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ASYMMETRIC SYNTHESIS OF UNUSUAL AMINO ACIDS: SYNTHESIS OF OPTICALLY PURE ISOMERS OF ß-METHYLPHENYLALANINE

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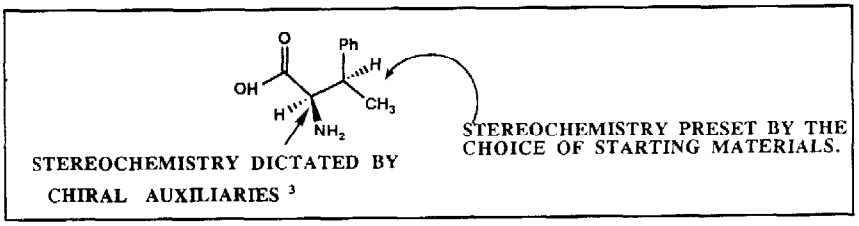
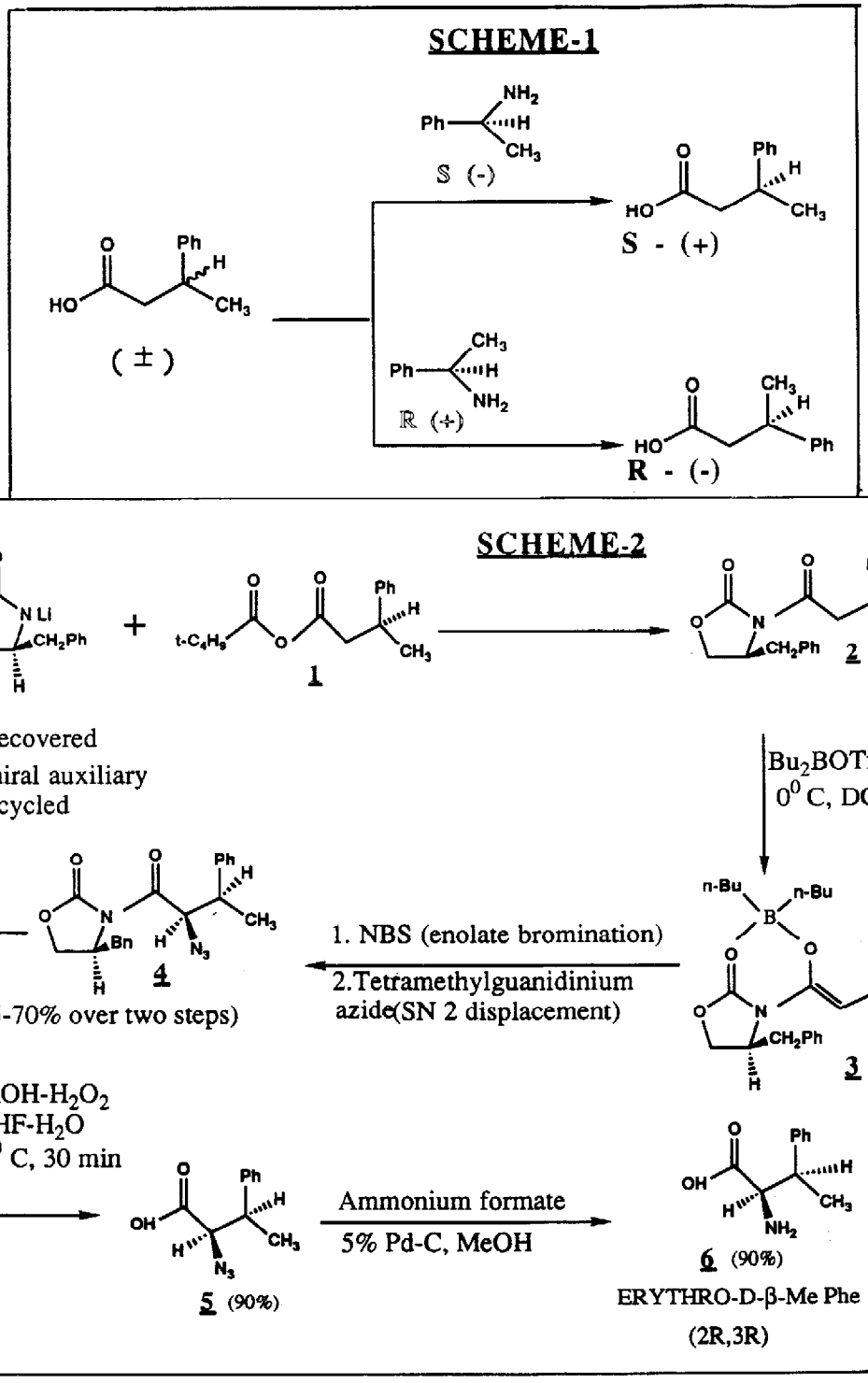
Abstract: All the four individual isomers of ß-methylphenylalanine have been synthesized in very high optical purities by utilizing in part the chiral imide enolate bromination methodology of Evans and co-workers.

Substitution of the diastereotopic ß-hydrogens of many α-amino acids provides in principle, an approach to topographic control of peptide structure. Asymmetric synthesis of the desired amino acids is needed to facilitate these studies. In this letter, we detail our approach[1] to the successful synthesis of all the four individual isomers of ß-methylphenylalanine in very high optical purity. In the recent years, several methods have been developed[2,3] for the asymmetric synthesis of α-aminoacids. Among them, the elegant method of Evans and co-workers[3] appealed to us as suitable for controlling the stereochemistry at the α-carbon of these compounds while the stereochemistry at the ß-carbon would be preset by the choice of starting materials.



Commercially available racemic 3-phenylbutyric acid was resolved[4] into its optical isomers via fractional crystallization of diastereoisomeric salts formed with S(-)methylbenzylamine (Scheme-1). Four recrystallizations gave pure S(+)3-phenylbutyric acid. From the partially enriched mother liquor, the R(-)isomer was obtained by fractional crystallization of diastereoisomeric salts formed with R-(+)methylbenzylamine. (The absolute configuration of the (-) acid was determined[5] to be R by chemical correlation with S-(+)hydratropic acid). The S-(+)-3-phenylbutyric acid thus obtained was converted into a mixed anhydride with pivalic acid and was attached to the chiral auxiliary derived from L-phenylalanine[6] (Scheme-2). The optical purity of S-(+)-3-phenylbutyric acid could be determined from the ^{1}H NMR (500 MHz) of N-acyloxazolidinone 2. When racemic 3-phenylbutyric acid was used, two multiplets centered around δ 4.60 and 4.45 ppm were observed for the proton attached to the C-4 of the chiral auxiliary. When optically pure S-(+)-3-phenylbutyric was used, only one multiplet at δ 4.45 ppm was observed. From this simple analysis it was determined that the resolution of racemic 3-phenylbutyric acid proceeded in >98% ee. The N-acyloxazolidinone was converted[3] to boron


SCHEME-1
S (-)
S - (+)
(±)
R (+)
R - (-)
SCHEME-2
1
2 (70%)
Recovered
chiral auxiliary
recycled
Bu2BOTf
0° C, DCM
1. NBS (enolate bromination)
2.Tetramethylguanidinium
azide(SN 2 displacement)
4
(65-70% over two steps)
3
LiOH-H2O2
THF-H2O
0° C, 30 min
Ammonium formate
5% Pd-C, MeOH
5 (90%)
6 (90%)
ERYTHRO-D-β-Me Phe
(2R,3R)

enolate 3 (Scheme-2). Stereoselective bromination of 3 by NBS and S_N2 displacement of the resulting bromide by tetramethylguanidinium azide at room temperature gave diastereoisomeric azides with high diastereo selectivity (Scheme 3).

Removal of the chiral auxiliary was effected[7] by using LiOH in presence of hydrogen peroxide. Catalytic hydrogenation of the resulting azido acid using 10% Pd-C was very slow and gave unidentified side products when longer reaction times were used. Utilizing Lindlar's catalyst[9] or attempted reduction of azido group with triphenylphosphine[10] resulted in mixtures. Finally the optimum yields were realized when catalytic hydrogen transfer[8,11] utilizing ammonium formate[8] in presence of 5% Pd-C was used. The diastereoisomeric purity of the resulting amino acid was determined by converting it to its N-acetyl derivative and comparing its HPLC[12] with a mixture of *threo-* and *erythro*-N-acetyl ß-MePhe prepared by the method[13] of Kataoka et al. In addition thin layer chromatography of these amino acids on chiral silica plates[14] provided a quick analysis of their optical purity. Utilizing L-chiral auxiliary and R-(-)3-phenylbutyric acid gave (2R,3S)ß-methylphenylalanine. The other two isomers were synthesized

SCHEME-3

DIASTEREOSELECTIVITY OF AZIDE 4 DEPENDS ON CHIRALITY OF SUBSTRATE 2

			RATIO OF AZIDES 4	
L-X_C + S-(+)-3-phenylbutyricacid	N-acyloxazolidinone **2a**	1.Bu_2BOTf 2.NBS 3.N_3^-	(2R,3R): (2S,3R)	99:1
L-X_C + S-(+)-3-phenylbutyricacid	N-acyloxazolidinone **2b**	1.Bu_2BOTf 2.NBS 3.N_3^-	(2R,3S): (2S,3S)	94:6
L-X_C + S-(+)-3-phenylbutyricacid	N-acyloxazolidinone **2c**	1.Bu_2BOTf 2.NBS 3.N_3^-	(2R,3R): (2S,3R)	6:94
L-X_C + S-(+)-3-phenylbutyricacid	N-acyloxazolidinone **2d**	1.Bu_2BOTf 2.NBS 3.N_3^-	(2R,3S): (2S,3S)	1:99

SCHEME-4

ALL THE FOUR INDIVIDUAL ISOMERS OF β-ME PHE HAVE BEEN SYNTHESIZED BY STARTING WITH D OR L CHIRAL AUXILIARY AND (+) OR (-) 3-PHENYLBUTYRIC ACID.

L-Chiral auxiliary + S-(+)-3-Phenylbutyric acid	⟶	Erythro-D-β-Me Phe (2R,3R) d.e= 98%
L-Chiral auxiliary + R-(-)-3-Phenylbutyric acid	⟶	Threo-D-β-Me Phe (2R,3S) d.e=94%
D-Chiral auxiliary + S-(+)-3-Phenylbutyric acid	⟶	Threo-L-β-Me Phe (2S,3R) d.e=94%
D-Chiral auxiliary + R-(-)-3-Phenylbutyric acid	⟶	Erythro-L-β-Me Phe (2S,3S) d.e=98%

from chiral auxiliary obtained from D-Phe and S-(+) or R-(-)3-phenylbutyric acid (Scheme-4). In conclusion, we have developed a straightforward method for the asymmetric synthesis of unusual amino acids such as ß-methylphenylalanine[15,16] in very high optical purities. Large scale synthesis of ß-methylphenylalanine and similar analogues suitable for incorporation into various peptides is in progress in our laboratory.

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References and Notes:

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13. (a) Kataoka, Y.; Seto, Y.; Yamamoto, M.; Yamada, T.; Kuwata, S.; Watanabe, H. Bull. Chem. Soc. Jpn. **1976**, 49, 1081-84. (b) We have resolved **erythro**-D-(2R,3R) and **erythro**-L-(2S,3S)ß-MePhe using Quinine. These optically pure isomers served as standards for products obtained by asymmetric synthesis.
14. Chiralplate® from Chemical Dynamics - Precoated with reverse phase silicagel and impregnated with a chiral selector and copper (II) ions was used. The separation of optical isomers is based on ligand exchange. R_f for threo-L, threo-D, erythro-L and erythro-D-ß-MePhe are 0.65, 0.54, 0.70 and 0.46 (4:1:1 acetonitrile:methanol:water), respectively.
15. For other synthesis of ß-methylphenylalanine in addition to reference 13(a), see (a) Effenberger, F.; Weber, T. Angew. Chem. Int. Ed. Engl. **1987**, 26(2), 142-143. (b) Tsuchihashi, G.; Mitamura, S.; Ogura, K. Bull. Chem. Soc. Jpn. **1979**, 52(7), 2167-68.
16. Spectroscopic data (IR, NMR, EI or CI/MS) and elemental analyses support the structures for all compounds shown.

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