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Asymmetric Synthesis of L-Carbidopa Based on a Highly Enantioselective α-Amination

Àlex Pericas, Alexandr Shafir, and Adelina Vallribera*

Department of Chemistry, Universitat Autònoma de Barcelona, Cerdanyola del Vallès, 08193 Barcelona, Spain

adelina.vallribera@uab.es

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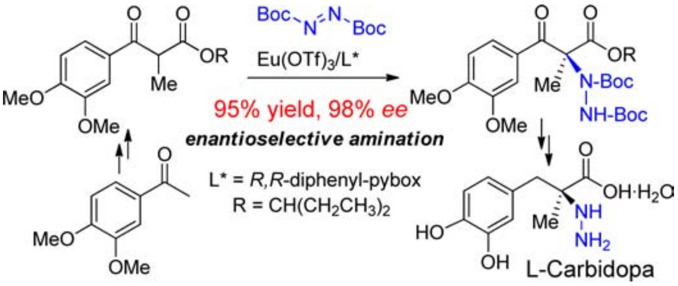
ABSTRACT



A stereoselective synthesis of L-carbidopa in seven steps and 50% overall yield from commercial compounds is described. The key step involves a highly enantioselective α-amination reaction of an acyclic *β*-ketoester with di-*tert*-butyl azodicarboxylate induced by europium and (*R*,*R*)-diphenyl-pybox.

Parkinson's disease, caused by the low concentration of the neurotransmitter dopamine in the brain, is the most common neurodegenerative illness. Traditionally, levodopa (L-DOPA), the biogenetic precursor of dopamine, has been used to temporarily diminish the disease's motor symptoms. This treatment, however, is not very efficient and produces side effects due to the drug undergoing decarboxylation to dopamine at the peripheral regions. Thus, levodopa is commonly administered in combination with L-carbidopa, **1**, an inhibitor of the peripheral aromatic L-amino acid decarboxylase (DDC), an enzyme responsible for the metabolism of levodopa to dopamine. Thus, the use of L-carbidopa helps increase the levodopa plasma half-life from 50 min to 1.30 h. Given that L-carbidopa cannot cross the blood brain barrier, only the peripheral DDC is inhibited. This reduces the side effects caused by dopamine on the periphery, as well as increasing the concentration of L-DOPA and dopamine in the brain.[1]

As part of our research on enantioselective Michael[2] and aza-Michael reactions,[3] we became interested in applying a metal-catalyzed α-hydrazination procedure to perform an enantioselective synthesis of L-carbidopa. Given that the bulk of previously described methods for the preparation of this drug have generally relied on the resolution of enantiomers and/or transformation of chiral precursors,[4] it was highly desirable to develop a new synthesis where an

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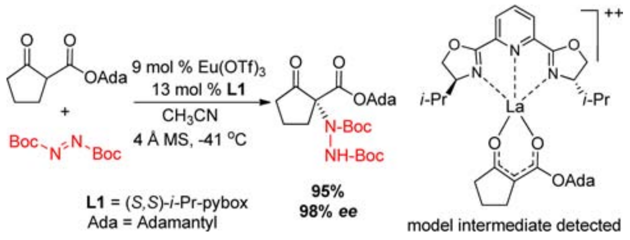
enantioselective catalytic transformation would be the key step.

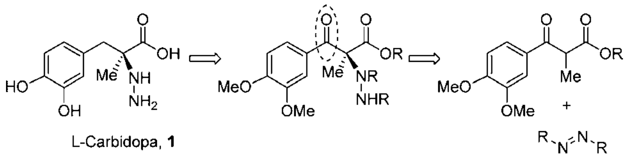
Our previous work in this area involved the use of lanthanides as versatile Lewis acids for asymmetric catalysis.[5] In particular, the potential of these metals for higher coordination numbers[6] makes them a favorable match for pybox ligands.[7] In 2007, we reported that a combination of europium triflate and (*S,S*)-*i*Pr-pybox (**L1**) catalyzed a highly enantioselective electrophilic hydrazination of cyclic β-ketoesters (Scheme 1).[3b] To account for the stereochemical outcome (*R* as major enantiomer), a model key complex was detected (ESI), consisting of the La ion bound to the C_2-symmetric pybox and a molecule of the ketoester. Enantioface differentiation would presumably take place upon differentiated azodicarboxylate binding to this complex. In addition to such binary L-M systems, Shibasaki and co-workers developed a series of lanthanum-catalyzed enantioselective hydrazination protocols. In these, excellent enenatioselective induction was achieved employing amino acid based ligands/additives.[8]The method was used to carry out a multigram synthesis of a spirosuccinimide derivative Ranirestat, identified as a promising aldose reductase inhibitor.[8b]

Scheme 1. Our Group's Previous Example of Enantioselective Aza-Michael Reaction (from Ref 3b)



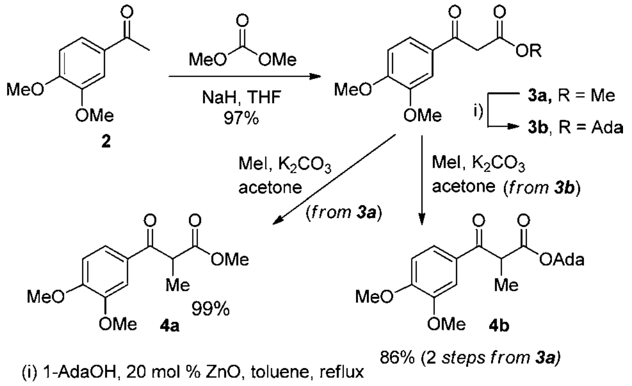
With these precedents, we set out to apply this methodology as a key step in the enantioselective synthesis of L-carbidopa. While ostensibly not a β-dicarbonyl derivative, the compound does feature a hydrazine moiety α to an ester and could, therefore, be envisioned as derived from an enantioselective amination of an open-chain β-ketoester, followed by the desoxygenation of the keto group (Scheme 2). Obviously, in order for this approach to succeed, the high enantioinduction obtained previously in cyclic β-ketoester would have to be extendable to the more flexible (and more challenging) open-chain substrates.

Scheme 2. Retrosynthesis of L-Carbidopa via α-Hydrazination



We envisioned the use of the commercially available 1-(3,4-dimethoxyphenyl)ethanone, **2**, as a precursor to the open-chain β-ketoester **4** (Scheme 3). Thus, reaction of **2** with dimethylcarbonate in the presence of 2 equiv of NaH afforded, after a 3 h reflux in toluene, the desired β-ketoester **3a** in 97% yield (Scheme 3). Subsequent alkylation of **3a** under classical conditions using methyl iodide and potassium carbonate in anhydrous acetone afforded the methyl ester **4a** in 99% yield. Our previous experience also suggested that a β-ketoester substrate bearing an OR group bulkier than the methoxy might be necessary to achieve efficient enantioinduction. Therefore, after testing a series of conditions, transesterification of **3a** with 1-adamantanol was accomplished using catalytic amounts of ZnO in refluxing toluene.[9] Treatment of the newly prepared **3b** with MeI and K_2CO_3 afforded the adamantyl-protected substrate **4b** in 86% yield over the two steps.

Scheme 3. Synthesis of Amination Substrates **4a** and **4b**



A series of experiments were then carried out in order to establish the best conditions for the lanthanide-catalyzed

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(9) The method was also found to be applicable to a wide range of substrates; see: Pericas, A.; Shafir, A.; Vallribera, A. *Tetrahedron* **2008**, *64*, 9258–9263.

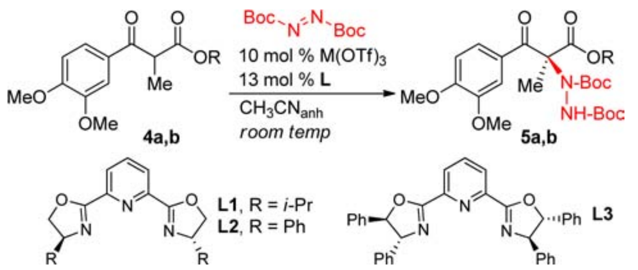
α-amination of substrates **4a** and **4b** with the BOC-protected azodicarboxylate (Table 1). In this preliminary screen, $Eu(OTf)_3$ and $Yb(OTf)_3$ were used in combination with the chiral pybox ligands **L1**, **L2**, and **L3** at room temperature. The study revealed that, in the case of the methyl ketoester **4a**, poor enantiomeric excesses (41−54%) were observed with both europium and ytterbium triflates and all three ligands (runs 1−5). The $Yb(OTf)_3$/pybox combination was found to be less effective, requiring up to 5 days to reach full conversion (down to 1.5 h using $Eu(OTf)_3$/**L2**). As expected, higher enantioselectivities were reached for the sterically hindered adamantyl ketoester **4b** (runs 6−10). Thus, we were pleased to find that **5b** was obtained in $>99.9\%$ ee using a combination of europium(III) triflate and the bis(diphenyloxazoline) derivative **L3** (run 8).

Next, reductive conversion of the ketone group in **5** to a methylene group was attempted. Reduction methods in acid medium had be avoided to preserve Boc protective groups. After numerous unsuccessful attempts, including a Raney nickel catalyzed desulfurization of the corresponding tioacetal[10] and a deoxygenation through reduction of the tosylhydrazones,[11] we concluded that the extremely sluggish reactivity was likely due to the steric hindrance of the bulky *N*-protecting groups. Thus, the Boc groups were easily removed with trifluoroacetic acid, and the free hydroazine intermediates were protected by treatment with 1 equiv of benzyl chloroformate and $NaHCO_3$ in toluene. This sequence afforded the Cbz-protected **6a** and **6b** in 92% and 95% yield, respectively (Scheme 4).

After this modification, the keto group of the methyl ketoester **6a** could be deoxygenated via an ionic hydrogenation procedure employing trialkylsilane in trifluoroacetic acid (TFA).[12] Conceptually, this method consists in delivering to the substrate the formal H_2 equivalents in the form of H^- (from silane)/H^+ (from TFA) pair. Best results were achieved by conducting the reaction under an Ar atmosphere (Scheme 4 and Table 2). Under these conditions, the deoxygenation of **6a** took place in the presence of triethylsilane (7.5 equiv) and TFA (as a solvent, ~50 equiv) and afforded the methylene product **7a** in 74% yield after 24 h (Table 2, run 1). The reaction time could be shortened by employing the less hindered ethyldimethylsilane (entry 2). This reduction method, unfortunately, failed for the more sterically congested adamantyl ketoester **6b**, leading to what appeared to be a retro-Claisen cleavage of the substrate (Table 2, entries 4 and 5).

These results indicated that the presence of a bulky 1-adamantyl group, while benefiting the enantioselectivity of the lanthanide-catalyzed α-amination of **4b**, was detrimental for the ionic deoxygenation. It was, therefore, necessary to find an R group bulky enough to maintain high levels of ee, while still allowing the subsequent ionic hydrogenation. After testing a number of substrates, we found that the secondary 3-pentyl group fulfills these requirements. As shown in Scheme 5, the new 3-pentyl *β*-ketoester substrate **4c** was prepared in three steps from the acetophenone **2** employing the previously developed procedure. Substrate **4c** then underwent enantioselective α-amination with di-*tert*-butyl azodicarboxylate using a $Eu(OTf)_3$/**L3** mixture as a catalyst. It was found that the enantiomeric excess of 95% achieved at room temperature could be further improved at −20 °C. At this temperature, the adduct **5c** was obtained in 95% yield and 98% ee.

Table 1. Ln-Catalyzed Enantioselective α-Aminations of **4** with Di-*tert*-butyl Azodicarboxylate[a]



run	substrate	ligand	$M(OTf)_3$	time[b]	% ee[c]
1	**4a**	**L1**	Eu	5 h	41
2	**4a**	**L2**	Eu	1.5 h	53
3	**4a**	**L3**	Eu	3 days	51
4	**4a**	**L1**	Yb	5 days	54
5	**4a**	**L2**	Yb	5 days	54
6	**4b**	**L1**	Eu	1 day	74
7	**4b**	**L2**	Eu	2 days	88
8	**4b**	**L3**	Eu	1 day	**>99.9**[d]
9	**4b**	**L1**	Yb	5 days	74
10	**4b**	**L2**	Yb	5 days	98

[a] Reactions were conducted in acetonitrile (2 mL) using 1 equiv of *β*-ketoester, 1.3 equiv of di-*tert*-butyl azodicarboxylate, 0.1 equiv of $M(OTf)_3$, and 0.13 equiv of pybox ligand. [b] At the indicated reaction time, the conversion was 100% in all the cases. [c] The ee's were determined by HPLC. [d] 83% yield

Scheme 4. Deprotection and Deoxygenation Steps Leading to **7a**

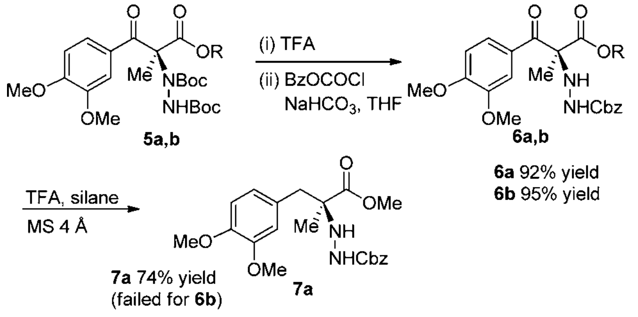


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Table 2. Ionic Reduction of **6** in Acidic Media (Scheme *4*)[a]

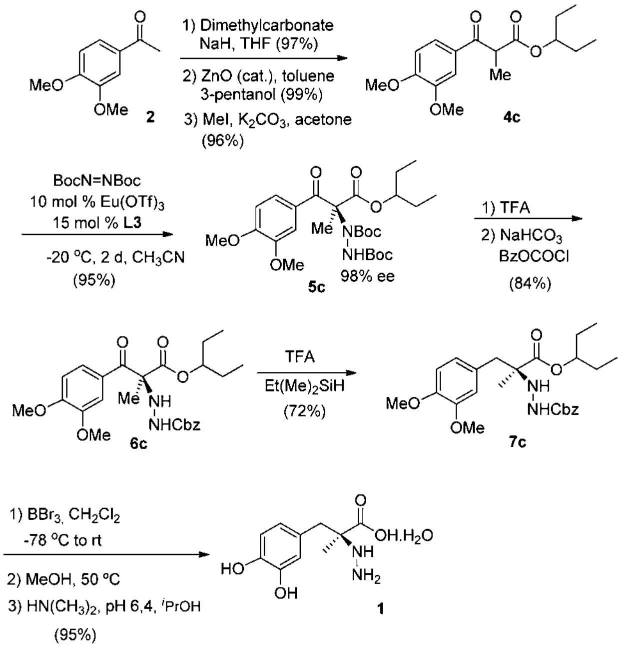
run	**6**	TFA (equiv)	silane	silane (equiv)	time (h)	% yield[b] **7**
1	**6a**	50	Et_3SiH	7.5	24	74
2	**6a**	15	$Et(Me)_2SiH$	7.5	18	74 (92)[c]
3	**6b**	15	Et_3SiH	7.5	24	3
4	**6b**	40	Et_3SiH	10	36	–

[a] All the reactions were carried out in the presence of 4 Å molecular sieves. [b] Yields are given for isolated products. Performed under an argon atmosphere. [c] Value in parentheses corresponds to the yield based on NMR.

The subsequent protecting group exchange led to the Cbz-protected **6c** in 84% yield; the keto group in **6c** underwent a smooth reduction using the $Et(Me)_2SiH$/TFA combination to give **7c** in 72% yield.[13] Finally, removal of the protecting groups from **7c** was accomplished with BBr_3, a reagent previously used for the deprotection of a variety of protected amino acids and peptides.[14] Under these conditions, the global deprotection of **7c** led directly to the L-carbidopa as a hydrobromide.[15] To get the monohydrate derivative **1**, the hydrobromic salt was dissolved in the minimum quantity of isopropanol and dimethylamine was added obtaining L-carbidopa hydrate in 95% yield. The assignment of the absolute configuration of **1** as *S* (98% ee) was based on the comparison of the specific rotation for the same compound in the literature.[16]

In summary, the chemistry described here constitutes a highly enantioselective synthesis for the drug L-carbidopa in seven steps and an overall yield of 50% with no need for diastereo- or enantiomeric resolution.[17] The key step is a highly enantioselective europium-catalyzed α-amination process applied to acyclic β-ketoesters.

Scheme 5. Concise Enantioselective Synthesis of L-Carbidopa[15]



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Supporting Information Available. General experimental details for the preparation of β-ketoesters and L-carbidopa. ^1H and ^{13}C NMR and IR of **1**, **3a**–**d**, **4a**–**d**, **5a**–**d**, **6a**–**d**, **7a**–**d**. HSQC NMR of **5b**, **6a**, **6d**, **7a**, **7b**, and **7d**. HPLC chromatograms of **5a**–**d**, **6c**, **6d**, **7c**.This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Higher enantioselectivity was achieved using 2,4-dimethylpentan-3-yl 3-(3,4-dimethoxyphenyl)-2-methyl-3-oxopropanoate, **4d**, having the more bulky secondary 2,4-dimethylpentyl group. Compound **5d** was obtained in > 99.9 ee. However, the deoxygenation step gave **7d** in a moderate 55% yield (for details, please see Supporting Information).

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(15) L-Carbidopa hydrobromide can be isolated at this stage and was completely characterized (see Supporting Information).

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The authors declare no competing financial interest.