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Synthesis of a Chiral C_2-Symmetric Sterically Hindered Pyrrolidine Nitroxide Radical via Combined Iterative Nucleophilic Additions and Intramolecular 1,3-Dipolar Cycloadditions to Cyclic Nitrones

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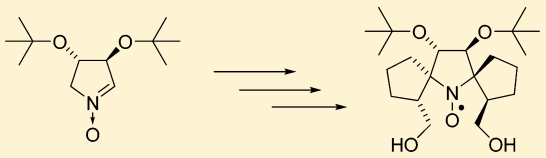
Supporting Information

ABSTRACT: A sterically hindered bis-spirocyclic C_2-symmetric chiral pyrrolidine-type nitroxide has been successfully synthesized starting from an L-tartaric derived nitrone. Starting from a pyrrolidine flanked by two methylene groups, complete quaternization of the two α-carbon atoms has been accomplished through iteration of completely regio- and stereoselective intramolecular cycloaddition reactions and organometallic additions to key nitrone intermediates, formed in turn by oxidation procedures. This method appears to be very useful for building up bulky spirocyclic moieties adjacent to a nitroxide group and provides an important supplementation to traditional methods of nitroxide synthesis. The synthesized chiral nitroxide showed a very high stability to reduction with ascorbate ($k \approx 8 \times 10^{-3}$ M^{-1} s^{-1}).



INTRODUCTION

The range of applications of stable nitroxides is extremely broad, since they are used in living polymerization (nitroxide-mediated polymerization, NMP);[1] in the construction of magnetic materials;[2] as reagents for selective oxidation;[3] as functional probes for measurement of oxygen,[4] pH, thiols, and NO[5] in various heterogeneous media (including living tissues); for imaging of cellular oxidative stress;[6] in structural studies of biological macromolecules;[7] as therapeutic agents,[8] MRI contrast agents,[9] electrode active and charge storage materials in rechargeable batteries;[10] etc. Most of the widely used nitroxides have two pairs of methyl groups at the α-carbon atoms of the nitroxide moiety. It is known that replacing the methyl groups with bulkier substituents can improve their properties for NMP.[11] Moreover, increase in steric requirements of substituents at the α-carbon atoms retards reduction of nitroxides by low-molecular biogenic reductants and enzymatic systems.[12] Recently it has been found that nitroxides with spirocyclic moieties flanking the nitroxide group may give tremendous advantages over their tetramethyl analogues in structural studies using high-field EPR.[13] Here we use the term "sterically hindered" for nitroxides with four substituents larger than methyl (or two spirocyclic moieties) at carbon atoms adjacent to the nitroxide group.

Methods for preparation of sterically hindered nitroxides with different skeletons have been developed, including piperidine,[11a,12c,14] piperazine,[15] isoindoline,[16] oxazolidine,[17] and imidazoline[12b,18,19] derivatives. However, introduction of several bulky groups to the α-carbons of a nitroxide group is still a challenging task. Concerning the pyrrolidine-type nitroxides, the method developed by Keana consisting of iterative nucleophilic addition of methyl organometals to pyrroline *N*-oxides has been used extensively,[20] usually for synthesizing 2,2- or 2,5-dimethyl-substituted nitroxides and in a few cases also for accessing enantiomerically pure nitroxides.[21] 1,3-Dipolar cycloaddition reaction of nitrones,[22] a powerful method for the synthesis of nitrogen heterocycles that allows facile preparation of rather complex molecules, has been less employed to this aim. The feasibility of applying an intermolecular nitrone cycloaddition reaction for the introduction of bulky groups to the α-carbon atoms was first demonstrated by Hideg et al. in their synthesis of 2-(2-hydroxy-2-carboxyethyl)-substituted pyrrolidine nitroxides.[23] Recently, we published an example of imidazoline nitroxide synthesized by intramolecular 1,3-dipolar cycloaddition from nitrones with alkenyl moiety in the α-position in the 4*H*-imidazole-3-oxide series.[24]

In this work, we have considered the use of either intermolecular or intramolecular 1,3-dipolar cycloaddition reactions, in combination with the organometallic addition methodology, for accessing enantiomerically pure C_2-symmetric sterically hindered pyrrolidine nitroxides, starting from (3*S*,4*S*)-3,4-di-*tert*-butylpyrroline *N*-oxide (**1**).[25] The planned synthesis

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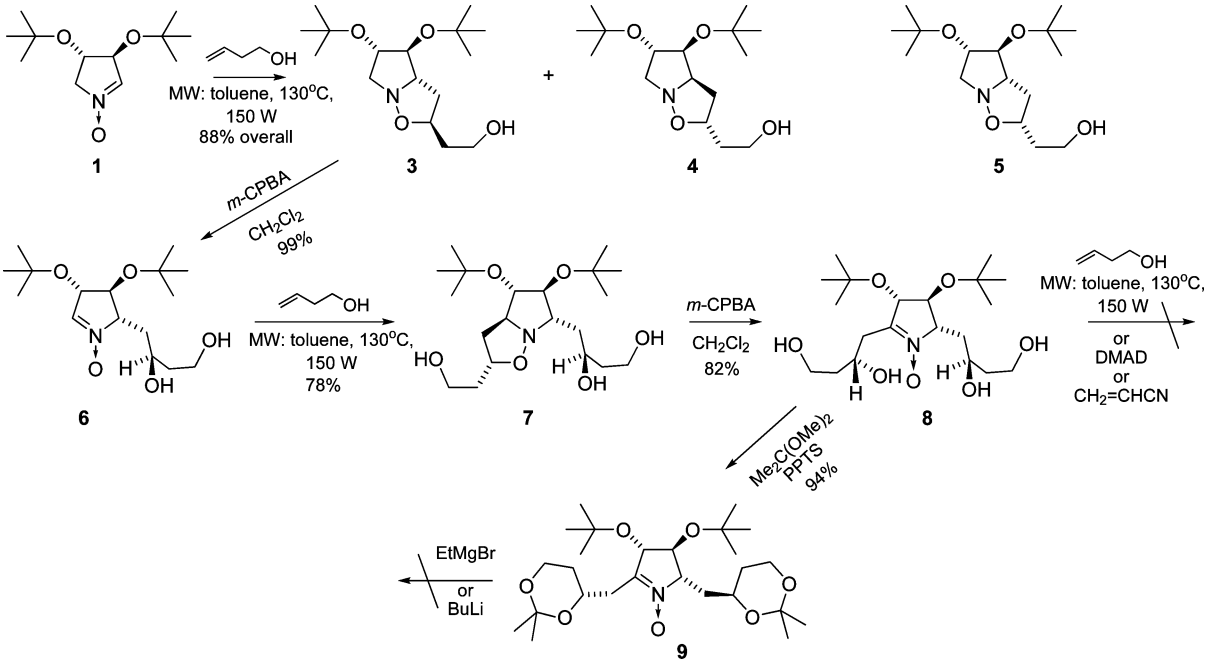
Scheme 1



implied introduction of two pairs of bulky substituents or two bulky spirocyclic moieties to the positions 2 and 5 of the pyrrolidine ring using repetitive sequences of chemical transformations, including both organometallic additions and cycloaddition reactions to five-membered cyclic nitrones, formed in turn by redox steps. The choice of **1** as a starting material in this work is based on the unusual reactivity of this nitrone. Nitrone **1** is known to show high reactivity in 1,3-dipolar cycloadditions, reacting readily even with non-activated alkenes.[26] Thus, it was reasonable to expect that iteration of alkene addition and isoxazolidine ring-opening procedures could afford 2,2,5,5-tetrasubstituted pyrrolidines, which then could be converted into the corresponding nitroxides. The bulky *tert*-butoxy group at C^3 of pyrroline ring strongly disfavors addition reactions from the same face of the nitrone group. As a result of this effect, both organometallic reagent addition and 1,3-dipolar cycloaddition reactions proceed with high stereoselectivity.[27,26] Moreover, the C_2-symmetry of this material was deemed appropriate for avoiding undesired side reactions and regioselectivity issues and for planning convergent strategies in a multistep synthesis.

The synthetic strategy based on intramolecular 1,3-dipolar cycloaddition was successful, enabling the synthesis of enantiomerically pure (1*S*,2*R*,3′*S*,4′*S*,5′*S*,2″*R*)-dispiro[(2-hydroxymethyl)cyclopentan-1,2′-(3′,4′-di-*tert*-butoxy)-pyrrolidine-5′,1″-(2″-hydroxymethyl)-cyclopentane]-1′-oxyl (**2**). This sterically hindered nitroxide showed very high stability to reduction by ascorbic acid.

RESULTS AND DISCUSSION

Reaction of enantiomerically pure nitrone **1** ($[\alpha]^{25}_D$ = +153.4, *c* 0.68, CCl_4) with but-3-en-1-ol under thermal conditions has been reported to give a mixture of three diastereoisomers, **3**, **4**, and **5**, in a 10:2:1 ratio, 48 h heating in toluene at reflux being necessary to reach 100% conversion (Scheme 1).[26] We have found that this reaction proceeds much faster and more selectively in the microwave oven, affording 100% conversion after 20 min of heating at 130 °C and 150 W microwave power. Only the two major isomers **3** and **4** were detected in a 10:1 ratio under these conditions. The diastereoisomers **3** and **4** were easily isolated from the reaction mixture using column chromatography.

In order to open the isoxazolidine ring by N−O bond cleavage and install concomitantly another nitrone moiety for the subsequent addition, we took into account the LeBel−Tufariello oxidation methodology.[28] A few examples of this method have been reported on related adducts obtained from a malic acid derived nitrone; the reaction furnished regioisomeric aldo- and ketonitrones,[29] with moderate to excellent regioselectivity, in a solvent-dependent manner, as previously shown by Ali for the oxidation of less substituted hexahydropyrrolo[1,2-*b*]isoxazoles.[30]

The regioselectivity of the oxidation could be controlled to afford exclusively the aldonitrone regioisomer when aprotic chlorinated solvents were used.[29,30] Accordingly, when the major isomer **3** was treated with *m*-CPBA in dichloromethane, it afforded, to our delight, only the desired regioisomer **6**. The NMR spectra of **6** reveal typical aldonitrone features, i.e., a singlet at 6.88 ppm in the ^{1}H NMR spectrum and a signal of CH carbon at 135.7 ppm in the ^{13}C NMR spectrum. The electronic effect of the nitrone group produces significant downfield shifts of the CH protons at C^3 and C^5 of pyrrolidine ring compared to these atoms signals in the ^{1}H NMR spectrum of **3**. In contrast, the protons at C^1 and C^2 of 2,4-dihydroxybutyl group are shifted upfield after cleavage of the isoxazolidine ring. It is interesting to note that the CH protons of the heterocycle do not show significant spin−spin interactions, presumably due to nearly planar geometry of the heterocycle that places the corresponding CH bonds close to a 90° dihedral angle. The COSY ^{1}H−^{1}H and ^{13}C−^{1}H correlations were used to perform assignments in the NMR spectra (see Tables 1 and 2).

The aldonitrone **6** was again subjected to heating with but-3-en-1-ol in the microwave oven. The reaction proceeded with even higher selectivity than addition to nitrone **1**, confirming that steric encumbrance at C^5 of the pyrroline ring contributes

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Table 1. Data from ^{1}H NMR Spectra of Pyrrolidines and Pyrrolines, δ_{H^i}, $CDCl_3$,[a] for Designations See Chart 1

entry	1, 1H	2, 1H	3, 1H	4	5/5′	6/6′	7/7′	8/8′	9/9′	*t*-BuO, s
6	3.99 t (7.2)	3.82 s	4.41 s	6.88 s 1H	1.99–2.03 m 2H	4.16–4.21 m 1H	1.60–1.67 m 1H, 1.75–1.79 m 1H	3.80–3.84 m 2H		1.20 18H
7	3.16 td (3.4, 7.6)	3.76–3.82 m 2H		3.45–3.56 m 1H	1.53–1.93 m 2H 2.11 ddd (9, 9.4, 12.1) 1H, 2.29 ddd (5, 6.4, 12.1) 1H	4.16–4.28 m 1H 4.31–4.42 m 1H	1.53–1.93 m 4H, 3.63–3.75 m 4H			1.15 9H, 1.16 9H
8	4.06 dd (5.1, 9.8)	3.67 s	4.34 s		1.60–1.77 m 2H 2.55 dd (8.2, 14.6) 1H, 2.73 dd (2.9, 14.6) 1H	4.11–4.18 m 1H 4.19–4.25 m 1H	1.60–1.77 m 2H, 1.86–2.00 m 2H	3.74–3.82 m 4H		1.19 9H, 1.23 9H
9[b]	4.02 dd (3.1, 11.7)	3.48 s	4.45 s		1.53–1.76 m 2H 2.37 dd (6.8, 13.4) 1H, 2.73 dd (4.4, 13.4) 1H	4.25–4.38 m 4H	1.53–1.76 m 2H, 1.87–1.99 m 2H	3.75–3.97 m 2H		1.21 9H, 1.25 9H
10	2.73 dt (5.3, 6.5)	3.62 dd (2.2, 6.5)	3.90 dt (2.2, 5)	3.14 d (5) 2H	1.52–1.59 m 4H		2.01–2.09 m 2H	5.78 tdd (6.5, 10, 17) 1H	4.90 d (10) 1H, 4.97 dd (1.5, 17) 1H	1.14 9H, 1.17 9H
11	3.61 dd (3, 13.7) 1H, 4.10 dd (6.4, 13.7) 1H	3.89 dd (3, 6.4)	4.40 s		2.24 ABt (7.7, 13.4) 1H, 2.36 ABt (7.7, 13.4) 1H	1.54 tt (7.6, 7.7) 2H	1.98 dt (7, 7) 2H	5.66 tdd (6, 10, 17) 1H	4.82 d (10) 1H, 4.89 d (17) 1H	1.05 9H, 1.11 9H
12	3.63 t (5.5)	3.78 s	4.32 s	6.77 s 1H	1.87 m 2H	1.47 m 2H	2.03 dt (6.5, 14.2) 2H	5.73 tdd (6.5, 13.4, 18.7) 1H	4.89 d (13.4) 1H, 4.94 dd (1.4, 18.7) 1H	1.13 9H, 1.14 9H
13	2.67 dd (7.6, 10.9) 1H, 3.43 dd (5.8, 10.9) 1H	3.76 ddd (5.8, 6.3, 7.6)	3.82 d (6.3)		1.45–1.50 m 1H, 1.85–1.92 m 1H	1.62–1.66 m 2H	1.45–1.50 m 1H, 1.62–1.66 m 1H	2.64–2.73 m 1H	3.59 dd (1.6, 8.8) 1H, 4.13 dd (6.5, 8.8) 1H	1.12 9H, 1.14 9H
15		3.83 d (1.5)	4.25 t (1.5)	6.99 d (1.5) 1H	2.00–2.05 m 1H, 2.20–2.25 m 1H	1.38–1.48 m 1H, 1.83–1.93 m 1H	1.65–1.74 m 1H, 1.83–1.93 m 1H	2.21–2.30 m 1H	3.59 dd (6.1, 12.4) 1H, 3.69 dd (2.5, 12.4) 1H	1.14 9H, 1.16 9H
16		3.63 d (0.8)	4.26 d (0.8)		1.85–1.99 m 1H, 2.18–2.24 m 1H 2.38 ddd (5.6, 9.6, 13.8) 1H, 2.64 ddd (6.2, 9.8, 13.8) 1H	1.41–1.49 m 1H, 1.54–1.64 m 1H 1.71–1.83 m 2H	1.54–1.64 m 1H, 1.85–1.99 m 1H 2.05–2.15 m 2H	2.20–2.30 m 1H 5.78 tdd (6.8, 10.3, 17) 1H	3.50 dd (5, 12.5) 1H, 3.70 dd (2.2, 12.5) 1H 4.96 d (10.3) 1H, 5.02 dd (1.8, 17) 1H	1.21 9H, 1.25 9H
17	3.04 m		3.69 d (4.5)	3.04 m 1H	1.45–1.70 m 4H		1.98–2.11 m 2H	5.79 tdd (6, 10, 17) 1H	4.91 d (10) 1H, 4.97 d (17) 1H	1.17 18H
18	3.75 t (6)	3.62 s	4.29 s		2.20–2.35 m 1H, 2.40–2.55 m 1H 1.90 dt (7, 7) 2H	1.36–1.74 m 4H	2.01–2.10 m 4H	5.67–5.84 m 4H	4.83–5.05 m 4H	1.15 9H, 1.19 9H
19	2.76–2.89 m	3.52 t (3.7)	3.80 d (3.4)		1.42–1.82 m 4H, 1.99–2.12 m 4H		1.99–2.12 m 2H 1.42–1.82 m 2H	5.83 tdd (6.5, 10.2, 17.1) 1H 2.76–2.89 m 1H	4.92 d (10.2) 1H, 4.99 dd (1.6, 17.1) 1H 3.59 d (8.2) 1H, 4.11 dd (6.8, 8.2) 1H	1.20 9H, 1.21 9H

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Table 1. continued

entry	1, 1H	2, 1H	3, 1H	4	5/5′	6/6′	7/7′	8/8′	9/9′	*t*-BuO, s
							1.31–1.76 m 2H	2.22–2.28 m 1H	3.55 dd (6.6, 11.5) 1H, 3.79 dd (3.6, 11.5) 1H	1.13 9H,
23		3.57 s	3.40 s	2.97–3.03 m	1.31–1.76 m 4H, 1.97–2.08 m 4H		1.97–2.08 m 2H	5.75 tdd (6.5, 10.2, 17) 1H	4.90 d (10.2) 1H, 4.96 dd (1.9, 17) 1H	1.14 9H
					1.69–1.74 m 1H, 2.25–2.34 m 1H	1.40–1.44 m 1H, 1.69–1.78 m 1H		2.25–2.34 m 1H	3.70 d (5.1) 2H	1.20 9H,
24		3.82 d (4)	3.58 d (4)		1.47–1.57 m 1H, 1.83–1.91 m 1H	1.47–1.57 m 2H	1.58–1.68 m 4H	2.78–2.82 m 1H	3.50 dd (2, 7.5) 1H, 3.93 dd (7.5, 7.5) 1H	1.22 9H
25			3.80 s		1.51–1.70 m 2H, 1.98–2.07 m 2H	1.51–1.70 m 8H		2.08–2.16 m 2H	3.64 dd (6.5, 11.5) 2H, 3.77 dd (3.5, 11.5) 2H	1.20 18H

[a]Spin–spin coupling constants are shown in brackets (Hz). [b]1.39 s, 1.39 s, 1.45 s, 1.49 s (2*$(CH_3)_2C$).

additional shielding. Indeed, the *trans,trans* relative trisubstitution pattern in substrate pyrroline *N*-oxides has often resulted in virtually complete stereoselective cycloadditions;[31] however, less selective examples have also been reported.[32] The cycloadduct **7** was isolated as a single product with 78% yield, and only trace amounts of another product, presumably an isomeric cycloadduct, were observed by TLC. The $^1H-^1H$ COSY correlations were used to perform assignments.

Treatment of **7** with *m*-CPBA afforded a single product **8**, which showed UV absorption at 239 nm and a low-field signal at 146.3 ppm in ^{13}C NMR spectrum, typical for ketonitrones. The ^1H NMR spectrum of the new nitrone **8** showed its structural similarity to **6**. In analogy to **6**, the spectra of **8** revealed weak spin–spin interaction between CH protons of pyrrolidine ring. The signals of 5-(2,4-dihydroxybutyl) group, similar to those observed in spectra of **6**, are partly overlapped with signals of another 2,4-dihydroxybutyl fragment. The signals of methylene protons at C^1 of the second 2,4-dihydroxybutyl group are shifted downfield to 2.55 and 2.73 ppm due to electron-withdrawing effect of the nitrone group and the interaction with adjacent CH proton, which produces additional splitting of the AB system signals. Spectral assignments were confirmed by $^1H-^1H$ COSY correlations. Formation of a single nitrone from **7** provides additional confirmation of the configuration of the cycloadduct, originating from two subsequent cycloadditions to butenol occurred with the same orientation of the partners, since a different stereoisomer would have afforded two different nitrones upon isoxazolidine ring cleavage.

Nitrone **8** was again reacted with dipolarophiles. However, no conversion was observed by treating **8** with but-3-en-1-ol or even with very reactive dipolarophiles, such as dimethyl acetylenedicarboxylate (DMAD), upon either refluxing in toluene for 24 h or heating for 5 h at 130 °C and microwave power 150 W. Heating of **8** with acrylonitrile under similar conditions led to polymerization of the alkene. A diminished reactivity of the ketonitrone **8** compared to that of aldonitrones **1** and **6** was expected. However, we hoped to be able to pursue its complete substitution at C^2 and C^5 by using highly reactive C-nucleophiles. Unfortunately, treatment of **8** with organometallic reagents was also unsuccessful, and only the starting material was isolated from reaction mixtures after addition of large excesses of CH_3MgBr or CH_3Li. With the argument that low reactivity of **8** toward organometallic reagents could derive from formation of insoluble alkoxide salts, **8** was treated with 2,2-dimethoxypropane in presence of pyridinium tosylate (PPTS) to give the bis-acetal **9** and protect the 1,3-dihydroxyalkyl moieties from metalation. However, attempted methylation of the resulting nitrone **9** failed to give any adduct as well. Presumably, bulky substituents around the reactive center of **8** and **9** prevent any reagent from approaching the nitrone, thus blocking our synthetic route toward a nitroxide.

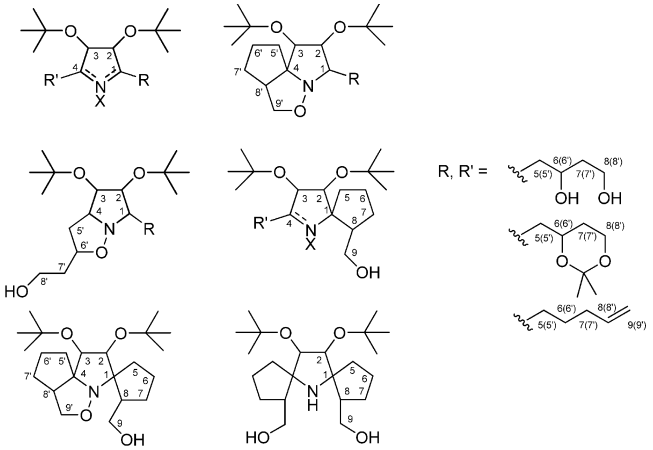
To circumvent this hurdle and accomplish our aim, we envisaged that an intramolecular 1,3-dipolar cycloaddition reaction, being entropically favored, might proceed much more easily than its intermolecular counterpart, provided that the nitrone moiety and dipolarophile are connected by an appropriate spacer.[22] It has been demonstrated that a related, albeit less substituted, chiral pyrroline *N*-oxide afforded readily the corresponding cycloadduct by an intramolecular mode when a dipolarophile was connected to its oxygen atom.[33] Moreover, we have shown recently that cyclization of a nitrone with an alkenyl moiety followed by isoxazolidine ring opening

Table 2. Data from ^{13}C NMR Spectra of Pyrrolidines and Pyrrolines, δ_{C^i}, $CDCl_3$; for Designations see Chart 1

entry	1	2	3	4	5/5′	6/6′	7/7′	8/8′	9/9′	*t*-BuO
6	77.4	78.2	79.0	135.7	39.7	68.1	38.3	61.5		28.4, 28.6, 75.1, 75.1
7	69.7	77.8, 85.6		69.9	39.9, 43.8	74.9, 84.6	44.2, 44.3	62.8, 62.9		31.7, 32.3, 77.9, 78.2
8	78.4	76.4	81.7	146.3	40.6 34.8	67.5, 68.2	38.5, 38.9	60.8, 60.9		28.5, 28.7, 75.2, 76.1
9[a]	79.5	74.5	81.1	142.4	39.0, 29.9	66.1, 67.3	31.1, 30.5	59.4, 59.9		28.1, 28.1, 73.7, 74.2
10	63.8	81.6	72.9	64.4	25.5, 28.4		33.8	138.7	114.3	28.7, 28.9, 73.6, 73.8
11	147.9	80.6	72.3	67.8	33.3	23.6	33.3	137.4	114.8	28.0, 28.3, 74.2, 74.7
12	78.0	79.9	77.3	134.2	39.4	24.2	33.3	137.8	114.7	28.4, 28.5, 74.3, 74.7
13	82.2	80.2	74.9	57.0	34.0	25.2	32.8	53.5	72.9	28.4, 28.8, 73.7, 73.8
15	86.9	80.0	76.7	135.4	30.1	23.0	28.6	51.7	61.1	28.3, 28.5, 74.8, 75.1
16	150.0	78.3	77.6	88.5	33.3 28.2	23.0 24.7	29.1 23.9	137.7 50.1	115.3 62.2	28.7, 28.8, 74.6, 75.2
17	71.8	83.4		71.81	26.4, 30.0		33.8	138.7	114.4	29.0, 73.8
18	80.4	80.5	74.8	145.0	24.2 29.9	23.8 23.9	33.2 33.2	137.6 137.7	114.6 114.4	28.1, 28.3, 74.0, 74.2
19	70.0	80.9	79.9	84.3	33.1 33.3	25.2 25.9	34.8 33.4	138.7 52.4	113.7 73.2	28.3, 28.6, 73.3, 73.6
23	65.8	84.6	81.6	76.1	28.3 34.3	21.9 26.2	33.4 33.0	138.4 43.3	114.5 64.9	28.6, 28.8, 73.1, 73.4
24	83.9	80.1	79.5	80.9	35.5 33.7	24.9 22.1	27.3 26.3	53.5 46.9	76.6 64.1	28.9, 29.0, 73.7, 73.9
25	74.0	79.6		74.0	34.3	20.6	26.34	44.3	62.6	29.2, 71.4

[a]For $C(CH_3)_2$: 29.4, 29.6, 97.7, 97.9

Chart 1. Designations of Atoms in the NMR Tables



and oxidation may afford a nitroxide.[24] Therefore, we considered the combination of organometallic additions and intramolecular cycloadditions a suitable strategy for the synthesis of a nitroxide from nitrone **1** and planned the synthetic sequence reported in Scheme 2. Iteration of similar procedures, with small variations, demonstrated the general character of the methods used.

Additions of methyl- or arylmagnesium bromide to nitrone **1** are known to proceed in a highly stereoselective manner, anti to the substituent at C^3, due to concurrent steric and stereoelectronic effects of the bulky *tert*-butoxy group at the position 3 of pyrroline ring.[27,34] Accordingly, addition of 4-pentenylmagnesium bromide to **1** afforded a single stereoisomeric *N*-hydroxypyrrolidine **10**.[35] The IR spectrum of **10** showed strong absorption bands at 1641, 990, and 910 cm^{-1} typical for terminal ethylene bond vibrations. Assignments of signals for the 3,4-di-*tert*-butoxy-pyrrolidine moiety of **10** in the ^1H and ^{13}C spectra were based on similarity to the literature data for (2*S*,3*S*,4*S*)-1-hydroxy-3,4-di-*tert*-butyl-2-methylpyrrolidine.[27a]

As expected on the basis of previous related results,[27a,36] oxidation of hydroxylamine **10** occurred with moderate regioselectivity, affording the two isomeric nitrones **11** and **12**, which were separated using column chromatography. The signals of 4-pentenyl group in ^1H NMR spectra of both isomers are similar, except for methylene protons at C^1 of the substituent, which undergo stronger downfield shift in the spectra of the ketonitrone **11**. The NMR spectra showed structural similarity of the heterocyclic fragment of **12** to that of **6** (see Tables 1 and 2). In analogy to the above description for **6**, ^1H NMR of **12** does not show significant spin−spin interaction between protons at C^3 and C^4 of pyrrolidine ring. In ^1H NMR of **11** the proton at C^3 gives a singlet at 4.40 ppm, while the signal of proton at C^4 (3.89 ppm) shows spin−spin interaction constants with both methylene protons at C^5 (3.0 and 6.4 Hz), which in turn form an AB system, J = 13.7 Hz.

The **11**/**12** regioisomeric ratio was dependent upon the oxidation method used (see table in scheme 3), however, the aldonitrone **12** was always the major isomer. This observation is in agreement with the interpretation given previously, based on stereoelectronic effects.[37,38] Oxidation of hydroxylamines to nitrones may proceed via the corresponding nitroxides[39] or via the oxoammonium cation.[28b] The radical mechanism implies bimolecular reaction of nitroxides with β-hydrogen abstraction. In this case hydrogen abstraction from less hindered methylene group, leading to aldonitrone, should be preferable. In turn, proton elimination from oxoammonium cation should be controlled by electronic effects of substituents. The electron-withdrawing effect of a vicinal substituent has been shown to promote elimination of the *trans*-proton.[38,38] Therefore, removal of CH proton in the position 2 of the heterocycle, which is *cis*-located to the vicinal acceptor *tert*-butoxy group, should be less favored than elimination of the *trans*-proton from the methylene group at position 5. Thus, formation of

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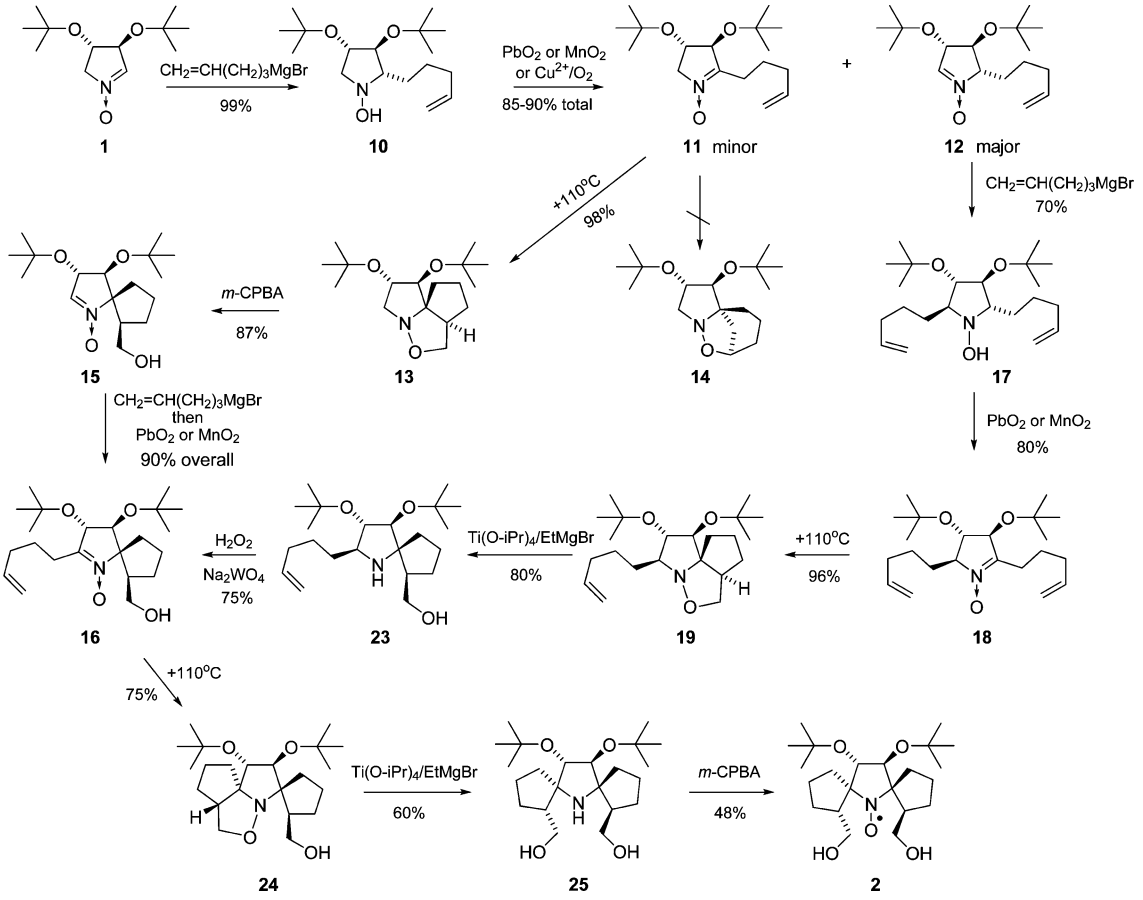
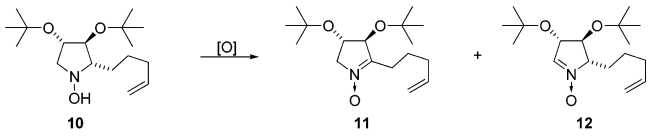
Scheme 2



Scheme 3



Oxidant	PbO_2	MnO_2	O_2/Cu^{2+}
Ratio **11** : **12** (NMR)	1 : 6	1 : 8	1 : 5

aldonitrone is favored by both mechanisms. Remarkably, the oxidation is much more selective than observed for related hydroxylamines,[27a,36] showing up to a satisfactory 8:1 regioselectivity when MnO_2 was used.[40] Nonetheless, we envisaged and managed an appropriate synthetic sequence which allowed proper elaboration of both nitrones **11** and **12** to the same final nitroxide in a convergent manner.

Heating **11** at 110 °C in toluene for 2.5 h resulted in its quantitative conversion into a single product, which did not show any significant absorption in UV, and no absorption band was present in its IR spectrum in the region 1550−1700 cm^{-1}. In addition, its NMR spectra showed no signals at low field, denoting that both the terminal ethylene and nitrone group were engaged in the cycloaddition reaction. Taking into account the directing effect of the bulky *tert*-butoxy group at C^3 of the pyrroline ring, one could expect that 1,3-dipolar cycloaddition in **11** give two regioisomeric products **13** and **14** as a result of *exo-anti* attack.[41] However, cycloaddition of similar nitrones was reported to lead to hexahydro-1*H*-cyclopenta[*c*]isoxazole exclusively, with no formation of 7-oxa-6-aza-bicyclo[3.2.1]octane ring system.[34,42] Indeed, appearance of a relatively high-field signal of the CH group carbon at 53.49 ppm and low-field signal of the CH_2 carbon at 72.88 ppm in the ^{13}C NMR spectrum of the cycloadduct allowed ruling out the structure **14**. Assignments of the signals in the ^1H NMR spectrum of **13** were based on comparison with literature data for substituted octahydrocyclopenta[*c*]pyrrolo[1,2-*b*]-isoxazoles.[42,43]

Treatment of **13** with *m*-CPBA in chloroform afforded the nitrone **15** in quantitative yield. UV, IR, and ^1H and ^{13}C NMR spectra of **15** revealed typical features of an aldonitrone group (see Experimental Section). Besides that, isoxazolidine ring opening in **15** produced remarkable changes in ^1H NMR spectral parameters of the cyclic system. For example, the spin−spin interaction constant between vicinal CH protons at the positions 3 and 4 of pyrrolidine ring decreased from 6 to 1.5 Hz. Another interesting effect is a strong upfield shift of the CH proton of the cyclopentane ring (from 2.68 to 2.12 ppm). The detailed assignments of the signals in the ^1H NMR spectrum of **15** were performed using COSY $^1H-^1H$ correlations.

Again, the aldonitrone **15** was treated with excess 4-pentenylmagnesium bromide, and the resulting hydroxylamine was oxidized *in situ* with PbO_2 to give nitrone **16**. Signal assignments in the NMR spectra of **16** were performed using comparison to spectral data of starting aldonitrone **15** and the ketonitrone **11** (see Experimental Section). The same nitrone **16** was obtained from **12** using an alternative multistep

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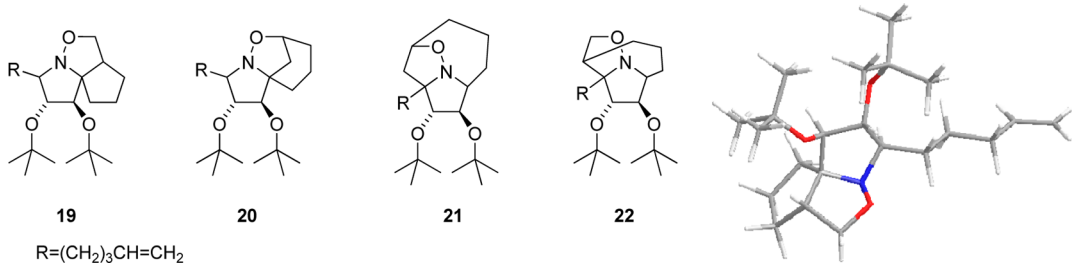

Figure 1. Possible intramolecular cycloaddition products and X-ray structure of **19**.

sequence, which also allowed confirmation of its structure and configuration.

Treatment of the aldonitrone **12** with 1.5 equiv of 4-pentenylmagnesium bromide afforded the all-*trans* *N*-hydroxypyrrolidine **17** as a single product. The ^{1}H and ^{13}C NMR spectra of **17** revealed a half-number set of signals, according to its C_2-symmetric structure, thus providing confirmation of the stereoselectivity of Grignard reagent addition.[27a] Oxidation of hydroxylamine **17** with PbO_2, due to its symmetry, gave only the nitrone **18**. Assignments of the signals in the spectra of **18** were performed by analogy with spectra of **11** and **12**.

Intramolecular cycloaddition in **18** may, in principle, involve one of two terminal ethylene bonds, producing a set of isomers **19**–**22**. However, heating of **18** in toluene afforded a single product. As described before for cyclization of **11**, the ^{13}C NMR spectrum of the isolated product allowed structures **20** and **21** to be discarded, using comparison of chemical shifts of the CH_2 and CH groups carbons. Among the structures **19** and **22**, the latter is more strained and therefore less probable, but it cannot be discarded unambiguously on the basis of the NMR data because of superposition of the signals in the spectra. Definitive confirmation of the structure **19** was achieved by an X-ray analysis (Figure 1).

It is well-known that N–O bond cleavage in isoxazolidines can be performed using either oxidative[28,44] or reductive methods.[45,24] Treatment of **19** with *m*-CPBA as described above for **3**, **7**, and **13** may result in terminal ethylene bond oxidation. Therefore, the cycloadduct **19** was treated with low-valent titanium (LVT) reagent[24] to give the aminoalcohol **23**. The IR spectrum of **23** (neat) revealed a strong and broad absorption at 3312 cm^{-1}, attributed to hydrogen-bonded OH and NH stretching. It has been demonstrated above that spin–spin interaction between CH protons at the positions 3 and 4 of pyrrolidine ring is negligible for (3*S*,4*S*)-3,4-di-*tert*-butoxypyrrolidines (including spirocyclic derivatives), but relatively high (up to 6 Hz) for strained (1*S*,2*S*,6a*R*,9a*S*)-1,2-di-*tert*-butoxy-octahydrocyclopenta[*c*]pyrrolo[1,2-*b*]-isoxazoles (cf. **6**–**12**,**15**–**18**, and **13**, **19**, Table 1). The ^{1}H NMR spectrum of **23** showed no spin–spin interaction between CH protons of pyrrolidine ring, which denotes isoxazolidine ring opening.

Remarkably, oxidation of the aminoalcohol **23** with H_2O_2/Na_2WO_4 afforded nitrone **16**,[46] identical to that obtained from **11**, completely chemoselectively, with no involvement of the C=C double bond. Formation of **16** confirms all the stereochemical assignments occurred in the previous transformations.

The nitrone **16** underwent intramolecular 1,3-dipolar cycloaddition upon heating in toluene. The single cycloadduct formed was assigned the structure **24** on the basis of COSY correlations and using comparison with the NMR spectra of **13** and **19**. Reductive isoxazolidine ring cleavage using LVT reagent[24] afforded the aminodiol **25**. Similarly to **17**, its NMR spectra showed a half-number set of signals, according to its C_2 symmetry. Noteworthy, **25** was obtained as a single enantiomer, it is optically active, as well as all its precursors listed in scheme 2, and the whole sequence of chemical transformations (Scheme 2) proceeded in highly stereoselective manner. The regioselectivity was incomplete only in the oxidation of hydroxylamine **10**; however, both nitrones **11** and **12** could be conveniently transformed into the same pyrrolidine **25**, thus bypassing this shortcoming.

It is known that oxidation of highly sterically hindered amines into nitroxides is sometimes problematic.[15,17a,24] In agreement to these observations, treatment with H_2O_2/Na_2WO_4 did not lead to the desired nitroxide. Conversely, oxidation of **25** with *m*-CPBA afforded **2**, albeit with a moderate 48% yield. The structure of the nitroxide was confirmed by X-ray analysis (Figure 2). Since the nitroxide was prepared from enantiomerically pure amine **25** and isolated as a chromatographically homogeneous compound, the X-ray data should be considered as a direct confirmation of its absolute configuration. It should be noted that enantiomerically pure spin probes and labels might be of interest for biophysical studies, because interaction of different enantiomers with chiral biomolecules should give different results.

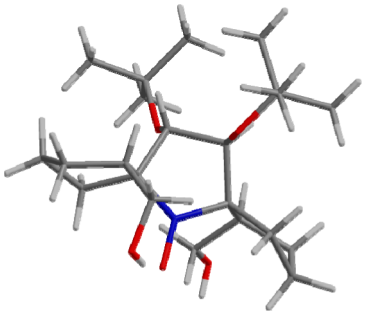

Figure 2. X-ray structure of **2**.

EPR spectrum of the nitroxide **2** is represented by a triplet with a line width of about 3 G (Figure 3 left). The broad EPR line is typical for nitroxides with bulky substituents or spirocyclic moiety at α-carbons of the nitroxyl group.[47,48] Another important characteristic of sterically hindered nitroxides is their stability to reduction. The nitroxide **2** was found to be remarkably stable toward reduction by ascorbic acid. EPR kinetics of the nitroxide reduction are presented in Figure 3. The nitroxide was only partly reduced even in the presence of a large excess of ascorbic acid. The incomplete reduction of the radical was apparently due to reversibility of the reaction.[49] The initial rate of EPR signal decay was used to estimate the rate

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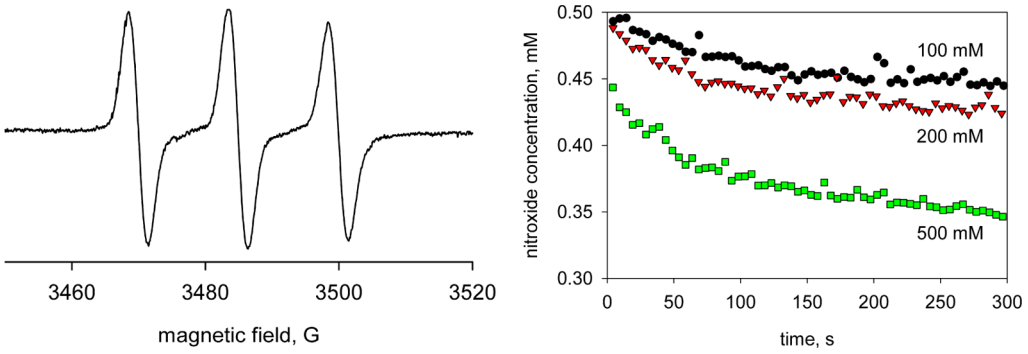

Figure 3. (left) EPR spectrum of 0.5 mM nitroxide **2** in phosphate buffer. (right) Reduction kinetics of the nitroxide **2** (0.5 mM) in the presence of different concentrations of ascorbic acid (100 mM, 200 mM and 500 mM).

constant of the nitroxide reduction by ascorbic acid, $k \approx 8 \times 10^{-3}$ M^{-1} s^{-1}, which is the lowest among known nitroxides, to the best of our knowledge.

CONCLUSIONS

We have demonstrated the synthetic potential of intramolecular 1,3-dipolar cycloaddition reaction applied to the synthesis of a chiral C_2-symmetric pyrrolidine nitroxide. Starting from a pyrrolidine flanked by two methylene groups, complete quaternization of the two α-carbon atoms has been accomplished through a series of mixed methodologies consisting of oxidation reactions aimed at forming the key nitrone intermediates, on which organometallic additions and intramolecular cycloaddition reactions have been carried out. This method appears to be very useful for building up bulky spirocyclic moieties adjacent to nitroxide group and provides an important supplementation to traditional methods of nitroxide synthesis. It should be noted that the hydroxymethyl groups in the spirocyclic moieties formed afford an opportunity for further increase in sterical hindrance or for introduction of functional groups, e.g., spin labels synthesis.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded at 300 or 400 MHz, and ^{13}C NMR spectra were recorded at 75 or 100 MHz. ^{1}H and ^{13}C chemical shifts (δ) were internally referenced to the residual solvent peak. IR spectra were acquired on FT-IR spectrometer in KBr and are reported in wave numbers (cm^{-1}). Reactions were monitored by TLC carried out using UV light as visualizing agent and/or aqueous permanganate. Column chromatography was performed on silica gel 60 (70−230 mesh).

The nitrone **1** was prepared from L-tartaric acid using a modified method.[25] It is worth mentioning that the use of absolute solvents on the second step of the synthesis and neutralization of the reaction mixture with dry K_2CO_3 before isolation of the (2*R*,3*R*)-dimethyl 2,3-di-*tert*-butoxysuccinate allowed us to increase the overall yield of nitrone **1** from 20% to 60%.

General Procedure for 1,3-Dipolar Cycloaddition Reaction of Nitrones with But-3-en-1-ol. A solution of the nitrone **1** or **6** (0.43 g, 1.4 mmol) and but-3-en-1-ol (0.49 g, 6 mmol) in toluene (2.5 mL) was placed into a microwave oven tube and sealed. The mixture was subjected to microwave irradiation for 20 or 40 min, respectively, at +130 °C (microwave power 150 W). Solution was concentrated in vacuum, and the residue was separated using column chromatography (silica gel, EtOAc/MeOH = 5:1) to give isomers **3** and **4** or **7**.

(2*S*,3a*S*,4*S*,5*S*)-4,5-Di-*tert*-butoxy-2-(2-hydroxyethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (3). Yield 80%. NMR data are identical to those previously published.[26]

(2*R*,3a*R*,4*S*,5*S*)-4,5-Di-*tert*-butoxy-2-(2-hydroxyethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (4). Yield 8%. NMR data are identical to those previously published.[26]

(*S*)-4-((2*S*,3a*S*,4*S*,5*S*,6*S*)-4,5-Di-*tert*-butoxy-2-(2-hydroxyethyl)hexahydropyrrolo[1,2-*b*]isoxazole-6-yl)butane-1,3-diol (7). Yield 78%, colorless solid, mp 78−81 °C (hexane); $[\alpha]^{23}_D$ = +54 (*c* 1.01, $CHCl_3$); IR (neat) ν 3321.2, 1638.0, 1474.5, 1461.6, 1438.7, 1391.3, 1365.3 cm^{-1}; Anal. Calcd for $C_{20}H_{39}NO_6$: C, 61.67; H, 10.09; N, 3.60. Found: C, 61.42; H, 10.00; N 3.66.

General Procedure for Isoxazolidine Ring Cleavage Using *m*-CPBA. A solution of **3**, **7** or **13** (2 mmol) in dry CH_2Cl_2 (20 mL) was cooled to −10 °C, then *m*-CPBA (0.35 g, 2 mmol) was added in one portion, and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (silica gel, EtOAc, developing with 1% aq. $KMnO_4$) and consumption of the starting material occurred within 3 to 5 h. Solution was concentrated in vacuum and the residue was separated using column chromatography as indicated below to afford the nitrone **6**, **8** or **15** correspondingly.

(2*S*,3*S*,4*S*)-3,4-Di-*tert*-butoxy-2-((*S*)-2,4-dihyroxybutyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (6). Separated using column chromatography (silica gel 60, EtOAc). Yield 99%, colorless oil: $[\alpha]^{23}_D$ = +38 (*c* 1.05, $CHCl_3$); IR (neat) ν 3393.1, 1586.2, 1465.6, 1437.5, 1392.0, 1368.3 cm^{-1}; UV (EtOH) λ_{max} (log ε) 238 (3.55) nm. Anal. Calcd for $C_{16}H_{31}NO_5$: C, 60.54; H, 9.84; N, 4.41. Found: C, 60.70; H, 9.72; N 4.36.

(2*S*,3*S*,4*S*)-3,4-Di-*tert*-butoxy-2,5-bis((*S*)-2,4-dihyroxybutyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (8). Separated using column chromatography (silica gel 60, EtOAc/MeOH = 7:1). Yield 82%, colorless oil: $[\alpha]^{21}_D$ = +76 (*c* 1.35, $CHCl_3$); IR (neat) ν 3371.1, 1607.5, 1468.4, 1431.3, 1392.5, 1368.8 cm^{-1}; UV (EtOH) λ_{max} (log ε) 239 (3.98) nm. Anal. Calcd for $C_{20}H_{39}NO_7$: C, 59.24; H, 9.69; N, 3.45. Found: C, 59.35; H, 9.60; N 3.52.

(3*S*,4*S*,5*S*,6*R*)-3,4-Di-*tert*-bytoxy-6-(hydroxymethyl)-1-azaspiro[4.4]non-1-ene 1-Oxide (15). Separated using column chromatography (silica gel 60, hexane/EtOAc 1/5). R_f = 0.35; yield 87%; colorless oil; $[\alpha]^{26.6}_D$ = +79 (*c* 0.98, $CHCl_3$); IR (neat) ν 3384.1, 2974.9, 2873.6, 1738.8, 1574.6, 1470.0, 1392.9, 1368.0, 1239.3, 1189.7, 1086.5, 896.5, 872.9, 754.0 cm^{-1}; UV (EtOH) λ_{max} (log ε) 242 (3.98) nm. Anal. Calcd for $C_{17}H_{31}NO_4$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.33; H, 9.63; N 4.14.

(2*S*,3*S*,4*S*)-3,4-Di-*tert*-butoxy-2,5-bis(((*S*)-2,2-dimethyl-1,3-dioxane-4-yl)methyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (9). A mixture of **8** (0.5 g, 1.2 mmol), dimethoxypropane (3.3 g, 32 mmol), and PPTS (80 mg, 0.3 mmol) in dry $CHCl_3$ (10 mL) was stirred for 2 h and then concentrated in vacuum, and the residue was separated using column chromatography (silica gel 60, EtOAc/MeOH = 8:1) to afford 0.55 g (94%) of **9** as a colorless oil: $[\alpha]^{22}_D$ = +69 (*c* 1.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 1.21 (s, 9H), 1.25 (s, 9H), 1.39 (s, 6H), 1.45 (s, 3H), 1.49 (s, 3H), 1.53−1.76 (m, 4H), 1.87−1.99 (m, 2H), 2.37 (dd, *J* = 6.8, 13.4 Hz, 1H), 2.73 (dd, *J* = 4.4, 13.4 Hz, 1H), 3.48 (s, 1H), 3.75−3.97 (m, 2H), 4.02 (dd, *J* = 3.1, 11.7 Hz, 1H), 4.25−4.38 (m, 4H), 4.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 28.1, 29.4, 29.6, 29.9, 30.5, 31.1, 39.0, 59.4, 59.9, 66.1, 67.3, 73.7, 74.2, 74.5, 79.5, 81.1, 97.7, 97.9, 142.4; IR (neat) ν 2719.2, 1714.5, 1592.9, 1463.4, 1434.3, 1368.2 cm^{-1}; UV (EtOH) λ_{max} (log ε)

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237 (3.97) nm. Anal. Calcd for $C_{26}H_{47}NO_7$: C, 64.30; H, 9.75; N, 2.88. Found: C, 64.35; H, 9.60; N 3.02.

General Procedure for Pent-4-enylmagnesium Bromide Addition to Nitrones. A solution of pent-4-enylmagnesium bromide was prepared via slow addition of a 5-bromopentene-1 (1.98 mL, 16.8 mmol) and Et_2O (5 mL) mixture to a suspension of Mg chips (0.46 g, 18.9 mmol) in dry Et_2O (15 mL). Then a solution of **1** or **12** (15 mmol) in dry Et_2O (10 mL) was added dropwise. The reaction mixture was stirred for 3−5 h, quenched with water (2 mL), and filtered. The organic layer was separated and concentrated in vacuum, and the residue was separated using column chromatography to afford **10** or **17**, respectively.

(2*S*,3*S*,4*S*)-3,4-Di-*tert*-butoxy-2-(pent-4-enyl)pyrrolidin-1-ol (10). Separated using column chromatography (silica gel 60, EtOAc), yield 2.07 g (99%), colorless oil: $[\alpha]^{22.4}_D$ = +28 (*c* 0.98, $CHCl_3$); IR (neat) ν 3249.2, 2975.4, 2868.6, 1741.5, 1641.0, 1461.7, 1390.6, 1365.8, 1235.2, 1193.2, 1080.4, 908.5 cm^{-1}. Anal. Calcd for $C_{17}H_{33}NO_3$: C, 68.19; H, 11.11; N, 4.68. Found: C, 68.59; H, 10.94; N 4.33.

(2*S*,3*S*,4*S*,5*S*)-3,4-Di-*tert*-butoxy-2,5-di(pent-4-enyl)-pyrrolidin-1-ol (17). Separated using column chromatography (silica gel 60, EtOAc). R_f = 0.9; yield: 1.28 g (70%); colorless oil; $[\alpha]^{22.9}_D$ = +29 (*c* 1.1, $CHCl_3$); IR (neat) ν 3243.4, 3076.7, 2976.2, 2934.5, 1641.0, 1461.0, 1415.2, 1389.7, 1365.0, 1193.3, 1067.9, 1022.4, 908.8 cm^{-1}. Anal. Calcd for $C_{22}H_{41}NO_3$: C, 71.89; H, 11.24; N, 3.81. Found: C, 71.88; H, 11.27; N 3.89.

General Procedure for Oxidation of Hydroxylamines 10 and 17 to Nitrones. *Method A.* An oxidant (PbO_2 or MnO_2) (12 mmol) was added to a solution of **10** or **17** (2.1 mmol) in $CHCl_3$ (10 mL), and the suspension was stirred for 4 h. The precipitate was filtered off, the solution was concentrated in vacuum, and the residue was separated using column chromatography (silica gel 60, EtOAc).

Method B. A solution of $CuSO_4$ (0.1 g) in water (1 mL) was mixed with 25% aqueous NH_3 (3 mL), and the resulting solution was poured into a solution of **10** (0.63 g, 2.1 mmol) in MeOH (10 mL). Then air was bubbled through the reaction mixture. The progress of the reaction was monitored by TLC (silica gel, EtOAc, developing with 1% aq $KMnO_4$), and consumption of the starting material occurred within 3−5 h. The solution was evaporated in vacuum, and the residue was separated as described above.

(3*S*,4*S*)-3,4-Di-*tert*-butoxy-5-(pent-4-enyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (11) and (2*S*,3*S*,4*S*)-3,4-Di-*tert*-butoxy-2-(pent-4-enyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (12) (from 10). Overall yield 90% (PbO_2) or 85% (MnO_2) or 90% (Cu^{2+}/O_2), for the ratio of isomers see Scheme 3. **11**: R_f = 0.4 (silica gel, EtOAc), colorless oil; $[\alpha]^{22.5}_D$ = +114 (*c* 1.1, $CHCl_3$); IR (neat) ν 3076.8, 2975.2, 2934.5, 1713.3, 1640.6, 1603.8, 1464.2, 1438.8, 1391.5, 1367.9, 1189.6, 1068.9, 1061.3, 911.9 cm^{-1}; UV (EtOH) λ_{max} (log ε) 233 (3.75) nm. Anal. Calcd for $C_{17}H_{31}NO_3$: C, 68.65; H, 10.51; N, 4.71. Found: C, 68.50; H, 10.31; N 4.50. **12**: R_f = 0.7 (silica gel, EtOAc), colorless oil; $[\alpha]^{26.9}_D$ = +63 (*c* 0.8, $CHCl_3$); IR (neat) ν 3076.5, 2975.1, 2933.6, 2871.3, 1739.0, 1640.7, 1575.9, 1462.3, 1391.5, 1366.9, 1238.2, 1191.1, 1079.8, 1051.9, 909.1, 869.7 cm^{-1}; UV (EtOH) λ_{max} (log ε) 230 (3.82) nm. Anal. Calcd for $C_{17}H_{31}NO_3$: C, 68.65; H, 10.51; N, 4.71. Found: C, 68.35; H, 10.80; N 4.64.

(2*S*,3*S*,4*S*)-3,4-Di-*tert*-butoxy-2,5-di(pent-4-enyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (18) (from 17). R_f = 0.65; yield: 0.51 g (80%); colorless oil; $[\alpha]^{27}_D$ = +45 (*c* 1.3, $CHCl_3$); IR (neat) ν 3435, 3077, 2975, 2869, 1719, 1666, 1641, 1462, 1390, 1366, 1192, 1075, 909 cm^{-1}; UV (EtOH) λ_{max} (log ε) 236 (3.24), 284 (3.08) nm. Anal. Calcd for $C_{22}H_{39}NO_3$: C, 72.28; H, 10.75; N, 3.83. Found: C, 72.40; H, 10.45; N 3.51.

General Method for Intramolecular 1,3-Dipolar Cycloaddition. A solution of **11**, **16**, or **18** (0.3 mmol) in toluene (2 mL) was stirred at +110 °C. The progress of the reaction was monitored by TLC (silica gel, EtOAc, developing with 1% aq $KMnO_4$), and consumption of the starting material occurred within 3−10 h. The solution was concentrated in vacuum and residue was separated by column chromatography (silica gel 60, EtOAc) to give **13**, **24**, or **19**, respectively.

(1*S*,2*S*,6a*R*,9^1*S*)-1,2-Di-*tert*-butoxyoctahydrocyclopenta[*c*]-pyrrolo[1,2-*b*]isoxazole (13). R_f = 0.75; yield 98%; colorless oil; $[\alpha]^{27.5}_D$ = +42 (*c* 1.2, $CHCl_3$); IR (neat) ν 2974.2, 2868.1, 1712.7, 1468.0, 1390.4, 1364.6, 1256.9, 1234.6, 1193.3, 1114.4, 1098.0 cm^{-1}. Anal. Calcd for $C_{17}H_{31}NO_3$: C, 68.65; H, 10.51; N, 4.71. Found: C, 68.45; H, 10.60; N 4.55.

((1*S*,1′*S*,2*S*,2′*R*,6a*R*,9′*S*)-1,2-Di-*tert*-butoxyhexahydro-1*H*-spiro[cyclopenta[*c*]pyrrolo[1,2-*b*]isoxazole-3,1′-cyclopentane]-2′-yl) Methanol (24). R_f = 0.65; yield 75%; colorless oil; $[\alpha]^{30.9}_D$ = −11 (*c* 0.15, $CHCl_3$); IR (neat) ν 2973.3, 2872.2, 1724.6, 1468.9, 1390.6, 1364.9, 1239.3, 1192.4, 1131.0, 1072.6 cm^{-1}. Anal. Calcd for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67. Found: C, 69.47; H, 10.18; N 3.73.

(1*S*,2*S*,3*S*,6a*R*,9^1*S*)-1,2-Di-*tert*-butoxy-3-(pent-4-enyl)-octahydrocyclopenta[*c*]pyrrolo[1,2-*b*]isoxazolidine (19). R_f = 0.75; yield 96%; colorless solid; mp 58−63 °C (hexane); $[\alpha]^{26.9}_D$ = +13 (*c* 0.4, $CHCl_3$); IR (KBr) ν 3444, 3079, 2974, 2942, 2865, 1643, 1461, 1390, 1363, 1253, 1233, 1192, 1102, 1088, 906 cm^{-1}. Anal. Calcd for $C_{22}H_{39}NO_3$: C, 72.28; H, 10.75; N, 3.83. Found: C, 72.20; H, 10.68; N 3.59.

(3*S*,4*S*,5*S*,6*R*)-3,4-Di-*tert*-butoxy-6-(hydroxymethyl)-2-(pent-4-enyl)-1-azaspiro[4.4]non-1-ene 1-Oxide (16). *Method A (from **15**).* The nitrone **15** was treated with pent-4-enylmagnesium bromide in analogy to the procedure described above for **1** and **12**. The crude product was dissolved in $CHCl_3$ and oxidized with PbO_2 as described above for **10** and **17**. The product was isolated using column chromatography (silica gel 60, EtOAc). Yield 90%.

*Method B (from **23**).* A solution of $Na_2WO_4{\cdot}2H_2O$ (6.6 mg, 0.02 mmol) and Na_2H_2EDTA (6.8 mg, 0.02 mmol) in H_2O (0.5 mL) was added to a solution of **23** (171 mg, 0.465 mmol) in MeOH (1 mL). Then H_2O_2 (0.2 mL, 30%) was poured into the mixture, and the solution was allowed to stand overnight. The solvent was removed under vacuum, and the residue was separated using column chromatography (silica gel 60, EtOAc); yield 75%; R_f = 0.65; colorless oil; $[\alpha]^{30.8}_D$ = +16 (*c* 0.1, $CHCl_3$); IR (neat) ν 3300.2, 2975.7, 1712.8, 1641.3, 1600.9, 1462.5, 1392.4, 1368.1, 1254.7, 1185.7, 1066.2, 1022.6, 898.0 cm^{-1}; UV (EtOH) λ_{max} (log ε) 240 (3.62) nm. Anal. Calcd for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67. Found: C, 69.20; H, 10.45; N 3.75.

General Procedure for Reductive Isoxazolidine Ring Cleavage Using LVT Reagent. Titanium(IV) *iso*-propoxide ($Ti(O\text{-}iPr)_4$, 3.01 g, 10.58 mmol) was injected with a syringe into a flask with dry Et_2O (5 mL) under a stream of inert gas (argon). A 2 M solution of EtMgBr in Et_2O (5.5 mL, 11 mmol) was added dropwise within 2 min upon vigorous stirring. The solution turned black over the course of EtMgBr addition. The reaction mixture was stirred at rt under argon for 15 min and then 15 min under reflux. A solution of **19** or **24** (3.5 mmol) in Et_2O (5 mL) was added dropwise, and then stirring under reflux was continued. The progress of the reaction was monitored by TLC (silica gel, EtOAc, developing with 1% aq $KMnO_4$), and consumption of the starting material occurred within 3−5 h. The reaction mixture was quenched carefully with H_2O (3 mL) and stirred under reflux for 24 h. The organic layer was separated, the solvent was evaporated in vacuum, and the residue was purified using column chromatography (silica gel 60, EtOAc) to give **23** or **25**, respectively.

((2*S*,3*S*,4*S*,5*S*,6*R*)-3,4-Di-*tert*-butoxy-2-(pent-4-enyl)-1-azaspiro[4.4]nonan-6-yl)methanol (23). R_f = 0.55; yield 80%; colorless oil; $[\alpha]^{30.1}_D$ = −6 (*c* 0.1, $CHCl_3$); IR (neat) ν 3312.5, 2974.9, 2871.1, 1641.2, 1460.1, 1389.2, 1364.9, 1191.7, 1068.0, 909.7, 733.3 cm^{-1}. Anal. Calcd for $C_{22}H_{41}NO_3$: C, 71.89; H, 11.24; N, 3.81. Found: C, 71.51; H, 11.51; N 3.88.

(1*S*,2*R*,3′*S*,4′*S*,5′*S*,2″*R*)-Dispiro[(2-hydroxymethyl)-cyclopentane-1,2′-(3′,4′-di-*tert*-butoxy)pyrrolidine-5′,1″-(2″-hydroxymethyl)cyclopentane] (25). R_f = 0.45; yield 60%; colorless solid; mp 152−152 °C (hexane); $[\alpha]^{30.9}_D$ = −71 (*c* 0.09, $CHCl_3$); IR (neat) ν 3307.4, 2972.2, 2942.8, 2871.8, 1457.5, 1392.5, 1362.0, 1192.1, 1133.0, 1093.7, 891.3 cm^{-1}. Anal. Calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.77; N, 3.65. Found: C, 68.78; H, 11.02; N 3.59.

1*S*,2*R*,3′*S*,4′*S*,5′*S*,2″*R*)-Dispiro[(2-hydroxymethyl)-cyclopentan-1,2′-(3′,4′-di-*tert*-butoxy)pyrrolidine-5′,1″-(2″-

hydroxymethyl)cyclopentane] 1′-Oxyl (2). To a solution of **25** (145 mg, 0.38 mmol) in $CHCl_3$ (4 mL) at −10 °C was added *m*-CPBA (65 mg, 0.38 mmol) in one portion. Then the mixture was stirred at 0 °C until the reaction was complete (control by TLC analysis, $CHCl_3$). Solvent was removed under vacuum, and the residue was separated by column chromatography (Kieselgel 60, $CHCl_3$); R_f = 0.3; yield: 72 mg (48%); light yellow solid; mp 114−116 (hexane); $[\alpha]^{30.9}_D$ = −54 (*c* 0.09, $CHCl_3$); IR (KBr) ν 3437.0, 3308.2, 2969.0, 2871.4, 1464.1, 1391.2, 1363.0, 1191.6, 1129.7, 1080.7 cm^{-1}; UV (EtOH) λ_{max} (log ε),nm: 225 (3.27), 285 (3.05). Anal. Calcd for $C_{22}H_{40}NO_5$: C, 66.30; H, 10.12; N, 3.51. Found: C, 66.65; H, 10.49; N 3.59.

Nitroxide Reduction with Ascorbic Acid. The experiments were carried out in phosphate buffer (50 mM, pH 7.4) containing 50 μM DTPA. Solutions of the nitroxide **2** (1 mM) and ascorbic acid (200 mM, 400 mM and 1 M) were prepared. The pH of the ascorbic acid solutions was adjusted to 7.4 with NaOH. All solutions were bubbled with argon for 10 min to remove dissolved oxygen. Aliquots of the radical (150 μL) were rapidly mixed with an equal volume of the ascorbic acid solutions, and the mixtures were immediately placed into 50 μL glass capillary tubes for EPR measurements. Kinetics of decrease in peak intensity of the low-field component of the nitroxide EPR spectrum were recorded. Initial rate of EPR signal decay was used to calculate the bimolecular rate constant of the nitroxide reduction by ascorbic acid. EPR spectrometer settings were as follows: magnetic field modulation, 1 G; microwave power, 20 mW.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of new products and X-ray structures in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661−3688.

(2) (a) Iwamura, H.; Inoue, K. Magnetic Ordering in Metal Coordination Complexes with Aminoxyl Radicals. In *Magnetism: Molecules and materials II. Molecule-Based Materials*; Miller, J. S., Drillion, M., Eds.; Wiley-VCH Verlag GmbH & Co KGaA: Weinheim, 2001; pp 61−108. (b) Ovcharenko, V. Metal−Nitroxide Complexes: Synthesis and Magnetostructural Correlations. In *Stable Radicals. Fundamentals and Applied Aspects of Odd-Electron Compounds*; Hicks, R. G., Ed.; Wiley: New York, 2010; pp 461−506.

(3) (a) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153−1174. (b) Bobbitt, J. M.; Brückner, C.; Merbouh, N. *Org. React.* **2009**, *74*, 106−424. (c) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979−1993.

(4) Halpern, H. J.; Yu, C.; Peric, M.; Barth, E.; Grdina, D. J.; Teicher, B. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 13047−13051.

(5) (a) Khramtsov., V. V.; Volodarsky, L. B. *Biological Magnetic Resonance, Vol. 14: Spin Labeling: The Next Millennium*; Plenum Press: New York, London, 1998. (b) Khramtsov, V. V.; Grigor'ev, I. A.; Foster, M. A.; Lurie, D. J.; Nicholson, I. *Cell. Mol. Biol.* **2000**, *46*, 1361−1374. (c) Khramtsov, V. V.; Grigor'ev, I. A.; Foster, M. A.; Lurie, D. J. *Antioxid. Redox Signaling* **2004**, *6*, 667−676.

(6) Ahn, H.-Y.; Fairful-Smith, K. E.; Morrow, B. J.; Lussini, V.; Kim, B.; Bondar, M. V.; Bottle, S. E.; Belfield, K. D. *J. Am. Chem. Soc.* **2012**, *134*, 4721−4730.

(7) Berliner, L. J. *Biological Magnetic Resonance, Vol. 14: Spin Labeling: The Next Millennium*; Plenum Press: New York, London, 1998.

(8) Soule, B. P.; Hyodo, F.; Matsumoto, K.-I.; Simone, N. L.; Cook, J. A.; Krishna, M. C.; Mitchell, J. B. *Free Radic. Biol. Med.* **2007**, *42*, 1632−1650.

(9) (a) Keana, J. F. W.; Pow, S.; Rosen, G. M. *Magn. Reson. Med.* **1987**, *3*, 83−88. (b) Winalski, C. S.; Shortkroff, S.; Mulkern, R. V.; Schneider, E.; Rosen, G. M. *Magn. Reson. Med.* **2002**, *48*, 965−972.

(10) Suga, T.; Nishide, H. Rechargeable Batteries Using Robust but Redox Active Organic Radicals. In *Stable Radicals. Fundamentals and Applied Aspects of Odd-Electron Compounds*; Hicks, R. G., Ed.; Wiley: New York, 2010; pp 507−520.

(11) (a) Wetter, Ch.; Gierlich, J.; Knoop, Ch. A.; Müller, Ch.; Schulte, T.; Studer, A. *Chem.—Eur. J.* **2004**, *10*, 1156−1166. (b) Miura, Y.; Nakamura, N.; Taniguchi, I. *Macromolecules* **2001**, *34*, 447−455.

(12) (a) Marx, L.; Chiarelli, R.; Guiberteau, T.; Rassat, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1181−1182. (b) Kirilyuk, I. A.; Bobko, A. A.; Grigor'ev, I. A.; Khramtsov, V. V. *Org. Biomol. Chem.* **2004**, *2*, 1025−1030. (c) Kinoshita, Yu.; Yamada, K.; Yamasaki, T.; Sadsue, H.; Sakai, K.; Utsumi, H. *Free Radic. Res.* **2009**, *43*, 565−571. (d) Yamasaki, T.; Mito, F.; Ito, Y.; Pandian, S.; Kinoshita, Y.; Nakano, K.; Murugesan, R.; Sakai, K.; Utsumi, H.; Yamada, K. *J. Org. Chem.* **2011**, *76*, 435−440.

(13) Rajca, A.; Kathirvelu, V.; Roy, S. K.; Pink, M.; Rajca, S.; Sarkar, S.; Eaton, S. S.; Eaton, G. R. *Chem.—Eur. J.* **2010**, *16*, 5778−5782.

(14) (a) Yoshioka, T.; Higashida, S.; Murayama, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 636−638. (b) Smythe, M. L.; Nakaie, C. R.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 10555−10562. (c) Schulte, T.; Siegenthaler, K. O.; Luftmann, H.; Letzel, M.; Studer, A. *Macromolecules* **2005**, *38*, 6833−6840. (d) Sakai, K.; Yamada, K. I.; Yamasaki, T.; Kinoshita, Y.; Mito, F.; Utsumi, H. *Tetrahedron* **2010**, *66*, 2311−2315.

(15) (a) Yoshioka, T.; Mori, E.; Murayama, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1855−1860. (b) Lai, J. T. *Synthesis* **1981**, 40−42.

(16) (a) Marx, L.; Rassat, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4494−4496. (b) Fairfull-Smith, K. E.; Brackmann, F.; Bottle, S. E. *Eur. J. Org. Chem.* **2009**, 1902−1915.

(17) (a) Braslau, R.; Burill, L. C.; Chaplinski, V.; Howden, R.; Papa, P. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3209−3212. (b) Morat, C.; Rassat, A. *Tetrahedron Lett.* **1979**, *19*, 4561−4564.

(18) Toda, T.; Morimura, S.; Murayama, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 557−561.

(19) Reznikov, V. A.; Volodarsky, L. B. *Tetrahedron* **1993**, *49*, 10669−10692.

(20) (a) Keana, J. F. W. Synthesis and Chemistry of Nitroxide Spin Labels. In *Spin Labeling in Pharmacology*; Holtzman, J. L., Ed.; Academic Press: Orlando, 1984; pp 1−85. (b) Keana, J. F. W.; Lee, T. D.; Bernard, E. M. *J. Am. Chem. Soc.* **1976**, *98*, 3052−3053. (c) Lee, T. D.; Birrell, G. B.; Keana, J. F. W. *J. Am. Chem. Soc.* **1978**, *100*, 1618−1619. (d) Keana, J. F. W.; Seyedrezai, S. E.; Gaughan, J. *J. Org. Chem.* **1983**, *48*, 2644−2647. (e) Keana, J. F. W.; Cuomo, J.; Lex, L.; Seyedrezai, S. E. *J. Org. Chem.* **1983**, *48*, 2647−2654. (f) Keana, J. F. W.; Prabhu, V. S. *J. Org. Chem.* **1986**, *51*, 4300−4301. (g) Benfaremo, N.; Steenbock, M.; Klapper, M.; Müllen, K.; Enkelmann, V.; Cabrera, K. *Liebigs Ann.* **1996**, 1413−1415. (h) Baracz, N. M.; Hankovsky, O. H.; Sár, C. P.; Jerkovich, G.; Hideg, K. *Synthesis* **1996**, 204−208. (i) Haire, D. L.; Janzen, E. G.; Chen, G.; Robinson, V. J.; Hrvoic, I. *Magn. Reson. Chem.* **1999**, *37*, 251−258.

(21) (a) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Gautier-Luneau, I.; Pierre, J. L. *J. Org. Chem.* **1997**, *62*, 9385−9388. (b) Shibata, T.; Uemae, K.; Yamamoto, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 2339−2346.
(22) (a) Merino, P. In *Science of Synthesis*; Padwa, A., Ed.; Thieme: Stuttgart, 2004; Vol. *27*, pp 511−580. (b) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. *2*, pp 83−168. (c) Frederickson, M. *Tetrahedron* **1997**, *53*, 403−425. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (e) Jones, R. C. F.; Martin, J. N. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; The Chemistry of Heterocyclic Compounds Vol. *59*, pp 1−81. (f) Grigor'ev, I. A. Nitrones: Novel Strategies in Synthesis. In *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis. Novel Strategies in Synthesis*; Feuer, H., Ed.; Wiley: New York, 2008; pp 129−434.
(23) Sár, C. P.; Ősz, E.; Jekő, J.; Hideg, K. *Synthesis* **2005**, 255−259.
(24) Morozov, D. A.; Kirilyuk, I. A.; Gatilov, Yu. V.; Bagryanskaya, I. Yu.; Bozhko, J. Yu.; Komarov, D. A.; Grigor'ev, I. A. *Synthesis* **2009**, 343−348.
(25) Cicchi, S.; Hőld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274−5275.
(26) (a) Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761−763. (b) Cardona, F.; Goti, A.; Picasso, S.; Vogel, P.; Brandi, A. *J. Carbohydr. Chem.* **2000**, *19*, 585−601.
(27) (a) Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Guarna, F.; Merino, P.; Tejero, T. *Org. Lett.* **2003**, *5*, 4235−4238. (b) Merino, P.; Tejero, T.; Revuelta, J.; Romero, P.; Cicchi, S.; Mannucci, V.; Brandi, A.; Goti, A. *Tetrahedron: Asymmetry* **2003**, *14*, 367−379. (c) Marradi, M.; Cicchi, S.; Delso, J. I.; Rosi, L.; Tejero, T.; Merino, P.; Goti, A. *Tetrahedron Lett.* **2005**, *46*, 1287−1290. (d) Cardona, F.; Moreno, G.; Guarna, F.; Vogel, P.; Schuetz, C.; Merino, P.; Goti, A. *J. Org. Chem.* **2005**, *70*, 6552−6555. (e) Delso, I.; Marca, E.; Mannucci, V.; Tejero, T.; Goti, A.; Merino, P. *Chem.—Eur. J.* **2010**, *16*, 9910−9919.
(28) (a) LeBel, N. A.; Spurlock, L. A. *J. Org. Chem.* **1964**, *29*, 1337−1339. (b) LeBel, N. A.; Post, M. E.; Hwang, D. *J. Org. Chem.* **1979**, *44*, 1819−1823. (c) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, Sk. A. *J. Am. Chem. Soc.* **1979**, *101*, 2435−2442.
(29) Iwamoto, O.; Sekine, M.; Koshino, H.; Nagasawa, K. *Heterocycles* **2006**, *70*, 107−112.
(30) Ali, Sk. A.; Wazeer, M. I. M. *Tetrahedron* **1993**, *49*, 4339−4354.
(31) (a) Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1863−1864. (b) Nagasawa, K.; Georgieva, A.; Nakata, T. *Tetrahedron* **2000**, *56*, 187−192. (c) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315−2318. (d) Liautard, V.; Christina, A. E.; Desvergnes, V.; Martin, O. R. *J. Org. Chem.* **2006**, *71*, 7337−7345. (e) Cardona, F.; Parmeggiani, C.; Faggi, E.; Bonaccini, C.; Gratteri, P.; Sim, L.; Gloster, T. M.; Roberts, S.; Davies, G. J.; Rose, D. R.; Goti, A. *Chem.—Eur. J.* **2009**, *15*, 1627−1636. (f) Bonaccini, C.; Chioccioli, M.; Parmeggiani, C.; Cardona, F.; Lo, Re, D.; Soldaini, G.; Vogel, P.; Bello, C.; Goti, A.; Gratteri, P. *Eur. J. Org. Chem.* **2010**, 5574−5585.
(32) (a) Carmona, A. T.; Whigtman, R. H.; Robina, I.; Vogel, P. *Helv. Chim. Acta* **2003**, *86*, 3066−3073. (b) Coutouli-Argyropoulou, E.; Xatzis, Ch.; Argyropoulos, N. *Nucleosides, Nucleotides Nucleic Acids* **2008**, *27*, 84−100. (c) Podolan, G.; Kleščíková, L.; Fišera, L.; Kožíšek, J.; Fronc, M. *Synlett* **2011**, 1668−1672.
(33) Goti, A.; Cacciarini, M.; Cardona, F.; Cordero, F. M.; Brandi, A. *Org. Lett.* **2001**, *3*, 1367−1369.
(34) Merino, P.; Revuelta, J.; Tejero, T.; Cicchi, S.; Goti, A. *Eur. J. Org. Chem.* **2004**, 776−782.
(35) Additions of pentenyl Grignard reagents (and similar) to cyclic nitrones aimed at successive intramolecular cycloaddition and ultimately at the synthesis of spiroannelated nitrogen heterocycles have been reported previously. (a) Gössinger, E.; Imhof, R.; Wehrli, H. *Helv. Chim. Acta* **1975**, *58*, 96−103. (b) Yang, S.-H.; Clark, G. R.; Caprio, V. *Org. Biomol. Chem.* **2009**, *7*, 2981−2990.
(36) (a) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Goti, A. *Synlett* **2007**, 2651−2654. (b) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929−2947.
(37) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743−4748.
(38) (a) Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 3119−3125. (b) Goti, A.; Cicchi, S.; Cordero, F. M.; Fedi, V.; Brandi, A. *Molecules* **1999**, *4*, 1−12.
(39) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988.
(40) Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **2001**, *42*, 6503−6505.
(41) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem.—Eur. J.* **2009**, *15*, 7808−7821.
(42) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399−10432.
(43) Dondas, H. A.; Grigg, R.; Hadjisoteriou, M.; Markandu, J.; Thomas, W. A.; Kennewell, P. *Tetrahedron* **2000**, *56*, 10087−10096.
(44) Holmes, A. B.; Hughes, A. B.; Smith, A. L. *Synlett* **1991**, *1*, 47−48.
(45) (a) Huisgen, R.; Grashey, R.; Hauck, H.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2043−2055. (b) LeBel, N. A.; Ojha, N. D.; Menke, J. R.; Newland, R. J. *J. Org. Chem.* **1972**, *37*, 2896−2898. (c) Bapat, J. B.; Black, D. St. C.; Brown, R. F. C.; Ichlov, C. *Aust. J. Chem.* **1972**, *25*, 2445−2450. (d) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134−1144. (e) Koizumi, T.; Hirai, H.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4004−4005. (f) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5048−5050. (g) DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686−1688. (h) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455−3462. (i) Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am. Chem. Soc.* **1986**, *108*, 4647−4648. (j) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3354. (k) Zhang, D.; Süling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885−888. (l) Revuelta, J.; Cicchi, S.; Brandi, A. *Tetrahedron Lett.* **2004**, *45*, 8375−8377.
(46) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736−1744.
(47) Okazaki, Sh.; Mannan, M. A.; Sawai, K.; Masumizu, T.; Miura, Y.; Takeshita, K. *Free Radic. Res.* **2007**, *41*, 1069−1077.
(48) Bobko, A. A.; Kirilyuk, I. A.; Gritsan, N. P.; Polovyanenko, D. N.; Grigor'ev, I. A.; Khramtsov, V. V.; Bagryanskaya, E. G. *Appl. Magn. Reson.* **2010**, *39*, 437−451.
(49) Bobko, A. A.; Kirilyuk, I. A.; Grigor'ev, I. A.; Zweier, J. L.; Khramtsov, V. V. *Free Radic. Biol. Med.* **2007**, *42*, 404−412.