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# Chemoenzymatic Enantioselective Synthesis of Amidinomycin

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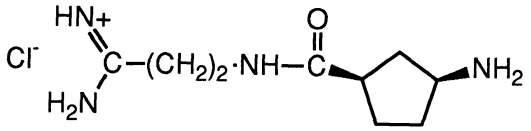
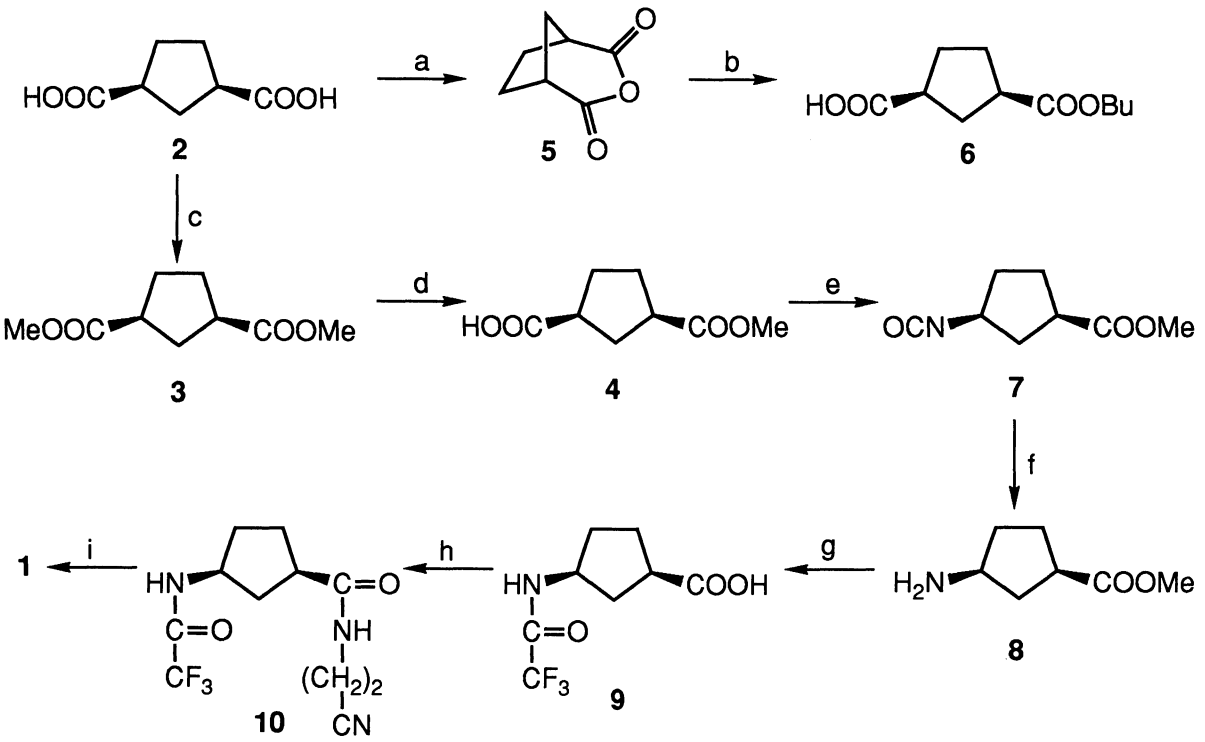
We report the first asymmetric synthesis of amidinomycin, an antiviral antibiotic metabolite. Amidinomycin of high enantiomeric purity (ee 91%) was prepared from norbornylene in 8 steps. The key step is an enzymatic discrimination of enantiotopic groups in meso cis-1,3-dicarbomethoxycyclopentane or in meso cis-cyclopentane-1,3-dicarboxylic acid anhydride.

Amidinomycin (**1**, synonym myxoviromycin) is an antiviral antibiotic metabolite, first isolated from the fermentation medium of various *Streptomyces* species.[1] Its chemical structure, N-(2-amidinoethyl)-3-aminocyclopentanecarboxamide was established by chemical degradation[2] and was confirmed by a total synthesis of the racemic mixture.[3] The absolute configuration was determined by X-ray crystallographic analysis.[4] Amidinomycin belongs to a family of natural oligopeptide antibiotics including distamycin, netropsin, anthelvencin, kikumycin, and noformycin.[5] Amidinomycin is also related to a series of synthetic aromatic diamidines such as pentamidine, beneril, and stilbamidine, many of which have antimicrobial properties.[6] These compounds have attracted considerable attention because of their DNA binding capacity. We report here a chemoenzymatic synthesis of amidinomycin (**1**).



**1**

The key feature of the present approach is an enzymatic discrimination of enantiotopic groups of meso cis-1,3-dicarbomethoxycyclopentane (**3**) or meso cis-cyclopentane-1,3-dicarboxylic acid anhydride (**5**). Esterification of diacid **2**, obtained from ozonolysis of norbornylene,[7] with methanol in the presence of an acidic resin as a catalyst gave diester **3** (Scheme 1). We did some preliminary screening to find suitable enzymes for the asymmetrization of meso **3** and **5**. The best results are summarized in Tables 1 and 2. Hydrolysis of **3** in the presence of cholesterol esterase or subtilisin gave the (1*S*, 3*R*) monoester **4** in high chemical and enantiomeric yields. Anhydride **5** was obtained by dehydration of **2** with acetic anhydride.




Reagents and conditions: (a) $Ac_2O$, 120 °C, 83%; (b) *Pseudomonas cepacia* lipase, BuOH, $iPr_2O$, 97%; (c) MeOH, $H^+$ resin, reflux, 91%; (d) cholesterol esterase, phosphate buffer, 1% MeCN, 92%; (e) i) ClCOOEt, $Et_3N$, acetone, −5 °C, ii) $NaN_3/H_2O$, iii) toluene, reflux, 74%; (f) HCl 8 N, MeOH 10%, 80%; (g) $CF_3COOMe$, tetramethyl guanidine, 93%; (h) 3-aminopropionitrile, EDC, $CH_2Cl_2$, 65%; (i) i) MeOH, HCl, −10 °C, ii) $NH_3$, 90%.

Scheme 1.

Lipases from *Pseudomonas fluorescens* and from *Pseudomonas cepacia* catalyzed the asymmetric ring opening of anhydride **5** with 1-butanol in diisopropyl ether to afford half ester 1*S*, 3*R*-**6** having 82 and 91% ee (Table 2). Enzyme catalyzed asymmetric alcoholysis of anhydrides has been reported by Oda *et al.*[8] and others,[9] but as far as we know, this is the first report of such a reaction on a bicyclic system. The enantiomeric purity of **4** and **6** was measured by reaction with (*S*)-(−)-1-(1-naphthyl)ethylamine in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) followed by NMR analysis of the resulting diastereomeric amides. The absolute configuration of **4** was determined by comparison of the specific rotation with reported values.[10] The absolute configuration of **6** was determined by trans-esterification of its naphthylethylamine derivative and correlation with the corresponding derivative of **4**.

The carboxyl group of **4** was converted to an amino group with retention of configuration through a Curtius rearrangement; thus, the mono-ester was first treated with ethyl chloroformate and then with sodium azide in acetone to give the corresponding acyl azide which was heated in toluene to give isocyanate **7**. Owing to its instability, this isocyanate was not purified but was directly converted to the amino-acid **8** by

Table 1. Enantioselective hydrolysis of substrate **3**

| Enzyme | Conditions | Monoester **4**[a] Yield/% | ee/% | Absolute configuration |
|---|---|---|---|---|
| Lipase | | | | |
| *Aspergillus niger* | buffer A | 50 | 55 | 1S, 3R |
| *Candida sp.* | buffer A | 80 | 63 | 1S, 3R |
| Protease | | | | |
| *Aspergillus sojae* | buffer A | 85 | 76 | 1S, 3R |
| | buffer B | 82 | 84 | 1S, 3R |
| *Streptomyces griseus* | buffer A | 90 | 80 | 1S, 3R |
| *Aspergillus oryzae* | buffer A | 78 | 70 | 1S, 3R |
| Chymotrypsin | buffer A | 90 | 30 | 1R, 3S |
| Subtilisin carlsberg | buffer A | 83 | 88 | 1S, 3R |
| | buffer B | 98 | 90 | 1S, 3R |
| Cholesterol esterase | buffer A | 95 | 88 | 1S, 3R |
| | buffer A 1% acetonitrile | 92 | 91 | 1S, 3R |

a) Conditions: Buffer A, phosphate 0.05 M, pH 7.00; Buffer B, TRIS·HCl 0.25 M, pH 7.00.

Table 2. Enantioselective alcoholysis of anhydride **5**

| Enzyme | Monoester **6**[a] Yield/% | ee/% | Absolute configuration |
|---|---|---|---|
| Lipase | | | |
| *Pseudomonas fluorescens* | 81 | 82 | 1S, 3R |
| *Pseudomonas cepacia* | 97 | 90 | 1S, 3R |

a) Conditions: Anhydride **5** (1.0 mmol), lipase (30 mg), butanol (2.0 mmol) in diisopropyl ether (10 ml) at 25 °C.

treatment with aqueous HCl. Amino-acid **8** was converted to the N-trifluoroacetyl derivative **9** with methyl trifluoroacetate in the presence of tetramethylguanidine. The enantiomeric purity of **9** was also checked by NMR analysis of the diastereoisomeric N-trifluoroacetyl amides obtained by reaction with (*R*)-1-(1-naphthyl)ethylamine as above. The result (90% ee) further confirm the expected retention of configuration during the rearrangement. Condensation of **9** with 3-aminopropionitrile in the presence of EDC afforded **10**. Pinner reaction of **10** with methanol in the presence of hydrogen chloride and subsequent ammonolysis of the trifluoroacetyl protecting group gave amidinomycin hydrochloride **1**. Also, amidinomycin was obtained similarly from **6** by the same reaction sequence.

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