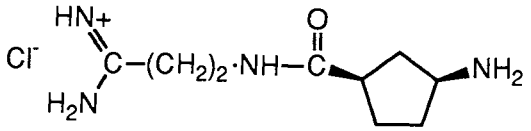
CHEMISTRY LETTERS, pp. 93-96, 1994.

Chemoenzymatic Enantioselective Synthesis of Amidinomycin

Robert CHÊNEVERT,* Michèle LAVOIE, Gabriel COURCHESNE, and Richard MARTIN
Département de Chimie, Faculté des Sciences et de Génie,
Université Laval, Québec (Québec), Canada G1K 7P4

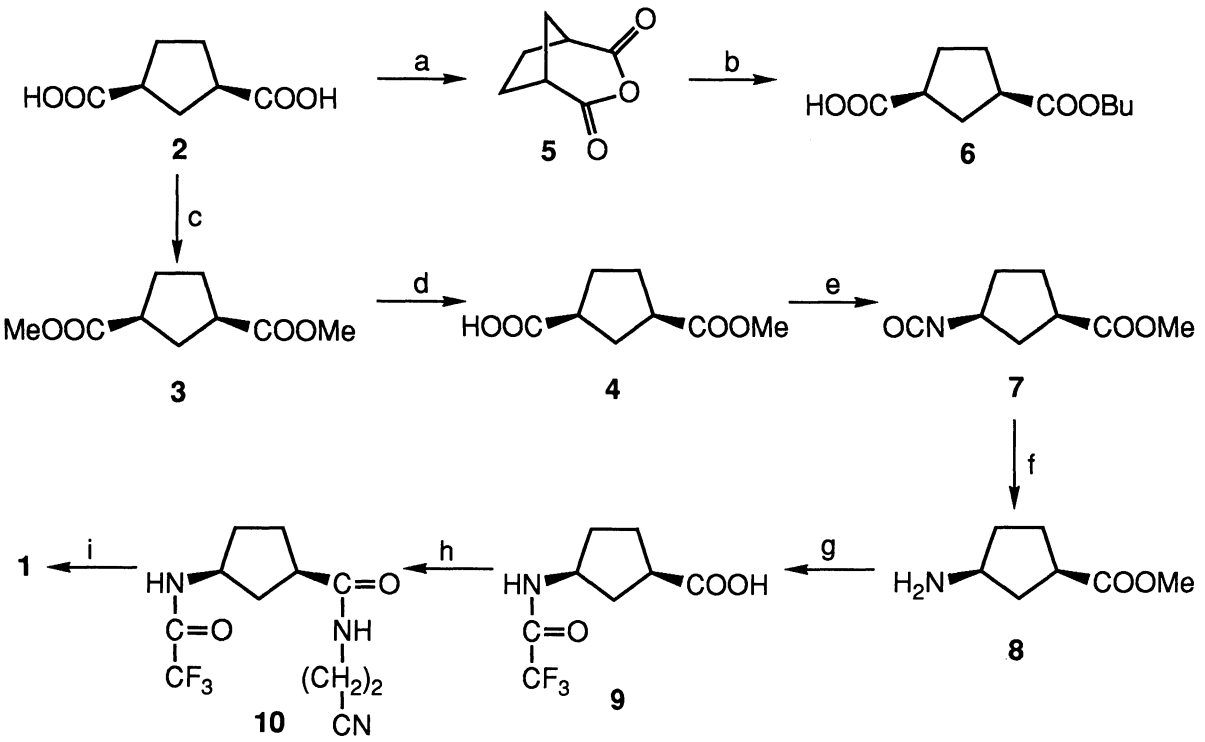
We report the first asymmetric synthesis of amidinomycin, an antiviral antibiotic metabolite. Amidinomycin of high enantiomeric purity (ee 91%) was prepared from norbornylene in 8 steps. The key step is an enzymatic discrimination of enantiotopic groups in meso cis-1,3-dicarbomethoxycyclopentane or in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

This research was supported by grants from the Natural Sciences and Engineering Research Council of Canada.[11)]

References

1) S. Nakamura, K. Karasawa, H. Yonehara, N. Tanaka, and H. Umezawa, *J. Antibiotics, Ser. A.*, **14**, 103 (1961); S. Nakamura, H. Umezawa, and N. Ishida, *ibid.*, **14**, 163 (1961).

2) S. Nakamura, *Chem. Pharm. Bull.*, **9**, 641 (1961); R.D. Allan, G.A.R. Johnston, and B. Twitchin, *Aust. J. Chem.*, **32**, 2517 (1979).

3) H. Paul, H. Berger, H. Boeden, and G. Hilgetag, *Arch. Pharmaz.*, **301**, 512 (1968); H. Berger, H. Paul, and G. Hilgetag, *Chem. Ber.*, **101**, 1525 (1968).

4) M. Kaneda, S. Nakamura, and Y. Iitaka, *J. Antibiotics*, **23**, 778 (1980).

5) K.E. Rao, Y. Batlini, and J.W. Lown, *J. Org. Chem.*, **55**, 728 (1990); J.W. Lown, K. Korwicki, J. Balzarini, R.A. Newman, and E. De Clercq, *J. Med. Chem.*, **32**, 2368 (1989).

6) R.R. Tidwell, S.K. Jones, J.D. Geratz, K.A. Ohemeng, M. Cory, and J.E. Hall, *J. Med. Chem.*, **33**, 1252 (1990); P.R. Lowe, C.E. Sansom, C.H. Schwalbe, and M.F.G. Stevens, *J. Chem. Soc., Chem. Commun*, **1989**, 1164.

7) R.H. Perry, *J. Org. Chem.*, **24**, 829 (1959).

8) Y. Yamamoto, M. Iwasa, S. Sawada, and J. Oda, *Agric. Biol. Chem.*, **54**, 3269 (1990); J. Hiratake, K. Yamamoto, Y. Yamamoto, and J. Oda, *Tetrahedron Lett.*, **30**, 1555 (1989); K. Yamamoto, T. Nishioka, and J. Oda, *ibid.*, **29**, 1717 (1988); Y. Yamamoto, K. Yamamoto, T. Nishioka, and J. Oda, *Agric. Biol. Chem.*, **52**, 3087 (1988).

9) R. Ozegowski, A. Kunath, and H. Schick, *Tetrahedron: Asymmetry*, **4**, 695 (1993).

10) J.B. Jones, R.S. Hinks, and P.G. Hultin, *Can. J. Chem.*, **63**, 452 (1985).

11) Presented, in part, at a NATO Advanced Research Workshop, Sestri Levante, Italy, March 23-27, 1992. Proceedings: "Microbial Reagents in Organic Synthesis", ed by S. Servi, Kluver Academic Publishers, Dordecht (1992).

(Received September 30, 1993)