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REDUCTION OF AMINO ACIDS TO AMINO ALCOHOLS. A COMPARISON OF VARIOUS METHODS WITH REGARD TO POTENTIAL RACEMIZATION

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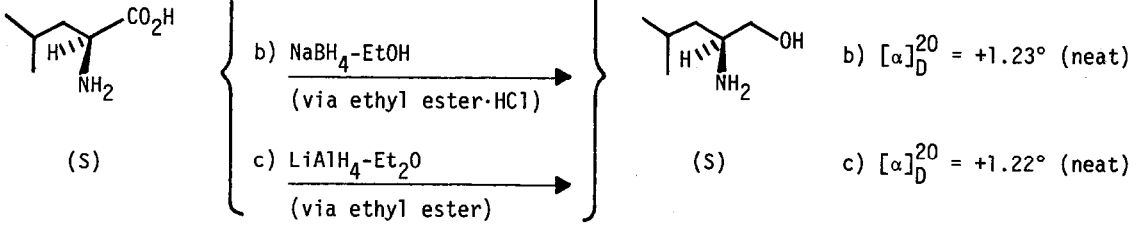
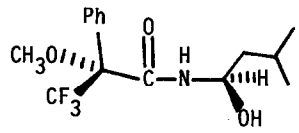
The reduction of naturally occurring amino acids has been reported using lithium aluminum hydride,[2] sodium borohydride[3] and borane-dimethylsulfide-BF_3.[4] Because of our need for chiral amino alcohols as reagents in asymmetric synthesis,[5] we prepared S-leucinol[6] using the borane reagent.[7] However, comparison of the rotation of leucinol with that obtained using lithium aluminum hydride[2] indicated a large variation although samples from the three reduction methods were determined to be >98% chemically pure (glc, nmr) (Scheme 1). The higher $[\alpha]_D$ for leucinol from the

SCHEME 1



borane reduction suggested that the other two methods may have proceeded with considerable racemization. That this was not the case was proven by ^{19}F-nmr of the Mosher amides (1)[8] which exhibited clean ^{19}F signal separations (~8 Hz) for racemic leucinol as its amide.[9] The leucinol derived from reduction of (S)-leucine using all three methods gave only a single sharp ^{19}F-signal indicating that none of these reduction methods was accompanied by any significant degree of racemization and the discrepancies in $[\alpha]_D$ are due to trace impurities. This technique has also been used to assess enantiomeric purities of other amino alcohols[10] derived from reduction of amino acids and the ^{19}F-spectra indicated no racemization regardless of the method employed. In most cases, however, the $[\alpha]_D$ varied from 50-200% suggesting that ^{19}F-nmr techniques are much more reliable than optical methods for determining % ee in this series of compounds.[10,11,12]



1

Reaction	^{19}F (CF_3)	Integration
(S)-leucine ethyl ester·HCl + $NaBH_4$	688 Hz	99±1
(S)-leucine ethyl ester + $LiAlH_4$	688 Hz	99±1
(S)-leucine + $BH_3 \cdot Me_2S$	688 Hz	99±1
(R,S)-leucine ethyl ester·HCl + $LiAlH_4$	682 Hz 690 Hz	1:1

NOTES AND REFERENCES

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3. H. Seki, K. Koga, H. Matsuo, S. Ohki, and S. Yamada, Chem. Pharm. Bull. (Japan), 13, 995 (1965).
4. C. F. Lane, U.S. Patent 3,935,280, Chem. Abstr., 84, 135101p (1976).
5. A. I. Meyers, M. L. Druelinger, and D. R. Williams, J. Am. Chem. Soc., 98, 3032 (1976).
6. A sample purchased from Aldrich Chem. Co. had $[\alpha]_D^{20}$ = 4.80° (neat) in our hands although the catalog lists $[\alpha]_D^{22}$ +1.3° (neat).
7. We thank Dr. C. Lane (Aldrich) for a gift of $BH_3 \cdot Me_2S$ for our studies.
8. J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969); S. Yamaguchi and F. Yashura, Tet. Letters, 89 (1977).
9. All samples were run at 94.1 MHz in acetone-d_6 using TFA as an external standard. We thank Dr. R. M. Riddle (University of Minnesota) for these measurements.
10. Similar studies were performed on valine, phenylglycine, and phenylalanine.
11. The ^{13}C-nmr spectra were also examined and gave very small peak separation (~0.1 ppm) which was not sufficient for meaningful integration on enantiomeric compositions.
12. The hydrochloride salts of leucinol obtained from reaction a) and b) were repeatedly recrystallized (EtOH-Et_2O) and gave $[\alpha]_D^{20}$ 10.7° and 11.1° (EtOH). The trace impurity from reaction a) was thus removed. The recovered leucinol then possessed $[\alpha]_D^{20}$ 1.23° (neat).

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