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Asymmetric Synthesis of Unusual Amino Acids : An Enantioselective Synthesis of the Four Isomers of D- and L-*O*-Methyl-2', β-Dimethyltyrosine

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Abstract: The four individual isomers of D- and L-O-methyl-2', β-dimethyltyrosines have been synthesized in high optical purity. The evidence for asymmetric induction was confirmed by the X-ray analysis of one of the key intermediates.

Michael-type additions in conjuction with an Oppolzer auxilliary have been used in the synthesis of L-allo-isoleucine.[1] In the procedure, the 1, 4-conjugate addition product was converted into the corresponding ketene silyl acetal followed by bromination to give a bromide as a key intermediate. In the preceeding letter,[2] we have reported our approach to the asymmetric synthesis of some key intermediates to unusual amino acids by using a modified Evans auxiliary[3] in conjuction with an asymmetric Michael-type conjugate 1,4-addition followed by direct bromination in a one-pot operation (Figure 1). In this letter, we detail our successful synthesis of all four individual isomers of β–2'-dimethyltyrosine analogues, which are important to the design of peptide and protein ligands with specific conformational and topographical features,[4] by using the above method starting from a set of four starting compounds **1a-1d**. The synthesis of the four optically pure bromides **2a-2d** required for the final amino acids **5a-5d** is described in Scheme I with the results listed in Table I.

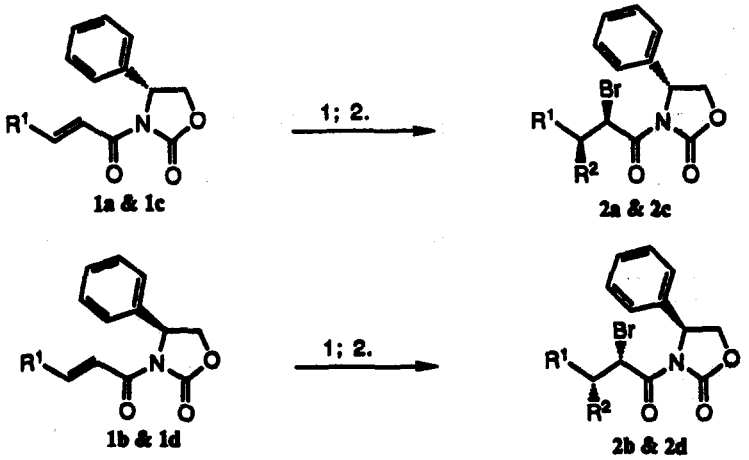
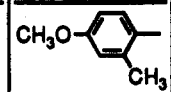
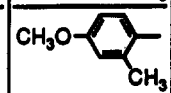
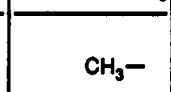
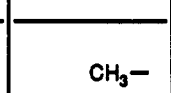


Figure 1. 1) R^2MgBr, $CuBr.S(CH_3)_2$; 2) NBS, -78°C

Table I

entry	R^1	R^2	chiral auxiliary	crude# de%	purified		config.	$[\alpha]_D^{27}$ ($CHCl_3$)
					yield%	de%		
a			R	>99.0*	76	>99	(2R,3S)**	-120.0 (c=2.6)
b			S	90.3	74	>99	(2S,3R)	+119.5 (c=2.4)
c			R	92.7	80	>99	(2R,3R)	-13.2 (c=3.2)
d			S	92.5	80	>99	(2S,3S)	+13.8 (c=2.8)

Only two isomers observed for b, c and d,
* >99% means no detection for the minors which is the best result among 20 repeated reactions
** X-ray structure provided

The stereochemistry of the asymmetric induction was confirmed by X-ray structure of 3(2R, 3S), 4R 3-[2-Bromo-3-(4'-methoxy-2'methylphenyl)-1-oxopropyl-4-phenyl-2-oxazolidinone, **2a** (Figure II).

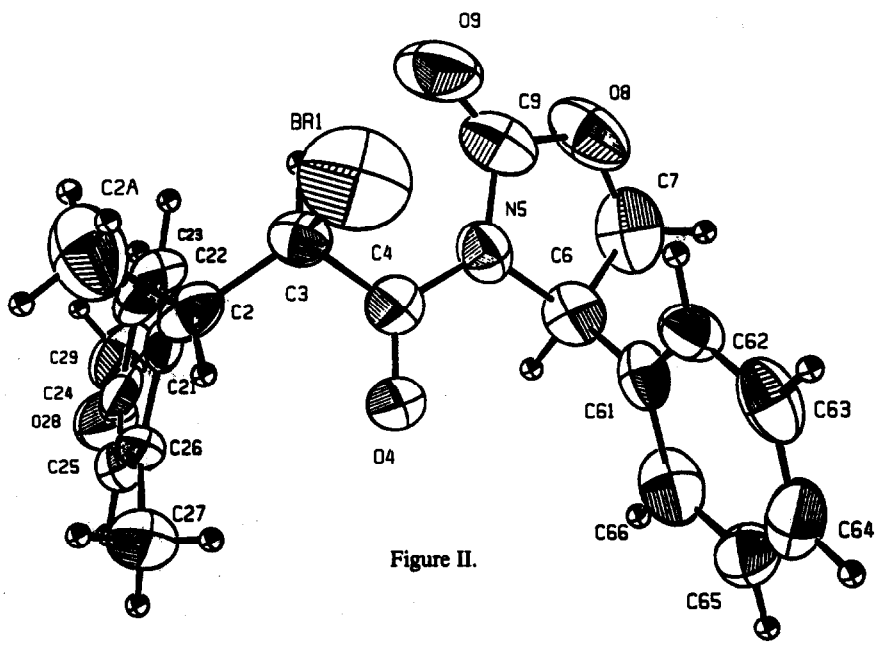
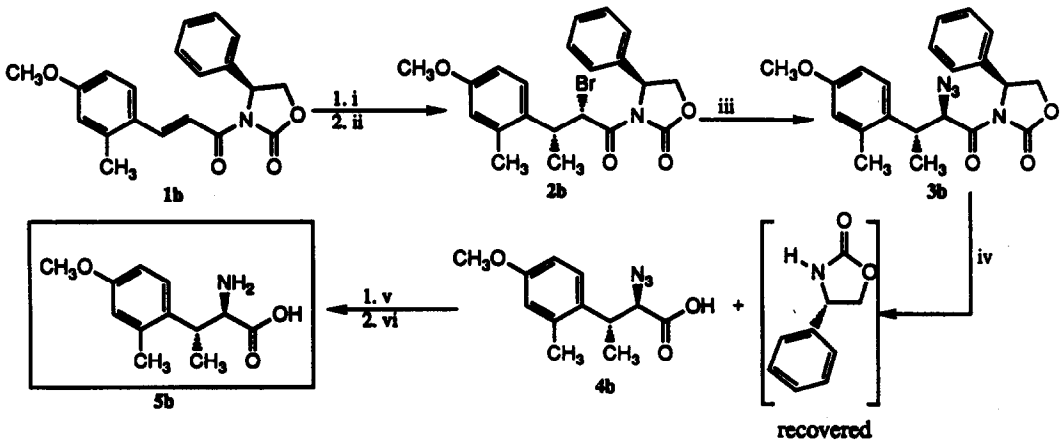


Figure II.

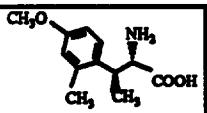
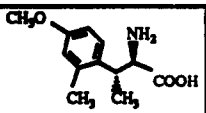
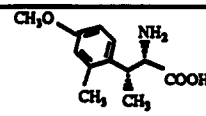
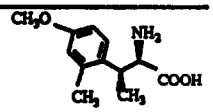
The procedure for preparing the bromides was demonstrated in our proceeding letter. The S_N2 displacement of the resulting four optically pure bromides **2a-2d** by tetramethylguanidinium azide[4] at 0 °C for 15 min and at room temperature for 3-4 hrs gave the corresponding azides **3a-3d** without recemization. Removal of the chiral auxiliary was effected by using LiOH in the presence of hydrogen peroxide.[5] The resulting azido acids **4a-4d** were subject to catalytic hydrogenation (10% Pd/C) at 34-38 Psi for 24 hrs. The crude amino acids **5a-5d** were purified by ion-exchange chromatogrophy on Amberlite IR-120 plus exchange resin. The detailed processes are illustrated by the synthesis of *erythro*-D-2',β-dimethyl-*O*-methyltyrosine **5b** (Scheme I); the optical rotation, mp, and overall yield for the four amino acids are listed in Table II.

Scheme I.



(i) CH_3MgBr, $CuBr.S(CH_3)_2$; (ii) NBS, THF, -78 °C; (iii) TMGA, CH_3CN; (iv) LiOH, H_2O_2 (v) Pd-C, H_2; (vi) ion-exchange resin.

Table II

Entry	 5a(2S,3S)	 5b(2R, 3R)	 5c(2S, 3R)	 5d(2R, 3S)
$[\alpha]_D^{27}$ (MeOH)	-32.0 (c=3.2)	+32.8 (c=3.0)	+20.8 (c=2.8)	-21.0 (c=3.0)
mp. (°C)	180-183	180-184	177-181	176-180
% Yields from 1a-1d	58	62	66	65

In summary, the proposed procedure is a practical method for the synthesis of β-alkyl-α-amino acids analogues of aromatic amino acids such as tyrosine which is used for advanced research in polypeptides and proteins. The synthesis of a series of unusual amino acid analogues on a large scale is underway in this laboratary.

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