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A NEW STRATEGY FOR THE SYNTHESIS OF FOUR INDIVIDUAL ISOMERS OF β-METHYLPHENYLALANINE

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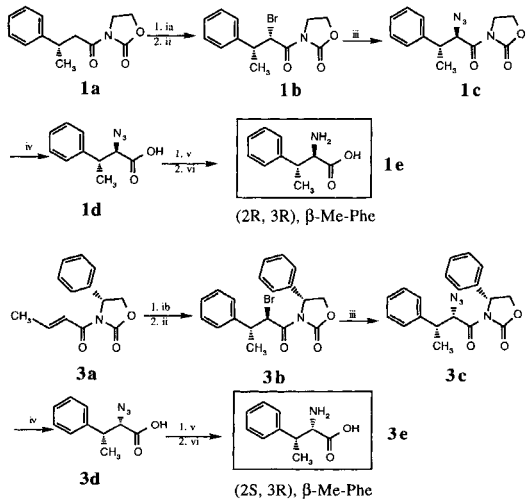
Abstract: The application of an allylic strain effect in boron enolates and asymmetric Michael-like addition/electrophilic bromination reactions is reported for the asymmetric synthesis of the individual isomers of unusual constrained amino acids. For β–substituted α-amino acids, all of the final optically pure products were identical to authentic samples, which provided further and unequivocal evidence to confirm the assignments of stereochemical control of the new methods in this report.

The design and synthesis of optically pure amino acid derivatives has become one of the most important research areas in biochemistry, bioorganic chemistry and medicinal chemistry.[1a-1f] At the same time, the study of specialized amino acids, their incorporation into peptides, and their many other applications has been at the forefront of chemical science for the past decade.[2] Recently, we and others have demonstrated that β–alkyl α-amino acids are very important for the design of biologically active peptide molecules with specific conformational and topographical features.[3a-3e] In connection with our studies of peptide molecular design and structure-biological activity relationships, extensive explorations for new synthetic methods and their application to the total synthesis of all of the individual isomers of such specific amino acids have been made in this laboratory.[4, 5]

Evans and coworkers first introduced the use of chiral boron enolates, produced by using the modified reaction conditions developed by Mukaiyama and colleagues [6], for the asymmetric synthesis of optically pure α-amino acids in which an oxazolidinone auxiliary was used to control the chirality of the α-carbon position.[7] In this communication, we wish to report the successful synthesis of all individual isomers of β-methylphenylalanine by using a boron enolate such that the β-chiral center can be used to direct the chirality of the α-position. This methodology can be used in conjuction with our newly developed tandem Michael-like addition followed by an electrophilic bromination reaction, such that all four isomers of β–methylphenylalanine can be obtained in high chiral purity. The detailed procedures are illustrated for the synthesis of (2R, 3R)- and (2S, 3R)-β-methylphenylalanine in Scheme 1.

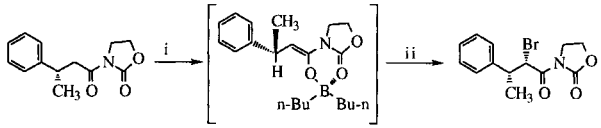


(ia) Bu_2BOTf, DIEA, DCM, -78 °C; (ib) PhMgBr, CuBr-$S(CH_3)_2$; (ii) NBS, THF, - 78 °C; (iii) Tetramethylguanidinium azide, CH_3CN; (iv) LiOH, H_2O_2; (v) Pd-C, H_2; (vi) ion-exchange resin.

Scheme 1

Both the (2R, 3R) and (2S, 3S) bromide precursors 3 and 4 were synthesized by tandem asymmetric Michael-like addition/electrophilic bromination reactions in which both α- and β-chiral centers were directed by the auxiliary. The syntheses of the (2S, 3R) and (2R, 3S) bromide intermediates[8] 1 and 2 were achieved by 1, 2-asymmetric *cis* induction through the boron enolates with allylic strain. To our knowledge this is the first documentation where such effects

are seen in boron enolates with a nonchiral oxazolidinone derivatives (Scheme 2). The reaction conditions are similar to those described in the literature for related reactions.[6,7]

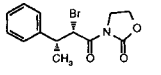
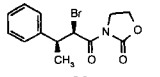
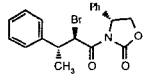
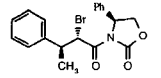


i. n-Bu_2BOTf, DIEA, Dichloromethane (DCM), -78 °C → 0 °C;
ii. NBS, DCM, -78 °C.

Scheme 2

The stereoselectivities of the bromination reactions were determined by using ^{1}H-NMR (250 MHz) through the integration of the down-field doublets of the α-protons of the bromides (**1b-4b**, ranging from 5.95 to 6.00 ppm). The crude products were readily purified by silica gel chromatography [E. Merck silica gel 60 (230-400 Å)]. The purified bromides were converted to the corresponding azides (**1c-4c**) by S_N2 displacement with tetramethylguanidinium azide in acetonitrile at 0 °C for 15 min and at room temperature for 3-4 h. Oxazolidinones were removed by hydrolysis with LiOH in the presence of hydrogen peroxide to yield the azido acids **1d-4d**. The azido acids were subject to catalytic hydrogenation (10% Pd/C) at 34-38 psi for 24 h, and the resulting crude products were purified by ion-exchange chromatography (Amberlite IR 120). No racemizations were observed in the above procedures (Scheme 1). The four final amino acids were found to be identical to authentic samples.

Table 1: The synthetic results of bromides and amino acids from the new strategy

Contents	 **1b**	 **2b**	 **3b**	 **4b**
Bromination Yield	82	67	79	89
Crude d.e% of Bromination	76	76	64	67
Purified d.e%	>99	>99	>99	>99
$[\alpha]^{25}_D$ ($CHCl_3$)	-6.0 (c=3.5)	+5.8 (c=1.8)	-30.0 (c=1.5)	+34.6 (c=2.0)
δ of α–H's (ppm)	6.00	6.00	5.95	5.95
Coupling Const.(Hz)	10.6	10.6	10.7	10.7
Bromide Precursor	(2S, 3R)-Bromide	(2R, 3S)-Bromide	(2R, 3R)-Bromide	(2S, 3S)-Bromide
Amino Acid Product	(2R, 3R)-β-Me-Phe	(2S, 3S)-β-Me-Phe	(2S, 3R)-β-Me-Phe	(2R, 3S)-β-Me-Phe
Yield of Amino Acids from **1a-4a**	69	54	57	65

In conclusion, this newly established method and procedure, which is expected to be applicable to the asymmetric synthesis of other specialized amino acids analogues, is highly effective for the total synthesis of β-methylphenylalanine. Further examples of this new strategy will be investigated in the future.

ACKNOWLEDGMENTS

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8. The optically pure β-branched caboxylic acids were obtained from the separation of racemic mixture by using 4R or 4S 4-phenyl-oxazolidinone as new chiral resolution reagents (Li, Patel and Hruby, The 10th Biennial Marvel Symposium, University of Arizona, abstract 27, **1993**, March 14-16); A similar method has been successfully used in the seperation of optically pure α- and β-amino acid derivatives (Li, Maruyama, Hoghes and Hruby, to be published, also presented at 207th ACS National Meeting, San Diego, March 13-17, 1994)

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