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Conversion of Chiral Amino Acids to Enantiomerically Pure α-Methylamines[1]

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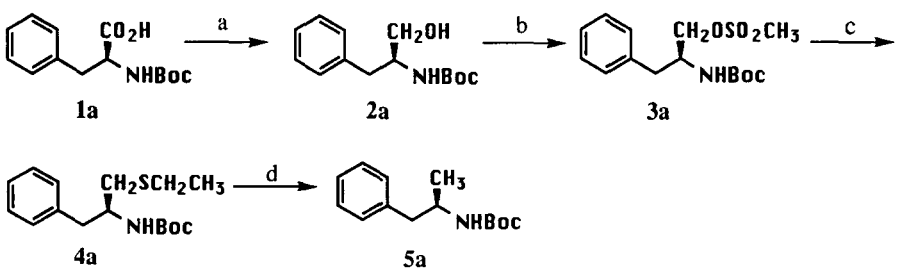
Abstract: *Enantiomerically enriched α-methylamines are obtained in high yield by Raney nickel reduction of N-Boc-protected, amino acid-derived thioethers.*

α-Methylamines, particularly those which might be derived from enantiomerically pure α-amino acids, are important targets in the synthesis of biologically active compounds.[2] The use of α-amino acids as starting materials in the synthesis of these amines, however, is precluded by the rigorous reaction conditions typically employed for the conversion of carboxyl groups to methyl groups.[3] With few exceptions, these conditions provide only modest yields or are incompatible with amino acids bearing acid or base-sensitive functionality. This report describes an efficient preparation of enantiomerically pure (≥98% ee) N-Boc-α-methylamines from the corresponding chiral amino acids.

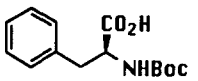
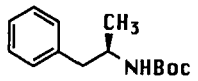
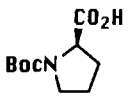
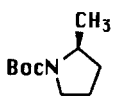
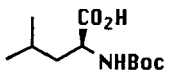
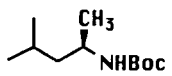
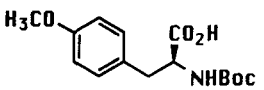
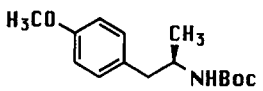
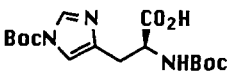
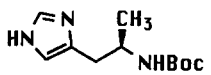
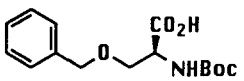
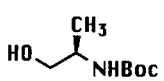
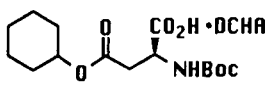
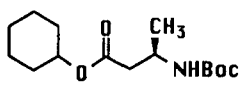
Raney nickel is a commonly used reagent for the desulfurization of thioethers.[4] Woo has also demonstrated the utility of this reaction in the synthesis of chiral, N-Boc-protected statine.[5] A similiar use was envisioned for reduction of N-Boc-protected thioethers **4a-g**, prepared from chiral amino acids **1a-g**, via a modification of the optically active taurine synthesis described by Ienaga and coworkers.[6] An illustrative synthesis of N-Boc-(R)-(+)-amphetamine is shown in Scheme 1.

Scheme 1[a]



[a] Reagents and conditions: a) BH_3·THF, 0°C, 2.5h; b) CH_3SO_2Cl, TEA, CH_2Cl_2, 0°C, 1h; c) NaH, THF, CH_3CH_2SH, 67°C, 2h; d) Ra-Ni, EtOH/H_2O, 70°C, 24h.

Table 1 Amino Acid-Derived α-Methylamines

Entry	Amino Acid	α-methylamine [7]	% Yield (4 steps)
a			95
b			94
c			88
d			97
e			88
f			96
g			76

The results are summarized in Table 1. Commercialy available N-Boc-α-amino acids **1a-g** were converted to the corresponding amino alcohols **2a-g** by treatment with 2.5 equivalents of diborane in THF.[8] The yields of this conversion ranged from 90 to 100%, depending on the nature of the amino acid side chain present. Entries **1d-g** provided the lower range yields, presumably due to irreversible ligation of the heteroatom-containing side chains with the reducing agent. Treatment of **2a-g** with 1.1 equivalents of methane sulfonyl chloride in the presence of base provided the mesylates **3a-g**.[9] These yields (88-97%) were notably dependent on the reaction conditions used but were optimized using triethylamine, dry (4Å sieves) CH_2Cl_2 and temperatures between -5 and 0°C. The conversion of **3a-g** to thioethers **4a-g** was effected with 3 equivalents of sodium thioethoxide in refluxing THF.[10] Formation of thioether **4e** was accompanied by deprotection of the imidazoyl side chain of **3e**. Raney nickel reduction of **4a-g** in refluxing ethanol/water gave the title N-Boc-α-methylamines **5a-g** in quantitative yields[11] with ee's ≥98%.

The enantiomeric purities of **5a-g** were confirmed by 300 MHz ^{1}H NMR analysis of the Mosher amide derivatives in $CDCl_3$.[12] (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid adducts of racemic α-methylamines, prepared under standard coupling conditions (1-ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride, 1-hydroxybenzotriazole), display well-separated α-methoxy proton absorbances. These diastereomeric proton signals were not observed for Mosher amides prepared from **5a-g** in over 90% yield. Thus the sequence described herein proceeds with retention of optical purity.

Scheme 1 represents a widely applicable means through which chiral amino acids are converted to enantiomerically pure α-methylamines. The deprotection of amino acid side chains of mesylate **3e** and thioether **4f** are noted as limitations of this method. Mild reaction conditions, suitable for milligram or multigram scale, allow a powerful alternative choice of routes to these ubiquitous structural intermediates.

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References and notes:

1. Preliminary results of this work were presented at the 205th National American Chemical Society Meeting in Denver, CO., March 28-April 2, 1993. Abstract Number 258.
2. Some representative examples include: (a) Gorczynski, R. J.; Anderson, W. G.; Stout, D. M. *J. Med. Chem.* **1981**, *24*, 835; (b) Yamanouchi Pharmaceutical Co., *US 4,703,063* **1987**; (c) Ye, Q.; Grunewald, G. L., *J. Med. Chem.* **1989**, *32*, 478; (d) Nichols, D. E.; Snyder, S. E.; Oberlender, R.; Johnson, M. P.; Huang, X. *Ibid.*, **1991**, *34*, 276; (e) Bennion, C.; Brown, R. C.; Cook, A. R.; Manners, C. N.; Payling, D.W.; Robinson, D. H. *Ibid.*, **1991**, *34*, 439; (f) Lipp, R.; Arrang, J.-M.; Garbarg, M.; Luger, P.; Schwartz, J.-C.; Schunack, W. *Ibid.*, **1992**, *35*, 4434; (g) Salvadori, S.; Bryant, S. D.; Bianchi, C.; Balboni, G.; Scaranari, V.; Attila, M; Lazarus, L. H. *Ibid.*, **1993**, *36*, 3748; (h) Lai, J-Y.; Wang, F-S.; Guo, G-Z.; Dai, L-X. *J. Org. Chem.* **1993**, *58*, 6944; (i) Vollinga, R. C.; de Koning, J. P.; Jansen, F. P.; Leurs, R.; Menge, W. M. P. B.; Timmerman, H. *J. Med. Chem.* **1994**, *37*, 332.
3. *Comprehensive Organic Transformations*; Larock, R. C.; VCH Publishers: New York, **1989**.
4. Other examples include: (a) Fleming, I.; Perry, D. *Tetrahedron* **1981**, *37*, 4027; (b) Vedejs, E.; Arnost, M. J.; Eustache, J. M.; Krafft, G. A. *J. Org. Chem.* **1982**, *47*, 4386; (c) Bravo, P.; Resnati, G.; Angeli, P.; Frigerio, M.; Viani, F.; Arnone, A.; Marucci, G.; Cantalamessa, F. *J. Med. Chem.* **1992**, *35*, 3102.
5. Woo, P. W. K. *Tetrahedron Lett.* **1985**, *26*, 2973-2976.
6. Higashiura, K.; Morino, H., Matsuura, H.; Toyomaki, Y.; Ienaga, K. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1479.
7. Proton NMR, mass spectral and combustion analyses were consistent with the assigned structures for all bulk final products for which yields are reported.
8. A mechanically stirred solution of Boc-Tyr, **1d**, (30.0 g, 101 mmol) in THF (337 mL) at 0°C was treated over 1h with 1M BH_3·THF (254 mL). Upon complete addition, the ice bath was removed and the solution was stirred at room temperature until the starting material was consumed as indicated by TLC ($CHCl_3$,CH_3OH,HOAc, 90:8:2). The reaction was cooled to 0°C and quenched over 1h by the dropwise addition of brine. The layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered and concentrated to provide 28.4 g (100%) of **2d**. Alcohols **2a** (100%), **2b** (99%), **2c** (100%), **2e** (93%), **2f** (97%) and **2g** (90%) were likewise obtained using this procedure.
9. A solution of **2d** (28.0 g, 99.5 mmol) and triethylamine (28 mL, 199 mmol) in CH_2Cl_2 (330 mL) at -3°C was treated over 2.5h with methane sulfonyl chloride (8.5 mL) in CH_2Cl_2 (8.5 mL). The resulting brown slurry was stirred for an additional 2.5h. All volatiles were removed under high vacuum (0.1 mm Hg) at 25°C. The residue was taken up in ethyl acetate and washed succesively with 0.1N HCl, 5% $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and reduced to provide a brown oil. Chromatography of the oil on silica gel with ethyl acetate/hexane provided 34.7 g (97%) mesyl ester **3d**. Esters **3a** (95%), **3b** (95%), **3c** (88%), **3e** (95%), **3f** (99%) and **3g** (88%) were likewise obtained using this procedure.
10. **3d** (34.0 g, 94.6 mmol) in THF (95 mL) was added to a mechanically stirred suspension of sodium thioethoxide (31.8 g, 378 mmol, prepared *in situ* from NaH and CH_3CH_2SH) in THF (500 mL) at room

temperature. The mixture was warmed to reflux for 2h, cooled and quenched with brine. The layers were separated, and the aqueous layer was washed twice with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered through a pad of silica gel and reduced to provide 30.8 g (100%) of thioether **4d**. Thioethers **4a** (100%), **4b** (100%), **4c** (100%), **4e** (100%) and **4g** (96%) were likewise obtained using this procedure. *CAUTION: ethanethiol is volatile and has an obnoxious odor! It should be used in an efficient fume hood.*

11. To Raney nickel (54.1 g, 922 mmol) in water (54.1 mL) was added a solution of **4d** in ethanol (184 mL).The mixture was refluxed for 18h, cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated to approximately one half of its original volume, saturated with NaCl, and extracted twice with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered through a pad of silica gel and concentrated to provide 24.5 g (100%) of α-methyl amine **5d**. **5a** (100%), **5b** (100%), **5c** (100%), **5e** (100%), **5f** (100%) and **5g** (100%) were likewise obtained using this procedure.
12. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org Chem.* **1969**, *34*, 2543.

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