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Asymmetric Syntheses of Highly Hydrophobic Chimeric Aromatic Amino Acids: 2-Amino-3,3´-Diarylpropionic Acids

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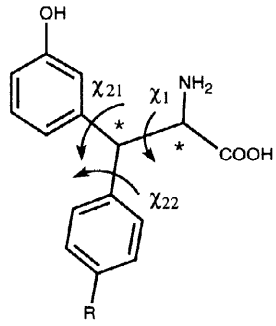
Abstract: Four conformationally constrained, highly hydrophobic, and enantiomerically pure chimeric aromatic amino acids have been asymmetrically synthesized in 7 steps with overall yields of 20-30%.

Conformational constraint is one major approach to modify the chemical and biological properties of endogenous bioactive peptide hormones and neurotransmitters. Much evidence indicates that such modifications of bioactive peptide analogues can significantly improve the physical and pharmacological properties of bioactive peptides and peptidomimetics including improvement in their affinities and selectivities for biological receptors/acceptors.[1] Therefore, design and synthesis of conformationally constrained amino acids with high hydrophobicity may provide a unique approach to obtain new insights into the stereochemical, conformational and topographical requirements of peptide ligand-receptor interactions and for signal transduction. As part of our continuing effort in this laboratory to obtain side-chain conformationally constrained, novel amino acids,[2] we have designed and synthesized a new type of chimeric aromatic amino acid, namely, 2-amino-3,3´-diarylpropionic acids of the general structure given.



These chimeric amino acids contain two bulky side chain groups, a phenol and a phenyl group. Therefore, these structure can be considered either as a phenylalanine derivative or as a tyrosine derivative. The interaction between these two bulky side-chain groups can produce strong constraints simultaneously for both

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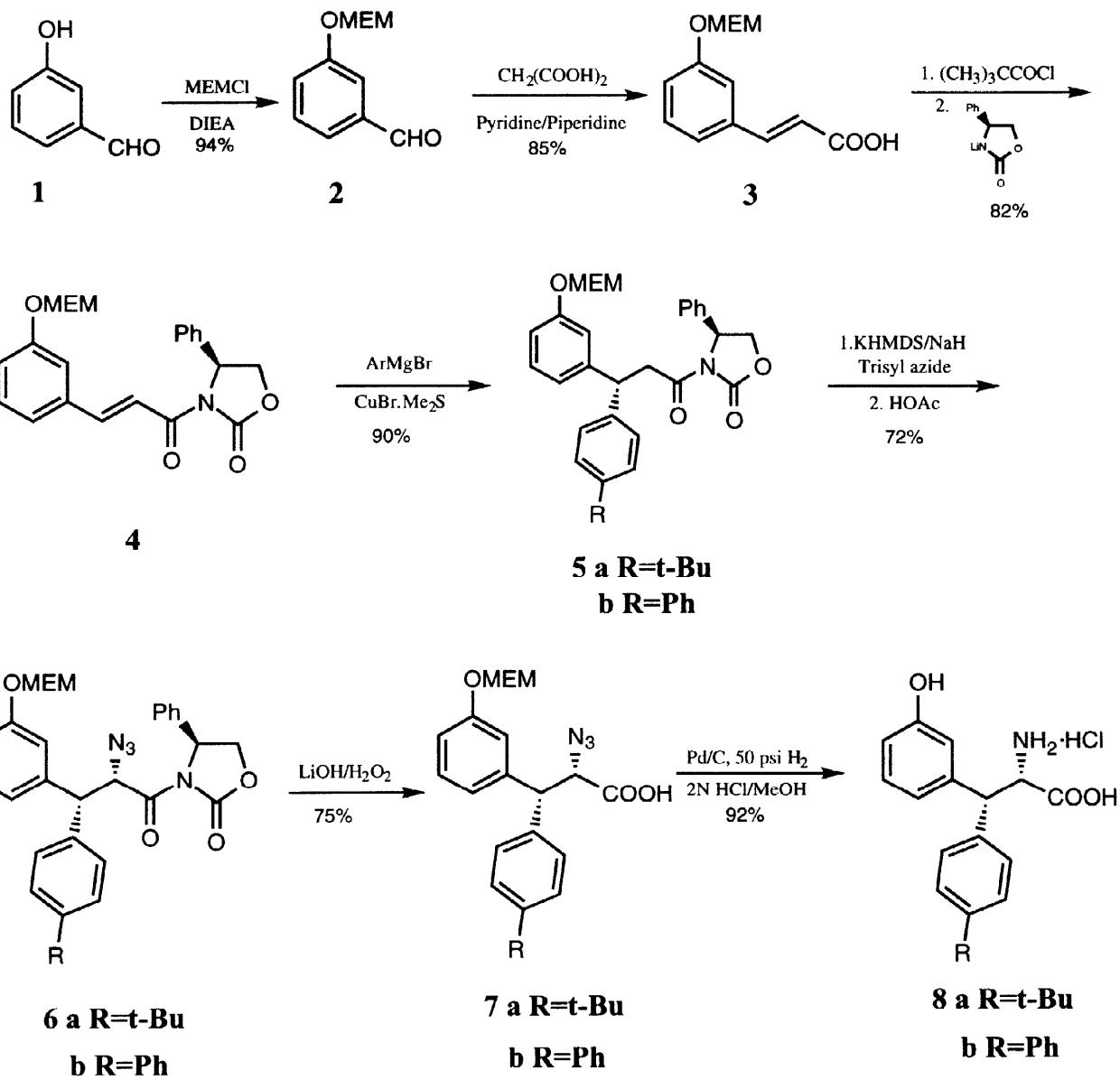
the χ^1 and χ^2 side chain torsional angles.[1b] Each diastereoisomer should thus favor a few specific low-energy side chain conformations separated by high energy barriers. Furthermore, the combination of 4-substituted phenyl groups and phenol groups, also can provide the possibility for dramatic increases in hydrophobic interactions with a receptor/acceptor. Thus, peptide ligands containing these unusual chimeric amino acids will possess unique physico-chemical and conformational properties, and provide useful information about the stereochemical requirements for peptide ligand-receptor interactions.

Scheme



The synthesis started from commercially available 3-hydroxylbenzylaldehyde **1**, in which the hydroxyl group was protected as a methoxyethoxymethyl ether **2**.[3] Then Knoevenagel reaction of the aldehyde with malonic acid formed the α,β-unsaturated acid **3**, which was coupled with the optically pure 4(S) or 4(R)-phenyloxazolidinone as a chiral auxiliary to form the imide conjugate **4**.[4] Asymmetric 1,4-Michael addition on the imide conjugate **4** with aromatic Grignard reagents produced β-aryl derivatives **5**.[5] Then direct azidation of intermediate **5** was carried out using a modified literature procedure to produce the α-azido derivatives **6**,[6,7] The cleavage of chiral auxiliary from **6** with lithium hydroxide in the presence of hydrogen peroxide was accomplished in over 75% yield using a modified procedure.[8] The final hydrogenolysis of the azido group in 2N HCl/methanol solvent resulted in the desired amino acids with simultaneous deprotection of the MEM ether.

The other two isomers **8c** and **8d** were synthesized using the same methodology as discussed above, and the (4R)-auxiliary was used to control the chiral centers. The use of these four unusual amino acids in design of novel bioactive peptidomimetics is currently under investigation.

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7. The azidation yield was significantly improved when 1:1 KHMDS/NaH was used as base.
8. Procedure to cleave the chiral auxiliary: After the cleavage of azido derivative **6**, the reaction mixture was acidified with 6N HCl, the organic phase was separated, and the aqueous phase was extracted with DCM. The combined organic phases were washed, dried and evaporated. Then hexanes/ethyl acetate (7:3) was added to precipitate and recover the auxiliaries. The mother liquid was evaporated and the residue was purified by column chromatography with chloroform/methanol (5:1) to give the desired azido acid **7.**
9. **(2S,3R)-2-Amino-3-(3′-hydroxyphenyl)-3-(4′-t-butylphenyl)propionic acid 8a:** ^{1}H NMR (δ ppm, CD_3OD): 7.35-6.52 (m, 8H, aromatic protons), 4.60 (d, J = 16.7 Hz, 1H, -C_αH), 4.8(d, J = 16.3 Hz, 1H, -C_βH), 1.18 (s, 9H, $(CH_3)_3$). MS for $C_{19}H_{24}O_3N$: $[M+H]^+$ (Calcd. 314.1756; Found: 314.1753). $[\alpha]_D^{22}$ = +18.3 (c = 0.50, MeOH). **(2S,3R)-2-Amino-3-(3′-hydroxyphenyl)-3-biphenylpropionic acid 8b:** ^{1}H NMR (δ ppm, CD_3OD): 7.56-6.68 (m, 13H, aromatic protons), 4.67 (d, J = 16.4 Hz, 1H, -C_αH), 4.27(d, J = 16.3 Hz, 1H, -C_βH). MS for $C_{21}H_{20}O_3N$: $[M+H]^+$ (Calcd. 334.1443; Found: 334.1453). $[\alpha]_D^{22}$ = +38.8 (c = 0.50, MeOH). **(2R,3S)-2-Amino-3-(3′-hydroxylphenyl)-3-(4′-t-butylphenyl)propionic acid 8c:** ^{1}H NMR(δ ppm, CD_3OD): 7.29-6.50 (m, 8H, aromatic protons), 4.58 (d, J = 16.6 Hz, 1H, -C_αH), 4.16 (d, J = 16.6 Hz, 1H, -C_βH), 1.16 (s, 9H, $(CH_3)_3$). MS for $C_{19}H_{24}O_3N$: $[M+H]^+$ (Calcd. 314.1756; Found: 314.1753). $[\alpha]_D^{22}$ = -23.6 (c = 0.50, MeOH). **(2R,3S)-2-Amino-3-(3′-hydroxyphenyl)-3-biphenylpropionic acid 8d:** ^{1}H NMR (δ ppm, CD_3OD): 7.48-6.47(m, 13H, aromatic protons), 4.62 (d, J = 16.7Hz, 1H, -C_αH), 4.21(d, J=16.1 Hz, 1H, -C_βH). MS for $C_{21}H_{20}O_3N$: $[M+H]^+$ (Calcd. 334.1443; Found 334.1446). $[\alpha]_D^{22}$ = -56.8 (c = 0.50, MeOH).