A Direct Preparation of Acetyl-(*S*)-phenylalanyl-(*S*)-phenylalanine Methyl Ester by a Double Asymmetric Hydrogenation

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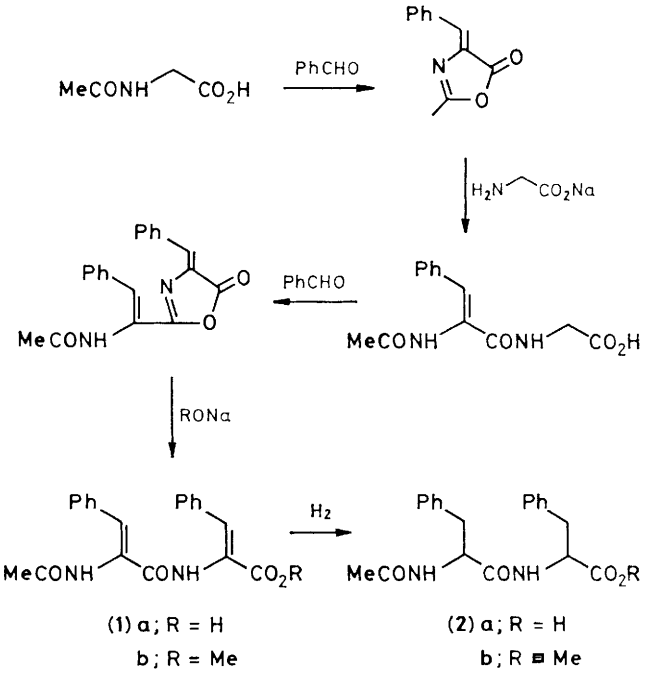
Acetyl-(*S*)-phenylalanyl-(*S*)-phenylalamine methyl ester [Ac(*S*)Phe(*S*)PheOMe] is obtained with high diastereoselectivity and enantioselectivity by catalytic hydrogenation, using [Rh(dipamp)(cod)]$^{+}BF_4^{-}$ (dipamp = *R*,*R*-1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane, cod = cyclo-octa-1,5-diene) as chiral catalyst, of a substrate containing two prochiral doubly bonded carbon atoms, which is easily available from glycine and benzaldehyde.

Asymmetric hydrogenation of dehydroamino-acids has been achieved with high enantioselectivity in the presence of chiral rhodium catalysts[1] and its mechanism clarified.[2] An extension of this method was recently described which involved the controlled reduction of various *N*-acetyl dehydropeptides.[3] We now describe a further development, the successful use of a bisdehydrodipeptide as the prochiral substrate.

Dehydropeptides are available by using various methods;[4] we chose compound (**1**) as a model. This compound was prepared with good yield, according to the method of Bergmann[5] (Scheme 1). Complete reduction of (**1a**) or (**1b**) can be performed with various rhodium catalysts in methanol or methanol–benzene solutions at room temperature under a normal pressure of hydrogen. Preliminary results on (**1a**) with the catalyst combination $[RhCl(C_2H_4)_2]_2$–(−)diop [diop = (2*S*,3*S*)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane] were not very useful since a mixture of the two diastereoisomeric dipeptides (**2a**) was obtained.[6] A reinvestigation of the reaction mixture using h.p.l.c. (reversed phase on C18 column and MeOH–H_2O 2:1 as eluant; elution order: *RR*+*SS* then *RS*+*SR*) showed a diastereoisomer ratio of 55 (*RR*+*SS*):45 (*RS*+*SR*). The enantiomeric excess (e.e.) of each diastereoisomer was 60% (*RR*) and 85% (*RS*), respectively {estimated by polarimetry and by n.m.r. spectroscopy with Eu(hfbc)$_3$ [Eu(hfbc)$_3$ = tris-(heptafluorobutyrylcamphorato)europium] as chiral shift reagent}.

We have now found that the use of the complex [Rh-(dipamp)(cod)]$^{+}BF_4^{-}$ as catalyst [catalyst concentration $1.5 \times 10^{-3} - 3.0 \times 10^{-3}$ M in methanol, 0.15 M in (**1**), 1 atm H_2] leads to complete reduction of (**1b**) with a very high diastereoselectivity, 98:2 as determined by h.p.l.c., to give (**2b**). In addition the major dipeptide (*S*,*S* configuration) has



Scheme 1

a very high optical purity (>95% e.e.) as estimated by n.m.r. spectroscopy with Eu(hfbc)$_3$ as chiral shift reagent.

In conclusion, we have achieved, with high efficiency, a one-pot synthesis of a dipeptide which involves two asymmetric syntheses.

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