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 diphenyloxazinones[4] 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 literature[6] were oxidized by ruthenium tetroxide (RuO_4) 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 RuO_4 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 dihydrochlorides[8] 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*-hydazoacetic 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 (±)-*trans*-

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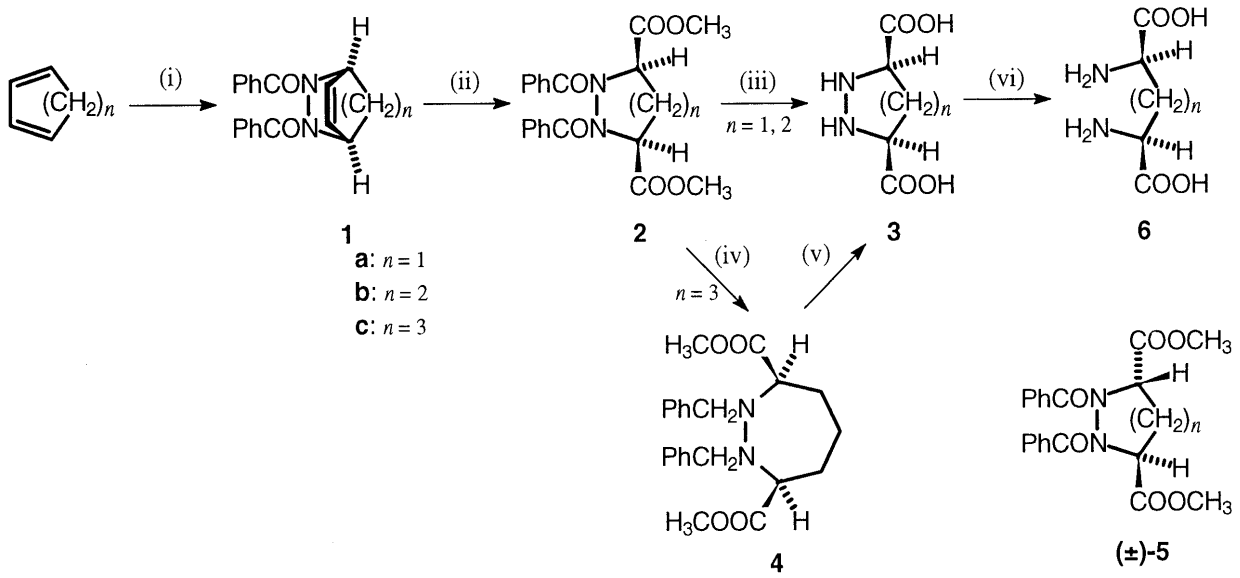
hydrazoacetic acid derivatives **5** took place by treatment of the five-membered dimethyl ester **2a** with sodium methoxide in methanol and by treatment of the six- and seven-membered **2b** and **2c** with triethylamine in methanol.

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) $(PhCON)_2$, CCl_4; (ii) RuO_2 (cat.), aq $NaIO_4$, AcOEt, 0°C, then CH_2N_2 or $SOCl_2$/MeOH; (iii) 6 N HCl-AcOH, 100°C; (iv) $BH_3{\cdot}(CH_3)_2S$, THF; (v) 20% $Pd(OH)_2$/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

REFERENCES AND NOTES

1) Y. Ren, Z. Jiang, Z. Liu, X. Yu, *Dalian Gongxueyuan Xuebao*, **25**, 75 (1986).
2) D. H. Simmonds, *Biochem. J.*, **58**, 520 (1954).
3) P. A. Sturm, D. W. Henry, *J. Med. Chem.*, **17**, 481 (1974); H. Newman, *J. Heterocycl. Chem.*, **11**, 449 (1974).
4) R. M. Williams, C. Yuan, *J. Org. Chem.*, **57**, 6519 (1992).
5) A. R. Jurgens, *Tetrahedron Lett.*, **33**, 4727 (1992).
6) C. Y-J. Chung, D. Mackay, T. D. Sauer, *Can. J. Chem.*, **50**, 1568 (1972); *idem*, *ibid.*, **50**, 3315 (1972).
7) The ^{1}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, 5.5Hz), 2.96 (1H, ddd, *J*=13.6, 9.2, 9.2Hz), 4.56 (2H, dd, *J*=9.2, 5.5Hz); **3b**: 2.01-2.07 (2H, m), 2.16-2.22 (2H, m), 4.20 (2H, dd, *J*=6.2, 4.0Hz); **3c**: 1.76-2.01 (4H, m), 2.38-2.45 (2H, m), 4.14 (2H, dd, *J*=10.4, 5.7Hz); **6a**: 2.39-2.46 (1H, m), 2.65-2.78 (1H, m), 4.36 (2H, dd, *J*=6.8, 6.8Hz); **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, 6.4Hz).
8) Free hydrazoacetic acids could be crystallized by adjustment of their salt solutions to pH 3-4 under argon atmosphere.

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