[29] The latter compound can be regarded as the paramagnetic derivative of menadione (vitamin K_3), one of the blood-clotting vitamins. The role of K vitamins, as essential cofactors for carboxylase which activates the proteins of blood-clotting cascade, is well documented,[30] although the effect of vitamin K is still under intense research.[31]

Oxidation of compound **8b** with H_2O_2 in the presence of Na_2CO_3 gave paramagnetic menadione epoxide **9**.[32] Reduction of compound **8b** with Fe/AcOH[33] resulted in the removal of oxygen from nitroxide moiety without reduction of quinone to hydroquinone to afford **10**. Further Diels–Alder reaction of diene **1** with **8a** followed by oxidation with activated MnO_2 and DDQ yielded 1,1,3,3,7,7,9,9-octamethyl-1,3,7,9-tetrahydro-2*H*,8*H*-anthra[2,3-*c*:6,7-*c*']dipyrrol-5,11-dione-2,8-bisyloxyl biradical (**11**) (Scheme 2).

The synthesis of 1,3-dihydro-5-phenyl-1,1,3,3-tetramethyl-2*H*,5*H*-pyrrolo[3,4-*c*]pyrrol-2-yloxyl radical was published earlier from our laboratory.[15] The synthesis of unsubstituted pyrrole derivative could be accomplished with Padwa annulation.[34] Alkylation of *p*-toluenesulfonamide with 3,4-bis(dibromomethyl)-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxyl radical (**12**)[15] under phase transfer conditions gave compound **13** which could be ar-



Reagents and conditions: (a) 1,4-benzoquinone or methyl-1,4-benzoquinone (1 equiv)/2 M $LiClO_4/Et_2O$, r.t., 12 h, then MnO_2 (4.5 equiv)/CH_2Cl_2, 62 °C, 2 h, 27–29%; (b) DDQ (1 equiv)/toluene, 110 °C, 5 h, 55–65%; (c) **8b**/H_2O_2 (3 equiv)/Na_2CO_3 (0.5 equiv)/EtOH, 10 °C, then H_2O, r.t., 20 min, 57%; (d) **8b**/Fe powder (7.1 equiv)/AcOH, 50 °C → r.t., 30 min, $H_2O/KHCO_3$, 31%; (e) **8a**/**1** (1 equiv)/2 M $LiClO_4/Et_2O$, r.t., 12 h, then MnO_2 (34.5 equiv)/CH_2Cl_2, 62 °C, 2 h, then DDQ (1 equiv)/toluene, 110 °C, 4 h, 28%;

Scheme 2

omatized at 110 °C in toluene with DDQ to *N*-tosylpyrrole derivative **14a**, but in low yield. Hydrolysis of this compound gave 1,3-dihydro-1,1,3,3-tetramethyl-2*H*,5*H*-pyrrolo[3,4-c]pyrrol-2-yloxyl radical (**14b**). Synthesis of a nitroxide annulated furan ring was achieved by partial oxidation of 3,4-bis(dihydroxymethyl)-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxyl radical (**15**)[15] with activated MnO_2 at 40 °C to give a mixture of 3-formyl-4-hydroxymethyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxyl (**17**) and the dialdehyde **16.** Compound **17** was cyclized with $BF_3.OEt_2$[35] to give 1,3-dihydro-1,1,3,3-tetramethyl-2*H*-furo[3,4-*c*]pyrrol-2-yloxyl radical (**18**) (Scheme 3).

In conclusion, we have extended the utilization of symmetric paramagnetic diene for synthesis of paramagnetic biomolecules such as gastric acid secretion inhibitor molecule, vitamin K_3 and pyrroline nitroxide fused five-membered heterocycles with one heteroatom. We hope these molecules will find applications in the future, especially those which are mimics of bioactive compounds, and can contribute to deeper evaluation of the mechanism of their activity.

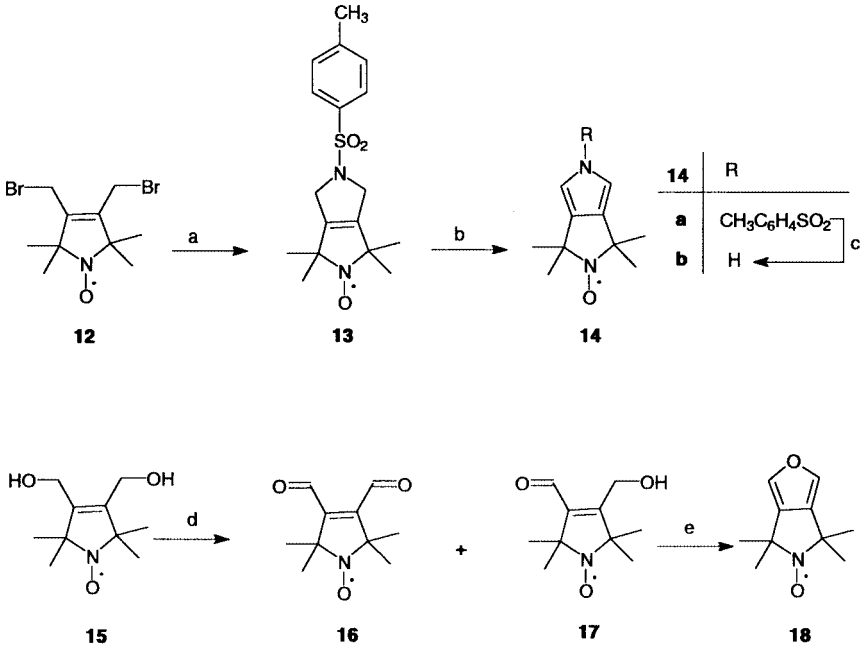
Melting points were determined with a Boetius micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N, S) were performed on Fisons EA 1110 CHNS elemental analyser. The IR (Specord 75) spectra were in each case consistent with the assigned structure. Mass spectra were recorded on a VG TRIO-2 instrument in the EI mode (70 eV, direct inlet) or with thermospray technique. Samples were analysed in the by-pass mode. A 10 μL solution of the sample in MeOH was introduced via the thermospray interface. The mobile phase was a mixture of MeOH/H_2O (1:1) containing 0.1 M NH_4OAc. Capillary tip temperature: 230 °C, electrode voltage: 180 V and the source temperature: 210 °C. The ESR spectra were obtained from 10^{-5} molar solution ($CHCl_3$), using Bruker ECS-106 spectrometer. All monoradicals exhibit three equidistant lines with a_N = 15.1−15.5 G. Biradical **12** exhibits quintet lines with 17.15 G splitting. ^{1}H NMR spectra were recorded with Bruker 400 spectrometer at 400 MHz. Chemical shifts are given in ppm, relative to TMS internal standard. Flash column chromatography was performed on Merck Kieselgel 60 (0.040−0.063 mm). Qualitative TLC was carried out on commercially prepared plates (20 × 20 × 0.02 cm) coated with Merck Kieselgel GF_{254}. Compounds **1,**[15] **12,**[15] **15,**[15] **16**[15] and *N*-(butoxycarbonylmethylene)-*p*-toluenesulfonamide[20] were prepared according to published procedures. The physical and spectral data of all new compounds are listed in the Table.

6-Butoxycarbonyl-1,3,4,5,6,7-hexahydro-1,1,3,3-tetramethyl-5-(*p*-toluenesulfonyl)-2*H*-pyrrolo[3,4-*c*]pyridine-2-yloxyl Radical (2)

A mixture of diene **1** (830 mg, 5.0 mmol) and of *N*-(butoxycarbonylmethylene)-*p*-toluenesulfonamide[20] (1.70 g, 6.0 mmol) in toluene (30 mL) was refluxed for 10 h, then the solvent was evaporated and the residue purified by flash column chromatography with hexane/EtOAc to give the title compound **2**; yield: 1.52 g (67%); orange oil; R_f 0.38 (hexane/EtOAc, 2:1).

6-Ethoxycarbonyl-1,3-dihydro-1,1,3,3-tetramethyl-2*H*-pyrrolo[3,4-*c*]pyridine-2-yloxyl Radical (3)

A solution of **2 (**1.40 g, 3.1 mmol) and KOH (2.0 g, 35.7 mmol) in anhyd EtOH (30 mL) was refluxed for 3 h and the brown solution was evaporated to dryness. To the residue was added EtOH saturated with HCl (50 mL) and the precipitated KCl was filtered. The resulting yellow solution was refluxed for 1 h and allowed to stay overnight at r.t. The solvent was evaporated to dryness, the residue taken up in $CHCl_3$ (30 mL) and to the stirred solution was added



Reagents and conditions: *p*-toluenesulfonamide (1.0 equiv)/K_2CO_3 (2 equiv)/KOH (0.1 equiv)/18-crown-6 (0.02 equiv)/dioxane, 101 °C, 6 h, 53%; (b) DDQ (1 equiv)/toluene, 110 °C, 4 h, 14%; (c) NaOH (13.8 equiv)/MeOH, 65 °C, 1 h, 78%; (d) MnO_2 (3 equiv)/CH_2Cl_2, 3 h, 40 °C, then r.t., 2 h, **16**: 18%, **17**: 28%; (e) **17**/$BF_3.OEt_2$ (1.2 equiv)/THF, 0 → 40 °C, 10 min, 55%

Scheme 3

Table Compounds **2**–**18** Prepared

Product	Yield (%)	Mp (°C)	IR (nujol) ν (cm^{-1})	MS *m*/*z* (%)
2	67	oil	1730 (C=O), 1590 (C=C)	449 (M^+, 77), 435 (44), 419 (46), 91 (100)
3	73	143−144	1700 (C=O), 1600, 1560 (C=C)	263 (M^+, 21), 249 (22), 176 (10), 161 (100)
4a	90	118−120	3200 (OH), 1600, 1565 (C=C)	221 (M^+, 42), 207 (66), 190 (100), 162 (37)
4b	30 90[a]	63−65	1600, 1560 (C=C)	239 (M^+, 44), 225 (26), 209 (44), 194 (100)
5	18	84−86	1605, 1560 (C=C)	383 (M^+, 40), 369 (42), 353 (100), 320 (67)
6	48	98−100	1605, 1560 (C=C)	399 (M^+, 10), 321 (37), 190 (65), 41 (100)
7a	29	205−207	1650 C=O, 1595 C=C	272 (M^+, 78), 257 (86), 242 (100), 225 (64)
7b	27	180−182	1640 C=O, 1610 (C=C)	286 (M^+, 73), 272 (93), 256 (95), 41 (100)
8a	55	233−234	1665 (C=O), 1600 (C=C)	270 (M^+, 61), 256 (100), 240 (63), 225 (79)
8b	65	202−204	1660 (C=O), 1600 (C=C)	284 (M^+, 50), 270 (100), 254 (82), 239 (74)
9	57	192−193	1685 (C=O), 1600 (C=C)	300 (M^+, 42), 286 (55), 270 (27), 43 (100)
10	41	180-182	3250 (NH), 1660 (C=O), 1590 (C=C)	269 (M^+, 2), 254 (100), 238 (47), 115 (11)
11	28	250 (dec.)	1670 (C=O), 1605 (C=C)	TSP 434[b] $(M + 2 H)^+$
13	53	171−172	1590 (C=C)	335 (M^+, 4), 321 (15), 305 (34), 91 (100)
14a	14	121−122	1590 (C=C)	333 (M^+, 2), 319 (13), 303 (22), 148 (100)
14b	78	213−215	3320 (NH), 1585 (C=C)	179 (M^+, 6), 165 (8), 149 (64), 134 (100)
17	28	93	3280 (OH), 1660 (C=O), 1620 (C=C)	198 (M^+, 21), 184 (49), 168 (27), 41 (100)
18	55	99−102	1560 (C=C)	180 (M^+, 15), 166 (21), 150 (91), 135 (100)

[a] Crude HCl salt.
[b] With N–OH formation.

dropwise a solution of $NaNO_2$ (690 mg, 10.0 mmol) in H_2O (10 mL). The solution was vigorously stirred for 10 min., the organic layer was separated, dried ($MgSO_4$), filtered and evaporated. Flash column chromatography using $CHCl_3$/MeOH afforded **3**; yield: 600 mg (73%); yellow solid; mp 143−144 °C; R_f 0.56 ($CHCl_3/Et_2O$, 2:1).

1,3-Dihydro-6-hydroxymethyl -1,1,3,3-tetramethyl-2*H*-pyrrolo[3,4-*c*]pyridine-2-yloxyl Radical (4a)

To a solution of **3** (526 mg, 2.0 mmol) in EtOH (20 mL) was added $NaBH_4$ (189 mg, 5.0 mmol) in one portion and stirred at r.t. for 30 min. EtOH was evaporated, the residue was dissolved in satd aq NH_4Cl solution (10 mL) and extracted with $CHCl_3$ (2 × 20 mL), organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography with $CHCl_3$/Et_2O to give **4a** 400 mg (90%) as a pale yellow solid; mp 118−120 °C; R_f 0.30 ($CHCl_3/Et_2O$/MeOH, 8:3:1).

6-Chloromethyl-1,3-dihydro-1,1,3,3-tetramethyl-2*H*-pyrrolo[3,4-*c*]pyridine-2-yloxyl Radical (4b)

To a stirred solution of **4a** (442 mg, 2.0 mmol) in anhyd CH_2Cl_2 (15 mL) was added dropwise a solution of $SOCl_2$ (357 mg, 3.0 mmol) in CH_2Cl_2 (5 mL) at r.t. The mixture was stirred for further 30 min, then the solvent was evaporated, and the crude hydrochloride salt of **4b** was used directly in the next step; yield: 500 mg (90%). For analytical identification **4b** (100 mg) was dissolved in H_2O (10 mL) and the pH was adjusted with $KHCO_3$ to 8. The aqueous solution was extracted with $CHCl_3$ (2 × 10 mL), dried ($MgSO_4$), filtered, and evaporated. After flash column chromatography of the residue with hexane/EtOAc **4b** was obtained as a brownish-yellow solid; yield: 30 mg (30%); mp 63−65 °C; R_f 0.26 (hexane/EtOAc, 2:1).

5-Methoxy-2{[(2-oxyl-1,3-dihydro-1,1,3,3-tetramethyl-2*H*-pyrrolo[3,4-*c*]pyridin-6-yl)methyl]thio}-1*H*-benzimidazole Radical (5)

A solution of the crude **4b**•HCl salt (400 mg, 1.44 mmol), 5-methoxy-2-benzimidazolethiol (260 mg, 1.44 mmol) and NaOH (120 mg, 3.0 mmol) in mixture of EtOH (10 mL) and H_2O (10 mL) was refluxed for 2 h. The EtOH was evaporated, the red coloured aqueous solution was saturated with NaCl and extracted with $CHCl_3$ (2 × 15 mL). The combined $CHCl_3$ extracts were dried ($MgSO_4$), filtered and evaporated and the residue was purified by flash column chromatography with $CHCl_3$ /MeOH to yield **5** 100 mg (18%) as an off-white solid; mp 84−86 °C; R_f 0.38 ($CHCl_3$/Et_2O/MeOH, 8:3:1).

5-Methoxy-2[((2-oxyl-1,3-dihydro-1,1,3,3-tetramethyl-2*H*-pyrrolo[3,4-*c*]pyridin-6-yl)methyl)sulfinyl]-1*H*-benzimidazole Radical (6)

To a stirred solution of **5** (100 mg, 0.26 mmol) in CH_2Cl_2 (10 mL) was added MCPBA (86 mg, 0.5 mmol) at 0 °C in two or three portions during 20 min, while the reaction was monitored by TLC ($CHCl_3$/Et_2O/MeOH, 8:3:1). When compound **5** had completely reacted, CH_2Cl_2 (10 mL) was added, the mixture filtered and the organic phase was washed with satd aq $NaHCO_3$ solution (10 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography with $CHCl_3$/MeOH to give compound **6** as an off-white solid; yield: 50 mg (48%); mp 98−100 °C; R_f 0.30 ($CHCl_3$/Et_2O/MeOH, 8:3:1).

Dihydrobenzoquinones 7a,b; General Procedure

To 2 M $LiClO_4$ ethereal solution (10 mL) of diene **1** (830 mg, 5.0 mmol) was added 1,4-benzoquinone (540 mg, 5.0 mmol) or methyl-1,4-benzoquinone (610 mg, 5.0 mmol) and the mixture was allowed to stay overnight at r.t. The mixture was then poured into H_2O (15 mL), the layers separated and the aqueous phase was extracted with Et_2O (2 × 10 mL) and then with $CHCl_3$ (10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in $CHCl_3$ (20 mL), activated MnO_2 (2.0 g, 23.25 mmol) was added and the mixture was stirred and refluxed for 2 h. Then MnO_2 was filtered off and the solvent evaporated. For analytical identification the residue was purified by flash column chromatography with hexane/Et_2O to give **7a** or **7b,** otherwise the crude product can be used in the next step.

1,1,3,3-Tetramethyl-1,3,4,9-tetrahydro-2*H*-benz[*f*]isoindol-5,8-dion-2-yloxyl Radical (7a)

Brownish-red crystals; yield: 400 mg (29%); mp 205−207 °C; R_f 0.23 (hexane/Et_2O, 2:1).

1,1,3,3,6-Pentamethyl-1,3,4,9-tetrahydro-2*H*-benz[*f*]isoindol-5,8-dion-2-yloxyl Radical (7b)

Brownish-red crystals; yield: 388 mg (27%); mp 180−182 °C; R_f 0.25 (hexane/Et_2O, 2:1).

Benzoquinones 8a,b; General Procedure

A solution of **7a** (272 mg, 1.0 mmol) or **7b** (286 mg, 1.0 mmol) and DDQ (227 mg, 1.0 mmol) in toluene (30 mL) was refluxed for 5 h. Then the mixture was filtered, the filtrate washed with EtOAc (15 mL) and the solvents were evaporated. The residue was dissolved in EtOAc (30 mL), washed with 10% aq K_2CO_3 solution (10 mL), the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was purified by flash column chromatography with hexane/Et_2O to give **8a** or **8b**.

1,3-Dihydro-1,1,3,3-tetramethyl-2*H*-benz[*f*]isoindol-5,8-dion-2-yloxyl Radical (8a)

Orange solid; yield: 150 mg (55%); mp 233-234 °C; R_f 0.30 (hexane/Et_2O, 2:1).

1,3-Dihydro-1,1,3,3,6-pentamethyl-2*H*-benz[*f*]isoindol-5,8-dion-2-yloxyl Radical (8b)

Orange solid; yield: 187 mg (65%); mp 202−204 °C; R_f 0.36 (hexane/Et_2O, 2:1).

1,3-Dihydro-6,7-epoxy-1,1,3,3,6-pentamethyl-2*H*-benz[*f*]isoindol-5,8-dione-2-yloxyl Radical (9)

To a solution of **8b** (100 mg, 0.35 mmol) in EtOH (5 mL) was added a mixture of Na_2CO_3 (20 mg, 0.14 mmol) and 30% aq H_2O_2 (0.1 mL) in H_2O (3 mL) at 10 °C. Then H_2O (10 mL) was added, upon which the title compound began to crystallize. The mixture was set aside for 20 min, then filtered to afford **9** as a yellow solid; yield: 60 mg (57%); mp 192−193 °C; R_f 0.30 (hexane/Et_2O, 2:1).

1,3-Dihydro-1,1,3,3,6-pentamethyl-2*H*-benz[*f*]isoindol-5,8-dione (10)

To stirred solution of **8b** (200 mg, 0.7 mmol) in AcOH (5 mL) was added Fe powder (280 mg, 5.0 mmol) and the mixture was warmed gently to 50 °C and kept for 30 min. The mixture was diluted with H_2O (20 mL), and the solution was decanted from the Fe powder. The solution was basified with $KHCO_3$ to pH 8 and extracted with $CHCl_3$ (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography with $CHCl_3$/Et_2O then $CHCl_3$/MeOH to give **10**; 78 mg (41%); a yellow solid; mp 180−182 °C; R_f 0.26 (?, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 6 H), 1.51 (s, 6 H), 2.19 (d, 3 H, *J* = 1.6 Hz), 6.82 (q, 1 H, *J* = 1.6 Hz), 7.81 (s, 1 H), 7.85 (s, 1 H).

1,1,3,3,7,7,9,9-Octamethyl-1,3,7,9-tetrahydro-2*H*,8*H*-anthra[2,3-*c*:6,7-*c*']dipyrrol-5,11-dione-2,8-bisyloxyl Biradical (11)

To 2 M $LiClO_4$ were added an ethereal (10 mL) solution of **8a** (270 mg, 1.0 mmol) and diene **1** (166 mg, 1.0 mmol) and the mixture was allowed to stay overnight at r.t. The mixture was poured into H_2O (10 mL), the organic phase was separated and the aqueous phase was extracted with $CHCl_3$ (15 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was dissolved in $CHCl_3$ (20 mL), activated MnO_2 (3.0 g, 34.5 mmol) was added and the mixture was stirred and refluxed for 2 h. The MnO_2 was filtered off, washed with $CHCl_3$ (5 mL), the filtrate was concentrated and the residue was dissolved in toluene (30 mL). DDQ (227 mg, 1.0 mmol) was added to this solution and the mixture was refluxed for 4 h. The same workup procedure as in the case of compounds **8a** and **8b** and purification with flash chromatography hexane/EtOAc afforded compound **11** as brownish-green crystals; yield: 122 mg (28%); mp 250 °C (dec.); R_f 0.36 (hexane/EtOAc, 2:1).

1,3,4,6-Tetrahydro-1,1,3,3-tetramethyl-5-toluenesulfonyl-2*H*,5*H*-pyrrolo[3,4-*c*]pyrrol-2-yloxyl Radical (13)

A mixture of **12** (1.63 g, 5.0 mmol), *p*-toluenesulfonamide (855 mg, 5.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), KOH (56 mg, 1.0 mmol), 18-crown-6 (26 mg, 0.1 mmol) in dioxane (30 mL) was stirred and refluxed for 6 h. The mixture was filtered, the filtrate washed with $CHCl_3$ (10 mL) and the solvents were evaporated. The residue was dissolved in $CHCl_3$ (30 mL), washed with brine (15 mL), the organic phase was separated, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography with hexane/EtOAc to give the title compound **13** (900 mg, 53%) as pale yellow solid; mp 171−172 °C; R_f 0.33 (hexane/EtOAc, 2:1).

1,3-Dihydro-1,1,3,3-tetramethyl-5-toluenesulfonyl-2*H*,5*H*-pyrrolo[3,4-*c*]pyrrol-2-yloxyl Radical (14a)

A solution of **13 (**670 mg, 2.0 mmol) and DDQ (454 mg, 2.0 mmol) in toluene (30 mL) was refluxed for 4 h. The mixture was filtered, the residue washed with EtOAc (10 mL) and the solvents were evaporated. The residue was dissolved in EtOAc (40 mL), washed with 10% aq K_2CO_3 solution (10 mL), the organic phase was separated, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography with hexane/EtOAc to give **14a** as a yellow solid 93 mg (14%); mp 121−122 °C; R_f 0.51 (hexane/EtOAc, 2:1).

1,3-Dihydro-1,1,3,3-tetramethyl-2*H*,5*H*-pyrrolo[3,4-*c*]pyrrol-2-yloxyl Radical (14b)

A solution of **14a** (60 mg, 0.18 mmol) and NaOH (100 mg, 2.5 mmol) in MeOH (10 mL) was refluxed for 1 h. After cooling the mixture was poured into H_2O (20 mL), extracted with Et_2O (2 × 20 mL), the organic phase was dried ($MgSO_4$), filtered and evaporated. Purification of the residue with flash column chromatography with hexane/EtOAc gave **14b** as a yellow solid 25 mg (78%); mp 213−215 °C; R_f 0.39 (hexane/EtOAc, 2:1).

2,5-Dihydro-3-formyl-4-hydroxymethyl-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxyl Radical (17)

To a stirred solution of **15** (1.0 g, 5.0 mmol) in CH_2Cl_2 (30 mL) was added activated MnO_2 (1.29 g, 15.0 mmol) in 3−4 portions at 40 °C during 3 h. The mixture was further stirred at r.t. for 2 h and the reraction was monitored by TLC. MnO_2 was filtered off, washed with $CHCl_3$ (10 mL), MeOH (10 mL) and the solvents were evaporated. The residue was purified by flash column chromatography with hexane/EtOAc to give the dialdehyde byproduct **16** as a brownish-red solid 180 mg (18%); R_f 0.55 (hexane/EtOAc, 2:1). Further elution with $CHCl_3$ gave **17** as a yellow solid 280 mg (28%); mp 93 °C; R_f 0.51 ($CHCl_3$/MeOH, 9:1).

1,3-Dihydro-1,1,3,3-tetramethyl-2*H*-furo[3,4-*c*]pyrrole-2-yloxyl Radical (18)

To stirred solution of **17** (99 mg, 0.5 mmol) and powdered molecular sieves (50 mg, 4 Å) in anhyd THF (5 mL) was added $BF_3.OEt_2$ (0.6 mmol) at 0 °C. The mixture was allowed to warm to r.t. and further stirred at 40 °C for 10 min. The solution was poured into crushed ice (30 g), extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography with hexane/Et_2O to afford compound **18** as a yellow solid 50 mg (55%); mp 99−102 °C, R_f 0.48 (hexane/Et_2O, 2:1).

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References

(1) Hideg, K.; Hankovszky, H. O. In *Spin-Labeling: Theory and Applications (3rd Compendium)*; Berliner, L. J.; Reuben, J., Eds.; Plenum Press: New York, 1989; Ch. 9, p 427.
(2) Rozantsev, E. G. *Free Nitroxide Radicals*; Plenum Press: New York, 1970.
(3) Altenbach, C.; Hubbell, W. L. In *Foundations of Modern EPR*; Eaton, G. R.; Eaton, S. S.; Salikov, K. M., Eds.; World Scientific: Singapore, 1998; Ch. G. 6, p 423.
(4) Herbelin, S. E.; Blough, N. V. *J. Phys. Chem. B* **1998**, *102*, 8170.
(5) Sosnovsky, G.; Li, W. S.; Rao, M. U. N. *Z. Naturforsch.* **1985,** *40b*, 1558.
Yokayama, H.; Sato, T.; Ogata, T.; Ohya-Nishiguchi, H.; Kamada, H. *J. Magn. Reson.***1997,** *129*, 201.
(6) Nooy, A. E. J.; Besemer, A. C.; Bekkum, van H. *Synthesis* **1996**, 1153.
Schnatbaum, K.; Schafer, H. J. *Synthesis*, **1999**, 864.
(7) Dugas, H. *Acc. Chem. Res.* **1977,** *10*, 47.
Trommer, W. E.; Vogel, P. D. In *Bioactive Spin Labels;* Zhdanov, R. I., Ed.; Springer-Verlag: Berlin, 1992; p 405.
(8) Hideg, K.; Csekö, J.; Hankovszky, H. O.; Sohár, P. *Can. J. Chem* **1986**, *64*, 1482.
(9) Hankovszky, H. O.; Sár, C. P.; Hideg, K.; Jerkovich, Gy. *Synthesis* **1991**, 91.
(10) Miyazaki, J.; Hideg, K.; Marsh, D. *Biochim. Biophys. Acta* **1992**, *1103*, 62.
(11) Sár, C. P.; Jekö, J.; Fajer, P. Hideg, K. *Synthesis* **1999,** 1039.
(12) Kikelj, D.; Pecar, S.; Debeljak, B.; Karba, D.; Krbavcic, A. *Synth. Commun.* **1984,** *14*, 547.
(13) Fellmann, P.; Zachowski, A.; Devaux, P. F. *Methods Mol. Biol., Vol. 27: Biomembrane Protocols: II;* Graham, J. M.; Higgins, J. A., Eds.; Humana Press Inc.: Totowa, 1994; Ch. 13, p 161.
(14) Cornish, V. W.; Benson, D. R.; Altenbach, C. A.; Hideg, K. Hubbell, W. L.; Shultz, P. G. *Proc. Natl. Acad. Sci., USA* **1994,** *91*, 2910.
(15) Kálai, T.; Balog, M.; Jekö, J.; Hideg, K. *Synthesis* **1999**, 973.
(16) Romero, F. M.; Ziessel, R. *Tetrahedron Lett.* **1999,** *40*, 1895.
(17) Kumai, R.; Matushita, M. M.; Izuoka, A.; Sugawara, T. *J. Am. Chem. Soc.* **1994,** *116*, 4523.
(18) Micallef, A. S.; Bott, R. C.; Bottle, S. E.; Smith, G.; White, J. M.; Matsuda, K.; Iwamura, H. *J. Chem. Soc., Perkin Trans 2* **1999,** 65.
Braslau, R.; Chaplinski, V.; Goodson, P. *J. Org. Chem.* **1998**, *63*, 9857.
(19) Kálai, T.; Balog, M.; Jekö, J.; Hideg, K. *Synthesis* **1998,** 1476.
(20) Baillargé, M.; Goffic, F. L. *Synth. Commun.* **1987**, *17*, 1603.
(21) Albrecht, R.; Kresze, G. *Chem. Ber.* **1965**, *98*, 1431.
(22) Krinitskaya, L. A.; Volodarskii, L. B. *Izv. Akad. Nauk. Ser. Khim* **1983**, 391; *Chem. Abstr.* **1983**, *98*, 197967.
Sosnovsky, G.; Cai, Z. A. *J. Org. Chem.*, **1995**, *60*, 3414.
(23) Junggren, U. K.; Sjöstrand, S. E. Eur. Patent Appl. 5, 129, 1979; *Chem Abstr.* **1980,** *92*, 1983962.
(24) Kromer, W. *Digestion* **1995**, *56*, 443.
(25) Nicolaou, K. C.; Sorensen, E. J.; Winssinger, N. *J. Chem. Ed.* **1998**, *75*, 1226.

(26) Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59.
(27) Shapiro, A. B.; Skripnichenko, L. N.; Pavlikov, V. V.; Rozantsev, E. G. *Izv. Akad. Nauk. Ser. Khim.* **1979**, 151; *Chem. Abstr.* **1979,** *90*, 203838.
(28) Cormier, R. A.; Conolly, J. S.; Pelter, L. S. *Synth. Commun.*, **1992**, *22*, 2155.
(29) Owton, M. W. *J. Chem. Soc., Perkin Trans 1* **1999,** 2409.
(30) Naganathan, S.; Hershline, R.; Ham, S. W.; Dowd, P. *J. Am. Chem. Soc.* **1993**, *115*, 5839.
Dowd, P.; Hershline, R.; Ham, S. W.; Naganathan, S. *Science* **1995**, *269*, 1684.
(31) Furie, B.; Bouchard, B. A.; Furie, B. C. *Blood* **1999**, *93*, 1798.
Bouchard, B.; Furie, B.; Furie, B. C. *Biochemistry* **1999**, *38*, 9517.
(32) Fieser, L. F.; Campbell, W. P.; Fry, E. M.; Gates, M. D. *J. Am. Chem. Soc.* **1939,** *61*, 3216.
(33) Sár, C. P.; Kálai, T.; Bárácz, M. N.; Jerkovich, Gy.; Hideg, K. *Synth. Commun.* **1995**, *25*, 2929.
(34) Hassner, A.; Stumer, C. *Organic Synthesis Based on Name Reactions and Unnamed Reactions*; Pergamon: Oxford, 1994; p 285.
Padwa, A.; Norman, H. B. *J. Org. Chem.* **1990,** *55*, 4801.
(35) Gribble, G. W. Silva, R. A.; Saulnier, M. A. *Synth. Commun.* **1999**, *29*, 729.

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