β-Phosphorylated Five-Membered Ring Nitroxides: Synthesis and ESR Study of 2-Phosphonyl-4-(hydroxymethyl)pyrrolidine Aminoxyl Radicals

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Intramolecular aminomercuration of the alkenyl α-amino phosphonate **6** followed by sodium borohydride reduction leads to the diethyl (4-(benzyloxymethyl)-2,5,5-trimethylpyrrolidinyl)-phosphonate **7**. Oxidation of the phosphonates **7** and **8** with 3-chloroperbenzoic acid led to the stable 2-phosphonylpyrrolidinyl aminoxyl radicals **9** and **10** bearing a 4-(hydroxymethyl)substituent.

Introduction

Stable aminoxyl radicals play a central role in a large number of spin-labeling[1,2] and spin-trapping[2,3] applications. Recently, their application as contrast-enhancing agents in magnetic resonance imaging (MRI) has been investigated.[4] In nonviscous solutions aminoxyl radicals bearing quaternary sp^3 carbon atoms adjacent to the nitroxide exhibit isotropic three-line ESR spectra, resulting from the coupling of the unpaired electron with the nitrogen atom. Stable aminoxyl radicals exhibiting a second very large hyperfine splitting with a one-half spin nucleus should present useful properties in spin-labeling investigations and in different applications involving their relaxivity.[5] In previous papers,[6-8] we reported our preliminary results on the synthesis of β-phosphorylated five-membered ring nitroxides of type A (Scheme I). We now report the complete synthesis of a functionalized system of type B, which will open the possibility of linkage of these new aminoxyl radicals to a wide array of biologically important substrates.

Results and Discussion

The nitroxides **9** and **10** were prepared by the reaction sequence described in Scheme II. Oxidation of 4-(benzyloxy)but-2-en-1-ol with activated manganese dioxide led to the aldehyde **2** as a mixture of *E* and *Z* isomers in varying proportions as already reported by Panek *et al.*[9] Following Grignard addition of methylmagnesium iodide, oxidation of the secondary alcohol to the ketone was realized with manganese dioxide in modest yield (27%), but the reaction with pyridinium dichromate, activated by molecular sieves,[10] led to **3** in better yield (57%). Although more sluggish than with other similar methyl ketones,[7,8] the aminophosphorylation reaction of **5**, under our modified Medved–Kabachnik reaction conditions, gave **6** as a 1:1 mixture of diastereoisomers, which were not resolved by chromatography.

Ring cyclization by intramolecular aminomercuration[11] of the sterically hindered primary amine followed by reduction with borohydride derivatives gave the phosphorylated pyrrolidine **7** as a mixture of diastereoisomers. When the reduction of the intermediate mercurial was performed with sodium borohydride, only a modest 30% yield was observed. However, use of sodium trimethoxyborohydride[12] led to a significantly improved yield (65%). Oxidation of **7** or **8** (after deprotection of the 4-(benzyloxy) substituent by palladium-catalyzed hydrogenation) with 1 equiv of 3-chloroperbenzoic acid yielded the corresponding nitroxides **10a,b** and **9a,b**. The diastereomer

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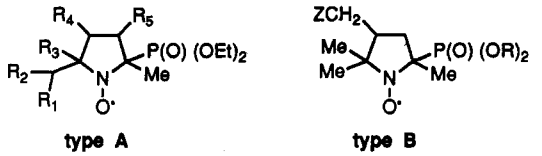
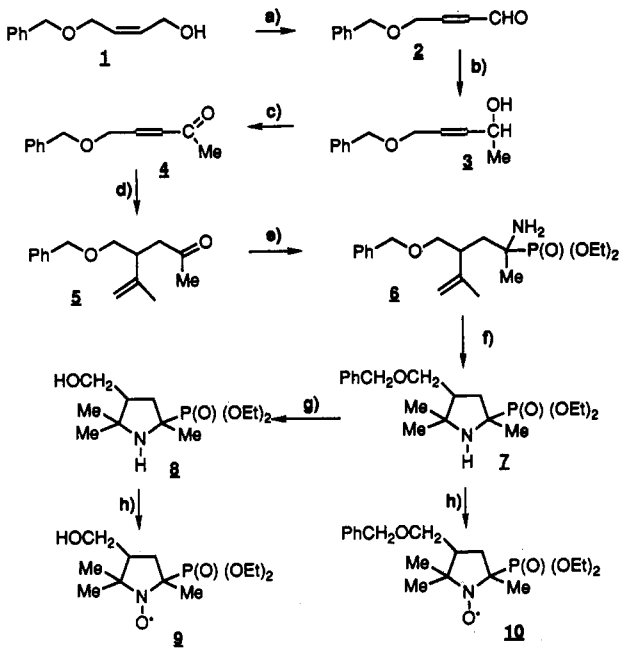
Scheme I



Scheme II[a]



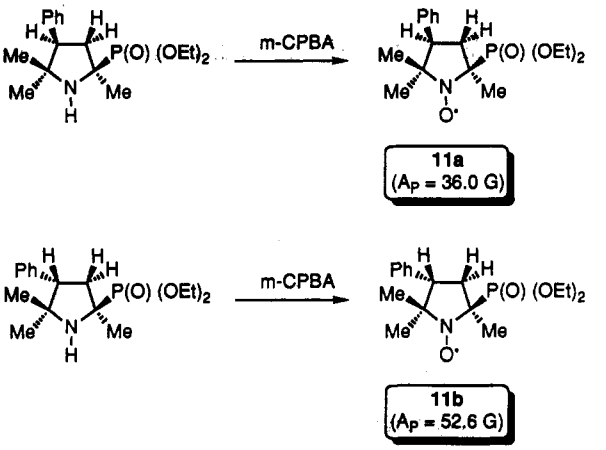
[a] Key: (a) MnO_2; (b) MeMgI; (c) pyridinium dichromate–molecular sieves; (d) 2-propenylMgBr; (e) NH_3–HP(O)$(OEt)_2$; (f) (1) $Hg(OAc)_2$, (2) $NaB(OMe)_3H$; (g) H_2–Pd/C; (h) *m*-CPBA.

Table I. Solvent Dependence of the ESR Data for Nitroxides 9a and 9b

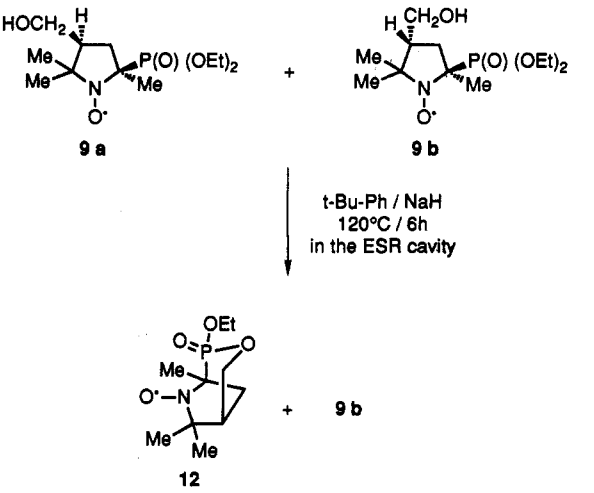
	9a			9b		
solvent	A_P	A_N	g	A_P	A_N	g
CH_2Cl_2	35.78	14.04	2.0058_6	53.20	14.10	2.0060_4
C_6H_6	36.79	13.95	2.0059_7	53.36	13.96	2.0061_3
THF	36.10	13.85		53.86	13.99	
n-pentane	38.01	13.70		54.12	13.67	
Ph-*t*-Bu	37.24	13.91	2.0059_6	52.83	13.65	2.0061_2

ratios **9a:9b** and **10a:10b** were estimated by integration of the corresponding ESR signals. In each case, a 3:1 ratio was observed. Preparative TLC on the diastereomeric mixture **9a–b** led to a pure sample of **9a**. The diastereomeric nitroxides **9a,b** and **10a,b** were shown to be stable in different organic solvents (including ethanol). Their ESR features (reported in Table I) exhibit very similar nitrogen couplings ($0.26\ G > \Delta A_N > 0.015\ G$ for **9a,b**) but very different phosphorus couplings ($17.7 > \Delta A_P > 15.4$ G for **9a,b**). Moreover, their ESR properties are close to other previously studied β-phosphorylated nitroxides[8] **11a,b** (Scheme III). It was possible to assign the stereochemistry of the nitroxides **11a** and **11b** by means of the full analysis of the ^1H NMR (400 MHz) spectra of the parent amines. In this way it was possible to conclude that the diastereomer with the lower A_P has the –P(O)$(OEt)_2$ group at C-2 on the same side as the substituent at C-4. Unfortunately, it was not possible to carry out a similar study with **7a,b** and **8a,b** because of the complexity of their ^1H-NMR spectra even at 400 MHz. Therefore, we proceeded by analogy assuming that **9a** and **10a** have the same configurations as **11a** (C-4 substituent and phosphorus group in cis) and that **9b** and **10b** have the same configurations as **11b** (C-4 substituent and phosphorus group in trans).

Scheme III



Scheme IV



If the stereochemistry assigned to **9a** was correct, we expected that heating **9a** in the presence of a base would promote an intramolecular transesterification resulting in the formation of the bicyclic nitroxide **12** (Scheme IV). Our assumption was confirmed when the diastereoisomeric mixture of **9a,b** was heated in *tert*-butylbenzene in the presence of sodium hydride[13] in the cavity of an ESR spectrometer. After 6 h the signal of **9a** had completely disappeared while the signal of **9b** remained unchanged and a new signal ($A_N = 13.40$ G; $A_P = 57.98$ G; $g = 2.0061$) assigned to **12** was observed. The phosphorus coupling in **12** is the highest coupling of this type ever observed in pyrrolidinyl-*N*-oxyl radicals bearing a β-dialkylphosphonyl [$(RO)_2P(O)$–] substituent. We have previously shown[14] that the phosphorus coupling for these radicals exhibit a $\cos^2\theta_P$ dependence ($A_P = B_P \cos^2\theta_P$), with $B_P \approx 60$ G. The phosphorus coupling observed for **12** corresponds to a very small value of the Karplus-like dihedral angle θ_P, in agreement with the blocked geometry of **12**. Force field calculations carried out with the nitroxide force field for the five-membered ring nitroxide we recently described[15]

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gave for **12** a θ_P value of 2°, which corresponds to a B_P value of 58 G.

Experimental Section

General Methods. ^{1}H- and ^{13}C-NMR spectra were recorded at 200 or 400 MHz, and the chemical shifts (δ) in ppm are referred to internal Me_4Si. Proton-decoupled ^{31}P-NMR spectra were recorded at 40.54 MHz, and the chemical shifts (δ) in ppm are referred to external 85% phosphoric acid. Mass spectra were recorded in EI$^+$ mode on a Carlo-Erba QMD 1000 GLC–MS spectrometer equipped with a direct probe apparatus. ESR spectra were recorded on a Bruker ESP 300 equipped with an ER 035N NMR gaussmeter for field calibration and an HP 5350B microwave frequency counter; hyperfine splitting coupling constants are given in Gauss (G). Chromatographic separations were performed using Merck silica gel 7734 (column chromatography) and Merck silica gel 7747 (preparative thin-layer chromatography). All solvents were purified by standard techniques.

Preparation of 4-(Benzyloxy)but-2-en-1-al (2). Activated manganese dioxide (35 g) was added to a solution of 4-(benzyloxy)-but-2-en-1-ol (5 g, Fluka, 30.4 mmol) in chloroform (35 mL) in small portions over 15 min. The mixture was then vigorously stirred for 2 h. After filtration over Celite, the solvent was distilled under vacuum to afford **2** (4.7 g, 95%) as a yellow oil: ^{1}H-NMR δ 9.57 (1H, d, J = 7.87 Hz, CHO), 7.34 (5H, s, ArH), 6.84 (1H, dt, J = 15.73 and 4.06 Hz), 6.4 (1H, qt, J = 1.92, 15.73, and 7.87 Hz), 4.58 (2H, s), and 4.28 (2H, dd, J = 4.06 and 1.92 Hz); ^{13}C-NMR δ 68.6, 73, 127.7, 128, 128.5, 131.9, 137.5, and 193.1.

Preparation of 5-(Benzyloxy)-3-penten-2-ol (3). Under an atmosphere of nitrogen, a solution of methylmagnesium iodide [prepared from 2.73 g of magnesium turnings and 14.5 g of methyl iodide in anhydrous diethyl ether (100 mL)] was added to a solution of **2** (6 g, 34 mmol) in anhydrous THF (150 mL). The reaction mixture was stirred for 3 h, poured into saturated aqueous ammonium chloride solution (200 mL), and then saturated with potassium chloride and extracted with dichloromethane (5 × 200 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure at 50 °C to afford **3** as a yellow oil (5.29 g, 91%): ^{1}H-NMR δ 7.34 (5H, ArH), 5.8 (2H, m), 4.33 (1H, tq, J = 6.4, 2.71, 4.54 Hz), 4.03 (2H, d, J = 4.02 Hz), 1.6 (1H, broad), and 1.29 (3H, d, J = 6.4 Hz); ^{13}C-NMR δ 23, 68, 70, 72.1, 126, 127.6, 128.2, and 137. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.52; H, 8.34.

Preparation of 5-(Benzyloxy)-3-penten-2-one (4). A solution of **3** (5.9 g, 31 mmol) in anhydrous dichloromethane (15 mL) was added dropwise over 30 min to a vigorously stirred mixture of pyridinium dichromate (17.3 g, 46 mmol) and powdered 4-Å molecular sieves (15 g) in anhydrous dichloromethane (15 mL) under an atmosphere of nitrogen. The mixture was stirred for 3 h and then filtered over Celite. After dilution with pentane, the reaction mixture was filtered five times. The solvents were evaporated, and the residue, dissolved in dichloromethane, was washed with aqueous HCl solution (3 × 200 mL). The organic layer was dried over sodium sulfate and the solvent distilled to afford **4** (4.06 g, 57%) as an oil: ^{1}H-NMR δ 7.35 (5H, ArH), 6.82 (1H, dt, J = 16.12 and 4.3 Hz), 6.36 (1H, dt, J = 16.12 and 1.9 Hz), 4.57 (2H, s), and 2.27 (2H, dd, J = 4.3 and 1.9 Hz); ^{13}C-NMR δ 27.1, 68.6, 72.8, 128.2, 130.8, 143.7 and 199. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.78; H, 7.48.

Preparation of 4-(Benzyloxymethyl)-5-methyl-5-hexen-2-one (5). Under an atmosphere of nitrogen, copper(I) iodide (0.165 g, 0.85 mmol) was added to a cooled (0 °C), stirred solution of the Grignard reagent, prepared from 0.5 g of magnesium turnings and 2.1 g of 2-bromo-1-propene in anhydrous THF (100 mL). A solution of ketone **4** (1.65 g, 8.5 mmol) in anhydrous THF (150 mL) was then slowly added over 30 min under a nitrogen stream at 0 °C. The resulting mixture was stirred for 1 further h at the same temperature and then poured into an aqueous ammonium chloride solution. After extraction with dichloromethane, the organic layer was dried (Na_2SO_4) and evaporated to dryness to give **5** (2.65 g, 89%) as a yellow oil: ^{1}H-NMR δ 7.32 (5H, ArH), 4.83 (1H, t, J = 1.5 Hz), 4.77 (1H, s), 4.49 (2H, s), 3.48 and 3.32 (2H, ABX, J = −9.34, 5.8 and 7.27 Hz), 2.95 (1H, dddd, J = 5.8, 7.27, 6.4 and 7.8 Hz), 2.67 and 2.53 (2H, ABX, J = −16.2, 6.4 and 7.8 Hz), 2.12 (3H, s), and 1.73 (3H, s); ^{13}C-NMR δ 21, 30.3, 42.3, 45.2, 72.4, 73, 111.9, 127.6, 138.3, 145.2, and 207.8. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.33; H, 8.67.

Preparation of Diethyl (1-Amino-3-(benzyloxymethyl)-1,4-dimethylpent-4-enyl)phosphonate (6). Gaseous ammonia was bubbled through neat 4-(benzyloxymethyl)-5-methyl-5-hexen-2-one (**5**) (5 g, 21.5 mmol) for 15 min. Diethyl phosphite (3.3 g, 24 mmol) was added and the reaction mixture stirred for 24 h at 60 °C under continuous bubbling of ammonia. The reaction mixture was then poured into water (40 mL), acidified to pH 1 with concentrated aqueous HCl, and extracted with diethyl ether (3 × 50 mL). Sodium carbonate was added to the aqueous layer up to pH 10, which was then saturated with potassium chloride and extracted with dichloromethane (5 × 30 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness. The residue dissolved in pentane–acetone (1/1) (30 mL) was passed through a silica gel flash chromatography column to give, after elution with dichloromethane, a mixture of diastereomers **6a,b** (2.87 g, 39%) as a yellow oil: ^{1}H-NMR δ 7.32 (5H, s, ArH), 4.88 (2H, multiplet), 4.51 (2H, s), 4.14 (2H, dd, J = 7.1 Hz, and J_{PH} = 7.92 Hz), 3.36 (2H, multiplet), 2.86 (1H, multiplet), 2.05 (2H, broad multiplet), 1.83 (2H, m), 1.74 (3H, s), 1.32 (1.5H, t(a), J = 7.04 Hz), 1.31 (1.5H, t(b), J = 7.04 Hz), 1.30 (1.5H, d(a), $^3J_{PH}$ = 16.65 Hz), and 1.26 (1.5H, d(b), J_{PH} = 16.34 Hz); ^{13}C-NMR δ 16.7 and 16.8, 20.1 and 20.2, 22.4 and 22.9 (d, J_{PC} = 1.83 Hz), 36.4 (d, J_{PC} = 4.48 Hz) and 36.5 (d, J_{PC} = 3.15 Hz), 41.6 (d, J_{PC} = 9.55 Hz) and 41.8 (d, J_{PC} = 12 Hz), 52.8 (d(a), J_{PC} = 147.54 Hz) and 53.9 (d(b), J_{PC} = 151 Hz), 62.7 (multiplet), 73.1 and 73.2, 73.9 and 74.1, 112.9 and 113.1, 128, 128.1, 128.8, 139, 147.8, and 148.2. ^{31}P-NMR ($CDCl_3$ δ 30.5 and 30.05. Anal. Calcd for $C_{19}H_{32}NO_4P$: C, 61.77; H, 8.73; N, 3.79. Found: C, 61.7; H, 8.7; N, 3.74%.

Preparation of Diethyl (4-(Benzyloxymethyl)-2,5,5-trimethylpyrrolidinyl)-2-phosphonate (7). Mercury(II) acetate (0.65 g, 2 mmol) was added in small portions over 30 min to a solution of **6a,b** (0.5 g, 1.35 mmol) in THF (50 mL) under vigorous stirring. After being stirred for 3 h, the reaction mixture was concentrated to a small volume under reduced pressure, diluted with dichloromethane (50 mL), washed with a saturated solution of $NaHCO_3$ (3 × 30 mL), and filtrated through Celite. The filtrate was dried over sodium sulfate and evaporated to dryness under reduced pressure. The resulting oil was dissolved in anhydrous THF (50 mL), and sodium trimethoxyborohydride (0.5 g, 4.05 mmol) under nitrogen bubbling was added. The mixture was stirred overnight, filtered over Celite, concentrated to *ca.* 2 mL, diluted with water (50 mL), and extracted with dichloromethane (4 × 50 mL). The organic layer was dried over sodium sulfate and evaporated *in vacuo* to afford a mixture of diastereomers **7a,b** (0.33 g, 65%) as a yellow oil: ^{1}H-NMR (C_6D_6) δ 7.2 (5H, m, ArH), 4.27 (2H, m), 4.06 (4H, m), 3.67 and 3.69 (1H, AB, J = −10.48 Hz), 3.26 (2H, m), 2.71 (1.5H, m), 1.72 (0.5H, m), 1.54 (1H, s), 1.43 (1.5H, d, $^3J_{PH}$ = 15.02 Hz), 1.38 (1.5H, s), 1.34 (1.5H, s), 1.30 (1.5H, d, $^3J_{PH}$ = 14.87 Hz), 1.11 (1.5H, t, J = 7.14 Hz), 1.10 (1.5H, t, J = 6.95 Hz), 1.08 (1.5H, t, J = 6.96 Hz), 1.07 (1.5H, t, J = 6.78 Hz), 0.85 (1.5H, s), and 0.78 (1.5H, s); ^{13}C-NMR (C_6D_6) δ 17.2, 22.6, 26.8 (multiplet), 31, 39.4 (multiplet), 42, 59 (d, J_{CP} = 199.8 Hz), 59.4 (d, J_{CP} = 199.5 Hz), 63.2 (multiplet), 67.8, 69.89, 70.1, 70.9, 71.1, 71.6, 73.7, 139.2, 139.4, and 139.7; ^{31}P-NMR δ ($CDCl_3$) 29.39 and 28.72; δ (C_6D_6) 29.64 and 28.44; MS *m/z* (rel int) 369 (M^+, 1.4), 368 (M − 1, 2.55), 353 (1.75), 213 (2.94), 179 (5.59), 145 (11.02), 139 (18.09), 97 (85.53), 91 (48.68), 57 (100). Anal. Calcd for $C_{19}H_{32}NO_4P$: C, 61.77; H, 8.73; N, 3.79. Found: C, 60.98; H, 8.71; N, 3.6.

Preparation of Diethyl (4-(Hydroxymethyl)-2,5,5-trimethylpyrrolidinyl)-2-phosphonate (8). A mixture of **7a,b** (2 g, 5.4 mmol), HCl (0.4 mL of a 37% aqueous solution), and 10% Pd/C (0.36 g) in ethanol (64 mL) was vigorously stirred under hydrogen atmosphere (1.3 bar) at 50 °C overnight. The mixture was filtered over Celite and the solvent distilled off under reduced pressure. The residue was stirred in a mixture of dichloromethane (150 mL), $NaHCO_3$ (8 g), and water (1 mL). After filtration, the solution was dried over sodium sulfate and evaporated to afford a mixture of diastereomers **8a,b** (0.7 g, 88%) as a yellow-orange oil: ^{1}H-NMR (C_6D_6) δ 4.05 (4H, m), 3.53 (2H, m), 2.64 (1H, m), 2.28 (1H, m), 1.92 (3H, m), 1.36 (1.5H, d, J_{PH} = 15.2 Hz), 1.35 (1.5H, d, J_{PH} = 15.71 Hz), 1.34 (1.5H, s), 1.33 (1.5H, s), 1.13 (3H,

t, J = 6.78 Hz), 1.12 (1.5H, s), 1.11 (3H, t, J = 7.14 Hz), and 0.86 (1.5H, s); ^{13}C-NMR (C_6D_6) δ 17.1, 20 (multiplet), 22.9, 25.6, 26.9 (d, J_{PC} = 7.52 Hz), 27.3 (d, J_{PC} = 7.73 Hz), 30.7, 31, 31.8, 32.8, 38.2, 38.9, 40, 42.9, 50.6 (d, J_{PC} = 6.81 Hz), 51.8, 57.1, 58.2 (d, J_{PC} = 169.1 Hz), 58.4 (d, J_{PC} = 172.8 Hz), 60.5 (d, J_{PC} = 4.27 Hz), 60.9 (d, J_{PC} = 6.51 Hz), 61.8 (d, J_{PC} = 8.85 Hz), 63 (multiplet), 65.7, 66.6, 70.4, and 71.2; ^{31}P-NMR (C_6D_6) δ 29.89 and 28.94; MS m/z (rel int) 280 (M + 1, 1.41), 279 (M^+, 2.65), 250 (1.36), 234 (7.64), 218 (2.82), 205 (5.03), 140 (6.68), 124 (19.97), 96 (100), 91 (20.83), 82 (44.44).

Preparation of Diethyl ((4-(Hydroxymethyl)-2,5,5-trimethylpyrrolidinyl-*N*-oxy)-2-phosphonate (9). To a solution of **8a,b** (1 g, 3.6 mmol) in diethyl ether (100 mL) was added 3-chloroperbenzoic acid (1.8 g, 85%, Fluka, 10.7 mmol) in small portions under stirring at room temperature over 30 min. After an additional 30 min of stirring, the reaction mixture was washed with a saturated solution of $NaHCO_3$ (5 × 100 mL) and with water (3 × 100 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative silica gel chromatography (eluant: acetone–benzene (1/1)). Extraction with dichloromethane of the first spot gave, after distillation of the solvent, 0.127 g (12%)[16] of a spectroscopically (ESR) pure mixture of diastereomers **9a** (75%) and **9b** (25%) as a dark oil. The ratio of the two diastereoisomers was calculated by integration of their ESR signals. The resulting diastereomeric mixture was submitted to preparative TLC separation over silica gel plates eluting with a benzene–acetone (95:5) mixture. From the first spot 50 mg of pure **9a** was obtained: MS m/z (rel int) 294 (M^+, 7.27), 236 (49.78), 221 (8.41), 206 (21.75), 191 (10.87), 157 (11.21), 145 (44.84), 118 (26.12), 104 (100), 97 (44.39); UV/vis (λ_{max} in MeCN) 235 (s), 440 (w); IR (neat) 1351 ($NO^\bullet$).

Preparation of Diethyl ((4-(Benzyloxymethyl)-2,5,5-trimethylpyrrolidinyl)-*N*-oxy)-2-phosphonate (10). Compound **7a,b** (1 g, 2.7 mmol) was treated with 3-chloroperbenzoic acid under the same reaction conditions and worked up as for **8**. The chromatographic separation afforded *ca.* 0.125 g (12%) of a spectroscopically pure (ESR) mixture of diastereomers **10a** (75%) and **10b** (25%) as a dark oil. The ratio of the two diastereomers was calculated by integration of their ESR signals: MS m/z (rel int) 385 (M + 1, 1.4), 384 (M^+, 2.89), 350 (3.04), 325 (1.47), 309 (2.23), 292 (2.74), 275 (2.61), 158 (55.19), 111 (100), 99 (17.92).

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(16) We are presently searching for a better oxidant in order to improve the yield of this oxidation step. In this respect, dimethyldioxirane[17] appears to be a much better oxidant than 3-chloroperbenzoic acid and is giving very encouraging preliminary results.

(17) Murray, R. W.; Singh, M. *Tetrahedron Lett.* **1988**, *37*, 4677–4680.