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Intramolecular Diels-Alder Route To 6-Oxodecahydroisoquinoline-3-Carboxylates: Intermediates For The Synthesis Of Conformationally Constrained Excitatory Amino Acid Antagonists

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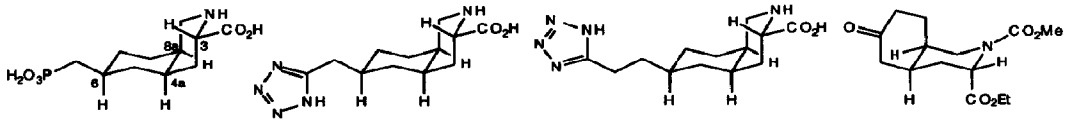
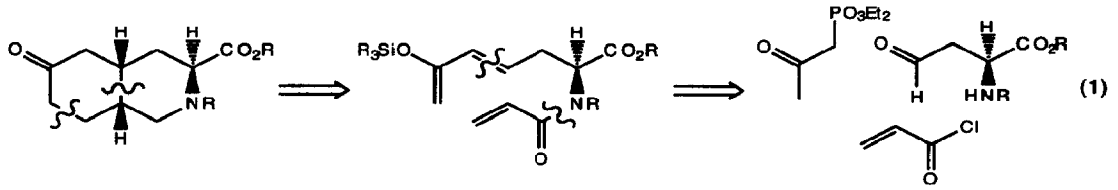
Abstract: We report the preparation of a hydroisoquinoline intermediate potentially useful for the synthesis of some excitatory amino acid antagonists. The requisite stereochemistry is established by an intramolecular Diels-Alder reaction, and the absolute stereochemistry is ultimately derived from *S*-aspartic acid. Also reported is an efficient synthesis of methyl *N*-CBZ aspartate β-aldehyde.

In our search for potent, subclass selective excitatory amino acid (EAA) receptor antagonists, we have found significant activity within a series of 6-substituted decahydroisoquinoline-3-carboxylates. For example, the phosphonate- and tetrazole-substituted amino acids (–)-**1** and (–)-**2** are antagonists of the *N*-methyl-D-aspartate (NMDA) subclass of EAA receptors,[1] while the tetrazole-substituted amino acid (–)-**3** is an antagonist of the 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) subclass of EAA receptors.[2] Many of the possible decahydroisoquinoline stereoisomers were prepared as a part of our structure activity study, and optimal NMDA and AMPA antagonist activity was observed with the diastereomer (and enantiomer) represented by (–)-**1**, (–)-**2** and (–)-**3**.[2,3] These conformationally constrained amino acids were all prepared from the same intermediate ketone (–)-**4**.[4] A liability in our synthesis of this ketone was the moderate diastereoselection observed in the formation of **4** and the need for a classical resolution to generate its enantiomers. We therefore sought an alternative synthetic strategy to ketones such as (–)-**4** that would allow us to prepare these compounds in a diastereo- and enantioselective fashion. In this communication we report the preparation of 6-oxodecahydroisoquinoline-3-carboxylates through an intramolecular Diels-Alder reaction.



Our retrosynthetic analysis of ketones such as **4** is shown in equation 1. Intramolecular Diels-Alder reaction between a silyloxy diene and an enamide should deliver an intermediate hydroisoquinolinedione, which can then be selectively reduced to afford the desired hydroisoquinolone.[5,6,7] Internal activation in the intramolecular Diels-Alder reaction is preferred for obtaining a cis-fused ring juncture, and some functionality (R) on the nitrogen is likely to be necessary in

order to obtain a sufficient population of intermediate where the enamide and diene are in a reactive conformation. We envisioned that the silyl enol ether could be obtained from the corresponding enone, which would be available from a Wittig or Horner-Emmons reaction of some protected β-aspartic acid aldehyde intermediate. And the enamide would be derived from acryloyl chloride.



(1)

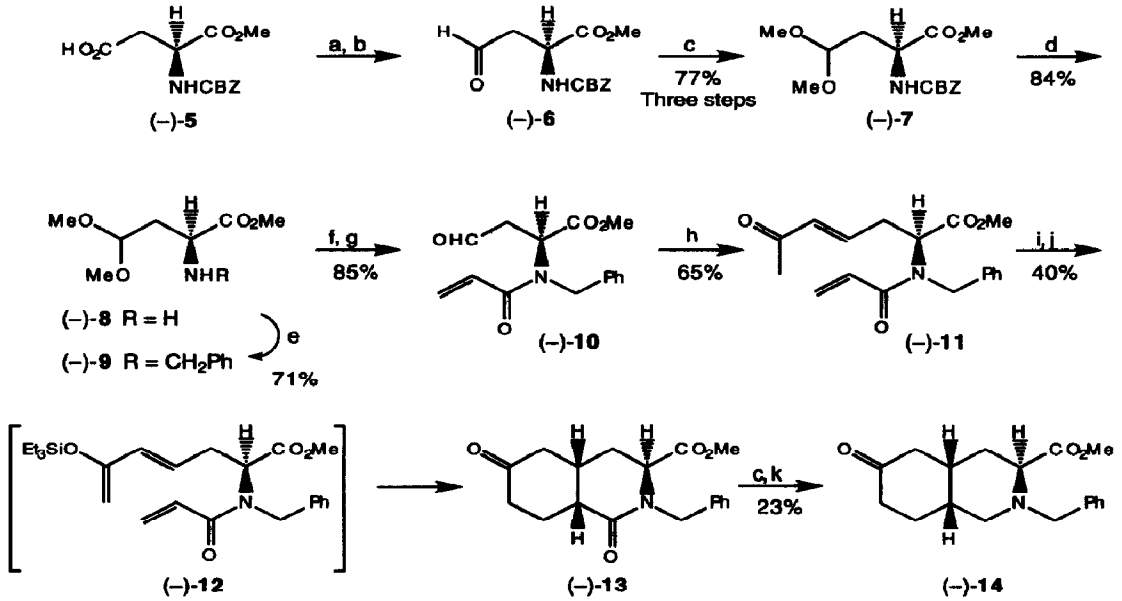
One critical feature of this synthesis was the need to obtain an enantiomerically pure β-aspartic acid aldehyde[8,9,10] intermediate (eq. 1), preferably in large quantity. Such aldehydes are usually obtained by oxidation of a suitably protected L-homoserine with, e.g., pyridinium chlorochromate,[8] 1,3-dicyclohexycarbodiimide/dimethyl sulfoxide[9] or chromium trioxide/pyridine complex.[10] However, L-homoserine is expensive, or it must be prepared from L-methionine;[6] and when protected, it 's prone to lactonize. We were able to obviate these issues by developing a facile two-step, one-pot preparation of methyl *N*-carbobenzoxy(CBZ)-aspartate β-aldehyde.

Commercially available *N*-CBZ-aspartate α-methyl ester ((–)-**5**) was converted to the acid chloride by treatment with thionyl chloride (Scheme 1). After removal of excess thionyl chloride in vacuo, the acid chloride was reduced to the corresponding aldehyde by treatment with tri-n-butyltin hydride in THF, in the presence of 7 mol% tetrakis(triphenylphosphine)palladium (0).[11] In the absence of palladium, the yield of the reduction was only 30%. While the aldehyde (–)-**6**[12] could be isolated, we found it more convenient to convert it to the acetal (–)-**7**,[12] by treatment at reflux with methanol, trimethylorthoformate and a trace of p-toluenesulfonic acid. The overall yield for the conversion of **5** to **7** was 77%, and this transformation could easily be carried out in the lab starting with 120 g of **5**. The optical integrity of **7** prepared in this manner was confirmed by hydrolysis of the acetal to the aldehyde (CH_3CN, 10% aq. HCl, room temperature) followed by Jones oxidation to afford the acid **5**. The optical rotation of this material was identical to commercially available **5**, so essentially no racemization was observed.

Hydrogenolysis of (–)-**7** afforded an 84% yield of the surprisingly stable amino ester (–)-**8**.[12] We chose to alkylate nitrogen with benzyl, which we felt would be easily removed either in conversion to **4** or to an acidic amino acid such as **1**. Treatment of (–)-**8** with benzyl bromide and triethylamine in DMF gave a 71% yield of the desired monobenzylamine (–)-**9**,[12] which was acylated with acryloyl chloride and then hydrolyzed to afford 85% of the aldehyde (–)-**10**.[12] Horner-Emmons reaction of (–)-**10** with the sodium salt of 1-diethylphosphono-2-propanone afforded the E-enone (–)-**11**[12] in 65% yield. The Wittig condensation of **10** with triphenylphosphoranylidineacetone was also highly E-selective, but it was difficult to separate the product from triphenylphosphine oxide. The presence of an E-olefin in **11** was confirmed by observation in the ^1H NMR of a 16 Hz coupling constant for the enone protons.

We found it most convenient to perform the Diels-Alder reaction using conditions similar to that of Martin and DiGrandi,[6] where an enone such as **11** is converted in situ to a silyl enol ether such as **12**, and then this reacts under mild conditions to deliver the desired cyclized product. To this end, a room temperature solution of the enone (–)-**11** in dichloromethane-d_2 was added to a preformed solution of triethylamine and triethylsilyl trifluoromethanesulfonate in dichloromethane-d_2, and the reaction was monitored by removal of an aliquot and ^{1}H NMR analysis; it was complete in one hour. After work-up, the enol silyl ether was hydrolyzed to afford a mixture of keto-amides. GC analysis of the reaction after Diels-Alder and enol ether hydrolysis shows three products in a ratio of 71:15:14,[13] from which the desired product (–)-**13**[12] was isolated diastereomerically pure in 40% yield after recrystallization from ethyl acetate. To obtain an intermediate that might be suitable for conversion to an EAA antagonist, the ketone of (–)-**13** was first protected as the dimethyl acetal, then the amide reduced (without purification) by treatment with borane/methyl sulfide in THF. Following workup of the reduction with aqueous hydrochloric acid, we obtained the N-benzyl keto-ester (–)-**14**[12] in 23% yield.

Scheme 1

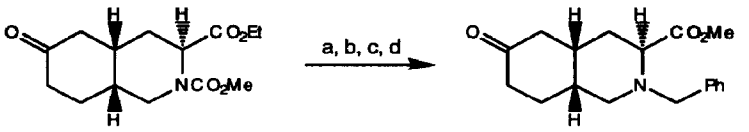


a. $SOCl_2$, room temperature. b. *n*-Bu_3SnH, 7 mol% $(Ph_3P)_4Pd$, THF, room temperature. c. $HC(OMe)_3$, p-TSA, MeOH, reflux. d. H_2, 5% Pd/C, MeOH, room temperature, 40 psi. e. $PhCH_2Br$, Et_3N, DMF, room temperature. f. CH_2=CHCOCl, Et_3N, CH_2Cl_2, room temperature. g. CH_3CN, 10% aq. HCl, room temperature. h. $Et_2O_3PCH_2C(O)CH_3$, NaH, THF, 0 °C. i. Et_3SiOTf, Et_3N, CH_2Cl_2, room temperature. j. KF, MeOH, reflux. k. BH_3•SMe_2, THF, reflux; HCl, H_2O, reflux.

The relative stereochemistry and enantiomeric purity of the intramolecular Diels-Alder product was confirmed by comparison with racemic **14**, prepared as shown in Scheme 2 from racemic **4**. The

methyl carbamate of (±)-**4** was removed with iodotrimethylsilane and the amine alkylated with benzyl bromide. The ethyl ester was then hydrolyzed and re-esterified with methanolic HCl to afford (±)-**14**. The intramolecular Diels-Alder product (–)-**14** was identical by GC and ^{1}H NMR analysis to (±)-**14**. Chiral HPLC analysis of (–)-**14** showed the enantiomeric excess to be >99%.[14]

Scheme 2



(±)-**4** (±)-**14**

a. TMSI, $CHCl_3$, reflux. b. $PhCH_2Br$, *i*-Pr_2NEt, DMF, 40 °C. c. 1N NaOH, EtOH, reflux. d. MeOH, HCl (g), reflux.

In summary, we have demonstrated that we can prepare 6-oxodecahydroisoquinoline-3-carboxylates through an intramolecular Diels-Alder reaction. A high degree of stereoselectivity is observed for the formation of a cis-ring juncture in this reaction, and the chirality introduced from *S*-aspartic acid can be efficiently transferred in this process. Further aspects of this reaction, along with applications to the synthesis of excitatory amino acid antagonists will be discussed in a forthcoming full account of this research.

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12. All new compounds gave satisfactory NMR, IR, mass spectral and elemental analysis consistent with the structure shown.
13. Gas chromatographic analysis of **13** was performed on an HP5890 Series II capillary GC with an Ultra 1 cross linked methyl silicone column, 25 m X 0.32 mm X 0.52 um, at a column temperature of 240 °C. Crude **13** prior to recrystallization showed three major products, with retention times of 10.14, 11.15 and 11.33 minutes, in a ratio of 71%:14%:15%, respectively. After recrystallization, GC analysis of **13** showed a single compound (>99%), with retention time of 10.14 minutes. The remaining two products have been difficult to separate and purify, and their structures have yet to be determined.
14. Chiral pack HPLC analysis of (±)-**14** on a Chiracel® OJ column, 4.6 X 250 mm, eluting with 4% ethanol/hexane, at a flow rate of 2.5 mL/min, with UV detection at 220 nm, shows two equal peaks with retention times of 7.66 and 9.00 minutes, whereas (–)-**14** shows a single peak with a retention time of 7.62 minutes, >99% enantiomerically pure.

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