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Asymmetric Synthesis of (2R, 3S) and (2S, 3R) Precursors of β-Methyl-Histidine, -Phenylalanine and -Tyrosine

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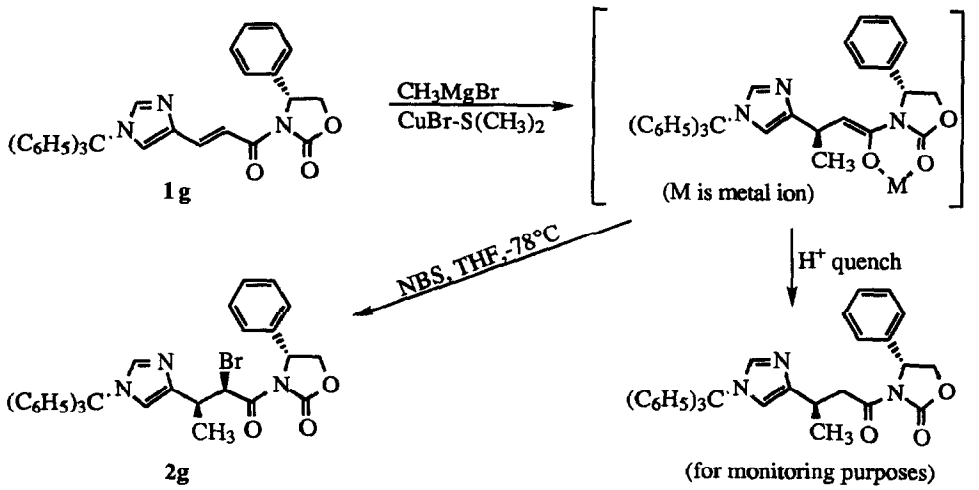
Abstract: A systematic series of (2S, 3R) and (2R, 3S) precursors to β-methyl-histidine, -phenylalanine and -tyrosine, which are of significant importance in the design of peptide and protein ligands, have been synthesized in high optically purity and yield.

The synthesis of conformationally and topographically constrained amino acids, peptides and peptide mimetics has become an important and rapidly developing area of bio-organic and medicinal chemistry[1,2]. The availability and ease of synthesis of a variety of unusual aromatic amino acids is crucial to future developments in this area. We have previously reported the asymmetric synthesis of all four individual isomers of unusual β-methyl α-amino acids, and their related (2S, 3S) and (2R, 3R) key intermediates by using modified or newly developed methodologies in our laboratory[3,4, 5]. Several of these unusual amino acids have demonstrated their importance in efforts to develop a rational approach to the design of highly selective peptide and protein ligands with specific conformational and topographical features[6]. Here we demonstrate the successful synthesis of a systematic series of (2S, 3R) and (2R, 3S) precursors to derivatives of β-methyl-histidine, a highly challenging and important synthetic target, together with those of β-methyl-phenylalanine and -tyrosine. Using an improved procedure, a convenient methodology is described in which a series of aromatic α,β-unsaturated analogs were used as the reaction substrates (**1a-1g**), and a simple copper reagent [$(CH_3)_2Cu$] was used as the addition ligand to facilitate the Michael-like addition and subsequent direct bromination reaction[3a,5c-e], both with high chiral purity.

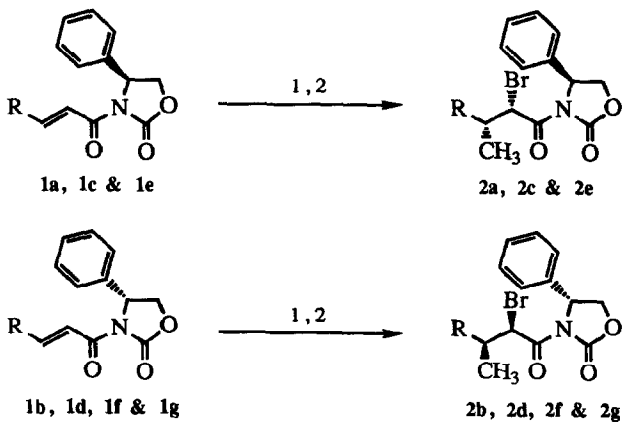
The overall syn-addition of organocuprates, and the tandem NBS bromination for directing the two new chiral centers, is controlled by an improved Evans auxiliary[5a,b], resulting in higher stereoselectivities than those previously obtained for the (2S, 3S) and (2R, 3R) reaction schemes[3a]. The reaction is demonstrated by the synthesis of 3(4R)-{3(2R,3S)-[4'-(1'-triphenylmethyl)imidazole]-2-bromo-1-oxobutyl}-4-phenyl-2-oxazolidinone (Scheme 1).

A synthetic procedure is described for example **g** (Table 1). To a copper(I)bromide-dimethyl sulfide complex (0.23g, 1.10mmol, 1.1eq) was added dimethyl sulfide (1.31 ml) and dry THF (2.2 ml). The resultant solution was cooled to -78°C to form a opaque mixture. Methyl magnesium bromide (0.49 ml of a 3M solution in ethyl ether, 1.47mmol, 1.47 eq) was added to the solution under a nitrogen atmosphere to yield a yellow slurry which was stirred at -78°C for 10 min, 0°C for another 10 min and re-cooled to -78°C before being transferred via a Teflon cannula to a pre-cooled (-78°C) slurry of **1g** (0.53g, 1.0mmol) in THF (4 ml) and dicholoromethene (2.4 ml). The resulting mixture was stirred at -78°C for 30 min, -10°C for 15 min (45 min for reactions **a-f**), (the color of the reaction changing from brown/yellow to green during this period). Following re-cooling to -78°C, the solution was transferred to a -78°C solution of NBS (2.3g) in THF (65 ml).



Scheme 1

The resultant mixture was stirred at -78°C for 45 min (90 min for reactions **a-f**), quenched with sodium sulfite (1.3M), and washed with water (100 ml) and brine (100 ml). Organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was evaluated by ^{1}H-NMR and purified by column chromatography to yield a glassy solid (0.50g, 80%) (Table 1).

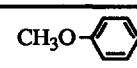
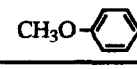
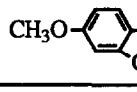
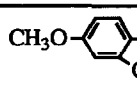
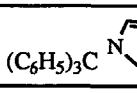


1. CH_3MgBr, $CuBr\text{-}S(CH_3)$; 2. NBS, -78°C.

Scheme 2

TLC and ^{1}H-NMR (250 MHz) provided convenient methods to monitor the progress and determine the stereoselectivities for both the asymmetric addition and bromination processes. TLC conditions employed EtOAc:hexane:CH_3CN = 2.7:6.3:1 for reaction **g**, and EtOAc:hexane=3:7 for reactions **a-f** respectively. The absolute stereochemistry was confirmed by the X-ray structure analysis of **2e** and by converting **2a** to (2R,3R) β-methylphenylalanine which was compared to an authentic sample obtained by alternative procedures[4c]. The downfield chemical shifts (5.9-6.47 ppm) of α-protons of the bromides and several ^{1}H signals from the chiral auxiliary can be used to evaluate the stereoselectivities following the bromination reactions. Only one isomer was observed for the reactions **a, b, f** and **g** (Table 1). The solid products obtained from **e** and **f**, could be easily crystallized, all other products remained as oils or glassy solids and failed most attempts at recrystallization.

Table 1: Analogs synthesized by the novel procedure

	R	crude * d.e. %	purified yield %	purified d.e. %	$\delta_{\alpha H}$ of bromides	chiral auxiliary	configuration	$[\alpha]_D^{25}$ ($CHCl_3$)
a		99.0	81.4	>99.0	6.06	S	(2S, 3R)	+67.7 (c=2.8)
b		99.0	77.5	>99.0	6.06	R	(2R, 3S)#	-68.0 (c=2.4)
c		78.0	71.9	>99.0	6.00	S	(2S, 3R)	+149.0 (c=1.5)
d		80.0	89.9	>99.0	6.00	R	(2R, 3S)	-145.4 (c=2.4)
e		90.3	74.0	>99.0	6.18	S	(2S, 3R)	+119.5 (c=2.4)
f		99.0	76.0	>99.0	6.18	R	(2R, 3S)†	-120.0 (c=2.4)
g		99.0	80.3	>99.0	5.92	R	(2R, 3S)	-67.5 (c=1.5)

* Only two isomers were observed in cases of c, d and e; >99.0% indicates only one isomer was observed.

The bromide has been converted into the authentic β-methyl amino acid.

† The X-ray structure has been determined [4a].

In summary, the described synthesis of the (2R, 3S) and (2S, 3R) precursors, in conjuction with the previously reported synthesis of (2S, 3R) and (2R, 3S) precursors[3a] has facilitated the total synthesis of all four isomers of several β-methyl α-amino acids. Furthermore, the new methodology described herein represents significant progress towards the enantioselective synthesis of all isomers of β-methylhistidine, which is among the most important and challenging special amino acids examined thus far.

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