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Sulfoxide-mediated diastereoselective Michael additions. New enantioselective synthesis of C-4 substituted 2-pyroaminoadipic acids

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Abstract

Diastereoselective reactions of suitably functionalized homochiral β-iminosulfoxides with Michael acceptors provide a new and efficient route for the asymmetric synthesis of C-4 substituted 2-pyroaminoadipates. Extension of the scope of the sulfoxide-mediated aza-enolate conjugate addition (Hua's reaction) has also been explored.

Keywords: amino acids and derivatives; sulfoxides; Michael reactions; asymmetric induction.

The synthesis of modified glutamic acids has recently attracted considerable attention due to their exceptional value for the exploration of excitatory amino acid receptors.[1] In this context, an increasing number of papers dealing with the preparation of the homologous 2-aminoadipic acid **1**[2,3] and their structurally constrained analogues and bioisosteres,[2b,c] as well as the synthesis of closely related substituted pipecolic acids **2**,[4] have recently appeared.

However, most of the reported stereoselective functionalizations of 2-pyroaminoadipates **3** were directed by the pre-existing chiral center in racemic systems. The lack of asymmetric routes to these kinds of structures with pharmacological activity, and our interest in the synthesis of non-proteinogenic aminoacids,[5] prompted the research described herein.

We envisioned that optically pure β-iminosulfoxides **4** (Scheme 1) could become precursors of 2-pyroaminoadipates via diastereoselective conjugate additions to α,β-unsaturated esters and cyclization. Sulfoxide-directed reduction of the imino group followed by oxidation of the terminal hydroxyl group in the final step would lead to C-4 substituted non-racemic systems **3** where the desired aminoadipic acid is protected as the internal lactam.

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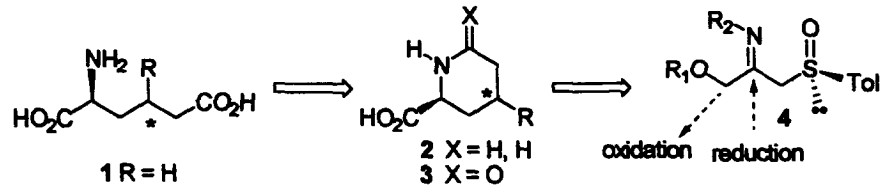
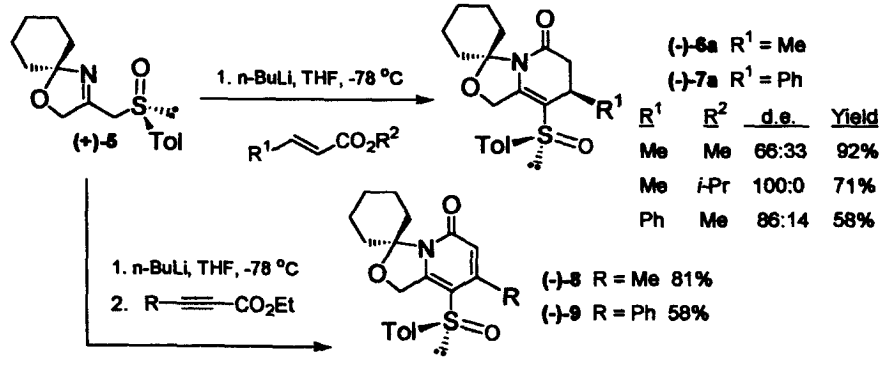


Scheme 1.

The sulfinyl group has proven to be an efficient chiral auxiliary for a wide variety of transformations in asymmetric synthesis[6a] and there are quite a few reports of its application to the synthesis of optically pure amino acids.[6b,c] On the other hand, Hua et al. have reported several remarkable and elegant syntheses of natural indolizidine and quinolizidine alkaloids using α-sulfinyl ketimine anions where the sulfoxide controlled the stereochemistry of different cyclic lactams.[7] Thus, we have tried to explore the application of Hua's reaction to pyroaminoadipate synthesis, starting from the 3-oxazoline-methylsulfoxide (+)-**5** which was prepared as described by Khiar.[8]

In a similar procedure as reported by Hua,[7b] lithiation of (+)-**5** (>98% e.e.) using *n*-BuLi in THF at −78°C, followed by addition of methyl crotonate afforded a 66:33 mixture of 4*R*:4*S*-3-sulfinyl piperidones in excellent overall yield and easily separable by silica gel chromatography (Scheme 2). It was observed that leaving the reaction at rt for 16 h was necessary to complete the second cyclization step.



Scheme 2.

The lack of stereoselectivity in the Michael reaction was overcome by using a more hindered Michael acceptor.[7b] By simply changing to isopropyl crotonate the reaction smoothly afforded the 4*R*-isomer (−)-**6a** as the only product.[‡] In order to extend the scope of this reaction, other acceptors not previously employed by Hua et al. were explored. The addition of methyl cinnamate took place with high selectivity favoring the 4*R*-isomer (−)-**7a**, which shows that changing the electronics of the unsaturated ester does not affect either the reactivity nor the stereochemistry of the reaction.[§]

It was also found possible to efficiently add the aforementioned lithium aza-enolate of (+)-**5** to ethyl propiolates[¶] in order to obtain the substituted homochiral pyrimidones (−)-**8** and (−)-**9**. In these reactions,

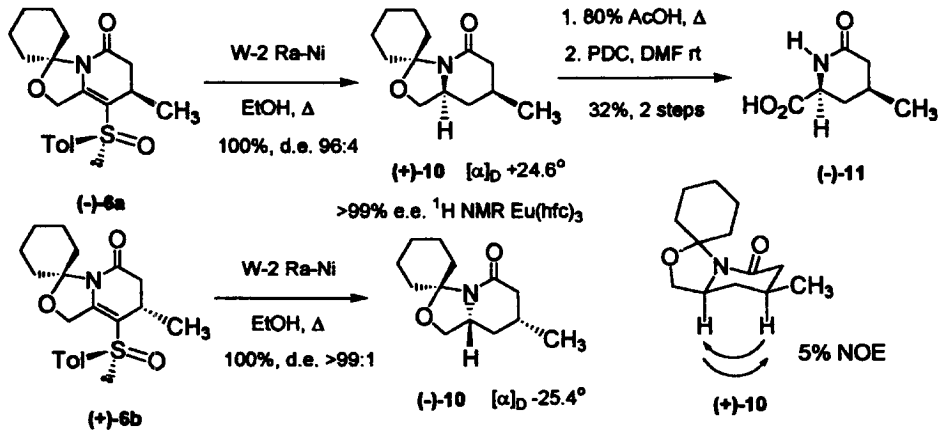
[‡] No traces of the corresponding 4*S* isomer (−)-**6b** could be detected within the detection limit of 300 MHz NMR. The absolute configuration was unambiguously established by comparison of the key ^{1}H NMR peaks with similar diastereomers obtained by Hua et al.[7b]

[§] A rationale to explain the observed stereochemistry has been proposed by Hua et al.[7b]

[¶] No reaction occurred and the starting material was fully recovered in the reaction with ethyl propiolate probably due to the acidity of the alkynyl proton.

the anionic intermediate produced after the conjugate addition must rearrange to the *cis* conjunction needed for the cyclization which is probably the driving force of the process.

The synthesis of the desired optically pure, substituted pyroaminoadipates was carried out in just three steps from the adduct (–)-**6a** (Scheme 3). Removal of the chiral auxiliary and reduction of the enamine *anti* to the methyl group was achieved in one pot and quantitative yield using freshly prepared Raney Nickel in refluxing ethanol.[9] The relative configuration of the new chiral center was assigned by differential NOE experiments. The comparison of the optical rotation of pure (+)-**10** with its enantiomer obtained from the same selective reduction of (+)-**6b**, and ^{1}H NMR chiral shift experiments with Eu(III) complexes confirm that no racemization occurred during the synthesis (Scheme 3).



Scheme 3.

Unfortunately, the deprotection of the cyclohexylidene acetal of the optically pure pyrimidone (+)-**10** was not trivial. After long experimentation[‖] we found that only refluxing in 80% aqueous AcOH cleaved the acetal although in modest yield. Final oxidation to the carboxylic acid afforded the L-(2*S*,4*R*)-4-methyl pyroaminoadipic acid (–)-**11**.

It is worth mentioning that from the minor isomer of the non-selective Michael addition to methyl crotonate (+)-**6b**, the reduction with Raney Nickel proceeded in a similar excellent manner to (–)-**10**,[††] which could lead to a D-aminoadipic acid analog. However, the overall strategy would allow the synthesis of L- or D-aminoacids by the simple choice of the *R*- or *S*-enantiomer of the chiral *p*-tolyl sulfoxide group in the starting material and using the isopropyl crotonate as the Michael acceptor.

In summary, a new short and efficient route to optically pure, 4-substituted pyroaminoadipic acids has been developed, where the chirality is controlled by the versatile and easily removable chiral sulfinyl group. We are currently: trying to extend the scope of this route to introduce different functionality in the pyroaminoadipates; exploring the chemistry of the interesting chiral β-iminosulfoxides[10]; as well as getting new insights in the mechanism of the conjugate addition.

[‖] Some other conditions were tested: 1N or 3N aqueous HCl, reflux; aq. TFA; H_2SO_4 in CH_3CN/H_2O; AlI_3.

[††] All new compounds have been satisfactorily characterized.

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