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Stereoselective Synthesis of All Individual Isomers of β-Methyl-2',6'-dimethylphenylalanine

Li Xiang, Huiwei Wu and Victor J. Hruby*

Department of Chemistry, University of Arizona, Tucson, AZ 85721

Abstract

Asymmetric synthesis of all four isomers of β-methyl-2',6'-dimethylphenylalanine was accomplished with complete stereoselectivities and high yields by using the Evans-like auxiliary 4-phenyl-oxazolidinone as a chiral auxiliary and as a chiral resolution reagent.

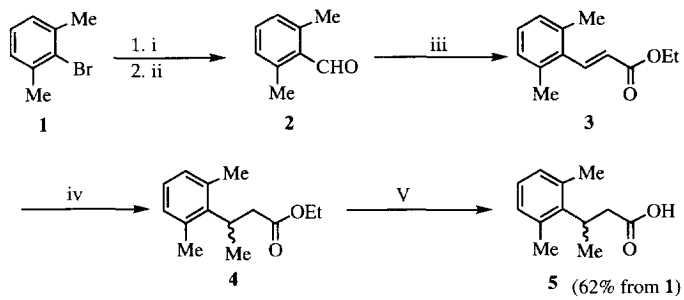
Key words: β-Methyl-2',6'-dimethylphenylalanine; Unusual amino acids; Asymmetric synthesis.

Peptide chemistry has been one of the most important research areas in modern life sciences because of the importance of peptides as hormones, neurotransmitters, growth factors, cytokins, enzyme inhibitors, neuromodulators, modulators of ion channels and many other biological functions. One of the central goals in peptide research is to develop better approaches for understanding the relationships of peptide structure, conformation and dynamics to the various biological activities by designing peptide molecules with specific topographical and conformational features.[1] The use of side chain constrained analogs has been shown to provide a useful rational approach to peptide design and to provide valuable insights regarding the mechanism of molecular recognition between peptide ligands and their specific receptors and receptor subtypes in binding and the consequent signal transduction processes.[2] The availability and ease of total synthesis of all individual isomers of unusual amino acids has become crucial to future developments in this research area.[3,4]

The asymmetric synthesis of several series of β-branched specialized amino acids has been studied in this laboratory with respect to synthetic methodologies and procedures.[4] However, the further exploration of practical and convenient asymmetric synthetic strategies of various specialized amino acids still remains as a central goal to meet the requirements of peptide molecular design. In this report, we wish to describe the total synthesis of all four isomers of the new χ_1 and χ_2 constrained amino acids β-methyl-2',6'-dimethylphenylalanine by using a newly developed method in our laboratory, in which (4R)- and (4S)-4-phenyl-oxazolidinone can be used as new chiral resolution reagents and

simultaneously as the chiral auxiliary to provide the desired compounds with high total yields and complete stereoselectivities.

In this method, optically pure (4R)- and (4S)-4-phenyl-oxazolidinone were coupled to racemic 3-(2',6'-dimethyl)-butyric acid, which was synthesized from 2-bromo-*m*-xylene (Scheme 1). In this procedure, the Grignard reagent prepared from 2-bromo-*m*-xylene (**1**) was reacted with dimethylformamide to yield 2',6'-dimethylbenzaldehyde (**2**), which was then transformed to the α,β-unsaturated ester **3** via a Wittig reaction.[5] The addition of lithium dimethylcuprate to the α,β-unsaturated ester **3** in the presence of chlorotrimethylsilane[6] and subsequent hydrolysis under basic conditions yielded the racemic 3-(2',6'-dimethylphenyl)-butyric acid (**5**).



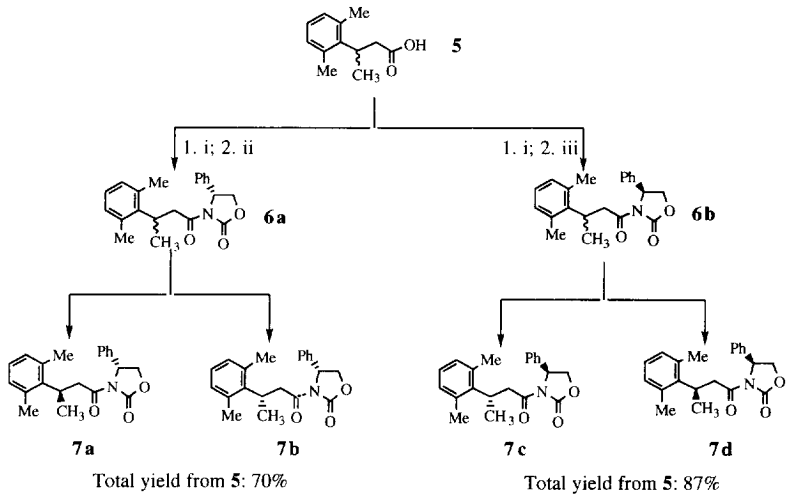
i. Mg, THF; ii. DMF, 0 °C –> rt; iii. $(EtO)_2P(O)CH_2CO_2Et$, t-BuOK, THF, rt;
iv. Me_2CuLi, Et_2O, TMSCl, -78 °C –> rt; v. LiOH, $MeOH/H_2O$, rt.

Scheme 1

The coupling reaction of the optically pure (4R)- and (4S)-4-phenyloxazolidinone to the racemic 3-(2',6'-dimethylphenyl)-butyric acid (**5**) was accomplished (Scheme 2) via the formation of the mixed anhydride with pivaloyl chloride to yield the (4R)- and (4S)-4-phenyl-3-[3-(2',6'-dimethylphenyl) butanyl)-2-oxazolidinone (**6a** and **6b** respectively). The resulting diastereomeric mixtures were resolved into their individual isomers **7a-7d** by crystallization employing a mixed solvent EtOAc:Hexane (v/v = 9/1).

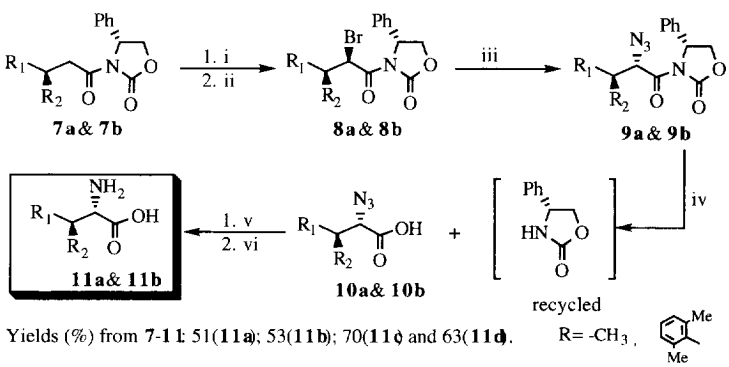
The conversion of **7a-7d** to the optically pure amino acids **11a-11d** respectively is demonstrated in Scheme 3. The bromination procedure was similar to that described by Evans and coworkers.[3b] ^{1}H-NMR (250 MHz) was used to determine the stereoselectivities of the crude products by observation of the sharp doublets of α-protons of bromides **8a-8d**. The improved stereoselectivity of the key bromination reaction in this system and some others from our group[4g] can be attributed to the presence of the sterically more hindered phenyl moiety of the Evans-type auxiliary used here, as compared with our initial asymmetric synthesis which used the less hindered benzyl moiety[4f] of the original Evans auxiliary. The absolute stereochemistry of the chiral induction was determined by comparing **8d** with a

known sample which was synthesized by an alternative method reported previously from our laboratory.[4b]



i. t-Bu-CO-Cl, Et_3N, THF, -78 °C –> 0 °C; ii. n-BuLi, 4R-auxiliary, THF, -78 °C –> rt; iii. n-BuLi, 4S-auxiliary, THF, -78 °C –> rt.

Scheme 2



Yields (%) from **7-11**: 51(**11a**); 53(**11b**); 70(**11c**) and 63(**11d**). R= $-CH_3$,

i. DIEA, CH_2Cl_2, n-Bu_2BOTf, -78°C; ii. NBS, -78°C; iii. TMGA, CH_3CN; iv. LiOH, H_2O_2; v. Pd-C, H_2; vi. ion-exchange resin.

Scheme 3

The bromides **8a-8d** were then subjected to S_N2 azide displacement reaction by using tetramethylguanidium azide[3b,4] in acetonitrile. The chiral auxiliary was removed and recycled by LiOH hydrolysis in the presence of hydrogen peroxide. The resulting azide acids **10a-10d** were subjected to hydrogenation (10% Pd-C) at 34-38 psi for 24-48 hrs to yield the crude amino acids **11a-11d** which were purified by ion-exchange chromatography on Amberlite IR-120 plus exchange resin. No racemization was observed in all cases examined in this study.

In summary, the first asymmetric synthesis of all four isomer of β-methyl-2',6'-dimethylphenylalanine has been achieved using this strategy. The application of this method to the synthesis of other analogs of unusual amino acids is currently under investigation in our laboratory and has shown preliminary success. Two of the four isomers already are being used in peptide molecular design and have provided some interesting preliminary results.

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