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

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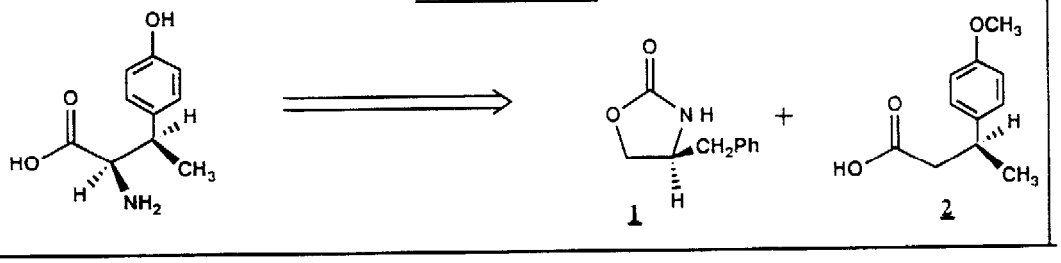
Abstract: Synthesis of optically pure isomers of ß-methyltyrosine has been accomplished.

In the preceeding letter, we have detailed our approach to the synthesis of optically pure isomers of ß-methylphenylalanine in very high optical purities, using in part the chiral imide enolate bromination methodology of Evans & coworkers.[1] Following protocols that are similar, we have synthesized the optically pure isomers of ß-methyltyrosine. In addition, we have converted erythro-D,L-ß-methylphenylalanine to erythro-D,L-ß-methyltyrosine. The details of these syntheses are described in this letter.[2]

To obtain optically pure isomers of ß-methyltyrosine following protocols described in the preceeding paper, we needed chiral auxiliary 1 and (+) or (-)4'-methoxy-3-phenylbutyric acid 2 (Scheme-1).

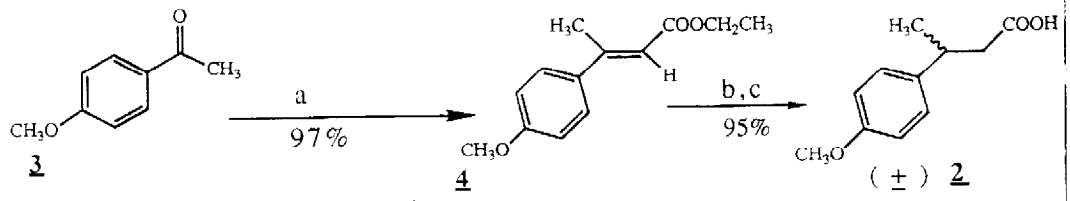
SCHEME-1



Since the desired acid 2 is not commercially available, we synthesized it from 4-methoxy-acetophenone using the Wittig reaction (Scheme-2). Utilizing potassium t-butoxide (instead of sodium hydride) as base and tetrahydrofuran as solvent (instead of diglyme) improved the reported[3] yields of 4 to 97%. The α,ß-unsaturated ester 4, was subjected to catalytic hydrogenation (10% pd/c), followed by hydrolysis to give the racemic acid 2 in 92% overall yield. It was resolved via fractional crystallization of diastereoisomeric salts formed with S-(-)- and R-(+)-α-methylbenzylamine, respectively. The absolute configuration of (+) and (-)4'-methoxy-3-phenylbutyric acid is not known and we have determined (Scheme-3) that the (+) acid has the S configuration by chemical correlation with the known[4] methyl ester of S-(+)-3-phenylburyricacid 7.

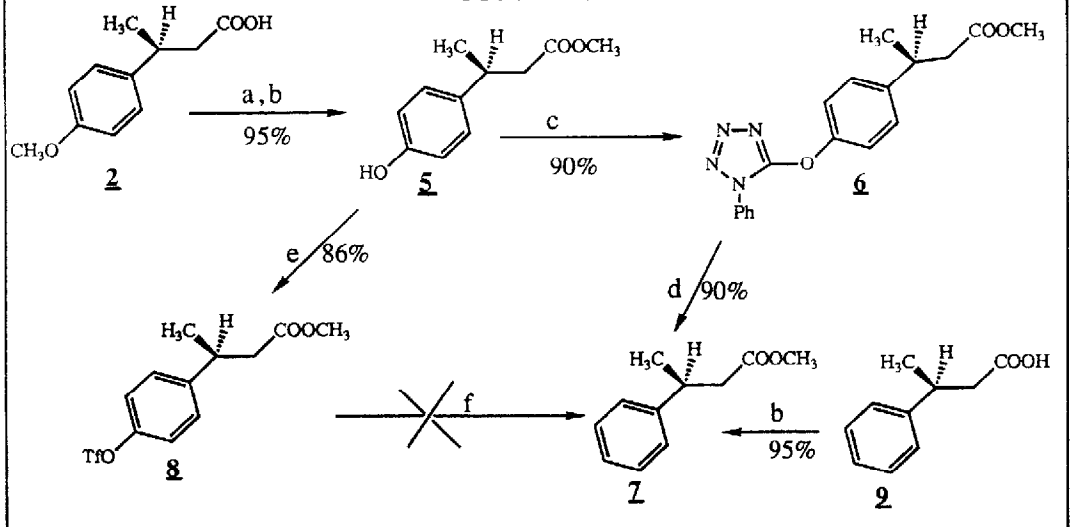
Thus, (+)-4'-methoxy-3-phenylbutyric acid 2 was demethylated[5] and esterified, but attempted deoxygenation[6] of the corresponding triflate 8 with triethylammoniumformate in the presence of a homogenous palladium catalyst[7] failed. The phenol 5 was converted[8] into tetrazole 6, followed by reductive removal of the tetrazolloxy functionality using catalytic transfer hydrogenation gave (+)methyl 3-phenylbutyrate ($[\alpha]^{23}_{546}$ + 74.4° (c 1.0, benzene)), identical in all respects (IR, NMR, MS) to an authentic sample ($[\alpha]^{23}_{546}$ + 75° (c 1.0, benzene)) of the ester prepared from S-(+)-3-phenylbutyric acid.

SCHEME -2

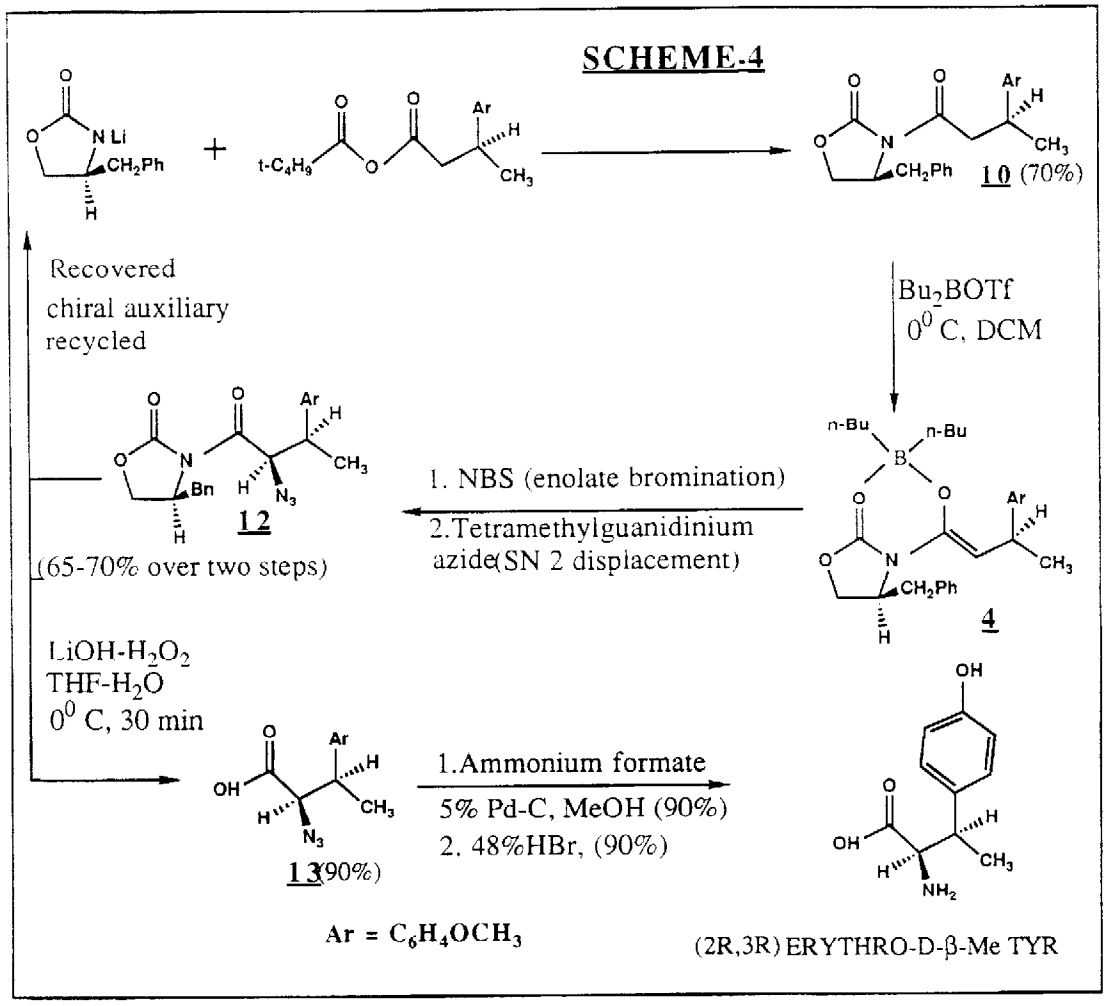


(a) $(EtO)_2P(O)CH_2COOEt$, KO^tBu ,THF. (b) H_2, 10% Pd/C .
(c) LiOH

SCHEME-3



(a) 48% HBr, AcOH. (b) HCl , MeOH.
(c) 5-Chloro-Tetrazole, K_2CO_3 , acetone, Δ
(d) Cyclohexene, MeOH, 5% Pd/C,Δ (e) Tf_2O, Et_3N.
(f) $Pd(OAc)_2(PPh_3)_2$, Et_3N, HCOOH,DMF, Δ



For the synthesis of ß-methyltyrosine, S-(+)-4'-methoxy-3-phenylbutyric acid was coupled with (Scheme-4) the chiral auxiliary derived from L-phenylalanine[9] to give the N-acyloxazolidinone 10. Enolate bromination followed by displacement with azide gave 12. Removal of the chiral auxiliary, followed by reduction of the azido group and hydrolysis of methyl ether gave *erythro*(2R,3R)-D-ß-methyltyrosine in 98% d.e. as judged by ^{1}H NMR. Utilizing R-(-)-4'-methoxy-3-phenylbutyric acid and the L-chiral auxiliary gave *threo*(2R,3S)-D-ß-methyltyrosine in 94% d.e. The synthesis of the other two isomers using the chiral auxiliary derived from D-phenylalanine is now in progress. We have synthesized racemic *erythro*-ß-methyltyrosine from racemic *erythro*-ß-methylphenylalanine via nitration, reduction, diazotization and hydroxylation (The racemic material was identical in all respects except for optical rotation to the material obtained by asymmetric synthesis.). In conclusion, unusual amino acids such as ß-methyltyrosine can be readily synthesized[10] in high optical purities, utilizing in part, the chiral imide enolate bromination methodology.[1]

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10. Spectroscopic data (IR, NMR, EI or CI/MS) and elemental analyses support the structures for all compounds shown.

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