Synthesis of Nitroxide-Annulated Carbocycles and Heterocycles

Tamás Kálai,[a,c] Balázs Bognár,[a] Dániel Zsolnai,[a] Zoltán Berente,[b] Kálmán Hideg*[a]

[a] Institute of Organic and Medicinal Chemistry, University of Pécs, Szigeti st. 12, 7624 Pécs, Hungary
Fax +36(72)536219; E-mail: kalman.hideg@aok.pte.hu

[b] Institute of Biochemistry and Medical Chemistry, University of Pécs, Szigeti st. 12, 7624 Pécs, Hungary

[c] Szentágothai Research Centre, Ifjúság st. 20, 7624 Pécs, Hungary

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Dedicated to Prof. Péter Mátyus on the occasion of his 60th birthday.

Abstract: New, pyrroline nitroxide annulated lactones, polycycles, and maleimide were synthesized by classical and microwave-assisted methodology. We report the application of the metathesis reaction in the presence of nitroxide yielding a pyrroline nitroxide condensed 1,4-benzoquinone as a paramagnetic dienophile. The formation of the isoselenazolone-fused pyrroline ring system was examined and different reactivity was observed with pyrrolin-1-oxyl and pyrroline derivatives.

Key words: free radicals, heterocycles, lactones, metathesis, quinones

Current interest in the chemistry of nitroxides is due to their wide practical applications. Nitroxides are widely used as classical[1] and orthogonal spin labels,[2] spin traps,[3] polymerization inhibitors[4] antioxidants,[5] co-oxidants,[6] and building blocks for functional molecular materials.[7] This tendency is well reflected in the increased number of reviews and monographs over the last few years.[8–11] Although the chemistry of nitroxides began 50 years ago, only limited numbers of basic scaffolds have been published. Among the various nitroxide structures, pyrroline and piperidine nitroxides are the most popular, as they are readily available from triacetonamine[12] and they are chemically more stable than other nitroxide scaffolds.

Moreover, piperidine and pyrroline nitroxides offer an alternative approach to various paramagnetic compounds via multistep synthesis. Because of the free radical moiety, these transformations are sometimes more sophisticated than those used in the synthesis of conventional (no free radical containing) materials. Despite the difficulties, the synthesis of various carbocycles and heterocycles condensed with pyrroline nitroxide have recently been published.[13–15] In this work we describe further extension of the synthesis of pyrroline nitroxide condensed carbocycles and heterocycles starting from β-bromo-α,β-unsaturated carboxylic acid **1**[16] and paramagnetic diene **2**[17] (Figure 1), which are the key compounds in the synthesis of aldehydes **8**[18] and **12**.[17]

We have previously published the synthesis of a coumarin-condensed pyrroline nitroxide.[19] Very recently Cai et al.[20] described a new approach to isocoumarins starting from 1,3-diketones and *o*-halobenzoic acids. Applying this copper(I)-catalyzed reaction, we have converted carboxylic acid **1** into lactone **3** with pentane-2,4-dione in *N*,*N*-dimethylformamide in the presence of tripotassium phosphate and copper(I) iodide. This reaction can be carried out by conventional heating to afford compound **3** in 10% yield after 24 hours, however this yield can be improved to 43% by heating in a microwave reactor for 2.5 hours. Unfortunately, further application of compound **3** as a diene failed.

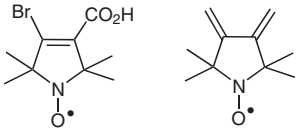

Figure 1 Key nitroxides for pyrroline nitroxide condensed carbocycles and heterocycles

As nitroxides are regarded as non-vitamin-like antioxidants, we have attached the nitroxide ring to antioxidant Ebselen [2-phenyl-1,2-benzoselenazol-3(2*H*)-one] to modulate its antioxidant properties.[21] In these analogues[22] mostly the *N*-phenyl ring was substituted with the nitroxide ring. We proposed that another analogue will be accessible by the method of Balkrishna[23] et al. who utilized *o*-halobenzanilides to achieve new Ebselen analogues.

To study this possibility, we converted carboxylic acid **1** into its *N*-phenylcarboxamide **4** by treatment of the corresponding carbonyl chloride[12] with aniline in the presence of triethylamine in dichloromethane. Reaction of compound **3** with copper(I) iodide, 1,10-phenanthroline, selenium powder, and potassium carbonate in *N*,*N*-dimethylformamide offered biradical **5** instead of isoselenazolone ring formation. This was confirmed by a mass spectral ($m/z = 676$) and EPR study (quintet line). This experiment suggested that incorporation of selenium was successful; however, because of oxidation of the selenol intermediate by the nitroxide, the diselenide **5** resulted. The same reaction from the diamagnetic derivative **6**, obtained by iron powder/acetic acid reduction of **4**,[24] now offered the pyrrolo[3,4-*d*][1,2]selenazol-3(4*H*)-one skeleton **7** although with low (15%) yield (Scheme 1). The

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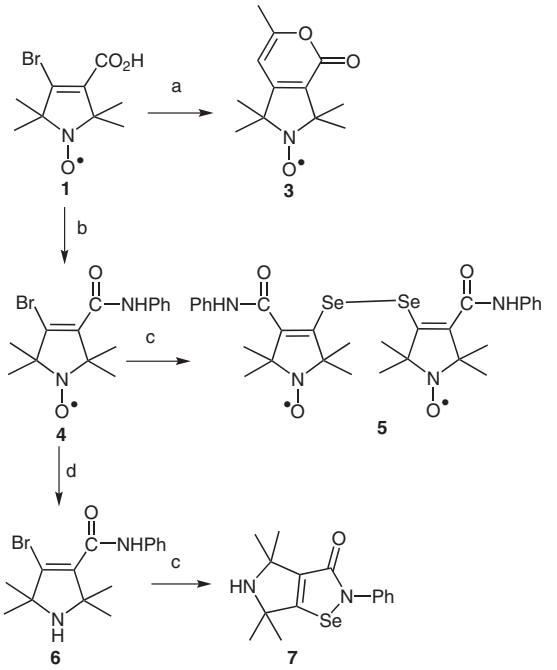
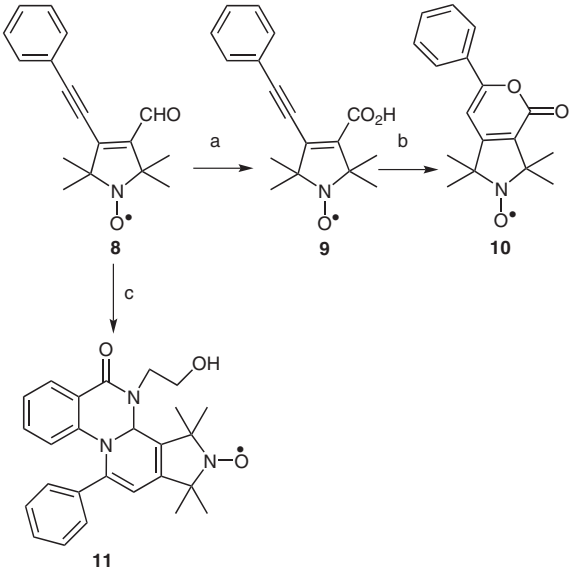
^{77}Se NMR signal of diamagnetic compound **7** was found at 916 ppm, which is close to that of Ebselen (940 ppm).



Scheme 1 *Reagents and conditions*: (a) pentane-2,4-dione (1.0 equiv), CuI (0.1 equiv), K_3PO_4 (2.0 equiv), DMF, 100 °C, 24 h, 10% or microwave, 100 °C, 2.5 h, 43%; (b) 1. $SOCl_2$ (3 equiv), pyridine (3 equiv), benzene, 0 °C to r.t., 1 h, then filtration and evaporation; 2. aniline (1.0 equiv), Et_3N (1.0 equiv), CH_2Cl_2, r.t., 1 h, 66%; (c) CuI (0.25 equiv), 1,10-phenanthroline (0.25 equiv), Se powder (1.6 equiv), K_2CO_3 (1.5 equiv), DMF, N_2, 110 °C, 26 h, 15–22%; (d) 1. Fe powder (10 equiv), AcOH, 70 °C, 30 min; 2. K_2CO_3, 38%.

β-Ethynyl-α,β-unsaturated carbonyl compounds are versatile intermediates for various heterocyclic ring synthesis.[25–27] We have used aldehyde **8** to achieve the pyrrolo[3,4-*c*]pyridine skeleton.[18] Here we report that oxidation of aldehyde **8**[18] to carboxylic acid **9** with hydrogen peroxide and sodium chlorite in aqueous acetonitrile followed by cyclization with gold(III) chloride in acetonitrile[28] offered lactone **10**, a phenyl analogue of compound **3**. Compound **8** was also used in an ytterbium(III) triflate catalyzed multicomponent reaction[29] with isatoic anhydride and ethanolamine in 1,2-dichloroethane to give pentacyclic compound **11** (Scheme 2). Similar isoquinolino[2,1-*a*]quinazolin-6(5*H*)-ones exhibited TNF-α inhibitory activity *in vitro*. In this experiment we demonstrated that this synthesis can be extended to tetrahydropyrrolo[3′,4′:3,4]pyrido[1,2-*a*]quinazolin-5(1*H*)-ones for the purpose of biological (TNF-α inhibitory) activity. For the synthesis of further pyrroline-annulated heterocycles, the functionalization of dialdehyde **12**[17] was obvious. Its oxidation with hydrogen peroxide and sodium chlorite in aqueous acetonitrile gave dicarboxylic acid **13**. This was converted into paramagnetic 'maleic anhydride like' compound **14** by heating in acetic anhydride.[13] This compound can be used as acylating spin label agent as its reaction with glycine methyl ester gave the acid amide at ambient temperature in dichloromethane. This was cyclized with acetic anhydride in the presence of anhydrous sodium acetate to offer maleimide derivative **15**.

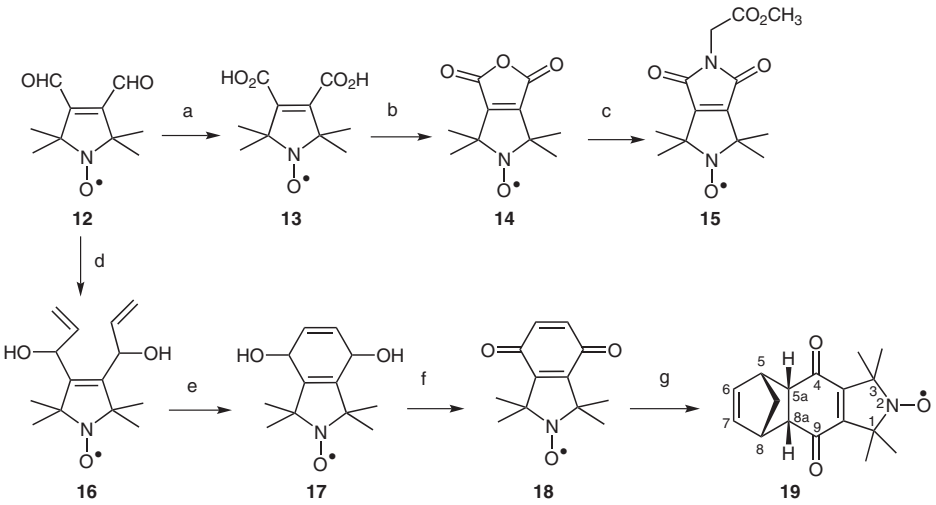


Scheme 2 *Reagents and conditions*: (a) 1. $NaClO_2$ (1.1 equiv), H_2O_2 (1.0 equiv), KH_2PO_4, MeCN–H_2O, 0 °C to r.t., 1 h; 2. $Na_2S_2O_5$, H^+, 72%; (b) $AuCl_3$ (0.05 equiv), MeCN, reflux, 30 min, 78%; (c) isatoic anhydride (1.0 equiv), ethanolamine (1.0 equiv), $Yb(OTf)_3$ (0.1 equiv), DCE, r.t., 48 h, 28%.

Reaction of aldehyde **12** with excess vinylmagnesium bromide in tetrahydrofuran gave diol **16**. This was converted into compound **17** by a ring-closing metathesis reaction in toluene in the presence of 5 mol% Grubbs II catalyst. Compound **17** was oxidized to pyrroline nitroxide condensed 1,4-benzoquinone **18** with manganese dioxide in chloroform. Although a naphthoquinone-condensed nitroxide has previously been reported by us,[30] this is the first example of 1,4-benzoquinone-annulated nitroxide, and as far as we know this is the first example of a metathesis[31] conducted in the presence of a nitroxide function, fortunately without loss of activity of the catalyst or devastation of nitroxide free radical moiety. To test the usefulness of compound **18** as a paramagnetic dienophile, freshly distilled cyclopentadiene was added to a solution of **18** in 3.0 M lithium perchlorate in diethyl ether[32] at ambient temperature to give *endo*-adduct **19** (Scheme 3).

The ^{1}H NMR chemical shifts of compound **19**, reduced with hydrazobenzene, suggest the formation of the *endo* isomer according to an analogous example published earlier; H5 and H8 positions gave signals at 3.51 ppm and H5a and H8a protons gave signals at 3.19 ppm.[33]

In summary, starting from nitroxides containing a β-bromo-α,β-unsaturated carboxylic acid, dicarbaldehyde, or β-ethynyl-α,β-unsaturated aldehyde moiety, various new carbocycles (1,4-benzoquinone and its adduct) and heterocycles (lactones, maleimides, isoselenazoles, pyrido[1,2-*a*]quinazolin-5(1*H*)-ones) condensed with



Scheme 3 *Reagents and conditions*: (a) 1. $NaClO_2$ (2.2 equiv), H_2O_2 (2.0 equiv), KH_2PO_4, MeCN–H_2O, 0 °C to r.t., 1 h; 2. $Na_2S_2O_5$, H^+, 53%; (b) Ac_2O (excess), reflux, 3 h, 61%; (c) 1. glycine methyl ester hydrochloride (1.0 equiv), Et_3N (2.0 equiv), r.t., 15 min; 2. **14**, r.t., 1 h,; 3. evaporation; 4. Ac_2O (excess), NaOAc (0.5 equiv), reflux, 3 h, 46%; (d) vinylmagnesium bromide (2.5 equiv), THF, 0 °C to r.t., 2 h, 55%; (e) Grubbs II catalyst (0.05 equiv), toluene, N_2, 90 °C, 3 h, 64%; (f) MnO_2 (5.0 equiv), $CHCl_3$, reflux, 1 h, 78%; (g) cyclopentadiene (5.0 equiv), 3.0 M $LiClO_4$ in Et_2O, r.t. 2 h, 69%.

nitroxides were obtained. Considering the new processes and transformations which are allowed in the presence of the nitroxide free radical function, it should be of great benefit in the synthesis of polycyclic nitroxides for biological study. We hope these findings also support the extension of the applied reactions in other transformations.

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 analyzer. Mass spectra were recorded on a Thermoquest Automass Multi. ^{1}H NMR spectra were recorded with Varian Unity Inova 400 WB spectrometer and Bruker Avance 3 Ascend 500; chemical shifts are referenced to Me_4Si. The paramagnetic compound was reduced with hydrazobenzene. Measurements were run at 298K probe temperature in $CDCl_3$ soln. ESR spectra were taken on Miniscope MS 200 in 10^{-4} M $CHCl_3$ soln and all monoradicals gave triplet line a_N = 14.4 G, biradical **5** a_{N1} = 7.2 G, a_{N2} = 14.4 G gave a quintet line. The microwave assisted reaction for synthesis of **3** was carried out in Milestone MicroSYNTH labstation in a sealed tube with temperature control (100 °C, fiber-optic probe). The total irradiation time was 2.5 h. The IR spectra was taken with Specord 85 instrument in Nujol or neat. Flash column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm). Qualitative TLC was carried out on commercially available plates (20 × 20 × 0.02 cm) coated with Merck Kieselgel GF254. Compounds **1**,[16] **8**,[18] **12**[17] were prepared according to published procedures. Grubbs II catalyst {benzylidene[1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene]dichloro(tricyclohexylphosphine)ruthenium} and other reagents were purchased from Aldrich.

1,1,3,3,6-Pentamethyl-4-oxo-1,2,3,4-tetrahydropyrano[3,4-*c*]pyrrol-2-oxyl Radical (3)

Method A: A tube was charged with a mixture of **1** (2.62 g, 10.0 mmol), pentane-2,4-dione (1.0 g, 10.0 mmol), CuI (190 mg, 1.0 mmol), and K_3PO_4 (4.24 g, 20.0 mmol) in DMF (10 mL) and the mixture was stirred 30 min at r.t. under N_2. The tube was sealed and stirred at 100 °C in an oil bath for 24 h. After cooling, the mixture was diluted with H_2O (30 mL), extracted with EtOAc (3 × 20 mL), and dried (anhyd $MgSO_4$). The mixture was filtered, evaporated, and purified by flash column chromatography (hexane–EtOAc, 2:1) to yield **3** (225 mg, 10%) as a yellow solid; mp 136–138 °C; R_f = 0.27 (hexane–EtOAc, 2:1).

IR (Nujol, KBr): 1710 (C=O), 1620, 1570 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 222 (M^+, 46), 207 (75), 192 (100), 149 (52).

Anal. Calcd. for $C_{12}H_{16}NO_3$: C, 64.85; H, 7.26; N, 6.30. Found: C, 64.76; H, 7.30; N, 6.25.

Method B: A tube was charged with a mixture of **1** (2.62 g, 10.0 mmol), pentane-2,4-dione (1.0 g, 10.0 mmol), CuI (190 mg, 1.0 mmol), and K_3PO_4 (4.24g, 20.0 mmol) in DMF (15 mL) and the mixture was stirred for 30 min at r.t. under N_2. The tube was sealed and stirred at 100 °C in a multimode microwave reactor for 2.5 h. After cooling the mixture was diluted with H_2O (30 mL), extracted with EtOAc (3 × 20 mL), and dried (anhyd $MgSO_4$). The mixture was filtered, evaporated, and purified by flash column chromatography (hexane–EtOAc, 2:1) to yield **3** (950 mg, 43%) as a yellow solid; mp 137–138 °C. The spectroscopic and physical data were identical with the sample achieved by method A.

4-Bromo-2,2,5,5-tetramethyl-3-[(phenylamino)carbonyl]-2,5-dihydro-1*H*-pyrrol-1-oxyl Radical (4)

To a stirred soln of **1** (1.31 g, 5.0 mmol) in benzene (10 mL) was added pyridine (1.21 mL, 15.0 mmol), followed by the dropwise addition of $SOCl_2$ (1.1 mL, 15.0 mmol) at 0 °C. The ice bath was removed and the mixture was stirred for a further 1 h at r.t. Pyridinium hydrochloride was filtered off, most of the solvent was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 (20 mL) and immediately added to a stirred soln of aniline (465 mg, 5.0 mmol) and Et_3N (505 mg, 5.0 mmol) and the mixture was stirred at r.t. for 1 h. The mixture was washed with 5% aq H_2SO_4 soln (15 mL) and brine (15 mL), and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc 2:1) to give **4** (1.11 g, 66%) as a yellow solid; mp 214–215 °C; R_f = 0.50 (hexane–EtOAc, 2:1).

IR (Nujol, KBr): 3300 (NH), 1685 (C=O), 1605, 1540 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 339/337 (M^+, 13/13), 309/307 (34/34), 228 (100), 77 (62).

Anal. Calcd for $C_{15}H_{18}BrN_2O_2$: C, 53.27; H, 5.36; N, 8.28. Found: C, 53.11; H, 5.25; N, 8.13.

4-Bromo-2,2,5,5-tetramethyl-*N*-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxamide (6)
To a stirred soln of **4** (1.35 g, 4.0 mmol) in AcOH (10 M), Fe powder (2.24 g, 40.0 mmol) was added and the mixture was stirred at 70 °C for 30 min. After cooling H_2O (50 mL) was added and the soln was decanted into a large, 500-mL beaker. Then the soln was basified (pH 10) by the addition of solid K_2CO_3 (intense foaming!) and the aqueous soln was extracted with $CHCl_3$ (2 × 20 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography ($CHCl_3$–Et_2O, 2:1) to give **6** (490 mg, 38%) as a white solid; mp 123–125 °C; R_f = 0.58 ($CHCl_3$–Et_2O–MeOH, 4:1.5:0.5).

IR (Nujol, KBr): 3300, 3176 (NH), 1660, 1630 (C=O), 1596, 1520 cm^{-1} (C=C).

^1H NMR ($CDCl_3$): δ = 7.91 (br s, 1 H), 7.60–7.58 (m, 2 H), 7.37–7.33 (m, 2 H), 7.17–7.13 (m, 1 H), 1.51 (6 H), 1.38 (6 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 165.73, 143.65, 139.42, 129.88, 129.28, 125.80, 121.75, 68.25, 68.01, 29.73, 28.66.

MS (EI): *m*/*z* (%) = 309/307 (M^+ – 15, 77/77), 227 (67), 136 (100).

Anal. Calcd for $C_{15}H_{19}BrN_2O$: 55.74; H, 5.92; N, 8.67. Found: C, 55.68; H, 5.88; N, 8.58.

Selenium-Containing Compounds 5, 7; General Procedure
A tube was charged with DMF (6 mL) and CuI (95 mg, 0.5 mmol); 1,10-phenanthroline (90 mg, 0.5 mmol) was added and the mixture was stirred for 15 min. Compound **4** or **6** (2.0 mmol), Se powder (253 mg, 3.2 mmol), and K_2CO_3 (414 mg, 3.0 mmol) were added sequentially and the mixture was degassed with N_2 for 5 min. Then the tube was sealed and the mixture was stirred for 26 h at 110 °C. After cooling the mixture was poured into a beaker containing brine soln (30 mL) and the mixture was stirred for 1 h. The mixture was extracted with EtOAc (3 × 20 mL) the combined organic extracts were dried (anhyd $MgSO_4$), filtered, and concentrated on a rotary evaporator under vacuo to give a brownish residue. This residue was and purified by flash column chromatography (hexane–EtOAc, 2:1 and $CHCl_3$–Et_2O, 4:1) to yield **5** and **7**.

4,4′-Diselenobis{2,2,5,5-tetramethyl-3-[(phenylamino)carbonyl]-2,5-dihydro-1*H*-pyrrol-1-oxyl) Biradical (5)
Deep yellow solid; yield: 148 mg (22%); mp 225–226 °C; R_f = 0.41 ($CHCl_3$–Et_2O, 2:1).

IR (Nujol, KBr): 3300 (NH), 1675 (C=O), 1595, 1530 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 676 (M^+, <1), 338 (9), 323 (35), 307 (100), 214 (52).

Anal. Calcd for $C_{30}H_{36}N_4O_4Se_2$: C, 53.42; H, 5.38; N, 8.31. Found: C, 53.30; H, 5.19; N, 8.27.

4,4,6,6-Tetramethyl-2-phenyl-5,6-dihydro-2*H*-pyrrolo[3,4-*d*][1,2]selenazol-3(4*H*)-one (7)
White solid; yield: 97 mg (15%); mp 175–176 °C; R_f = 0.52 ($CHCl_3$–Et_2O–MeOH, 4:1.5:0.5).

IR (Nujol, KBr): 3450 (NH), 1600 (C=O), 1570, 1540 cm^{-1} (C=C).

^1H NMR (CD_3OD): δ = 7.54–7.53 (m, 2 H), 7.42–7.38 (m, 2 H), 7.27–7.23 (m, 1 H), 1.56 (6 H), 1.53 (6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.22, 160.49, 139.50, 135.94, 129.17, 126.58, 124.96, 64.90, 64.70, 31.26, 29.07.

^{77}Se NMR (CD_3OD): δ = 916.

MS (EI): *m*/*z* (%) = 322 (M^+, 2), 307 (100), 188 (69), 136 (88).

Anal. Calcd for $C_{15}H_{18}N_2OSe$: C, 56.08; H, 5.65; N, 8.72. Found: C, 56.01; H, 5.59; N, 8.63.

Oxidation of Aldehydes to Carboxylic Acids 9, 13; General Procedure
To a well-stirred soln of aldehyde **8** or **12** (5.0 mmol), KH_2PO_4 (340 mg, 2.5 mmol) in MeCN–H_2O, (5:3, 24 mL), 30% aq H_2O_2 (0.5 mL for **9** and 1.0 mL for **13**), $NaClO_2$ (994 mg, 11.0 mmol for **9** and 1.98 g, 22.0 mmol for **13**) dissolved in H_2O (10 mL) was added dropwise over 30 min at 0 °C. The soln was stirred at r.t. for 1 h, then $Na_2S_2O_5$ (500 mg for **9** and 1.0 g for **13**) was added and the soln was cautiously acidified with 1.0 M aq HCl and the soln was extracted with $CHCl_3$ (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography ($CHCl_3$–MeOH, 9:1) to give the carboxylic acids as yellow solids.

3-Carboxy-2,2,5,5-tetramethyl-4-(phenylethynyl)-2,5-dihydro-1*H*-pyrrol-1-oxyl Radical (9)
???; yield: 1.02 g (72%); mp 220–222 °C; R_f = 0.65 ($CHCl_3$–MeOH, 9:1).

IR (Nujol, KBr): 3100 (OH), 2195 (C≡C), 1705 (C=O), 1605, 1550 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 384 (M^+, 68), 269 (97), 254 (100), 211 (40), 77 (50).

Anal. Calcd for $C_{17}H_{18}NO_3$: C, 71.81; H, 6.38; N, 4.93. Found: C, 71.76; H, 6.29; N, 4.88.

3,4-Dicarboxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-oxyl Radical (13)
???; yield: 604 mg (53%); mp 228–230 °C; R_f = 0.40 ($CHCl_3$–MeOH, 2:1).

IR (Nujol, KBr): 3200 (OH), 1700 (C=O), 1640 cm^{-1} (C=C).

MS (EI): *m*/*z* = 228 (M^+, 58), 180 (100), 162 (73).

Anal. Calcd for $C_{10}H_{14}NO_5$: C, 52.63; H, 6.18; N, 6.14. Found: C, 52.58; H, 6.11; N, 5.98.

1,1,3,3-Tetramethyl-4-oxo-6-phenyl-1,2,3,4-tetrahydropyrano[3,4-*c*]pyrrol-2-oxyl Radical (10)
To a soln of acid **9** (384 mg, 1.0 mmol) in anhyd MeCN (10 mL), $AuCl_3$ (15 mg, 0.05 mmol) was added and the mixture was heated at reflux temperature until the complete consumption of the starting material (~30 min.). After cooling the mixture was filtered through a Celite pad, the solvent was evaporated in vacuo, and the residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to yield **10** (221 mg, 78%) as a yellow solid; mp 224–226 °C; R_f = 0.46 (hexane–EtOAc, 2:1).

IR (Nujol, KBr): 1700 (C=O), 1620, 1545, 1535 cm^{-1} (C=C).

MS (EI): *m*/*z* = 384 (M^+, 20), 269 (50), 254 (100), 211 (30), 77 (31).

Anal. Calcd for $C_{17}H_{18}NO_3$: C, 71.81; H, 6.38; N, 4.93. Found: C, 71.78; H, 6.33; N, 4.85.

4-(2-Hydroxyethyl)-1,1,3,3-tetramethyl-5-oxo-11-phenyl-1,2,3,3b,4,5-hexahydropyrrolo[3′,4′:3,4]pyrido[1,2-*a*]quinazolin-2-oxyl Radical (11)
A mixture of aldehyde **8** (268 mg, 1.0 mmol), isatoic anhydride (163 mg, 1.0 mmol), ethanolamine (61 mg, 1.0 mmol), and $Yb(OTf)_3$ (62 mg, 0.1 mmol) was stirred in DCE (5 mL) for 48 h at r.t. under N_2. After evaporation the solvent, the residue was dissolved in $CHCl_3$ (15 mL), the organic phase was washed with brine (10 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography ($CHCl_3$–Et_2O, 2:1); the most significant product at R_f = 0.65 ($CHCl_3$–Et_2O–MeOH, 4.5:1.5:0.5) was isolated to give **11** as a yellow solid; yield: 120 mg (28%); mp 138–140 °C.

IR (Nujol, KBr): 3430 (OH), 1640 (C=O), 1590, 1570, 1510 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 430 (M^+, 3), 400 (9), 277 (19), 180 (35), 120 (100).

Anal. Calcd for $C_{26}H_{28}N_3O_3$: C, 72.54; H, 6.56; N, 9.76. Found: C, 72.42; H, 6.49; N, 9.59.

4,4,6,6-Tetramethyl-1,3-dioxo-3,4,5,6-tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5-oxyl (14)
A soln of **13** (456 mg, 2.0 mmol) in Ac_2O (5 mL) was heated at reflux temperature for 3 h. After cooling, the solvent was evaporated and the residue was purified by flash column chromatography (anhyd Et_2O) to yield **14** (256 mg, 61%) as a yellow solid; mp 37–39 °C; R_f = 0.54 (hexane–EtOAc, 2:1).

IR (Nujol, KBr): 1850, 1740 (C=O), 1650 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 210 (M^+, 1), 180 (100), 165 (33), 162 (56).

Anal. Calcd for $C_{10}H_{12}NO_4$: C, 57.14; H, 5.75; N, 6.66. Found: C, 57.08; H, 5.68; N, 6.60.

5-[(Methoxycarbonyl)methyl]-1,1,3,3-tetramethyl-4,6-dioxo-1,2,3,4,5,6-hexahydropyrrolo[3,4-*c*]pyrrol-2-oxyl Radical (15)
To a soln of glycine methyl ester hydrochloride (251 mg, 2.0 mmol) in CH_2Cl_2 (10 mL), Et_3N (404 mg, 4.0 mmol) was added and the mixture was stirred for 15 min at r.t. To this soln **14** (420 mg, 2.0 mmol) was added in one portion and the mixture was stirred at r.t. for 1 h. Then the organic phase was washed with brine, dried ($MgSO_4$), filtered, and evaporated to give a yellow oil. This oil was dissolved in Ac_2O (5 mL), NaOAc (82 mg, 1.0 mmol) was added and the mixture was stirred and refluxed for 3 h. After cooling the inorganic salt was filtered off, the solvent was evaporated and the residue was subjected to flash column chromatography (hexane–EtOAc, 2:1) to afford **15** (264 mg, 46%) as a yellow oil; R_f = 0.51 (hexane–EtOAc, 2:1).

IR (neat, KBr): 1750, 1720 (C=O), 1660 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 281 (M^+, 3), 251 (74), 236 (67), 191 (63), 93 (100).

Anal. Calcd for $C_{13}H_{17}N_2O_5$: C, 55.51; H, 6.09; N, 9.96. Found: C, 55.48; H, 6.01; N, 9.90.

3,4-Bis(2-hydroxyprop-2-enyl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-oxyl Radical (16)
To a stirred soln of **12** (980 mg, 5.0 mmol) in THF (30 mL), 1.0 M vinylmagnesium bromide in THF (12.5 mL, 12.5 mmol) was added dropwise at 0 °C. The mixture was stirred at r.t. for 2 h, and then sat. aq NH_4Cl soln (10 mL) was added. After dilution with Et_2O (20 mL) the organic phase was separated, the aqueous phase was extracted with $CHCl_3$ (2 × 20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography ($CHCl_3$–Et_2O) to yield **16** (693 mg, 55%) as a pale yellow solid; mp 92–94 °C; R_f = 0.65 ($CHCl_3$–Et_2O–MeOH, 4.5:1.5:0.5).

IR (Nujol, KBr): 3400 (OH), 1610, 1600, 1545 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 252 (M^+, 100), 238 (27), 204 (57), 189 (82).

Anal. Calcd for $C_{14}H_{22}NO_3$: C, 66.64; H, 8.79; N, 5.55. Found: C, 66.58; H, 8.61; N, 5.48.

4,7-Dihydroxy-1,1,3,3-tetramethyl-1,3,4,7-tetrahydro-2*H*-isoindol-2-oxyl Radical (17)
To a stirred and deoxygenated soln of **16** (504 mg, 2.0 mmol) in toluene (120 mL) Grubbs II catalyst (85 mg, 0.1 mmol) was added at 90 °C in one portion and the mixture was stirred at this temperature for 3 h under N_2. After cooling, the mixture was filtered through a Celite pad, the solvent was evaporated, and the brown residue was purified by flash column chromatography ($CHCl_3$–Et_2O, 2:1) to give **17** (286 mg, 64%) as a dark brown solid; mp 155–158 °C; R_f = 0.21 ($CHCl_3$–Et_2O, 2:1).

IR (Nujol, KBr): 3400 (OH), 1600 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 224 (M^+, 46), 194 (16), 161 (58), 42 (100).

Anal. Calcd for $C_{12}H_{18}NO_3$: C, 64.26; H, 8.08; N, 6.25. Found: C, 64.20; H, 7.98; N, 6.13.

1,1,3,3-Tetramethyl-4,7-dioxo-1,3,4,7-tetrahydro-2*H*-isoindol-2-oxyl Radical (18)
To a stirred soln of **17** (448 mg, 2.0 mmol) in $CHCl_3$ (25 mL), activated MnO_2 (870 mg, 10.0 mmol) was added and the mixture was stirred and refluxed for 1 h. After cooling, the MnO_2 was filtered off on a Celite pad and washed with $CHCl_3$ (30 mL), the solvents were evaporated off, and the residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to give **18** (343 mg, 78%) as a brown solid; mp 125–127 °C; R_f = 0.65 (hexane–EtOAc, 2:1).

IR (Nujol, KBr): 1655 (C=O), 1620 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 220 (M^+, 37), 190 (8), 175 (100), 160 (33).

Anal. Calcd for $C_{12}H_{14}NO_3$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.40; H, 6.38; N, 6.23.

1,1,3,3-Tetramethyl-4,9-dioxo-2,3,4,4a,5,8,8a,9-octahydro-1*H*-5,8-methanobenzo[*f*]isoindol-2-oxyl Radical (19)
To a stirred soln of 3.0 M $LiClO_4$ in Et_2O (10 mL) and **18** (220 mg, 1.0 mmol), freshly distilled cyclopentadiene (330 mg, 5.0 mmol) was added and the mixture was stirred for a further 2 h at r.t. The mixture was poured into H_2O (20 mL) and diluted with Et_2O (20 mL), the organic phase was separated, the aqueous phase was washed with EtOAc (20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to give **19** (197 mg, 69%) as an orange solid; mp 126 °C; R_f = 0.56 (hexane–EtOAc, 2:1).

IR (Nujol, KBr): 1675 (C=O), 1620 cm^{-1} (C=C).

^1H NMR ($CDCl_3$–PhNHNHPh): δ = 6.05 (s, 2 H), 3.51 (s, 2 H), 3.19 (s, 2 H), 1.54 (d, 1 H), 1.43 (t, 1 H), 1.41 (s, 6 H), 1.33 (s, 6 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 196.62, 152.50, 134.75, 67.91, 50.45, 49.34, 49.02, 23.96, 23.70.

MS (EI): *m*/*z* = 286 (M^+, 15), 256 (2), 220 (55), 175 (100), 66 (45).

Anal. Calcd for $C_{17}H_{20}NO_3$: C, 71.37; H, 7.04; N, 4.89. Found: C, 71.28; H, 7.01; N, 4.82.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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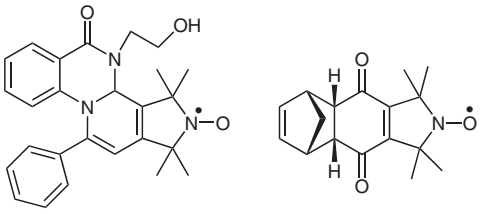

graphic abstract

