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Synthesis of Sterically Shielded Nitroxides of the *trans*-3,7-Diazabicyclo[3.3.0]octane series

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Abstract

A series of bicyclic nitroxides, (*3aR(S)*,*6aR(S)*)-1-X-1,3,3-triethyloctahydropyrrolo[3,4-*c*]pyrrol-2-oxyls, where X = Et or t-Bu, have been prepared from the corresponding 3,4-disubstituted bis(hydroxymethyl)pyrrolidine-1-oxyls, which are among the most stable nitroxides known. The formation of this bicyclic system occurs upon *in situ* generation of *trans*-3-(aminomethyl)-4-(((methylsulfonyl)oxy)methyl)pyrrolidin-1-oxyls by various methods. Although the resulting nitroxides have highly strained *trans*-3,7-diazabicyclo[3.3.0]octane scaffold, they demonstrate high resistance to reduction with ascorbate ($k_2 \sim 10^{-3}$ – 10^{-4} M⁻¹s⁻¹). A number of bicyclic conformationally rigid spin labels have been prepared.

Introduction

The conformational behavior of biomolecules plays a crucial role in their functioning and represents a challenge for structural biology, because the structure of biomolecules *in vitro* can significantly differ from that in their native intracellular environment [1, 2]. Site-directed spin labeling (SDSL) combined with pulsed electron paramagnetic resonance (EPR) spectroscopy is a powerful technique that can provide information on the folding and dynamics of proteins directly inside cells [2, 3, 4]. The stability of the spin label is a prerequisite for conducting such studies. Sterically shielded nitroxides of pyrroline and pyrrolidine series, which exhibit the highest resistance to chemical reduction in cellular compartments, are considered prospective candidates for application in biomolecules labeling [5, 6, 7, 8, 9]. We have previously shown that promising water-soluble spin labels can be synthesized starting from 2,2,5,5-tetraethyl-3,4-bis(hydroxymethyl)pyrrolidin-1-oxyl (**1**) [10]. Compound **1** and its derivatives show relatively slow reduction rates upon treatment with ascorbate, $k_2 = 3 - 8 \times 10^{-4}$ M⁻¹s⁻¹. However, these radicals are significantly inferior in stability to another nitroxide, 2,2,5-triethyl-5-*tert*-butyl-3,4-bis(hydroxymethyl)-pyrrolidine-1-oxyl (**2**) (Fig. 1), $k_2 = (7.0 \pm 2) \times 10^{-5}$ M⁻¹s⁻¹.

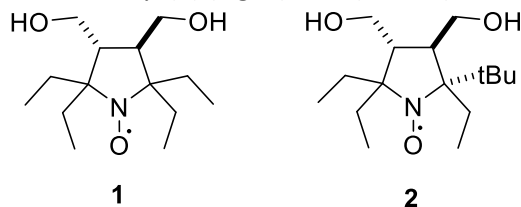


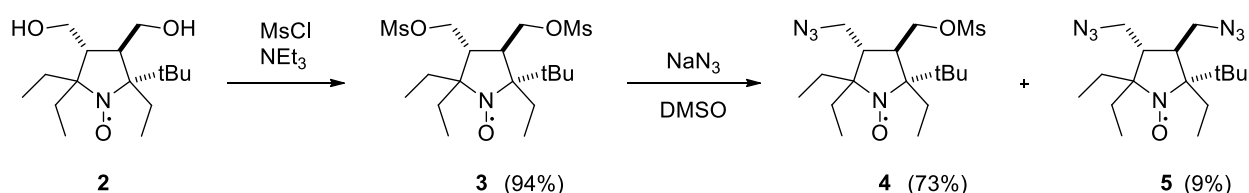
Figure 1. Structures of nitroxides **1** and **2**.

Recently, we proposed a convenient method for the preparation of **2**, which does not require the tricky hydrogenation procedure and renders this nitroxide more accessible than **1** [11]. We aimed to develop a method for the regioselective conversion of **2** into heterobifunctional derivatives (spin labels) without the formation of diastereomeric mixtures. In the course of these studies, we have found that the *in situ* generation of *trans*-3-(aminomethyl)-4-(((methylsulfonyl)oxy)methyl)pyrrolidin-1-oxyls via various routes invariably leads to cyclization yielding bicyclic nitroxides with a highly strained *trans*-3,7-diazabicyclo[3.3.0]octane core. This ring system represents an attractive scaffold for advanced spin label

design due to its inherent structural rigidity and the well-defined spatial orientation of the intracyclic secondary amino group relative to the nitroxide moiety. The rates of reduction of the new nitroxides with ascorbate were measured and a set of bicyclic spin labels has been prepared.

Results and discussion

To obtain heterobifunctional derivatives starting from nitroxide **2**, we attempted to use a previously developed approach involving a reaction with methanesulfonyl chloride followed by substitution of the mesylate group with an sodium azide [10]. Unlike compound **1**, nitroxide **2** is asymmetric; thus, if the amount of reagent is insufficient, complex mixtures of mesylation products are formed which are difficult to separate. Therefore, exhaustive mesylation was performed with three equivalents of methanesulfonyl chloride in the presence of triethylamine to afford nitroxide **3** in 94% yield as a crystalline racemate (Scheme 1). The assigned structure was supported by NMR spectra (recorded after reduction of the nitroxide group with Zn/CF₃COOH [12]), IR spectroscopy, high-resolution mass spectrometry, elemental analysis (see Supporting Information, pp. S6, S16, S29) and single-crystal X-ray diffraction data (CCDC 2586974, Fig. 2).



Scheme 1. Synthesis of azides **4** and **5**.

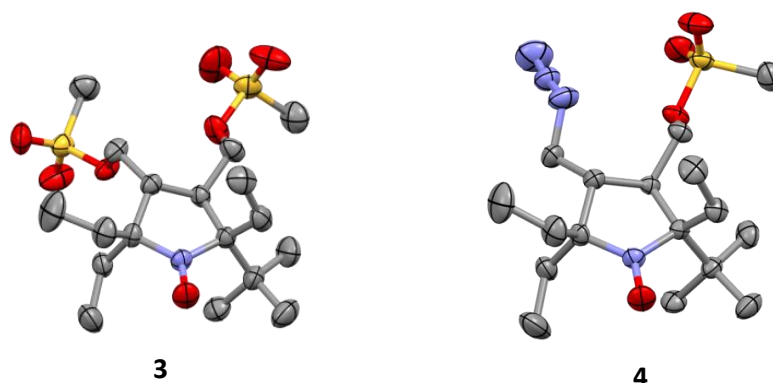
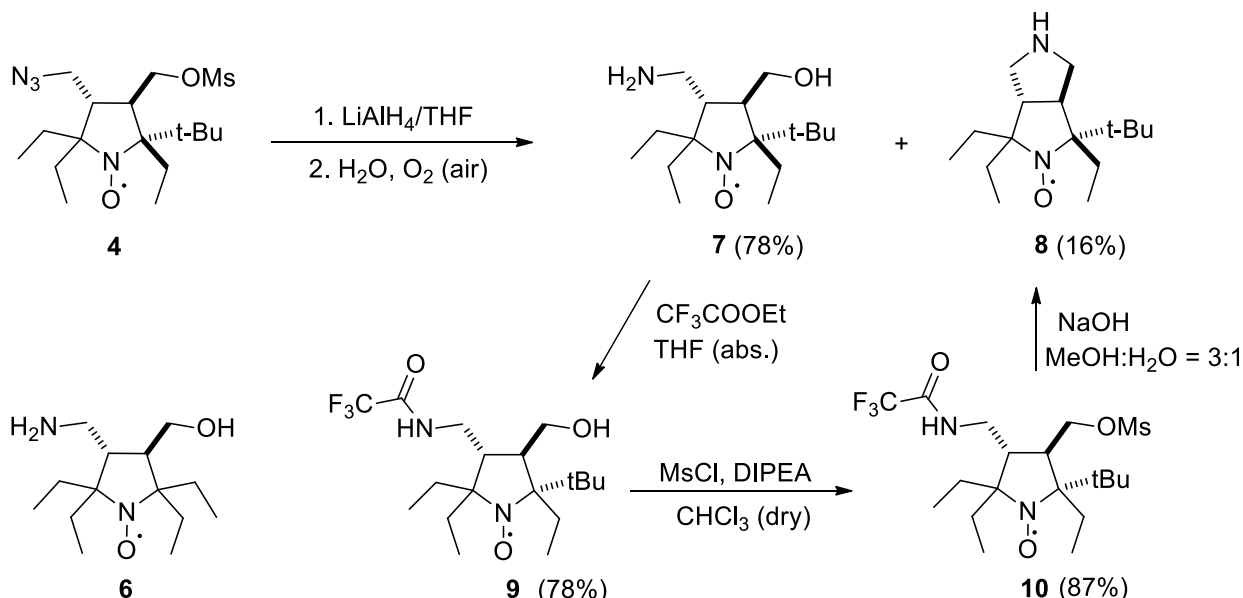


Figure 2. Single-crystal X-ray structures of nitroxides **3** and **4**.

Nitroxide **3** was heated with sodium azide in DMSO. The substitution of the mesylate groups occurred regioselectively, resulting in compound **4** in 73% yield. Diazide **5** was isolated as a by-product in 9% yield. Presumably, the access of the azide anion to one of the mesylate groups is sterically hindered by the bulky *tert*-butyl group at the adjacent position on the pyrrolidine ring (Scheme 1). The structure of **4** was unambiguously confirmed by single-crystal X-ray diffraction data (CCDC 2586975, Fig. 2).

In our previous work [10], we used 3-(aminomethyl)-4-(hydroxymethyl)-2,2,5,5-tetraethylpyrrolidin-1-oxyl (**6**) (Scheme 2) as an important precursor for hydrophilic spin labels. To synthesize the *tert*-butyl-substituted analog of this radical, nitroxide **4** was slowly added to an excess of LiAlH₄ in THF. The reaction of alkyl mesylates with LiAlH₄ is commonly used for deoxygenation of alcohols to alkanes, known to proceed via nucleophilic substitution of the mesylate by the hydride anion [13]. However, as noted above, steric hindrance retards the substitution of the mesylate group by azide; therefore, alternative pathways of this reaction should be expected, such as elimination [13, 14] or reduction to the corresponding alcohol [13, 15]. After quenching the reaction mixture, two nitroxides were isolated by column chromatography. The ¹H NMR spectrum of the major product, **7**, recorded after

the reduction of the nitroxide group with Zn/CF₃COOH, closely resembled the spectrum of **6** [10], with two pairs of well-resolved multiplets at 4.10, 3.76 and 3.30, 3.03 ppm assigned to the methylene protons of the CH₂OH and CH₂NH₂ groups respectively. The signal at 61.43 ppm in the ¹³C NMR spectrum was unambiguously assigned to the hydroxymethyl carbon. The structure of nitroxide **7** was supported with IR spectroscopy, high-resolution mass spectrometry, elemental analysis (see Supporting Information, pp. S7, S17, S30), and single-crystal X-ray diffraction data (CCDC 2586976, Fig. 3).



Scheme 2. Synthesis of aminoalcohol **7** and formation of the *trans*-3,7-diazabicyclo[3.3.0]octane system.

The minor product **8** was isolated in 16% yield. This nitroxide resisted crystallization. High-resolution mass spectrometry revealed the presence of an ion at *m/z* 267.2433, which corresponds to the loss of H₂O from nitroxide **7**. The absence of olefinic proton signals in the ¹H NMR spectrum of nitroxide **8**, reduced with Zn/CF₃COOH, indicated that the loss of H₂O resulted from cyclization rather than an elimination reaction. The proton signals were assigned based on ¹H-¹H COSY and ¹H-¹H NOESY correlations. Full lineshape simulation of the ¹H NMR spectrum using the gNMR program [16] revealed a coupling constant between the vicinal CH protons indicative of a *trans*-pseudodiaxial arrangement with a dihedral angle close to 180° (³J_{HH} = 13.5 Hz) [17], which is consistent only with a *trans*-fused bicyclic system (see Supporting Information, Fig. S47).

Recently, it has been shown that *trans*-3,7-diazabicyclo[3.3.0]octanes can be formed from the reaction of *trans*-3,4-bis(mesyloxymethyl)pyrrolidines with amines [18]. However, *trans*-fused 5,5-bicyclic frameworks are widely regarded as highly strained systems [19]. Therefore, the formation of the *trans*-3,7-diazabicyclo[3.3.0]octane scaffold prompted us to investigate this cyclization in more detail. As a first step, we attempted to obtain **8** from nitroxide **7**. The amino group in compound **7** was protected via trifluoroacetylation, and the resulting nitroxide **9** was treated with methanesulfonyl chloride in the presence of DIPEA to give mesylate **10** (Scheme 2). Nitroxides **9** and **10** were fully characterized by IR spectroscopy, HRMS, elemental analysis, and ¹H/¹³C NMR (the latter recorded after reduction of the nitroxide group with Zn/CF₃COOH). In addition, the structure of **9** was confirmed by single-crystal X-ray diffraction (CCDC 2586977, Fig. 3). Removal of the trifluoroacetyl group from compound **10** under alkaline conditions resulted in cyclization to afford nitroxide **8**.

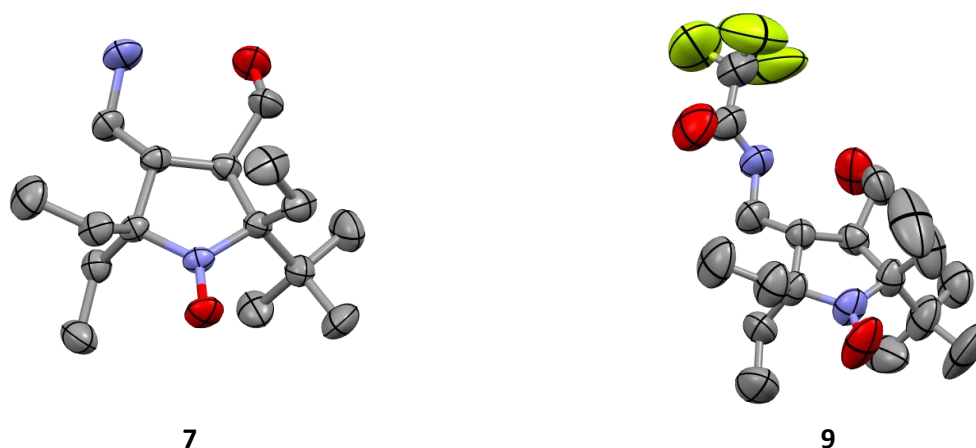
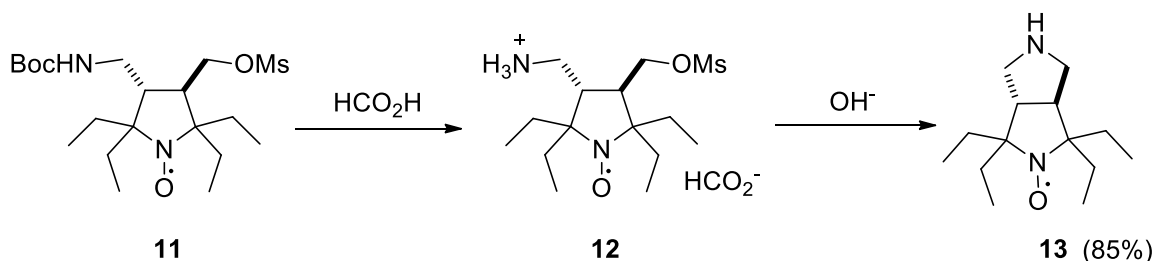


Figure 3. Single-crystal X-ray structures of nitroxides **7** and **9**.

In the pathways described above for the formation of **8** (Scheme 2), cyclization occurred upon heating in an alkaline medium. To verify whether alkaline conditions are required for the formation of the *trans*-3,7-diazabicyclo[3.3.0]octane scaffold, we used a *tert*-butoxycarbonyl-protected analog of **10**, nitroxide **11**, previously synthesized [10]. Reaction of nitroxide **11** with 95% formic acid at 25 °C was complete within 4 hours. The mixture was evaporated to dryness affording a crystalline solid. The IR spectrum of the resulting compound showed strong absorption bands at 1350 and 1174 cm^{-1} , characteristic of methanesulfonic acid esters. A sample of this compound was dissolved in CD_3OD and reduced with Zn in the presence of ND_4Cl at 0–5 °C. The ^1H and ^{13}C NMR spectra of the resulting solution indicated an asymmetric structure. Indeed, the ^{13}C NMR spectrum of this compound shows four signals for nonequivalent methyl groups at 8.33, 8.54, 8.72 and 9.28 ppm, two signals for methine carbons (CH) at 45.77 and 48.15 ppm, and two signals for methylene carbons (CH_2NH_3^+ and CH_2OMs) at 40.53 and 69.56 ppm, respectively. The significant difference in the chemical shifts of the methylene carbons is consistent with structure **12** (Scheme 3). These data indicate that cyclization to afford compound **13** does not occur under acidic conditions.

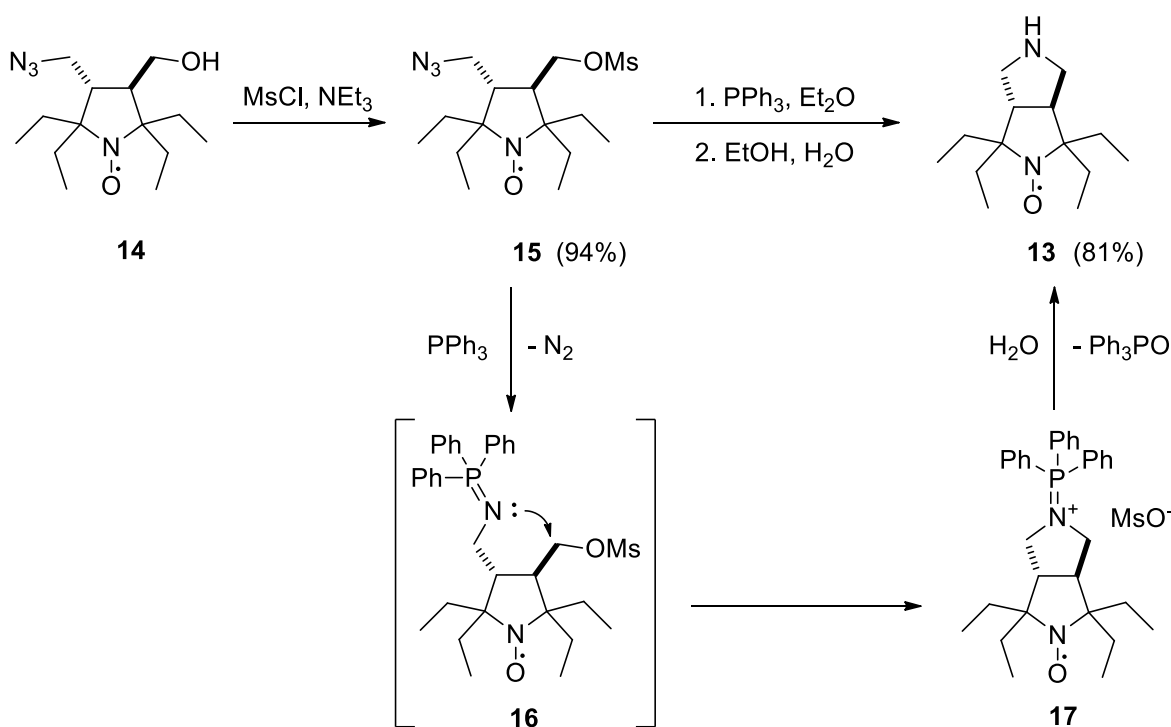


Scheme 3. Synthesis of bicyclic amine **13**.

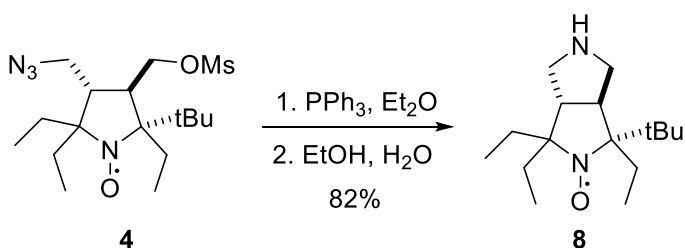
Dissolution of salt **12** in 0.33 M aqueous NaOH afforded bicyclic amine **13**, which was isolated in 85% yield as a crystalline solid (Scheme 3). The ^1H NMR spectrum recorded after reduction of nitroxide **13** with Zn/ CF_3COOH was similar to that of **8** in the region of 1.5–4.0 ppm. Full lineshape simulation of the ^1H NMR spectrum revealed that the coupling constants follow the same patterns as that of **8** (see Supporting Information, Figure S49). The ^{13}C NMR spectrum of reduced nitroxide **13** exhibited only half the expected number of signals, which is consistent with C_2 symmetry. The structure of **13** was further supported by HRMS and elemental analysis.

Amines **8** and **13** can also be prepared via the Staudinger reaction from the corresponding azidomesylates **4** and **15** (Schemes 4 and 5). Nitroxide **15** was prepared in 95% yield from **14** by treatment with methanesulfonyl chloride. Treatment of **15** with an equimolar amount of triphenylphosphine in diethyl ether upon heating afforded a yellow precipitate. The IR spectrum of the isolated compound showed no significant absorption in the 1350–1375 cm^{-1} region, where a strong band

of methanesulfonate esters typically appears. Instead, it displayed intense bands at 1211 and 1041 cm^{-1} , which can be attributed to the methanesulfonate anion [20]. HRMS revealed a peak at m/z 500.2947, which corresponds to the formula $\text{C}_{32}\text{H}_{41}\text{PN}_2\text{O}$, while elemental analysis was in agreement with structure **17**. Formation of **17** supports a mechanism involving intramolecular cyclization via nucleophilic attack of the iminophosphorane nitrogen on the mesylate-bearing carbon (intermediate **16**, Scheme 4), accompanied by elimination of the methanesulfonate anion. Hydrolysis of **17** in aqueous ethanol afforded **13** in 81% yield. A similar two-step Staudinger procedure was applied to azidomesylate **4** to afford bicyclic amine **8** in 82% yield (Scheme 5).



Scheme 4. Synthesis of bicyclic amine **17** via the Staudinger reaction and subsequent intramolecular cyclization.



Scheme 5. Synthesis of bicyclic amine **8** via the Staudinger reaction.

The EPR spectral parameters of bicyclic nitroxides **8** and **13** are summarized in Table 1. Data for their 4-(aminomethyl)-3-(hydroxymethyl)pyrrolidine derivatives **6** and **7** as well as 3,4-bis(hydroxymethyl)pyrrolidine precursors **1** and **2** are provided for comparison. The EPR spectral features of sterically hindered five-membered cyclic nitroxides have been discussed in detail previously [21, 22, 23]. It has been shown that, besides the typical triplet splitting from the ^{14}N nucleus, these radicals may exhibit large additional hyperfine coupling constants ($hfcc$) for certain γ -protons in their side chains. In the spectra of 3,4-disubstituted 2,2,5,5-tetraethylpyrrolidine nitroxides, two $hfcc$ of 0.20–0.25 mT are observed, one for each pair of geminal ethyl groups. This coupling arises from the overlap of the small lobe of the sp^3 -hybridized carbon orbital in the C–H bond with the nitroxide π^* orbital. The

highest $hfcc$ is expected for the conformation in which the ethyl group is in the pseudo-axial position and the CH_2-CH_3 bond is parallel to the nitroxide N–O bond [22]. Replacement of one ethyl group with a *tert*-butyl group renders this conformation unfavorable and results in the disappearance of the large $hfcc$ on the methylene proton of the adjacent ethyl group [22, 24].

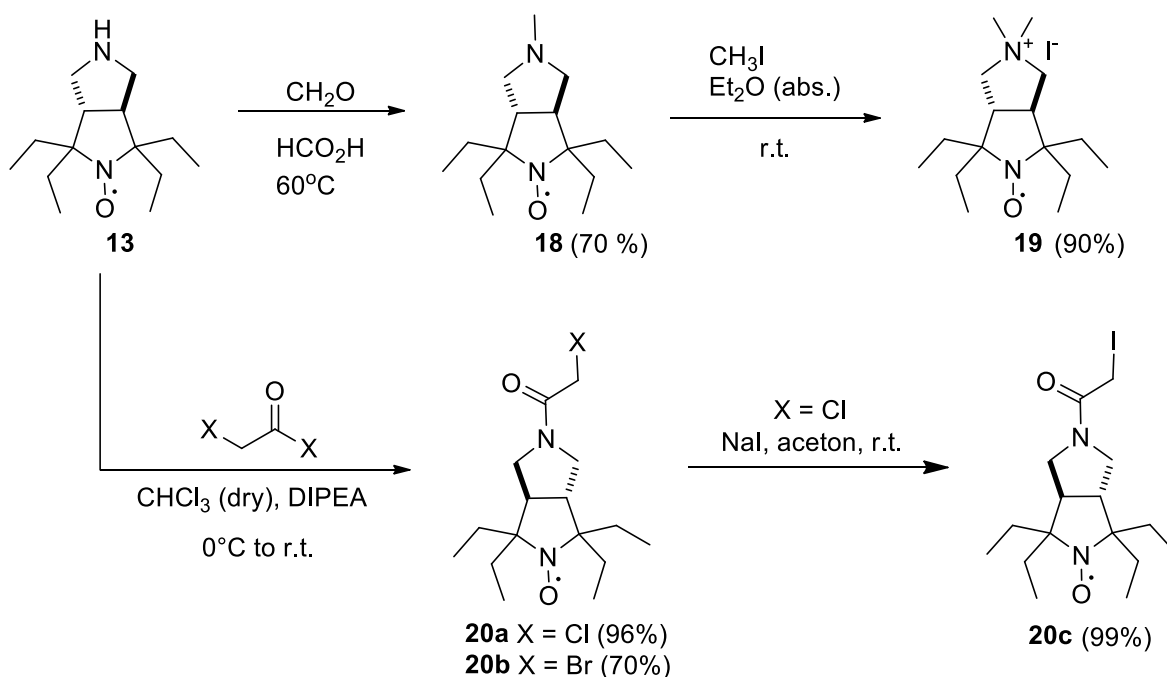
The additional $hfcc$ values on γ -protons in the EPR spectra of bicyclic radicals **8** and **13** are 0.07–0.08 mT smaller than those in the spectra of **1**, **2**, **6**, and **7**. The formation of the bicyclic structure restricts the conformational mobility of the substituents at the 3- and 4-positions of the pyrrolidine ring. This restriction shifts the conformational equilibrium towards less shielded states, where the ethyl groups deviate from alignment with the N–O bond. The decrease in steric shielding of the nitroxide group partly explains the higher rates of reduction of diazabicyclooctane nitroxides by ascorbate compared to those of similar pyrrolidine radicals (Table 1). The reduction rate can also be influenced by the electronic effects of the functional groups. Notably, nitroxides **6–8** and **13** exist as protonated cations at pH 7 [25, 26]. It has been shown that amino nitroxides are stronger oxidants than the corresponding hydroxyl-substituted nitroxides. This difference arises because the basic amino group undergoes protonation to an ammonium group, which exerts a stronger electron-withdrawing inductive effect than a hydroxyl group [27].

Table 1. Hyperfine coupling constants and second-order reduction rate constants for nitroxides **1**, **2**, **6**, **7**, **8**, and **13**.

Nitroxide	a_N , mT	a_H , mT	k_2 , $M^{-1}s^{-1}$
1	1.527	0.225×2 [28]	$(3.3 \pm 0.8) \times 10^{-4}$ [28]
2	1.580	0.255 [24]	$(7.0 \pm 2) \times 10^{-5}$ [11]
6	1.531	0.23×2	$(7.1 \pm 0.6) \times 10^{-4}$
7	1.534	0.27	$(1.6 \pm 0.2) \times 10^{-4}$
8	1.569	0.19	$(4.4 \pm 0.3) \times 10^{-4}$
13	1.573	0.15×2	$(1.1 \pm 0.1) \times 10^{-3}$

The conformational rigidity of the *trans*-3,7-diazabicyclo[3.3.0]octane scaffold fixes the position of the secondary amino group relative to the nitroxide moiety in **8** and **13**. Therefore, despite the modestly lower stability of these radicals compared to those of nitroxides **1** and **2**, the new bicyclic nitroxides may find applications in molecular biology and materials science. The syntheses of several derivatives of **8** and **13** are outlined below.

Amine **13** was methylated via the Eschweiler-Clarke reaction using 21% formalin and 95% formic acid, affording methylamine derivative **18** in 70% yield (Scheme 6). The IR spectrum of **18** showed an absorption band at 2783 cm^{-1} , characteristic of C–H stretching vibrations in a methyl group attached to a nitrogen atom [29]. HRMS and elemental analysis data for **18** were consistent with the proposed molecular formula. Interestingly, the 1H NMR spectrum of nitroxide **18**, recorded after reduction by the Zn/ CF_3COOH system, showed significant broadening of the signals from the fused pyrrolidine ring protons, presumably due to slow nitrogen inversion.



Scheme 6. Alkylation of **13** and synthesis of haloacetamido spin labels **20a–c**.

Treatment of methylamine derivative **18** with methyl iodide in diethyl ether at room temperature gave quaternary ammonium salt **19** as a precipitate, which was isolated in 90% yield (Scheme 6).

Acylation of **13** with the corresponding haloacetyl halides afforded the chloro- and bromoacetamides **20a,b** in 96% and 70% yields, respectively. Iodoacetamide **20c** was obtained from **20a** via halide exchange with sodium iodide (Scheme 6). The IR spectra of nitroxides **20a–c** exhibit a characteristic amide C=O stretching band at 1648–1660 cm^{-1} . HRMS and elemental analysis data for **20a–c** were consistent with the expected formulas. The structure of **20a** was further confirmed by single-crystal X-ray diffraction (CCDC 2586978, Fig. 4).

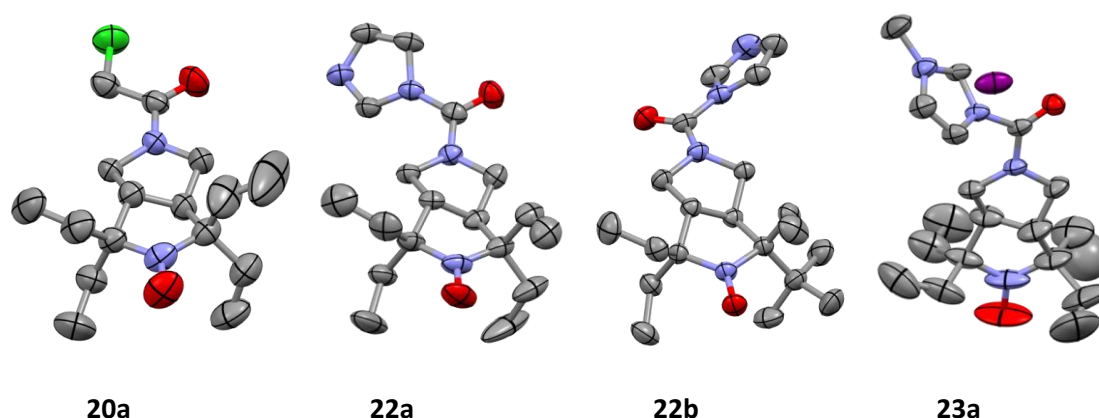
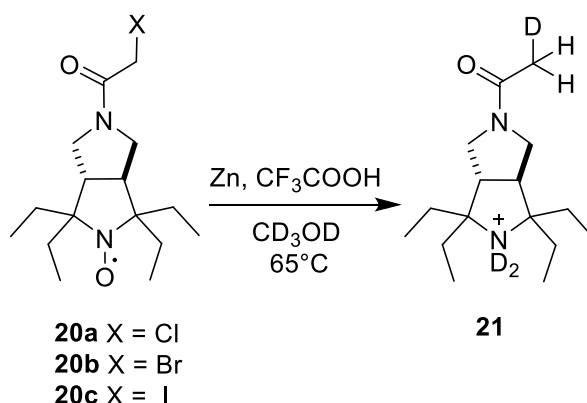


Figure 4. Single-crystal X-ray structures of nitroxides **20a**, **22a**, and **22b**.

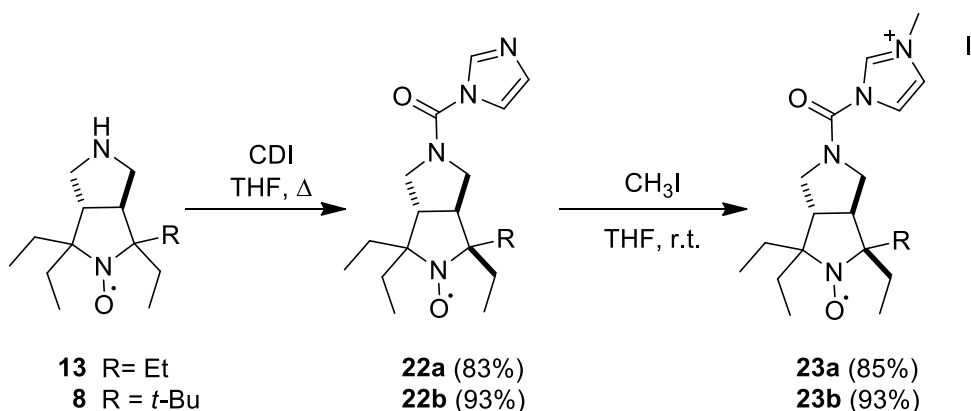
Reduction of nitroxides **20a–c** with the $\text{Zn}/\text{CF}_3\text{COOH}$ system in CD_3OD yielded the same diamagnetic product, as evidenced by ^1H NMR spectroscopy. The observed ^1H NMR signals matched those expected for the *trans*-2,2,4,4-tetraethyl-3,7-diazabicyclo[3.3.0]octane framework. The observed coupling constants within the six-spin system of the bicyclic core closely resemble those of reduced nitroxide **13**. Notably, the loss of molecular symmetry relative to precursor **13** reflects the restricted rotation about the C–N amide bond. The appearance of a characteristic triplet ($^1J_{\text{C-D}} = 20 \text{ Hz}$) at 21.5 ppm in the ^{13}C NMR spectra revealed that the reduction of the nitroxide group to diamagnetic amine

was accompanied by reductive dehalogenation of the haloacetamide fragments, whereby the halogen was replaced by deuterium (Scheme 7).



Scheme 7. Reduction of **20a-c** with the Zn/CF₃COOH system.

Carbamoylimidazoles and carbamoylimidazolium salts are versatile reagents that react readily with amino, hydroxyl, and thiol groups [30,31,32,33]. Recent studies have shown that these reactions can be performed in aqueous media [32]. This characteristic renders them highly advantageous for *in vivo* spin labeling. Moreover, carbamoylimidazolium-functionalized nitroxides have been successfully used in the synthesis of polarizing agents for dynamic nuclear polarization (DNP) experiments in water [34]. Here, we have synthesized bicyclic carbamoylimidazole and carbamoylimidazolium spin labels from **8** and **13** via modified literature protocols [30]. Treatment of bicyclic amines **8** and **13** with *N,N'*-carbonyldiimidazole (CDI) in THF afforded carbamoylimidazoles **22a,b** in 83% and 93% yields, respectively (Scheme 8). The molecular structures of both compounds were unambiguously confirmed by single-crystal X-ray diffraction (CCDC 2586979, 2586980, Fig. 4). Subsequent methylation of **22a,b** with methyl iodide in anhydrous THF afforded imidazolium salts **23a,b** in 85% and 93% yields, respectively. The products were isolated as solids after trituration with diethyl ether. Due to the high reactivity of the synthesized salts, attempts to isolate analytically pure samples for elemental analysis were unsuccessful. The structure of **23a** was confirmed by single-crystal X-ray diffraction (CCDC 2586981, Fig. 4).



Scheme 8. Synthesis of carbamoylimidazolium salts **23a,b**.

Conclusion

In summary, this work presents the first synthesis and characterization of a novel class of nitroxides featuring a *trans*-fused 3,7-diazabicyclo[3.3.0]octane core. By employing efficient strategies such as the Staudinger reaction and acid- and base-induced cyclizations, we achieved a high-yielding synthesis of these target bicyclic structures. While the inherent conformational constraint of the system

leads to a slight decrease in reductive stability relative to monocyclic analogues, the scaffold provides exceptional rigidity and regioselectivity. The successful preparation of functionalized derivatives (haloacetamides and carbamoylimidazoles) highlights the potential of this system as a robust and versatile platform for developing rigid spin labels for EPR and DEER/PELDOR applications.

Supporting Information

Detailed experimental procedures, representations of the NMR, IR, and EPR spectra, line shape analysis of NMR and X-ray crystallographic data. Crystallographic data for structures **3**, **4**, **7**, **9**, **20a**, **22a,b**, **23a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 2586977-2586981.

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