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Fluorinated Amino Acids
Part 2: [1] Synthesis of Diastereomeric N-Acyloxazolidinone Precursors

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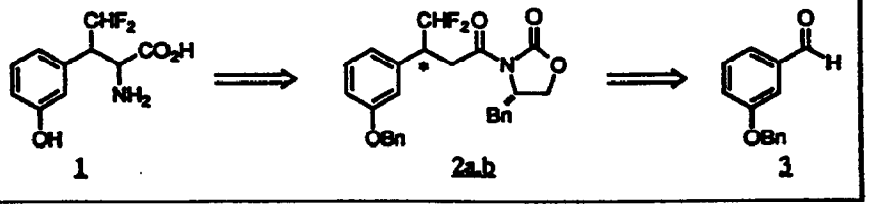
Abstract: Evans' chiral auxiliary is used to resolve 3-difluoromethyl-3-(3-benzyloxyphenyl)propionic acid (8), which provides key building blocks for the synthesis of chiral β-substituted m-tyrosine derivatives.

The development of potent, site-selective inhibitors of monoamine oxidase (EC 1.4.3.4, MAO) resulted in the design and synthesis of (E)-β-fluoromethylene-m-tyrosine.[2] In this dual enzyme-activated approach, the bioprecursor is actively transported across the blood brain barrier and into adrenergic nerve endings whereupon the action of aromatic L-amino acid decarboxylase (AADC) liberates the actual MAO inhibitor, (E)-β-fluoromethylene-m-tyramine. To further explore this concept we targeted β-difluoromethyl-m-tyrosine (1) for synthesis.[3] Retrosynthetically, our approach employs the well established electrophilic amination of chiral imide enolates to introduce an amino group in the final stage of the synthesis (Scheme I).[4] This communication reports the synthesis of the imide diastereomers 2a and 2b from commercially available 3-benzyloxybenzaldehyde (3).

Scheme I:



The synthesis (Scheme II) commences with a Wadsworth-Emmons olefination[5] of aldehyde 3 with triethyl phosphonoacetate. Reduction of the resulting α,β-unsaturated ester with diisobutylaluminum hydride (DIBAL) afforded the (E)-allylic alcohol 4 in 76% overall yield. Johnson ortho ester Claisen rearrangement[6] on a 50 mmol scale provided an 85% yield of the ester 5. The first attempt to introduce the difluoromethyl moiety from 5 was only partially successful. Although ozonolysis of 5 proceeded uneventfully to the aldehyde, numerous attempts to convert the aldehyde to the required gem-difluoromethyl group proceeded in poor yield, with starting material being the major component

in the reaction mixtures. This problem could be avoided by the reduction of the ester prior to ozonolysis. Thus, DIBAL reduction of 5 and protection of the resulting alcohol as the acetate afforded 6 in 78% yield. Ozonolysis of 6, followed by treatment with diethylaminosulfur trifluoride (DAST),[7] proceeded very well to afford the gem-difluoride 7 in 75% overall yield on a 20-30 mmol scale. Hydrolysis of the acetate and pyridinium dichromate (PDC)[8] oxidation of the resulting alcohol furnished the carboxylic acid 8 in 75% yield. In this way, multigram quantities of 8 were readily prepared.

In the next phase of the approach (Scheme III) which sets the scene for the use of Evans' stereoselective carboximide amination methodology,[4] the required N-acyloxazolidinone (2) was prepared from 8 in a one-pot procedure.[9] Formation of the mixed anhydride with pivaloyl chloride was followed by reaction with lithiated (4S)-4-phenylmethyl-2-oxazolidinone. We were fortunate that a 1:1 mixture of diastereomers was produced in 50% yield; separation was readily achieved by silica gel chromatography[10] leading to multigram quantities of 2a and 2b. Proof that a resolution of the carboxylic acid 8 had actually been obtained was demonstrated by removal of the chiral auxiliary from 2a and 2b which led to the enantiomers 9a and 9b, respectively.

The approach has provided the key intermediates 2a and 2b which can be further elaborated to amino acids 1.[4] In order to complete this work, the absolute configuration at the stereocenters in 2a and 2b needs to be unequivocally established. This would be best achieved by an independent asymmetric synthesis of either 9a or 9b. These issues are the subject of the accompanying paper.[11]

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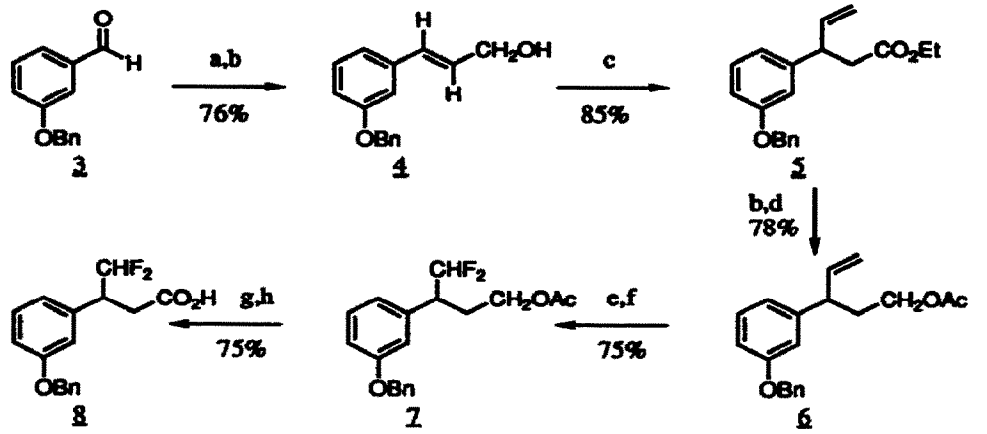
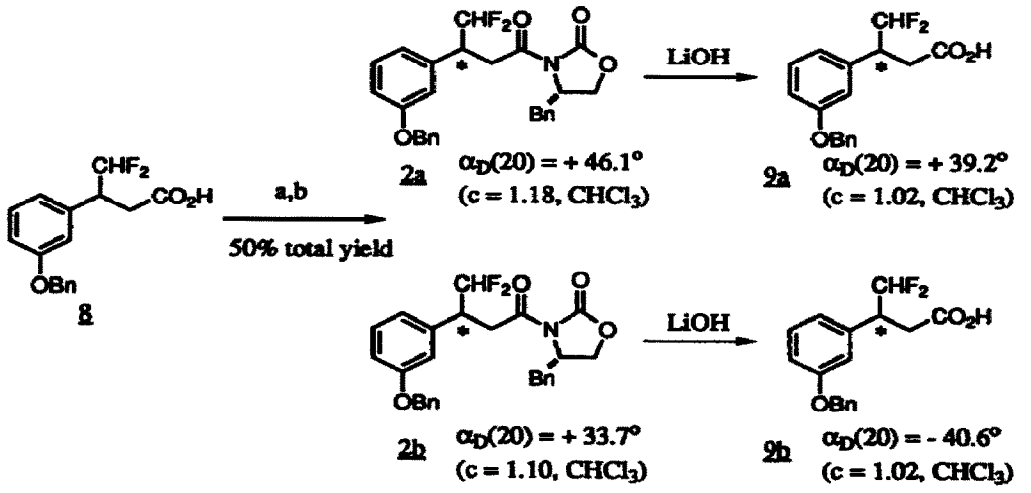
Scheme II:



Conditions: a) $(C_2H_5O)_2P(O)CH_2CO_2C_2H_5$, THF, $LiN(Si(CH_3)_3)_2$, 0°C to RT (1 h); b) DIBAL, toluene, rt (1 h); c) $CH_3C(OC_2H_5)_3$, $CH_3CH_2CO_2H$ (0.1 eq), 135°C (2 h); d) $(CH_3CO)_2O$, DMAP, THF, Et_3N, RT (1 h); e) O_3, 10:1 CH_2Cl_2:CH_3OH, Ph_3P (1.5 eq), -70°C to RT; f) DAST (1.5 eq), CH_2Cl_2, RT (1 h); g) K_2CO_3 (1.5 eq), CH_3OH, RT (1 h); h) PDC (3.5 eq), DMF, RT (15 h).

Scheme III:

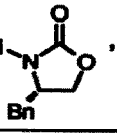


2a $\alpha_D(20) = +46.1°$ (c = 1.18, $CHCl_3$)

9a $\alpha_D(20) = +39.2°$ (c = 1.02, $CHCl_3$)

2b $\alpha_D(20) = +33.7°$ (c = 1.10, $CHCl_3$)

9b $\alpha_D(20) = -40.6°$ (c = 1.02, $CHCl_3$)

Conditions: a) $(CH_3)_3CC(O)Cl$, THF, Et_3N; b)  , THF

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