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Asymmetric Hetero Diels-Alder Reaction of *N*-Benzylimines Derived from *R*-Glyceraldehyde: A New Approach to Homochiral Piperidine Building Blocks and its Application to the Synthesis of (2*R*)-4-Oxopipecolic Acid

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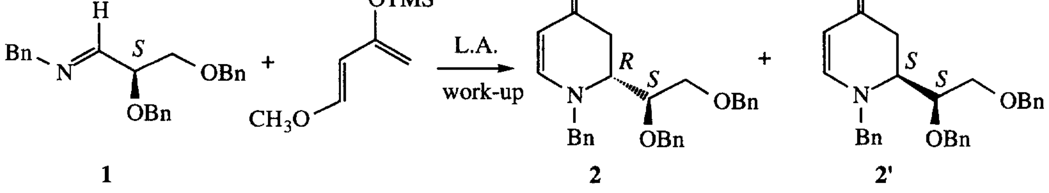
Abstract: The N-Benzyl imine derived from 2,3-di-*O*-benzyl-D-glyceraldehyde reacts with Danishefsky's diene to afford the corresponding hetero Diels-Alder adduct with a high diastereoselectivity. This compound can be transformed to enantiomerically pure (2*R*)-4-oxopipecolic acid .

The piperidine ring is one of the most abundant molecular fragments in both natural products and synthetic compounds with biological activity.[1] For this reason, the development of methods for the asymmetric synthesis of homochiral piperidine building blocks has recently received considerable attention.[2] The asymmetric hetero Diels-Alder cycloaddition using imines as dienophiles has given access to a wide variety of possibilities for the synthesis of the piperidine ring. The low reactivity of common deactivated imines is counteracted by the use of electron-rich butadiene derivatives such as Brassard's diene and Danishefsky's diene and/or the use of Lewis acids. The diastereoselectivity of this reaction has been investigated with chiral imines derived from chiral amines,[3] chiral amino alcohols,[4] chiral amino sugars,[5] or chiral amino acid derivatives,[6] as well as with the use of chiral Lewis acids,[7] and more recently with the use of chiral dienes.[8] Nevertheless, to the best of our knowledge and excluding the work of Akiba *et al.*,[9a] that describes the use of the benzylimine derived form (*S*)-lactaldehyde as the starting material, and the work of Midland and McLoughlin,[9b] that studies the cycloaddition reaction of a chiral imine derived from (2*R*,3*S*)-2,3-*O*-cyclohexylidene-2,3-dihydroxybutyraldehyde with Brassard´s diene, there are no examples in the literature of hetero Diels-Alder cycloaddition reactions using chiral imines as dienophiles in which the chiral matrix is the carbonyl moiety.

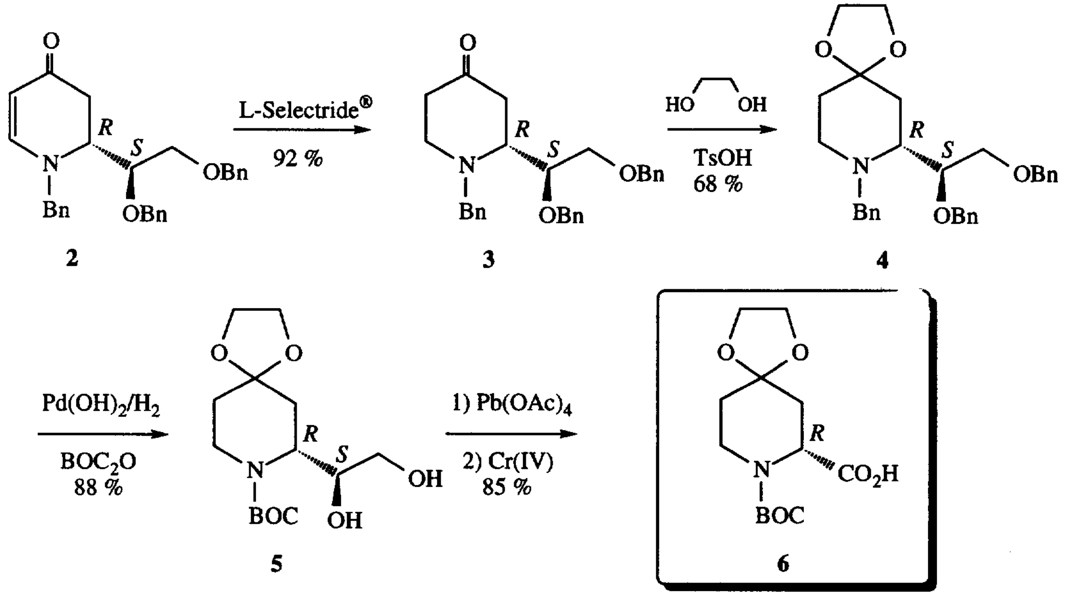
Our recent work has been directed towards the synthesis of highly functionalised amino acids from chiral imines derived from conveniently protected D-glyceraldehyde,[10] a useful starting material from the chiral pool. During the course of this research we have studied the behaviour of imine **1**, prepared from 2,3-di-*O*-benzyl-D-glyceraldehyde and benzylamine in the presence of anhydrous magnesium sulphate, [10b] towards Danishefsky's diene.



Scheme 1

Danishefsky's diene (1.2 eq) reacts with imine **1** under standard conditions (i.e. in dichloromethane (2 ml/mmol) in the presence of 1.1 eq of a Lewis acid catalyst) to give the corresponding hetero Diels-Alder adduct in low to acceptable yields depending on the Lewis acid and reaction temperature used (Scheme 1). In most cases good stereoselectivities are obtained. The reaction in the presence of $MgBr_2$ or $Eu(fod)_3$ works slowly, even at room temperature, and the imine decomposes in solution. However, ZnI_2, $BF_3.Et_2O$ and Et_2AlCl were all found to be effective catalysts to activate the imine, and good levels of induction and acceptable yields were obtained that improved on decreasing the reaction temperature from room temperature to -40 °C. A rather different situation was observed when the reaction was carried out in the presence of $SnCl_4$ or $TiCl_4$. Both catalysts promoted a rapid decomposition process, even at -78 °C, and no adducts were detected in either case. From this study we conclude that the best catalyst system is $ZnCl_2$ in dichloromethane at -40 °C. Under these reaction conditions a 90/10 diastereomeric mixture of the desired hetero Diels-Alder adducts **2, 2'** was obtained in 65 % isolated yield. We subsequently studied the influence of solvent polarity in the hetero Diels-Alder reaction catalysed by ZnI_2 and we observed that, with aprotic solvents, an increase in the solvent polarity led to an improvement in the diastereoselectivity of the cycloaddition reaction. When the reaction was carried out in acetonitrile or nitroethane at -40 °C a 95/5 diastereomeric mixture of the desired hetero Diels-Alder adducts **2, 2'** was obtained in about 65 % isolated yield. At this point it is worth noting that the same results were obtained when a less than stoichiometric amount on ZnI_2 (0.2 eq) was used as catalyst.

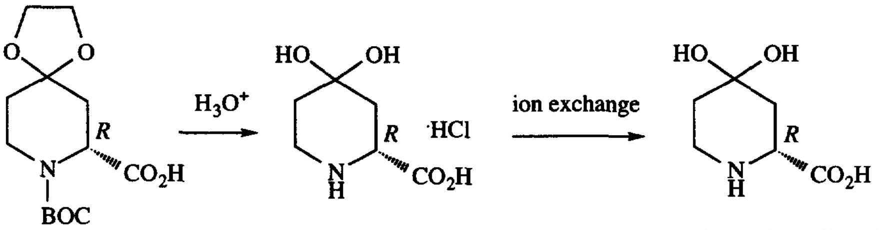
The diastereomeric ratios were determined directly from the crude reaction mixtures by ^{1}H-NMR (major: δ 6.90 (dd), minor 7.02 (dd)), and the absolute configuration of the newly formed stereogenic carbon was ascertained to be (*R*) after conversion to a compound of known configuration as detailed below.



Scheme 2

Enamidone **2** can be a versatile intermediate for the construction of a wide variety of enantiomerically pure compounds containing the piperidine ring. The alkene moiety can act as a Michael acceptor in asymmetric conjugate additions, the carbonyl group can be stereoselectively transformed into several functional groups and finally, the 1,2-diol moiety at C(2) can be conveniently elaborated to furnish a wide variety of substituents of known stereochemistry. To illustrate the synthetic utility of this compound we have performed the synthesis of conveniently protected (2*R*)-4-oxopipecolic acid, an interesting compound recently used in the synthesis of selective NMDA antagonists,[11] in 45 % overall yield from compound **2** accordingly to scheme 2.

Conversion of compound **2** (90 % de)[12] into the corresponding saturated compound **3** was conveniently performed, in 92 % yield, with the use of L-Selectride® through a selective reduction of the double bond. Subsequent debenzylation of the diol moiety, followed by oxidative cleavage, required prior protection of the carbonyl group. For this reason, ketone **3** was treated with ethylene glycol in the presence of *p*-toluenesulphonic acid to afford ketal **4** in 68 % yield as a single diastereoisomer as revealed by NMR spectroscopy. Compound **4** was debenzylated by hydrogenolysis in the presence of di-*tert*-butyldicarbonate, using palladium hydroxide as a catalyst, to afford *N*-Boc derivative **5** in high yield (88 %). Oxidative cleavage of the 1,2-diol moiety of compound **5** by successive treatment with lead tetraacetate followed by Jones oxidation of the intermediate aldehyde, gave (2*R*)-4-oxopipecolic acid **6** in a form conveniently protected for peptide syntheses.[13]



7

***(2R)*-4-oxopipecolic acid monohydrate**

Scheme 3

In order to determine the absolute stereochemistry of C(2), this compound was further elaborated to give the known compound (*R*)-4-oxopipecolic acid as its hydrate (scheme 3). Acid hydrolysis of **6** with a mixture of 6N hydrochloric acid-THF under reflux conditions for 7 days cleanly afforded the amino acid hydrochloride monohydrate **7**. The specific rotation value measured for this compound ($[\alpha]_D^{25} = -4.0$ (c = 0.55, H_2O)) compared with the known value for (2*S*)-4-oxopipecolic acid hydrochloride monohydrate[14] clearly indicates an (*R*)-configuration at the stereogenic centre. Elution of the hydrochloride salt through an ion exchange chromatography column afforded the hydrate of (2*R*)-4-oxopipecolic acid in enantiomerically pure form.

In conclusion, a simple method which allows the synthesis of a versatile building block for the synthesis of compounds containing the piperidine ring is described, starting from a common, commercially available precursor - D-mannitol. The synthetic utility of this chemistry has been illustrated by its application to the synthesis of enantiomerically pure (2*R*)-*N*-*tert*-butoxycarbonyl-4-(1,3-dioxolane-2-yl)-piperidine-2-carboxylic acid **6**. Additional studies on the synthetic utility of this chiral building block are currently underway and will be published in due course.

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