Spectra. ^{11}B NMR spectra were recorded on a Varian FT-80A instrument. The chemical shifts are in δ relative to $BF_3 \cdot OEt_2$. ^1H NMR (60 MHz), IR, and mass spectra were recorded on Varian T-60, Perkin-Elmer 137, and Finnegan GC/mass spectrometers, respectively.

GC Analyses. All GC analyses were carried out with a Hewlett-Packard 5890 chromatography using 9 ft × 12 ft × 0.125 in. columns packed with 10% Carbowax 20M on Chromosorb W (100–120 mesh).

Materials. Borane–methyl sulfide (BMS) and 9-borabicycl-9[3.3.1]nonane (9-BBN) in THF were purchased from Aldrich Chemical Company and were estimated according to the standard procedure.[14] Tetrahydrofuran (THF) was distilled over benzophenone ketyl and stored under nitrogen atmosphere in an ampule. *N*-Benzyl-3-pyrroline and *N*-(*n*-butyl)-3-pyrroline were prepared from *cis*-1,4-dichloro-2-butene according to the literature procedures.[8,15] *N*-Methyl-3-pyrroline and *N*-(trimethylsilyl)-pyrroline (contains 25% of the corresponding pyrrolidine) were prepared from 3-pyrroline (containing 25% of the corresponding pyrrolidine) by similar literature procedure.[16] The internal standard, hexadecane (Phillips) was kept over 4-Å molecular sieves under atmosphere and used as such.

Disiamylborane[3] and diisopinocampheylborane[17] were prepared as described in the literature.

Hydroboration with BMS. A typical experiment is as follows. In a 25-mL flask equipped with a septum inlet, magnetic stirring bar, and connecting tube leading to a mercury bubbler was placed 0.32 g (2 mmol) of *N*-benzyl-3-pyrroline in 1.3 mL of THF. To it was added 0.05 g (0.2 mmol) of hexadecane. The reaction flask was cooled to 0 °C. To it was added 0.28 mL (2.66 mmol) of BMS (9.7 M) via syringe. The reaction mixture was kept at room temperature under stirring. The reaction was followed by taking 0.1-mL aliquots and hydrolyzing by adding them to a solution of THF/glycerol/3 N HCl (1:1:1) medium. The hydrogen evolved was measured and the residual hydride was calculated. After the completion of the reaction, the reaction mixture was oxidized by using 6 N sodium hydroxide and 30% hydrogen peroxide. After 5 h, the aqueous phase was saturated with anhydrous K_2CO_3 and was extracted with 3 × 5 mL of ethyl acetate. The crude reaction mixture was dried over anhydrous Na_2SO_4 and analyzed by GC. The percentage of the products was calculated by using a correction factor. The results are summarized in Table I.

N-Substituted-3-pyrrolidinols were isolated on doing the reaction on a 15-mmol scale.

Hydroboration with 9-BBN, Chx_2BH, and Sia_2BH. The reactions were done as described above for BMS.

Asymmetric Hydroboration of *N*-Benzyl-3-pyrroline. Diisopinocampheylborane [(−)-Ipc_2BH, derived from (+)-α-pinene, 50 mmol] in THF was cooled to −25 °C. To it was added 4 g (25 mmol) of *N*-benzyl-3-pyrroline via syringe. The reaction mixture was kept under stirring. After 24 h, the solid Ipc_2BH dissolves. The trialkylborane thus obtained was treated with 25 mL of 6 N sodium hydroxide, followed by 7.5 mL of 30% hydrogen peroxide at 0 °C. The reaction mixture was stirred at room temperature for 5 h. The aqueous layer was saturated with anhydrous potassium carbonate. The organic layer was separated and the aqueous layer was extracted with 3 × 25 mL of ethyl acetate. The combined organic extracts were mixed and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was subjected to column chromatography using silica gel; ether/pentane (1:1) eluents removed α-pinene and isopinocampheol, whereas, ether eluents yielded the required alcohol. It was further distilled to obtain GC pure material: bp 88–90 °C/1 mm [lit.[7] bp 83–84 °C/0.23 mm]; yield 3.9 g, 89%; $[\alpha]^{23}_D$ − 3.145° (*c* 1.2, chloroform), ~100% ee [lit.[10] $[\alpha]^{25}_D$ − 2.47° (*c* 1.175, chloroform, 84% ee]. IR, ^1H NMR, and mass spectra are in agreement with the structure.

Isolation of Diethyl (*N*-Benzyl-3-pyrrolidinyl)boronate. Ethyl (*N*-benzyl-3-pyrrolidinyl)boronate was prepared by the reaction of diisopinocampheyl(*N*-benzyl-3-pyrrolindinyl)borane (10 mmol) with 100% excess (2.3 mL, 40 mmol) of CH_3CHO. The reaction mixture was stirred at 25 °C for 24 h. The excess acetaldehyde and the solvent were pumped off under reduced pressure. The residue was taken in 10 mL of ether and cooled to 0 °C. To it was added 3 mL of dry HCl in ether (4 M), and the solution was stirred for 0.5 h. The solid obtained was filtered and washed with 2 × 10 mL of ether. The solid was suspended in 10 mL of ether and to it was added 1 mL of isopropylamine, the solution was stirred at room temperature for 3 h. The solid was filtered. The filtrate was concentrated to obtain boronate.

Acknowledgment. We gratefully acknowledge support from the National Institutes of Health (Grant GM 10937-23) in this research. We also acknowledge Professor M. M. Joullié calling to our attention the apparent discrepancy between her successful hydroboration of *N*-benzyl-3-pyrroline and our reported unsuccessful hydroboration of *N*-methyl-3-pyrroline.

Registry No. **3**, 554-15-4; **7**, 31970-04-4; **8**, 6913-92-4; **10**, 6831-60-3; 9-BBN, 280-64-8; $(CH_3)_2S \cdot BH_3$, 13292-87-0; *N*-benzyl-3-pyrrolidinol, 775-15-5; *N*-methyl-3-pyrrolidinol, 13220-33-2; *N*-butyl-3-pyrrolidinol, 51045-30-8; *N*-carbobenzyloxy-3-pyrrolidinol, 95656-88-5; diisiamylborane, 1069-54-1; diisopinocampheylborane, 64234-27-1; *N*-benzyl-3(*S*)-pyrrolidinol, 101385-90-4; diethyl (*N*-benzyl-3-pyrrolidinyl)boronate, 104351-33-9; diisopinocampheyl(*N*-benzyl-3-pyrrolidinyl)borane, 104351-84-0; dicyclohexylborane, 1568-65-6.

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A More Efficient Synthesis of DMPO-Type (Nitrone) Spin Traps

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Ever since its inception, the spin-trapping technique[1] has employed nitrones extensively[2] to detect and identify a wide range of reactive free radicals generated from a variety of chemical environments. The cyclic nitrone, 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO), introduced as a spin trap in the early seventies,[3] has been shown kinetically to be an effective scavenger of alkyl,[4] hydroxyalkyl,[5] as well as alkoxy[6] radicals. The marked ability of DMPO to intercept hydroxyl[7] and superoxide radicals,[7a,c]

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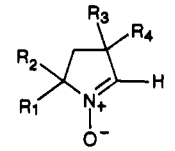
however, has been in large part responsible for its presently burgeoning useage, particularly in the biochemical/biomedical realm.[8] This aside, biological spin trapping with DMPO has unearthed several carbon-centred radicals (e.g., phenyl)[9] and very recently a number of a new heteroatom-centred species including the aminyl,[10] azidyl,[11] and sulfite anion[12] radicals, as well as alkylperoxyls[13] and alkylthiyls (e.g., cysteinyl).[14]

The current procedure to synthesize DMPO-type spin traps was devised several years ago by Todd and coworkers[15] and involves intramolecular condensation of aldehyde and hydroxylamine moieties to effect cyclic nitrone formation. The method calls for aldehyde protection/deprotection steps directly preceding and succeeding the zinc reduction of the nitro functionality. Protection of the nitro aldehyde proceeds in 75% yield while the nitro acetal is converted to the nitrone in a yield of 79% or only 59% overall (from the aldehyde). Failure to protect the aldehyde function reduces the overall yield to a mere 27%.[15] A recent report that described excellent yields for arylalkylnitrones,[16] modified from an earlier procedure for arylarylnitrones,[17] suggested to us that good yields of alkylalkylnitrones, such as DMPO, might also be attainable while avoiding the necessity of Todd's[15] aldehyde protection/deprotection steps.

Following this new procedure by Huie and Cherry,[16] with a few minor modifications (see Experimental Section), the crude nitrone (e.g., DMPO) was obtained in 94% yield (from the nitro aldehyde) which was >95% pure according to ^{1}H NMR. Distillation of the crude nitrone, a yellow oil, under reduced pressure provided the pure nitrone as a colorless, hygroscopic solid that melts around room temperature. The purified nitrone is suitable for spin-trapping studies because even concentrated solutions (e.g., 0.5 M) yield "clean" electron paramagnetic resonance (EPR) control spectra.

The general procedure described here improves the synthesis of DMPO analogues (see below) such as the water-soluble SCMPO (sodium 5-carboxy-5-methyl-1-pyrroline *N*-oxide)[18] and the lipid soluble RMPO series (e.g., 5-decyl-5-methyl-1-pyrroline *N*-oxide, DeMPO)[19] as well as the novel spiro nitrone, 5-spirocyclopentyl-1-pyrroline *N*-oxide (S_5PO)[20], or 1-azaspiro[4.4]-1-nonene N-oxide. This nitrone, purified by sublimation (25 °C, 0.05 torr), is a white crystalline solid, mp 80 °C, which is easier to handle than DMPO while its spin-trapping characteristics (e.g., spin-adduct spectra and spin-trapping rate constants) are essentially equivalent. For instance, the EPR hyperfine splitting constants for the methyl and hydroxyl adducts of S_5PO are, $a^N = 14.30$ $a_\beta^H = 20.22$ G (in benzene), and $a^N = a_\beta^H = 14.8$ G (in water), respectively. The rate constant for spin-trapping hydroxyl in water is approximately 1.0×10^9 M^{-1} s^{-1}. Other alicyclic nitrone spin traps such as 3,3,5,5-tetramethyl-1-pyrroline *N*-oxide (M_4PO)[21] as well as the hydrophobic derivative 5-octadecyl-3,3,5-trimethyl-1-pyrroline *N*-oxide (OMPO)[22] should also benefit from the good yields and relative ease of this general procedure.



structures of DMPO-type spin traps

$R_1 = R_2 = CH_3$, $R_3 = R_4 = H$ (DMPO)

$R_1 = CO_2^-Na^+$, $R_2 = CH_3$, $R_3 = R_4 = H$ (SCMPO)

$R_1 = n$-alkyl, $R_2 = CH_3$, $R_3 = R_4 = H$ (RMPO)

$R_1 + R_2 = (CH_2)_4$, $R_3 = R_4 = H$ (S_5PO)

$R_1 = R_2 = R_3 = R_4 = CH_3$ (M_4PO)

$R_1 = n$-octadecyl, $R_2 = R_3 = R_4 = CH_3$ (OMPO)

Experimental Section

5,5-Dimethyl-1-pyrroline *N*-Oxide. 4-Methyl-4-nitropentanal[23] (14.5 g, 0.1 mol) and (activated) zinc dust (13.1 g, 0.2 mol) were added to 300 mL of 95% ethanol that had been precooled to 2 °C. Under brisk mechanical stirring, glacial acetic acid (24 g, 0.4 mol) was added dropwise over a period of 1 h while maintaining the reaction temperature below 15 °C. The mixture was stirred vigorously for 2 h and stored in the refrigerator for 2 days (~1 °C). The sample was filtered to remove the zinc acetate. The zinc acetate was rinsed with 100 mL of ethanol and the combined ethanol portions were rotoevaporated. The crude nitrone was dissolved in 200 mL of dichloromethane which was washed twice with 50 mL of saturated sodium bicarbonate solution. The organic layer was dried with sodium sulfate and the solvent was rotoevaporated to give 10.7 g (94%) of the crude nitrone. Double distillation (bp 53 °C, 0.1 torr, lit.[15] bp 66 °C, 0.6 torr) provided 6.8 g (60%) of the pure nitrone as a white hygroscopic solid, not an oil as previously reported:[15] ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 6.80 (t, 1 H, vinyl, J = 2.8 Hz), 2.59 (td, 2 H, allyl, J = 7.2, 2.8 Hz), 2.14 (t, 2 H, methylene bound to quaternary C, J = 7.2 Hz), 1.43 (s, 6 H, methyls); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si) δ 132.4 (vinyl), 73.5 (quaternary), 34.1 (allyl), 25.3 (methylene bound to quaternary C), 24.4 (methyls).

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Registry No. 5,5-Dimethyl-1-pyrroline *N*-oxide, 3317-61-1; 4-methyl-4-nitropentanal, 57620-49-2; 5-spirocyclopentyl-1-pyrroline *N*-oxide, 104322-61-4; 4-cyclopentyl-4-nitropentanal, 104322-62-5; nitrocyclopentane, 2562-38-1; 2-propenal, 107-02-8.

trans-2,5-Dimethyl-2,5-bis(3-aminopropyl)-pyrrolidinyl-1-oxy: A *trans*-Diamino Azethoxyl Nitroxide

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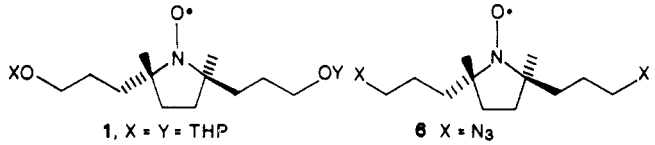
2,5-Disubstituted-2,5-dimethylpyrrolidinyl-1-oxy (azethoxyl[1]) nitroxides differ from most of the other stable nitroxide free radicals used in biophysical spin-labeling studies[2] and under evaluation as magnetic resonance imaging (MRI) contrast-enhancement applications[3] in two important ways. The canted nature of the nitroxide *z* axis with respect to the long molecular axis allows for the detection of restricted motion along this axis using ESR spin-labeling techniques.[4] In MRI applications, the azethoxyl nitroxide substitution pattern allows for the placement of functional groups in the vicinity of the paramagnetic nitroxide moiety. Certain of these groups might improve the resistance of the nitroxide group toward in situ reduction while enhancing the water-relaxing property of the nitroxide moiety. At present, nitroxide reduction seriously limits the use of nitroxides as MRI contrast-enhancing agents.[5] Herein, we describe the synthesis of the title *trans*-diamino azethoxyl nitroxide **7** from azethoxyl diol **3**.[6] The relative stability of **7** and several other nitroxides of novel structure toward reduction by liver homogenate, microsomes, and hepatocytes will be reported elsewhere.



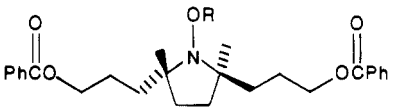
1, X = Y = THP
2, X = THP; Y = H
3, X = Y = H
4, X = Y = SO_2CH_3
5, X = Y = COPh

6 X = N_3
7 X = NH_2
8, X = NH_3^+; $HC_2O_4^-$

In our earlier study[6] diol **3** was obtained in variable yield by acid-catalyzed hydrolysis of a cis–trans mixture of bis(tetrahydropyranyl (THP) ether) **1**.[7] We now find that pure trans bis ether **1** can be obtained by careful chromatography of the mixture. This substance can be hydrolyzed to trans diol **3** consistently in 50–55% yield, accompanied by some starting **1** and mono derivative **2** which may be recycled.[8] More vigorous hydrolysis conditions, however, led to decomposition of the acid-sensitive nitroxide group.

Diol **3** was converted[9] into bis(methanesulfonate) **4**, but attempts to prepare diamine **7** directly from **4** using NH_3 in MeOH or THF in a pressure reactor[10] led to complex mixtures. Therefore, **4** was converted into bis azide **6**[11] which was then allowed to react with triphenylphosphine to give the corresponding bis(phosphinimine).[12] This was then hydrolyzed to the desired bis(amine) **7**, which was isolated and analyzed as the oxalate salt **8**.

The trans geometry of diol **3**, and hence of **7**, was established as follows. Diol **3** was converted into bis(benzoate) **5** which was then hydrogenated catalytically to *N*-hydroxy intermediate **9**. Esterification[1] of **9** with optically active Mosher's reagent[13] gave trifluoro ester **10**, which was shown to be a 1:1 mixture of diastereoisomers by the appearance of the methoxy groups as two singlets (δ 3.491 and 3.513) in the 360-MHz NMR spectrum. If ester **9** had been a cis azethoxyl nitroxide derivative, then it would have been a meso compound and it would have produced **10** as a single stereoisomer. The trans assignment of this series was confirmed by the observation of two singlets (δ −71.767 and −71.809) in a 1:1 ratio for the trifluoromethyl group in the ^{19}F NMR spectrum.



9, R = H
10, R = COC(OCH$_3$)(CF$_3$)Ph

Experimental Section[14]

***trans*-2,5-Dimethyl-2,5-bis[3-(tetrahydropyranyloxy)-propyl]pyrrolidinyl-1-oxy (1).** A cis–trans mixture (1.349 g) of **1** was prepared essentially as described.[6] The mixture was flash chromatographed over silica gel (5 g). Elution with 100 mL of hexane–ether, 3:2, gave 0.5005 g of *trans*-**1** (ESR, CH_2Cl_2, 3 lines, a_N = 14.5 G). Continued elution with this solvent (400 mL) followed by 100 mL of hexane–ether, 1:1, gave 0.638 g of the cis isomer (ESR, CH_2Cl_2, 3 lines, a_N = 14.5 G).

***trans*-2,5-Dimethyl-2,5-bis(3-hydroxypropyl)-pyrrolidinyl-1-oxy (3).** A solution containing 200 mg of **1**, 15 mg of *p*-toluenesulfonic acid monohydrate, 10 mL of MeOH, and 3 drops of water was stirred at 25 °C for 10 h. The reaction was monitored by TLC so as to maximize formation of **3**. Several drops of saturated $NaHCO_3$ were added and the mixture was evaporated to dryness. The residue was dissolved in CH_2Cl_2 and filtered through Celite. Evaporation gave 0.131 g of a mixture of **1**, **2**, and **3** which was flash chromatographed over silica gel (3 g). Elution with ether (65 mL) gave 52 mg of a mixture of **1** and **2**.

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(7) Compounds are racemic; only one enantiomer is shown. Each intermediate that bears a THP ether group is almost certainly a mixture of diastereoisomers owing the additional chiral center present in the THP ether grouping.
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