

STEREOSPECIFIC SYNTHESIS OF *MESO*-DIAMINODICARBOXYLIC ACIDS

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The hetero Diels-Alder adducts **1** derived from azodibenzoyl and cyclic dienes were transformed to the *meso*-diaminodicarboxylic acids **6** via the new cyclic hydrazoacetic acids **3**.

KEY WORDS *meso*-diaminodicarboxylic acid; hydrazoacetic acid; Diels-Alder adduct; ruthenium tetroxide; azodibenzoyl; *meso*-diaminopimelic acid

Diaminodicarboxylic acids play important parts in organic chemistry and biochemistry as “bis”-amino acids. Diaminoglutaric acid complexed with platinum indicates antitumor activity.¹⁾ Diaminoadipic acid is an inhibitor of bacterial growth,²⁾ and its *meso*-form is an important source of some medicinal compounds.³⁾ The usual methods to synthesize their *meso*-forms start with non-stereocontrolled α,α' -dibromination of α,ω -dicarboxylic acids followed by separation of the stereoisomers.³⁾

Diaminopimelic acid (DAP) is an important amino acid biosynthesized in bacteria and higher plants. *meso*-DAP is a biosynthetic precursor of the essential amino acid L-lysine and serves as a cross-linking constituent of virtually all Gram-negative and some Gram-positive bacterial peptidoglycans and also serves to anchor various membrane-associated macromolecules, such as lipoproteins, to the cell wall.⁴⁾ In spite of the simplicity of the molecular structure, there are few reports on the stereochemically evident chemical synthesis of *meso*-DAP or its derivatives, except for two recent reports.^{4,5)} In those reports, Williams and Yuan used optically active diphenyloxazinones⁴⁾ and Jurgens used optically active Garner oxazoline.⁵⁾ Both methods seem to be expensive and troublesome.

We now wish to report the stereospecific synthesis of the diaminodicarboxylic acids utilizing hetero Diels-Alder adducts via the new cyclic hydrazoacetic acids (Chart).

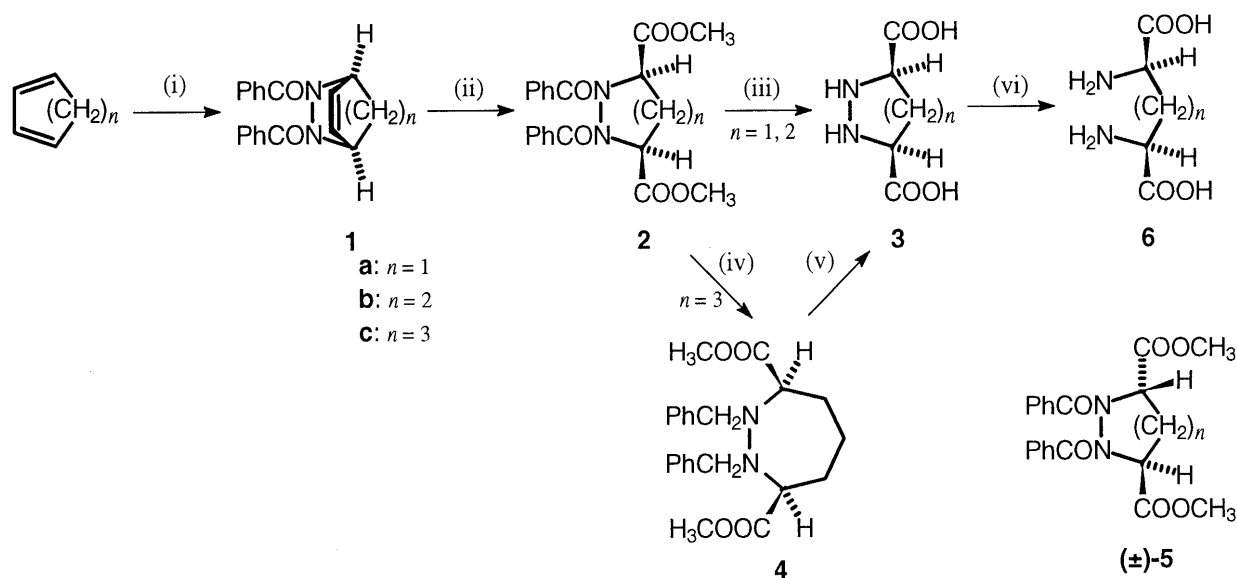
The hetero Diels-Alder adducts **1** prepared according to the literature⁶⁾ were oxidized by ruthenium tetroxide (RuO₄) in ethyl acetate at 0°C to afford *cis*-dicarboxylic acids selectively without spoiling the benzene ring and α -methine of the nitrogen atom, although it is well known that RuO₄ oxidizes not only double bond but also aryl group and α -carbon of nitrogen. Esterification of the dicarboxylic acids by diazomethane or thionyl chloride-methanol gave dimethyl esters **2a**, **2b**, and **2c** in 88%, 95%, and 90% yields, respectively, from **1**. New five- and six-membered cyclic hydrazoacetic acids **3a** and **3b**⁷⁾ (*cis*-3,5-pyrazolidinedicarboxylic acid and *cis*-3,6-piperidazinedicarboxylic acid) were easily obtained as their dihydrochlorides⁸⁾ in 96% and 87% yields, respectively, by hydrolysis of **2a** and **2b** with 6 N HCl-AcOH at 100°C for 24h. The dimethyl ester **2c** bearing a seven-membered ring was similarly hydrolyzed, but a little epimerization occurred to give a mixture of *cis*- and *trans*-dicarboxylic acids which were difficult to separate. Therefore, an alternative deprotection method was attempted, in which *N*-benzoyl groups of compound **2c** were reduced by borane-dimethyl sulfide in tetrahydrofuran (THF) to give di-*N*-benzyl compound **4** in 60% yield, which was then debenzylated by hydrogenolysis with 20% Pd(OH)₂/C and hydrolyzed with 2 N HCl at 50°C for 12h to give the seven-membered *cis*-hydrazoacetic acid **3c** (*cis*-1,2-diazepane-3,7-dicarboxylic acid) in 82% yield without formation of the epimer. On the other hand, efficient epimerizations to cyclic ($\pm$)-*trans*-

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hydrazoacetic acid derivatives **5** took place by treatment of the five-membered dimethyl ester **2a** with sodium methoxide in methanol and by treatment of the six- and seven-membered **2b** and **2c** with triethylamine in methanol.

Hydrogenolysis of *N-N* bonds of those *cis*-hydrazoacetic acids **3** obtained above was accomplished with PtO_2 in 2 N HCl to give *meso*-2,4-diaminoglutaric acid (**6a**), *meso*-2,5-diaminoadipic acid (**6b**), and *meso*-2,6-diaminopimelic acid (**6c**, *meso*-DAP) in 97%, 97%, and 92%, respectively.

In conclusion, we developed a new way to synthesize stereospecifically the new cyclic hydrazoacetic acids and the *meso*-diaminodicarboxylic acids.



Reagents and conditions: (i) $(\text{PhCON})_2$, CCl_4 ; (ii) RuO_2 (cat.), aq NaIO_4 , AcOEt , 0°C , then CH_2N_2 or $\text{SOCl}_2/\text{MeOH}$; (iii) 6 N HCl-AcOH , 100°C ; (iv) $\text{BH}_3 \cdot (\text{CH}_3)_2\text{S}$, THF ; (v) 20% $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , 2 N HCl-AcOH , 4 atm, then 2 N HCl , 50°C ; (vi) PtO_2 , H_2 , 2 N HCl , 4 atm.

Chart

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- 7) The $^1\text{H-NMR}$ data of the amino acids in this paper were as follows (400MHz, 1 N DCl): **3a**: 2.69 (1H, ddd, $J=13.6, 5.5, 5.5\text{Hz}$), 2.96 (1H, ddd, $J=13.6, 9.2, 9.2\text{Hz}$), 4.56 (2H, dd, $J=9.2, 5.5\text{Hz}$); **3b**: 2.01-2.07 (2H, m), 2.16-2.22 (2H, m), 4.20 (2H, dd, $J=6.2, 4.0\text{Hz}$); **3c**: 1.76-2.01 (4H, m), 2.38-2.45 (2H, m), 4.14 (2H, dd, $J=10.4, 5.7\text{Hz}$); **6a**: 2.39-2.46 (1H, m), 2.65-2.78 (1H, m), 4.36 (2H, dd, $J=6.8, 6.8\text{Hz}$); **6b**: 2.11-2.18 (4H, m), 4.18 (2H, brs); **6c**: 1.50-1.56 (1H, m), 1.64-1.70 (1H, m), 1.91-2.08 (4H, m), 4.11 (2H, dd, $J=6.4, 6.4\text{Hz}$).
- 8) Free hydrazoacetic acids could be crystallized by adjustment of their salt solutions to pH 3-4 under argon atmosphere.

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