An Improved Synthesis of Homoproline and Derivatives

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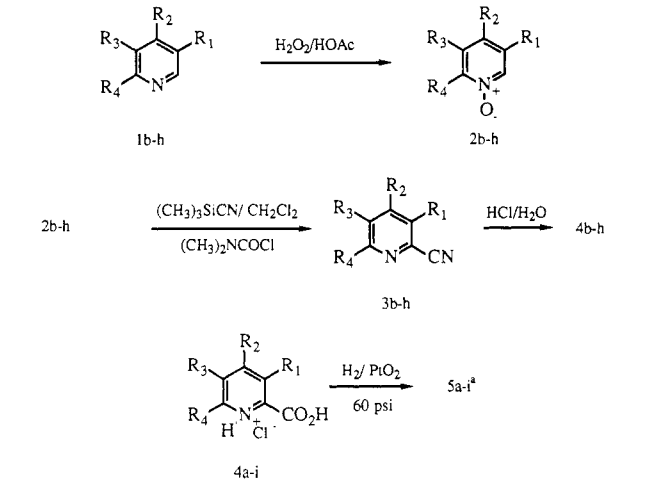
An improved, general synthesis of substituted homoprolines has been developed by using readily available substituted pyridines (1). A key step in this synthetic procedure involves the known conversion of pyridine *N*-oxides to 2-cyanopyridines (3) in nearly quantitative yields. The resulting nitriles are hydrolyzed to the corresponding pyridine-2-carboxylic acids (4). Subsequent reduction of the aromatic ring with PtO_2/H_2 gives the homoprolines (5) in good yields as racemic cis isomers. This procedure also can be utilized for the preparation of 5,6-benzohomoprolines from the appropriate quinoline precursors. The *N*-*tert*-butyloxycarbonyl (Boc) derivatives of these amino acids (useful intermediates for peptide synthesis) were also prepared in good yields.

The use of unnatural amino acids is becoming an important factor in peptide synthesis. Their incorporation into biologically relevant peptides can increase binding affinity to receptors, improve metabolic stability, or impart unique pharmacological properties. For example, substitution of D-alanine for glycine and *N*-methylmethionine amide for methionine in methionine enkephalin[1] resulted in an analogue with approximately a 100-fold increase in biological half-life. In addition, improved agonists or antagonists have been generated by substitution of D-amino acids at selected sites in LH-RH.[2] Thus, new and general routes for the synthesis of unnatural α-amino acids are of considerable importance.

We required the unnatural amino acid homoproline (sometimes called pipecolinic acid, or 2-carboxypiperidine) and closely related derivatives in order to complete a synthetic study of peptide-based enzyme inhibitors. Syntheses of homoprolines have been reported,[3-8] but these procedures generally suffer from low overall yields. In addition, many of these procedures involve a cyclization reaction, cumbersome reaction schemes, or extensive chromatographic purifications.

We now report an improved, general synthesis of substituted homoprolines. The key to this synthesis (Scheme I) is the selective 2-cyanation of pyridines and quinolines via the corresponding *N*-oxide.[9] By utilizing a modification of the Reissert–Henze reaction, reported by Fife,[10] high yields (nearly quantitative) of 2-cyanopyridines were obtained. The resulting nitriles were hydrolyzed to the corresponding pyridine-2-carboxylic acids (Table I). Subsequent reduction of the aromatic ring with platinum oxide gave the homoprolines in good yields[11] (Table II).

Scheme I



compound	R_1	R_2	R_3	R_4
4-5a	H	H	H	H
1-5b	H	H	H	Me
1-5c	Me	H	H	H
1-5d	H	Me	H	H
1-5e	H	Et	H	H
1-5f	H	MeO	H	H
1-5g	H	t-Bu	H	H
1-5h	H	Me	b	b
4-5i	H	H	b	b

[a] All compounds isolated as HCl salt except **5a** and **5i**, which were prepared from the pyridine and quinoline carboxylic acids. For simplicity the stereochemistry is represented as the L-cis isomers; however, the synthesis gives the racemic cis isomers. [b] Fused ring.

In this fashion 3-, 4-, and 6-substituted homoprolines were generated.

Several limitations of this procedure should be noted. The Fife modification has been reported to give exclusively the 2-cyano-3-substituted-pyridines when 3-substituted pyridine *N*-oxides are used as starting material. Therefore, 5-monosubstituted homoprolines are not directly available by this procedure. Attempted preparation of 4-methoxyhomoproline, **5f**, by reduction of **4f** resulted in generation of a mixture of two amino acids. Amino acid analysis of the crude reduction product gave two peaks, one of which coeluted with the desmethoxy compound (homoproline).

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(11) While this work was in progress a synthesis of the series of 3- and 4-(phosphonoalkyl)pyridine- and -(phosphonoalkyl)piperidine-2-carboxylic acids (as NMDA antagonists) was reported using the same general experimental protocol: Ornstein, P. L.; Schaus, J. M.; Chambers, J. W.; Huser, D. L.; Leander, J. D.; Wong, D. T.; Paschal, J. W.; Jones, N. D.; Deeter, J. B. *J. Med. Chem.* **1989**, *32*, 827.

0022-3263/90/1955-0738$02.50/0

Table I. Physical Data of Substituted Pyridine-2-carboxylic Acid Hydrochlorides

compd	mp, °C	yield, %	^{1}H NMR (DMSO-d_6/external TSP) δ (ppm)
4b	204–205	96	2.60 (s, 3 H), 7.65 (b d, 1 H), 7.98 (b d, 1 H), 8.05 (m, 1 H)
4c	206–207	80	2.50 (s, 3 H), 7.65 (dd, 1 H), 7.95 (d, 1 H), 8.60 (d, 1 H)
4d	188–190	93	2.50 (s, 3 H), 7.80 (d, 1 H), 8.15 (s, 1 H), 8.70 (d, 1 H)
4e	173–175	61	1.25 (t, 3 H), 2.85 (q, 2 H), 7.85 (dd, 1 H), 8.20 (s, 1 H), 8.75 (d, 1 H)
4f	148–150	71	4.10 (s, 3 H), 7.55 (dd, 1 H), 7.80 (d, 1 H), 8.70 (d, 1 H)
4g	208–209	73	1.38 (s, 9 H), 8.02 (dd, 1 H), 8.25 (s, 1 H), 8.78 (d, 1 H)
4h	210–212	75	2.85 (s, 3 H), 7.82 (ddd, 1 H), 7.95 (ddd, 1 H), 8.10 (s, 1 H), 8.20–8.30 (d, 2 H)

The ratio of homoproline to **5f** was estimated to be 2:1 by integration of the 4-MeO resonance in the ^{1}H NMR spectrum. Varying the amount of catalyst and reaction times failed to improve this result. The reaction of 4-methyl-2-quinolinecarboxylic acid to give compound **5h** resulted in a product which was contaminated with an equal amount of the completely saturated material. Attempts to prevent this over reduction were unsuccessful.

Several of the homoprolines generated by this procedure were converted to their corresponding *N-tert*-butyloxycarbonyl (Boc) derivatives (Table III). When attempts were made to protect the amino group of **5b** the yields were unacceptably poor (i.e. 1% of Boc-**5b** was isolated and judged pure by ^{1}H NMR spectroscopy), presumably due to steric hindrance by the methyl substituent at C_6. The attempted preparation of Cbz-**5b** using standard proce-

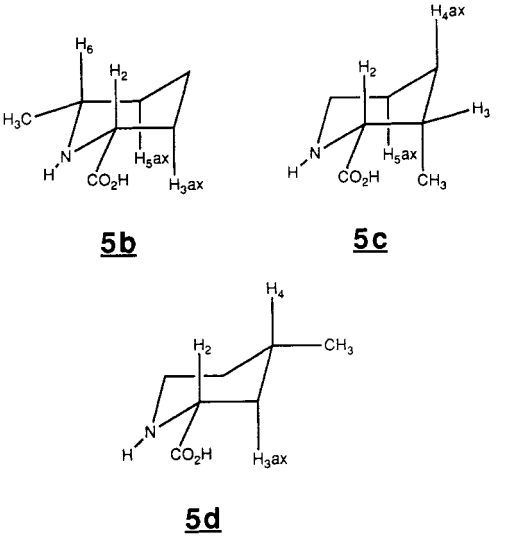

Figure 1.

Table II. Physical Data on Substituted DL-Homoproline Hydrochlorides

product	conditions for hydrogenation[a]	yield,[b] %	mp, °C	elemental analysis: found (calcd) C	H	N	MS *m/e* (MH^+)	^{1}H NMR (D_2O/external TSP) δ (ppm)
5a	5 h/H_2O	100	265–266[c]	55.60 (55.80)	8.34 (8.58)	10.54 (10.84)	130	1.40–1.80 (m, 5 H), 2.10 (dd, 1 H), 2.80 (t, 1 H), 3.30 (d, 1 H), 3.85 (dd, 1 H)
5b	24 h/EtOH–H_2O	87	247–249	46.82 (47.07)	7.56 (7.34)	8.01 (7.84)	144	1.37 (d, 3 H), 1.44 (m, 1 H), 1.65 (t, 2 H), 1.97 (s, 1 H), 1.98 (m, 1 H), 2.33 (b d, 1 H), 3.30 (m, 1 H), 3.92 (dd, 1 H)
5c	24 h/EtOH–H_2O	85	281–282	46.84 (47.07)	7.55 (7.34)	7.92 (7.84)	144	1.03 (d, 3 H), 1.70–1.90 (m, 4 H), 2.61 (m, 1 H), 3.02 (m, 1 H), 3.45 (dd, 1 H), 4.07 (d, 1 H)
5d	24 h/EtOH–H_2O	92	259–261	47.05 (47.07)	7.87 (7.34)	7.64 (7.84)	144	1.03 (d, 3 H), 1.33 (m, 1 H), 1.39 (m, 1 H), 1.84 (m, 1 H), 1.93 (d, 1 H), 2.33 (dd, 1 H), 3.06 (ddd, 1 H), 3.50 (m, 1 H), 3.94 (dd, 1 H)
5e	24 h/EtOH–H_2O	100	250–251	49.80 (49.61)	8.11 (8.33)	7.22 (7.23)	158	0.95 (t, 3 H), 1.30–1.45 (m, 4 H), 1.65 (m, 1 H), 2.00 (b d, 1 H), 2.40 (b d, 1 H), 3.05 (ddd, 1, H), 3.55 (m, 1 H), 3.94 (dd, 1 H)
5f	24 h/EtOH–H_2O	90[d]					130, 160	
5g	24 h/EtOH–H_2O	84	261–263	53.83 (54.17)	8.91 (9.09)	6.87 (6.31)	186	1.20 (s, 9 H), 1.70–1.90 (m, 3 H), 2.28 (b d, 1 H), 2.70 (b d, 1 H), 3.30 (m, 1 H), 3.85 (b d, 1 H), 4.18 (m, 1 H)
5h	4 h/HOAc	40[e]					192, 198	
5i	2 h/HOAc	81	193–194	45.33 (45.11)	6.11 (6.39)	5.16 (5.26)[f]	177	2.25 (m, 1 H), 2.55 (m, 1 H), 2.95–3.15 (m, 2 H), 4.41 (dd, 1 H), 7.30–7.50 (m, 4 H)

[a] 60 psi, 60 °C, PtO_2/H_2. [b] Isolated yield of PtO_2/H_2 reduction. [c] Zwitterion prepared from pyridine-2-carboxylic acid, lit.[19] mp 258–261 °C. [d] Reduction gave a mixture of expected product plus des-methoxy compound in approximtely a 1 to 2 ratio (estimate from ^{1}H NMR of 4-MeO resonance). [e] Mixture of expected product and completely reduced compound. [f] Zwitterion prepared from 2-quinolinecarboxylic acid, analyzed for 3 mol of H_2O.

Table III. Physical Data of Boc-DL-homoprolines

compd	mp, °C	yield, %	MS *m/e* (MH^+)	elemental analysis: found (calcd) C	H	N
Boc-**5a**	128–129[a]	74	231	57.42 (57.63)	8.19 (8.35)	6.36 (6.11)
Boc-**5c**	107–109[b]	25	244	67.67 (67.89)	10.68 (10.45)	6.67 (6.60)
Boc-**5d**	68–70	66	244	59.52 (59.24)	8.91 (8.70)	5.82 (5.76)
Boc-**5e**	161–162[b]	73	258	68.54 (68.45)	10.62 (10.57)	6.25 (6.38)
Boc-**5g**	105–106	68	286	62.93 (63.13)	9.57 (9.54)	4.89 (4.91)
Boc-**5i**	128–130[b]	33	277	70.34 (70.71)	9.01 (9.23)	6.53 (6.11)

[a] Boc-L-hPro: lit.[7] mp 123–124 °C; Boc-D-hPro: lit.[20] mp 123 °C. [b] Dicyclohexylamine salt.

dures[12] gave similar results to that of Boc-**5b**.

The sterochemistry of the disubstituted amino acids **5b**, **5c**, and **5d** was examined by ^{1}H NMR decoupling and NOE experiments at 500 MHz. Compound **5b** shows couplings of 12.07 Hz between H-2 and H-3$_{ax}$ and 11.40 Hz between H-5$_{ax}$ and H-6 (Figure 1). The magnitude of these couplings require that both methines (H-2 and H-6) occupy axial orientations, assuming a chair-like conformation for the piperidine ring. This allows only a cis configuration for **5b**. In compound **5c** the coupling between H-2 and H-3 is 4.07 Hz. The resonances of the 4 and 5 methylenes are overlapped and cannot be specifically assigned. However, there are NOE's from H-2 and 3-Me to these resonances which can be assigned to the following pairs of resonances, H-2/H-4$_{ax}$ and 3-Me/H-5$_{ax}$. Taken collectively, this data indicates that a cis configuration is also present and that H-2 is axial and H-3 is equatorial. In the case of compound **5d** the couplings of 13.08 and 12.07 Hz between H-2 and H-3$_{ax}$ and H-3$_{ax}$ and H-4, respectively, are observed. Thus, in a similar fashion to **5b**, a cis configuration is indicated.[13]

The amino acids generated by this synthetic protocol are racemic (DL-cis) due to the nonstereoselective nature of the final hydrogenation step.[14] However, procedures have been published for the chemical[15] or enzymatic[16] resolution of DL-α-amino acids. Furthermore, the use of racemic amino acids during peptide synthesis results in a pair of diastereomeric peptides which often are separable by reversed-phase HPLC techniques.[17]

In summary, the present method for the synthesis of substituted homoprolines will allow the ready access to this class of unnatural amino acids. This procedure uses inexpensive reagents, generally gives high yields, and eliminates the need for chromatographic purifications. Furthermore, Boc-substituted homoproline analogues, which are valuable derivatives for use in peptide synthesis, can be prepared by standard procedures.

Experimental Section

^{1}H NMR spectra were recorded with a General Electric QE-300 at 300 MHz or a Bruker AM500 at 500 MHz in D_2O using external TSP as a reference. Field desorption mass spectra were obtained by using a Varian MAT 731. Amino acid analyses were performed on a Beckman System 6300 high-performance amino acid analyzer equipped with a 3 mm × 20 cm column of cation exchange resin (Na^+ form). Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All reagents used in this study were obtained from commercial sources and used without additional purification.

The Preparation of *N*-Oxides. Typical Procedure: 4-Ethylpyridine *N*-Oxide (2e). Prepared by the method of Taylor and Crovetti.[18] 4-Ethylpyridine (32.1 g, 0.3 mol) was dissolved in glacial acetic acid (200 mL), 30% hydrogen peroxide (34 mL, 0.3 mol) was added, and the reaction mixture was refluxed for 24 h. The reaction mixture was concentrated in vacuo, and the resulting solid (36.9 g, 100%) was used without further purification or characterization.

The Preparation of 2-Cyanopyridines. Typical Procedure: 2-Cyano-4-ethylpyridine (3e). Prepared by the method of Fife.[10] 4-Ethylpyridine *N*-oxide, **2e** (24.6 g, 0.2 mol), was dissolved in dichloromethane (200 mL), dried over anhydrous $MgSO_4$, and added to trimethylsilyl cyanide (25 g, 0.253 mol) at room temperature. Dimethylcarbamyl chloride (23.2 mL, 0.253 mol) in dichloromethane (50 mL) was added dropwise with stirring to the reaction mixture over a 30-min period. The reaction mixture was stirred at room temperature for 24 h. A solution of 10% aqueous potassium carbonate (200 mL) was added dropwise, and stirring was continued for 10 min. The organic layer was separated, and the aqueous layer was extracted two times with dichloromethane (2 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to obtain **3e** (26 g, 98%) as an off-white solid. ^{1}H NMR, TLC, and FD mass spectral analysis indicated that **3e** was of greater than 90% purity and was used without further purification.

Hydrolysis of 2-Cyanopyridines. Typical Procedure: 2-Carboxy-4-ethylpyridine Hydrochloride (4e). A 250-mL round-bottomed flask was charged with **3e** (29 g, 0.22 mol) and 100 mL of 6 N HCl, and the reaction mixture was refluxed for 24 h. The reaction mixture was concentrated in vacuo, and the residue was crystallized from acetonitrile and recrystallized once from water/acetonitrile to give **4e** as a white solid (25.1 g, 61.2%) (see Table I for physical data).

Reduction of 2-Carboxypyridines. Typical Procedure: 4-Ethyl-DL-homoproline Hydrochloride (5e). A solution of **4e** (9.4 g, 0.05 mol) in ethanol–water (1:1, 100 mL) was reacted with hydrogen over platinum oxide (5 g) at 60 psi in a Parr shaker apparatus at 60 °C for 24 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was dissolved in water, treated with decolorizing carbon (5 g), filtered, and concentrated to dryness in vacuo to give pure **5e** (9.6 g, 100%) (see Table II for physical data).

The Preparation of Boc Amino Acids. Typical Procedure: 4-Ethyl-Boc-DL-homoproline (Boc-5e). A solution of **5e** (9.6 g, 0.05 mol) was dissolved in 2 N sodium hydroxide (50 mL, 0.1 mol) and *tert*-butyl alcohol (50 mL), and di-*tert*-butyl dicarbonate (13.1 g, 0.06 mol) was added to the reaction mixture. The pH was maintained at 9.5 with the addition of a small amount of 2 N sodium hydroxide during the first 2 h of reaction. After 24 h at room temperature the bulk of the *tert*-butyl alcohol was evaporated, and the resulting aqueous solution was extracted once with diethyl ether. The aqueous layer was separated and acidified with 2 N hydrochloric acid to pH 2.0 and extracted with ethyl acetate (2 × 100 mL). The extracts were dried over magnesium sulfate and concentrated to dryness in vacuo. The resulting oil was dissolved in diethyl ether (150 mL), and dicyclohexyl amine (9.9 g, 0.05 mol) was added to the solution. After standing at 4 °C (16 h) the precipitate was filtered washed with diethyl ether (2 × 25 mL) and dried in vacuo to afford pure product (16.1 g, 73%) (see Table III for physical data).

Acknowledgment. We thank Juel DeHoniesto for expert technical assistance (^{1}H NMR decoupling and NOE experiments), Dr. Douglas E. Dorman for discussions concerning ^{1}H NMR spectra, and Robert M. Ellis and Norman L. Holbrook for amino acid analysis data and discussions.

Registry No. **1b**, 109-06-8; **1c**, 108-99-6; **1d**, 108-89-4; **1e**, 536-75-4; **1f**, 620-08-6; **1g**, 3978-81-2; **1h**, 491-35-0; **2b**, 931-19-1; **2c**, 1003-73-2; **2d**, 1003-67-4; **2e**, 14906-55-9; **2f**, 1122-96-9; **2g**, 23569-17-7; **2h**, 4053-40-1; **3b**, 1620-75-3; **3c**, 20970-75-6; **3d**, 1620-76-4; **3e**, 92486-38-9; **3f**, 36057-44-0; **3g**, 42205-73-2; **3h**, 10590-69-9; **4a**, 636-80-6; **4b**, 87884-49-9; **4c**, 123811-72-3; **4d**,

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(13) The cis configuration was proven for a similar series of compounds (See ref 11).
(14) To obtain all four possible isomers (i.e. DL-cis and DL-trans) the reduction step can be carried out with nickel–aluminum alloy in the presence of 1 M KOH (See Lunn, G. *J. Org. Chem.* **1987**, *52*, 1043). In this fashion, 2-carboxy-4-methylpyridine hydrochloride, **4d**, was reduced to give a 60:40 mixture (estimate from integration of the 4-methyl resonances in the ^{1}H NMR) of the DL-cis, **5d**, and the DL-trans isomers.
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123811-73-4; **4e**, 79415-18-2; **4f**, 123811-74-5; **4g**, 123811-75-6; **4h**, 123811-76-7; **4i**, 89047-45-0; **5a**, 4043-87-2; BOC-**5a**, 98303-20-9; **5b**, 123878-70-6; **5c**, 123811-77-8; BOC-**5c**·DCHA, 123834-10-6; **5d**, 123878-71-7; BOC-**5d**, 123811-83-6; **5e**, 123811-78-9; BOC-**5e** (free acid), 123811-84-7; BOC-**5e**·DCHA, 123811-85-8; **5f**, 123811-79-0; **5g**, 123811-80-3; BOC-**5g**, 123811-86-9; **5h**, 123811-81-4; hexahydro-**5h**, 123811-89-2; **5i**, 123811-82-5; BOC-**5i**·DCHA, 123811-88-1.

Stereospecific Reductive Desulfurization of Vinyl Sulfoxides with *tert*-Butyllithium and an Internal Proton Source

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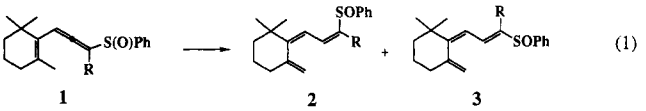
Trienyl and allenyl phenyl sulfoxides can be reduced stereospecifically with retention of configuration in good yields using *tert*-butyllithium with methanol (MeOH) as an internal (in situ) proton source. The method can be easily modified to give stereospecifically deuterium-labeled compounds. While simple monoene sulfoxides afford attenuated yields of reduced olefin, the method is useful for the reduction of the more sensitive and complex polyene sulfoxides as exemplified by the reduction of trienyl sulfoxides **2b**, **3b**, and **9** and allenyl sulfoxide **10** and by a brief review of additional examples which have emerged from this laboratory. That the reaction proceeds through the direct protonation of sulfurane intermediates such as **35** or **35'** is an attractive mechanistic hypothesis, but several other possibilities exist. A pathway involving a vinyllithium as a reactive intermediate is considered to be less likely.

Vinylallene sulfoxide **1** undergoes a facile sigmatropic [1,5]-hydrogen shift to afford triene sulfoxides **2** and **3** with the former *Z* sulfoxide predominating (eq 1).[1] The resulting triene sulfoxide necessarily has a (3*Z*)-1,3,5-hexatriene unit because of the intramolecular, cyclic nature of the process, but the ability of the phenylsulfinyl group to effect selective formation of geometric isomer **2** was unexpected. Nonetheless, this feature, in conjunction with the mild conditions required for the vinylallene variant[2] of the [1,5]-shift, was anticipated to be useful for polyene syntheses in general. The phenylsulfinyl group renders this route especially attractive because it represents a functional group which might be manipulated for further synthetic transformation. For example, if a vinyl sulfoxide could be converted stereospecifically to a vinyllithium compound, then the utility of this kind of substrate in synthesis could be greatly expanded.

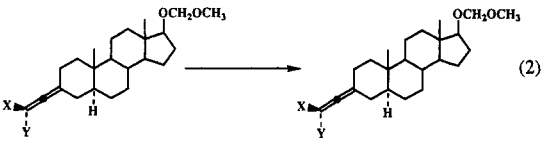


(1)

1 **2** **3**

a, R=H
b, R=CH_3

In earlier independent studies, Johnson and Durst reported the preparation of dialkyl sulfoxides, R'S(O)R, from aryl alkyl sulfoxides, ArS(O)R, by treatment with 4 equiv of the alkyllithium reagent R'Li at −78 °C.[3] It was suggested that the cleavage reaction proceeded by attack of R'Li on the sulfoxide in an S_N2-like fashion with expulsion of ArLi. Consistent with this hypothesis was the fact that essentially complete inversion of configuration at sulfur was observed (except in the case of *t*-BuLi). In a subsequent report, Neef and co-workers reported that allene sulfoxides could be desulfurized with retention of configuration in good yields with 4 equiv of CH_3Li (eq 2).[4] It was suggested that the reaction proceeded via formation of an allenyl anion, which was subsequently protonated.



(2)

4a, X = S(O)Ph; Y = CH_3
b, X = CH_3; Y = S(O)Ph

5a, X = H; Y = CH_3
b, X = CH_3; Y = H

Thus, based on these studies, it appeared feasible that formation of a vinyl anion (i.e., a vinyllithium species) could be achieved by reaction of a vinyl sulfoxide with excess RLi. In initial exploratory studies, we observed that treatment of **2b** with a variety of alkyllithium reagents in ether followed by proton quenching afforded a complex array of products and/or modest yields of triene **6a**. For example, when an ethereal solution of **2b** at −78 °C was treated with 3–4 equiv of *tert*-butyllithium in pentane followed by quenching with methanol, the hydrocarbon **6a** was obtained in only 47% yield at best. By contrast, it was serendipitously (but logically) discovered that when *tert*-butyllithium was added to an ethereal solution of **2b** containing methanol as an in situ proton source at −78 °C, the reduced hydrocarbon was obtained in significantly improved yields (72%) (eq 3). The observations that a deuterium label could be incorporated by simply employing methanol-d_1 (MeOD) as the in situ deuteron source and that an analogous transformation of **3b** to **8a** or **8b** (eq 4) render this procedure especially useful. From a mechanistic standpoint, it was particularly interesting of course that *tert*-butyllithium reacted with sulfoxide competitively with the proton source methanol. Accordingly,

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