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Clathration-Induced Asymmetric Transformation of Cefadroxil

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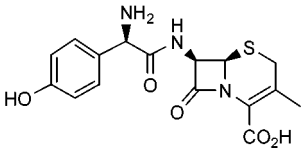
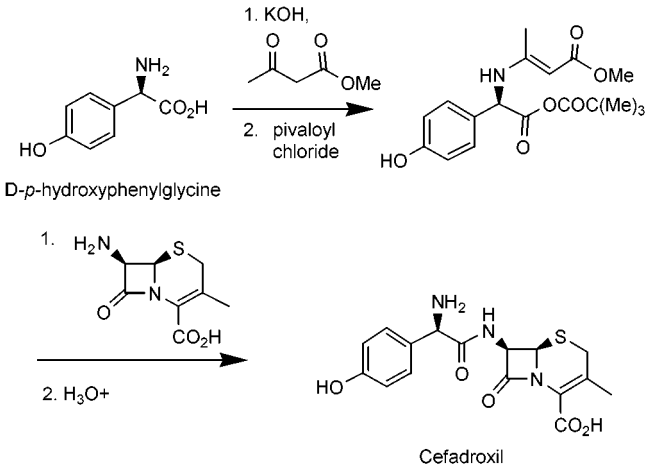
ABSTRACT



The cephalosporin antibiotic Cefadroxil can be epimerized at the α-carbon of its amino acid side chain using pyridoxal as the mediator. By clathration with 2,7-dihydroxynaphthalene, the desired diastereomer can be selectively withdrawn from the equilibrating mixture of epimers. In this way, an asymmetric transformation of Cefadroxil can be accomplished. This opens the possibility of the production of Cefadroxil starting from racemic *p*-hydroxyphenylglycine, in contrast to the current industrial synthesis that employs the D-amino acid in enantiopure form.

The cephalosporin antibiotics are important life saving medicines that already have been on the global market for more than 20 years. They are semisynthetic antibiotics consisting of a β-lactam nucleus and a D-amino acid side chain. Cefadroxil is an important member of this class, having a global market of approximately 300 tons per year. The β-lactam nucleus of Cefadroxil can be obtained via ring expansion of the penicillin nucleus[1] and recently also by direct fermentation.[2] Cefadroxil is produced by chemical coupling of the side chain (D)-*p*-hydroxyphenylglycine to the β-lactam nucleus, which proceeds via Dane-salt protection of the amino function and activation of the carboxylate of the side chain by pivaloyl chloride, as is depicted in Scheme 1.[3] Racemic *p*-hydroxyphenylglycine can be conveniently produced from basic organic chemicals. Classical resolution has been used for many years to obtain optically pure (D)-*p*-hydroxyphenylglycine.[4] Novel, more elegant approaches utilize enzymes or microorganisms for this purpose.[5] The

Scheme 1. Current Chemical Synthesis of Cefadroxil



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(3) (a) Dane, E.; Dockner, T. *Angew. Chem.* **1964**, *76*, 342. (b) Dane, E.; Dockner, T. *Chem. Ber.* **1965**, *98*, 789−796.

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resolution of the amino acid side chain constitutes a substantial cost factor in the price of the antibiotic.

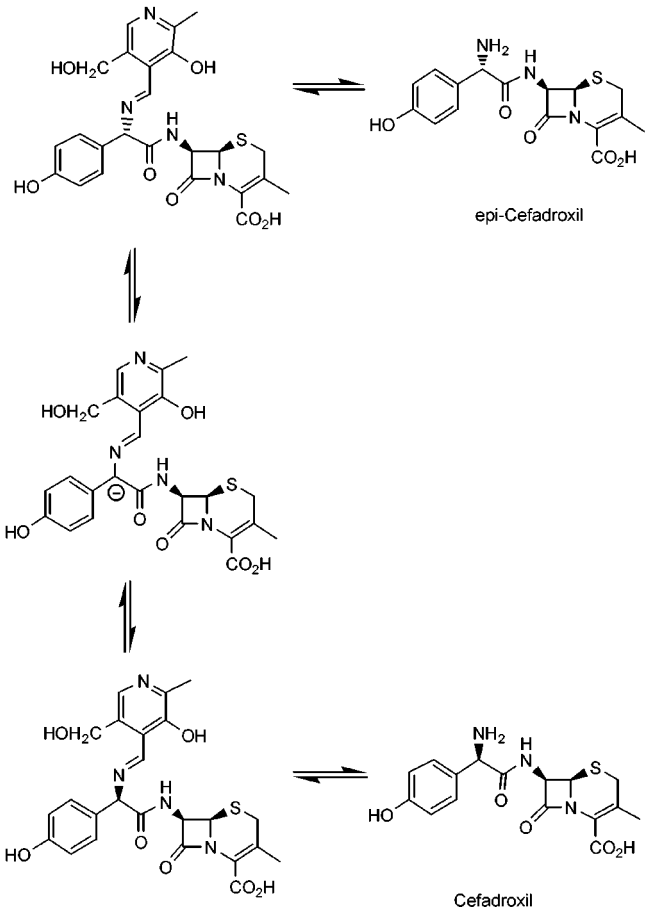
We have elaborated an asymmetric transformation of Cefadroxil that opens the way to produce Cefadroxil starting from racemic *p*-hydroxyphenylglycine. For this purpose we first investigated whether Cefadroxil could be epimerized under mild conditions. Subsequently, the possibility of selective isolation of the desired epimer of Cefadroxil by clathration was studied. By employing these techniques concurrently, an asymmetric transformation is conceivable.

Amino acids are usually optically stable and can only be racemized under extremely harsh conditions.[6] Their rate of racemization can be greatly enhanced by converting them first into their Schiff bases.[7,8] The racemization becomes even more effective when conducted in the presence of an organic acid.[9] In general, any amino acid can be racemized by heating in acetic acid, using a catalytic amount of aldehyde. A generally accepted mechanism for the racemization involves isomerization of the Schiff base.[6] Rate enhancement of the racemization in acetic acid supports this mechanism.[7]

Despite the major improvements of the racemization methods of amino acids, the conditions described above cannot be used for Cefadroxil. As a result of its β-lactam nucleus Cefadroxil is extremely susceptible to degradation. Exposure to a pH above 8 or to strong acidic conditions causes severe decomposition of the cephalosporin. Also, the temperatures needed in the methods described above are too harsh for this β-lactam antibiotic. Accordingly, the epimerization of Cefadroxil was investigated in aqueous solution under mild conditions. It was found that both salicylic aldehyde and pyridoxal could be used for the Schiff base mediated epimerization, whereby the latter showed a faster reaction. A catalytic amount of aldehyde (10%) appeared to be sufficient. Gratifyingly, the epimerization, according to Scheme 2, can be performed under these very mild conditions. A pH between 7 and 7.5 appeared to be appropriate to obtain an acceptable rate of epimerization at room temperature in water. The epimerization was monitored by HPLC. After 3 h the epimerization reached its thermodynamical equilibrium, at which 37% of *epi*-Cefadroxil had been formed.

As the solubility difference in water between Cefadroxil and *epi*-Cefadroxil is rather small, selective crystallization of the desired diastereomer cannot be achieved. However, clathration of Cefadroxil with 2,7-dihydroxynaphthalene is

Scheme 2. Epimerization of Cefadroxil via the Schiff Base Derived from Pyridoxal



an efficient method for the isolation of this antibiotic from aqueous solutions.[10] It was shown that this clathration process is highly selective. Only Cefadroxil is found in the precipitated clathrate, while its epimer remains in solution. By addition of 2,7-dihydroxynaphthalene to the reaction mixture of equilibrating epimers, an asymmetric transformation of *epi*-Cefadroxil to Cefadroxil could be accomplished. The formation of Cefadroxil from the epimeric mixture was followed with time using HPLC. The results are shown in Table 1.

Table 1. Asymmetric Transformation of Cefadroxil in the Presence of Pyridoxal and 2,7-Dihydroxynaphthalene

time (h)	Cefadroxil in the mixture (%)
0	63
1	66
3	73
5	84
7	89
24	94

After filtration, the precipitated clathrate was obtained in a yield of 86%. To obtain the pure antibiotic a subsequent

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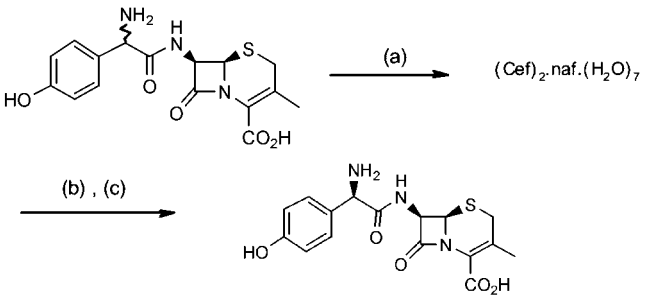
Scheme 3. Formation of Cefadroxil Starting from a Mixture of Diastereomers



(a) Pyridoxal, 2,7-dihydroxynaphthalene (naf), pH = 7.5. (b) 5% HCl, EtOAc. (c) NH_3.

decomplexation was necessary. This was accomplished by dissociation of the complex in diluted acid and extraction of the complexing agent with ethyl acetate. Subsequent neutralization of the concentrated aqueous solution, resulted in precipitation of the pure Cefadroxil monohydrate in a good yield. The entire sequence of the asymmetric transformation and the decomplexation is depicted in Scheme 3. This novel methodology of preparing Cefadroxil from racemic *p*-hydroxyphenylglycine has interesting prospects for a more cost-effective production of the antibiotic.[11]

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Supporting Information Available: Experimental details, HPLC results, and X-ray powder pattern of the product. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Patent has been filed by DSM Life Sciences, The Netherlands.