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Asymmetric Synthesis of Methyl *N*-(1-phenylethyl)-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]-4-oxo dec-8-en-6-carboxylate by an Intramolecular Diels-Alder Reaction

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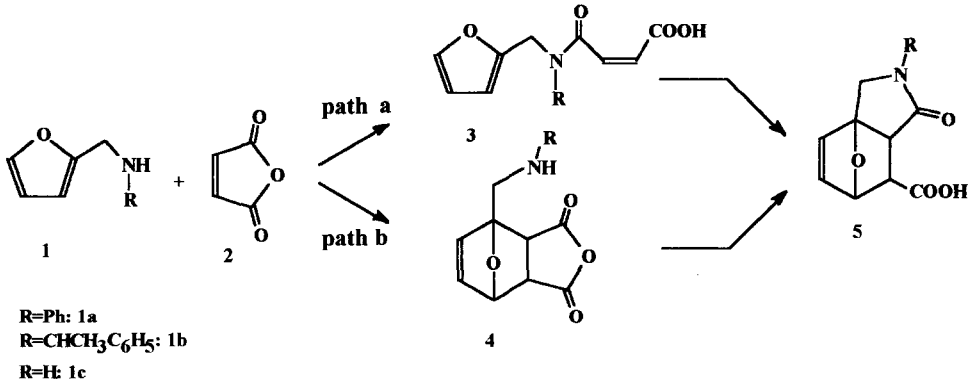
Abstract: The title compound can be obtained with up to five asymmetric centres of known absolute configuration by a diastereoselective intramolecular Diels-Alder reaction between optically active *N*-substituted furfurylamines and maleic anhydride, in which the chirality is transferred from one stereocentre to the four others.

Tricylic adducts containing a γ-lactam ring are formed in high yields when *N*-substituted furfuryl amines are reacted with maleic anhydride.[1] The reaction may proceed by condensation of the amine with maleic anhydride followed by an intramolecular Diels-Alder reaction (IMDA) (path **a**) or by an intermolecular Diels-Alder reaction between the furan nucleus and maleic anhydride and then, attack of the amino group on the anhydride moiety (path **b**) (Scheme 1).[2]

In an analogous reaction with an oxygen atom in place of the nitrogen atom these two pathways have been postulated.[3]



Scheme 1

We recently reported that path **a** is followed in such reaction when the nitrogen atom is substituted

by a phenyl (**1a**) or a 1-phenylethyl group (**1b**) and we have isolated and characterised the condensation adduct **3a** (R=Ph) which is quantitatively formed in the first step of the reaction.[4]

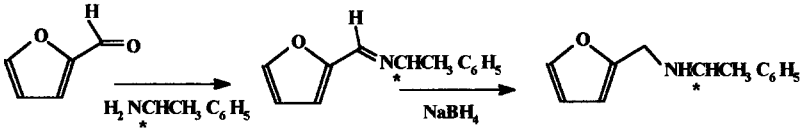
It must be noted that when the unsubstituted furfurylamine (**1c**) is used the condensation product **3c** is formed but the IMDA reaction is not observed in our conditions (room temperature, 1 to 100 h). This behaviour is identical to the one observed in analogous systems with a carbon chain or an ester group in the tether linking the furan diene and the dienophile for which it has been observed that the IMDA reaction is strongly accelerated when substituents are present on the sidearm chain. This is known as the "*gem*-dialkyl effect".[5]

It is also known that in such IMDA reactions, when the furan diene and the dienophile are linked by a short sidearm, only the cycloadduct with the sidearm *exo* (or *syn*) with respect to the oxa bridge is formed.[6] Such a diastereoselective reaction can therefore be used to prepare cycloadducts containing a γ-lactam ring system, in which up to five asymmetric centres of known absolute configuration are present.

A similar approach was recently described, using a furan nucleus and a dienophile tethered by a four carbon atoms sidearm containing an asymmetric carbon atom centre (bearing a methyl group). With this substrate a thermodynamically controlled asymmetric induction was observed.[7]

These results prompted us to report that such a reaction can be extended to substrates where a nitrogen atom bearing an asymmetric centre is included in the tether.

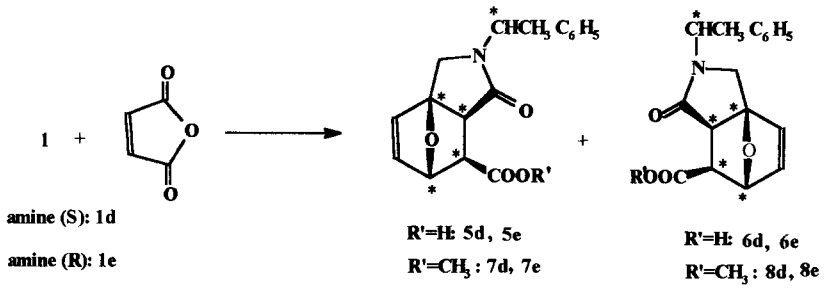
(*S*)- and (*R*)- 1-phenylethylamines were used as chiral source in this work. The preparation of the substrates **1d** and **1e** is illustrated in Scheme 2.



Scheme 2

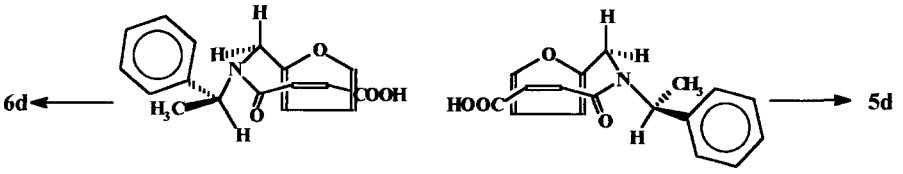
When reacted with maleic anhydride, amine **1d** or **1e** underwent the IMDA reaction at room temperature. Intermediate compounds were not isolated. The reaction can be performed without solvent or in diethyl ether (100%, 18h, 0°C) benzene (81%, 96h, r.t.) or methylene chloride (76%, 96h, r.t.). In a typical experiment 1 mM of the amine in 0.5 ml of solvent is added to a solution of 1 mM of maleic anhydride in 2.0 ml of solvent at 0°C or room temperature. In these conditions two diastereoisomeric adducts are obtained in which four new asymmetric centres are formed (Scheme 3).

Starting with amine **1d** the diastereomeric acids **5d** and **6d** are formed in a 65:35 ratio. After esterification with diazomethane, the corresponding methyl esters **7d** and **8d** can be readily isolated in their pure form by flash chromatography.



Scheme 3

The absolute configuration of the major adduct **5d** was established by X-ray crystallography of **7d** and was shown to be 1(*R*),5(*S*),6(*R*),7(*S*). With amine **1e** (*R*) the same diastereoselectivity is observed (65:35) with the major isomer **6e** - 1(*S*),5(*R*),6(*S*),7(*R*)- being the enantiomer of **5d**. The minor diastereoisomer **5e** is the enantiomer of **6d**. The diastereoselectivity could be explained by considering the steric repulsion between the phenyl group and methylene group of the tether in the approach leading to the minor isomer. This is illustrated in Scheme 4 for the (*S*) series.



Scheme 4

Such an attempt to control the diastereoselectivity of an IMDA reaction, involving an *N*-substituted amide very similar to **3** was previously reported to fail. The nitrogen atom was in this case substituted by an optically active 1-phenyl-2-hydroxy ethyl group.[8]

We also observed that if **7d**, **8d**, **7e** and **8e** are stable in their pure form, **7d** and **8d** are in equilibrium via a retro Diels-Alder reaction when dissolved in a solvent. Surprisingly this equilibration reaction is accelerated in polar solvents although it has been previously described that in analogous cyclization of such tertiary amide the reaction is unaffected by the polarity of the solvent.[9] In our case we observed that when pure **7d**, for instance, is dissolved in $CDCl_3$ it slowly equilibrates with **8d** reaching the same diastereomeric ratio 65:35 (**7d-8d**) after five months at room temperature. When the same experiment is performed in DMSO-d_6, the equilibration is achieved in fifteen days at room temperature while it takes only five hours at 50°C. This clearly indicates that the reaction is under thermodynamic control and that **7d** is the thermodynamically most stable cycloadduct. The same observations were made when pure **7e** or **8e** were submitted to the same conditions; they equilibrate in a 65:35 mixture of **8e** and **7e**. It is thus possible, starting from either **1d** or **1e**, to obtain more than 95% of one of the two

enantiomers **7d** or **8e** by two successive, flash chromatography separation-equilibration reaction sequences.

It has been shown previously that the acid or the ester function on C-6 can be easily and totally epimerized to the *endo* position by refluxing in a pyridine-acetic acid mixture, thus allowing the inversion of the configuration of C-6 stereocentre.[2] Furthermore the cleavage of the oxa bridge, leading to bicyclic systems is well documented and can be performed by highly stereoselective attack of organolithium reagents or by base-induced elimination.[10]

The methodology we have established for producing γ-lactam ring systems with up to five asymmetric centres, in which chirality is transferred from a stereocentre to four others in one step, is thus particularly versatile. The highly functionalized adducts are formed in high yields and can allow further elaboration.

Further work is currently in progress to evaluate the potential of others chiral amines in these thermodynamic asymmetric control approaches as well as to illustrate the usefulness of that type of chiron in more elaborated syntheses.

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