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SYNTHESIS OF METHYL 6-ARALKYL-2,5-DIKETOPIPERIDINE-3-CARBOXYLATES AS SYNTHONS OF CONFORMATIONALLY CONSTRAINED PSEUDOPEPTIDES

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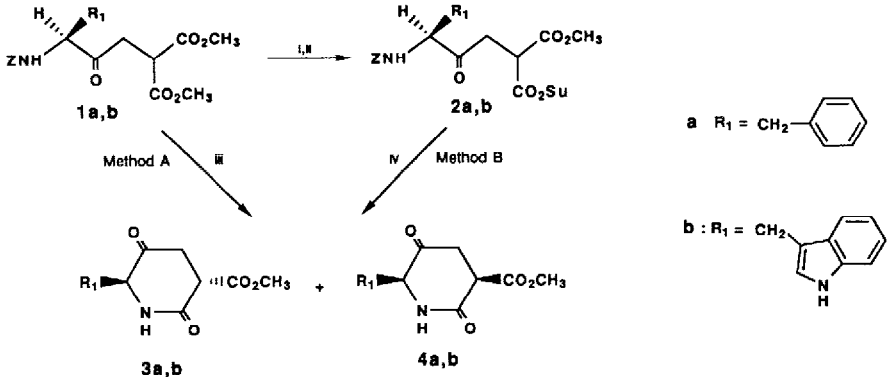
Abstract: Catalytic hydrogenation of the 4-ketoesters **1a,b** or **2a,b** and their 5R-enantiomers, obtained from the corresponding Z-L- and Z-D-amino acid halomethyl ketones, directly leads to the methyl 6-aralkyl-2,5-diketopiperidine-3-carboxylates **3a,b** and **4a,b** and their 6R-enantiomers with high or moderate stereoselectivity at C-3.

Dipeptides in which the scissile amide -CONH- bond has been replaced by an isosteric ketomethylene -$COCH_2$- group have been used to prepare metabolically stable peptides and various enzyme inhibitors.[1] However, this modification causes a loss of the peptide bond rigidity and, therefore, it increases conformational mobility.[2] The inclusion of lactams into peptides has gained wide acceptance for use as conformational constraints in peptides and for the design of peptidomimetics. Thus, the incorporation of 2-ketopiperazines into certain peptide neurotransmitters generates analogues with important biological activity[3] while 3-amino-2-ketopiperidine-6-carboxylic acid stabilizes ß-turns of peptides.[4] All these facts focused our attention on 2,5-diketopiperidines as conformationally restricted analogues of ketomethylene dipeptides. Here, we describe the synthesis of the 6-aralkyl-2,5-diketopiperidine-3-carboxylic acid derivatives **3a,b** and **4a,b** and the corresponding 6R-diastereomers, synthons which could be incorporated into peptides by standard procedures or, upon introduction of a suitable substituent in C-3, could be used as intermediates in the preparation of the corresponding ketomethylene dipeptide analogues cyclo[Aaaψ($COCH_2$)Xaa] (Aaa=Phe, Trp; Xaa=amino acid).

As shown in Scheme 1, 2,5-diketopiperidines **3a,b** and **4a,b** were obtained either from the 4-ketodimethyl esters **1a,b**,[5] prepared from Z-L-phenylalanine or Z-L-tryptophan chloromethyl ketone and dimethyl malonate, or, from the corresponding activated monohydroxysuccinimide ester analogues **2a,b**. In all cases, removal of the Z group and lactamization took place in one pot reaction, when the ketodiesters were hydrogenated at room temperature and 25 psi, using Pd/C as catalyst. Although predominance of 2,5-diketopiperidines **3a,b** having a trans disposition between substituents at C-3 and C-6 were always found, the degree of stereoselectivity was clearly dependent on the starting amino acid derivative. Thus, catalytic hydrogenation and subsequent cyclization of the phenylalanine derivatives **1a** (6 days) and **2a** (2 days) gave, with almost total stereoselectivity, **3a** [m.p. 147°C (from EtOH)] in 42 and 60% yield, respectively, along with traces

(< 5%) of the cis-diastereomer **4a** in both cases. However, a mixture of trans- and cis-diketopiperidines **3b** and **4b** were obtained in a 5:2 ratio (42% overall yield) from **1b**, and in a 3:2 ratio (40% overall yield) from **2b**, as determined by ^{1}H NMR spectroscopy. Similar results in yield and stereoselectivity were found when the corresponding D-amino acid derivatives were used as starting materials. Thus, the (3R,6R) enantiomer of **3a** was obtained almost exclusively from the 4-ketoesters derived from Z-D-phenylalanine, while (3R,6R) and (3S,6R) diastereomeric mixtures of diketopiperazines in a 5:2 ratio were obtained in the case of the D-tryptophan ester analogues.[6]



Scheme 1. Reagents and conditions: i, NaOH, ii, HOSu/DCC, iii, H_2/Pd-C, MeOH, iv, H_2/Pd-C, EtOAc

The ^{1}H NMR study of these 6-aralkyl substituted-2,5-diketopiperidines has demonstrated that, in a similar way to that reported for 2,5-diketopiperazines,[7] the preferred conformation of the arylmethylene side chain is one in which the aromatic ring folds over the diketopiperidine cycle.[8] According to this, the H-3 proton in compounds **3a** and **3b**, which is cis to the 6-aralkyl moiety, are more shielded than in the corresponding diastereomers **4a** and **4b** (δ=0.87 ppm), due to the aromatic ring current. This shielding allows to assign the stereochemistry at the C-3 center. Thus, the configurations of **3a,b** and **4a,b** were established as (3S,6S) and (3R,6S), respectively.

Studies on the influence of the starting amino acid derivative on the stereoselectivity of the lactamization are now in progress.

References and footnotes

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