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SIMULTANEOUS SYNTHESIS OF BOTH DIASTEREOMERS OF STEREOSELECTIVELY β-DEUTERATED PHENYLALANINES: (2S,3R)- AND (2R,3R)-PhCHDCH(NH_2)COOH

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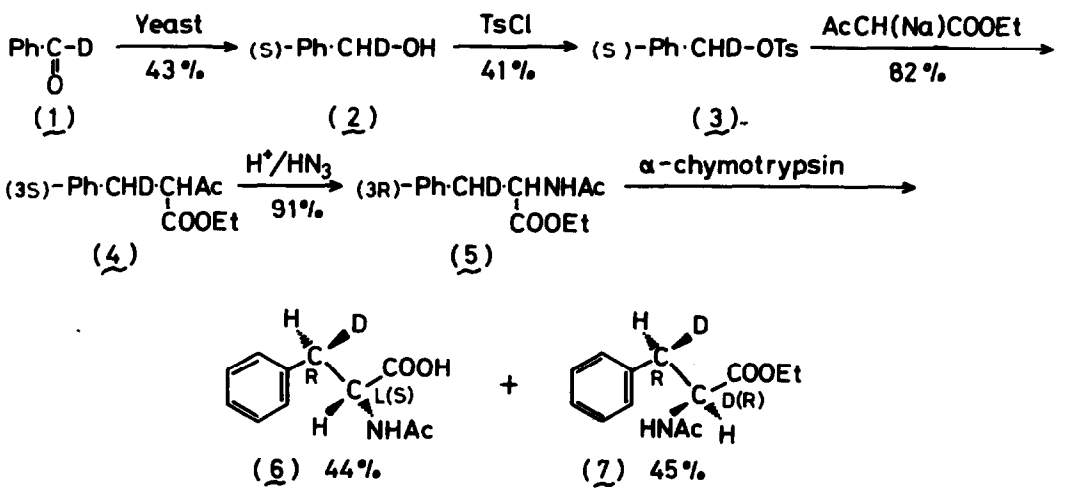
Precise ^{1}H NMR analysis of side chain conformation of amino acids having a β-methylene group requires discrimination of the two prochiral protons on the β-carbon.[1,2] It can be achieved by stereoselective deuteration. Stereoselective β-deuteration of several amino acids by chemical[3,4] and enzymatic[5] methods are published. Kirby and Michael[3] prepared (2S,3R)-phenylalanine-3-d_1 by catalytic hydrogenation of trans-α-acylamidocinnamic acid-3-d_1 and subsequent optical resolution. The method affords only one of the two possible diastereomers. Single diastereomer of known relative configuration suffices to discriminate the two β-protons when their signals are well separated in the NMR spectrum.[2] However, use of both diastereomers is desired for an unambiguous assignment when the two β-proton signals are in close proximity. Thus, we have designed the synthesis of both of the diastereomers as follows.

Reduction of benzaldehyde-α-d_1 (1) prepared from phenylglyoxylic acid by actively fermenting yeast afforded (S)-benzyl alcohol-α-d_1 (2),[6] whose d-content



was 93%(NMR) and the optical purity was confirmed by NMR using a chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]praseodymium, according to the reported procedure.[7] The methylene proton signal appears as a broad singlet corresponding to the pro-R proton signal (at a higher field) of the two methylene proton signals of benzyl alcohol (0.13 M in CCl_4) in the presence of 0.3 molar ratio of the chiral shift reagent. Tosylate (3) reacted with ethyl sodioacetoacetate to give α-benzylacetoacetate (4) with inversion of the configuration as discussed later.[8] Treatment of 4 with hydrazoic acid under the standard condition of Schmidt reaction gave N-acetyl-DL-phenylalanine-3-d_1 (5). Hydrolysis of 5 by α-chymotrypsin[9] afforded the desired products, (2S,3R)-N-acetyl-L-phenylalanine-3-d_1 (6) and (2R,3R)-N-acetyl-D-phenylalanine-3-d_1 ethyl ester (7) in 44% and 45% yield, respectively. This is the first synthesis of a (2R,3R)-phenylalanine derivative.

The optical purities of 6 and 7 were determined by molecular rotation ([φ]) at the trough (225 nm). Their $[\phi]_{225}$-values were +13200° for 6 and -11600 for 7 (c=1.25% in MeOH), which indicated the 91% and 94% purity, respectively, by comparison with the standard samples. The diastereomeric purity of 7 was determined by ^1H NMR in $CDCl_3$ with the aid of a shift reagent, $Eu(dpm)_3$, which separates the two β-methylene signals; the pro-R proton signals of the D-Phe derivative appear at a higher field. An intensity ratio of 83:17 observed corresponds to the epimeric purity of 92% at C-3 (calculated from the d-content and optical purity at C-2). The epimeric purity should be equal to that for 6 in consideration from the synthetic route. This result implies that almost complete inversion of the configuration was caused in the carbanionic reaction and the tosylation step.

The overall yield was about 6% for both 6 and 7, which is almost equal to that with the Kirby's procedure.[3] Our method takes two steps longer, but afford both diastereomers. The loss of deuterium was not observed through all the steps

Studies on a rotameric equilibrium of the side chain in phenylalanine derivatives are in progress using derivatives of 6 and 7. These compounds will also be useful for stereochemical studies on biogenesis including phenylalanine as a substrate or a product.

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