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ASYMMETRIC SYNTHESIS OF (R)-AND (S)- ENANTIOMERS OF NOVEL PHENYLALANINE HOMOLOGUES

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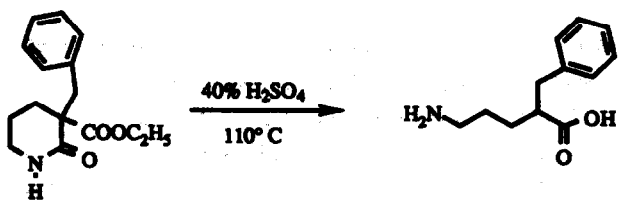
Key Words: Asymmetric synthesis; Phenylalanine homologues; Bradykinin antagonist

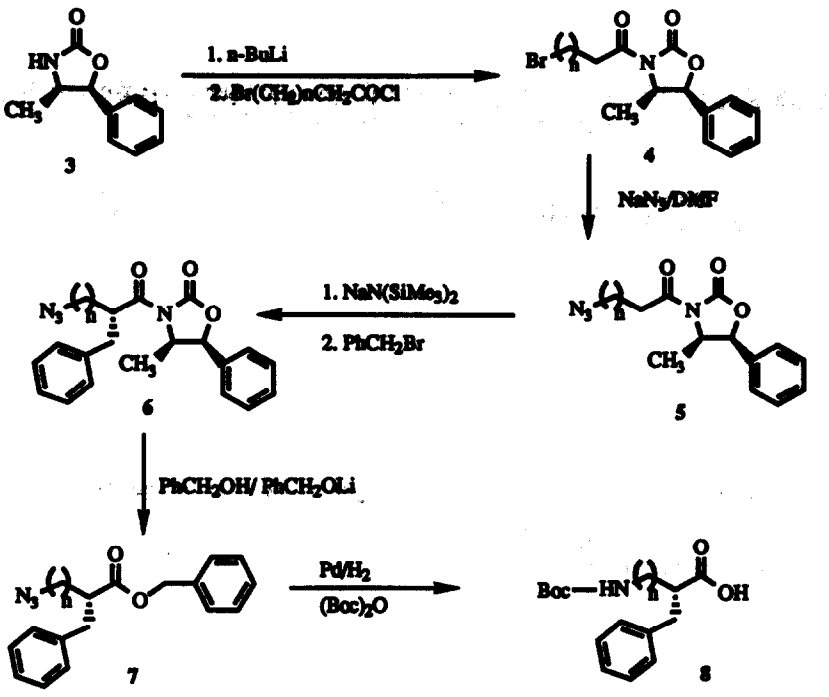
Abstract: Novel and efficient syntheses have been developed for the (R)- and (S)- enantiomers of a series of phenylalanine homologues.

Unusual amino acids are valuable building blocks in the study of natural peptides. Accordingly, β– amino acid substitutions have been extensively utilized in angiotensin,[1] gastrin,[2] oxytocin[3] and bradykinin[4] to explore structure- activity relationships and to obtain derivatives resistant to degradation by aminopeptidases. Several protected β-amino acids have been obtained by homologation of the corresponding amino acid derivatives.[4] Our interest in the synthesis of potential bradykinin antagonists necessitated the preparation of some hitherto unknown homologues of phenylalanine. Here we report a novel and efficient synthetic methodology based on chiral induction for the preparation of (R)- and (S)- enantiomers of phenylalanine homologues.



1 2

Racemic 5-amino-2-benzylvaleric acid (2) has been prepared by the hydrolysis of racemic 3-benzyl-3-ethoxycarbonyl-2- piperidone (1).[5] However, either separation of the enantiomers or an enantioselective synthesis is required to obtain the desired (R) and (S) isomers. As indicated in Scheme 1, enantioselective synthesis of Boc-protected 2, i.e. 8a, and several homologues (8b-8d) was achieved by adaptation of the chiral induction methodology of Evans.[6,7]



a, n=3; b, n=6, c, n=8; d, n=9

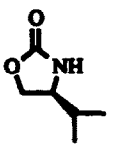
Scheme 1

The chiral auxiliary 3 was deprotonated with n-BuLi at -78°C and reacted with a series of bromoalkanoyl chlorides to give the corresponding amides 4 in excellent yields. The amides 4 were converted to the azides 5 by reacting them with sodium azide in DMF. Deprotonation of 5 with $NaN(SiMe_3)_2$ at -78°C followed by the addition of benzyl bromide gave the desired diastereoisomers 6. Diastereoselectivity of the alkylation reaction was established using ^{1}HNMR and HPLC techniques. Analyses of the reaction mixtures showed a kinetic ratio of 49:1 and after chromatographic separation the products had enantiomeric excesses (ee) of 100%. The chiral auxiliary was cleaved with $PhCH_2OH/PhCH_2OLi$ in THF at 0°C to provide the benzyl esters 7. Hydrogenation of 7 in presence of tert-butyldicarbonate followed by chromatographic separation provided the desired Boc protected (S) amino acids 8. The yields and physical constants for Boc protected (S)-5-amino-2-benzylvaleric acid (8a) and its intermediates are given in table 1.[8]

Table 1. Yields and Physical Constants for 8a and Intermediates.

Compound	Yield (%)[a]	m. p. (°C)	$[\alpha]_D^{25}$ (c = 1.0, CH_2Cl_2),[a]
4a	90	71-72	+ 23.6
5a	97	68-69	+ 23.6
6a	83	oil	+ 39.0
7a	98	oil	+ 9.8
8a	50	oil	+ 6.9

This novel methodology has been successfully applied for the preparation of the (R) isomer of Boc protected (R)-11-amino-2-benzylundecanoic acid **10** using (S)-2-isopropyloxazolidone[6,7] **9** as the chiral auxiliary.[9]



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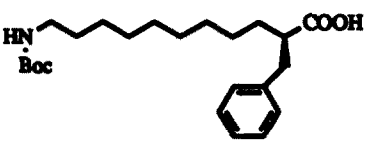

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8. Note: After chromatographic separation, all Boc protected amino acids were isolated as oils. Satisfactory elemental analysis have been obtained and the compounds were fully characterised by ^{1}HNMR, IR and specific rotation. Specific rotations were measured at c = 1, in methylene chloride and $[\alpha]_D^{25}$ for **8b** = +7.5°; **8c** = +6.0°; **8d** = +7.6°.

Yields (%) and physical constants (mp, $[\alpha]_D^{25}$) for intermediates were as follows:
4b (87%, 59-61°C, +21.7°), **5b** (96%, oil, +15.1°), **6b** (78%, oil, +26.5°), **7b** (90%, oil, +12.7°); **4c** (74%, 40-41°C, +20.7°), **5c** (90%, 45-46°C, +20.2°), **6c** (64%, oil, +27.6°), **7c** (79%, oil, +7.7°); **4d** (100%, 73-74°C, +25.9°), **5d** (70%, 53-54°C, +26.5°), **6d** (82%, oil, +29°), **7d** (90%, oil, +8.9°).

9. (R)-N-Boc-11-Amino-2-benzylundecanoic acid (**10**) was obtained as a colorless oil in 50% yield, $[\alpha]_D^{25}$ -7.8°. Yields (%) and physical constants (mp, $[\alpha]_D^{25}$ c = 1, CH_2Cl_2) for intermediates were as follows: (S)-1-(11-bromoundecanoyl)-2-isopropyloxazolidone (78%, 50-51°C, +54.2°); (S)-1-(11-azidoundecanoyl)-2-isopropyloxazolidone (95%, 23-24°C, +51.7°); (R)-1-[11-azido-2-benzylundecanoyl]-2-(S)-isopropyloxazolidone (45%, oil, -23.4°); (R)-benzyl 11-azido-2-benzylundecanoate (79%, oil, -9.8°).

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