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Synthesis of the proposed core of aeruginosins 205: the new α-amino acid (2*S*,3a*S*,6*R*,7a*S*)-2-carboxy-6-chlorooctahydroindole

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Abstract—The synthesis of enantiomerically pure α-amino acid (2*S*,3a*S*,6*R*,7a*S*)-2-carboxy-6-chlorooctahydroindole (L-Ccoi) is described. NMR data of L-Ccoi **3** are very different from those reported for the azabicyclic core of aeruginosins 205, indicating that the structure of these aeruginosins needs to be revised. © 2003 Elsevier Science Ltd. All rights reserved.

Aeruginosins constitute a new group of structurally related cyanobacterial peptides, bearing a C-6 functionalized *cis*-octahydroindole-2-carboxylic acid derivative as their common structural feature.[1–3] The most usual aeruginosin core is known as L-Choi [(2*S*,3a*S*,6*R*,7a*S*)-2-carboxi-6-hydroxyoctanhydroindole **I**], for which three approaches have been described: (a) from a reduced tyrosine derivative by means of a diastereoselective cyclization,[4] (b) from a tyrosine derivative via a diastereoselective cyclooxidation,[5] and (c) from a proline derivative and elaboration of the fused cylohexanol ring.[6] Additionally, syntheses of 3a,7a-*diepi*-L-Choi **II**[7] and 5β-hydroxy-L-Choi **III**, the latter from a proline derivative and ring-closing metathesis[8] have also been reported. Total syntheses of aeruginosin 298-A,[4b,5,9] 298-B,[4b] SF608,[10] and EI461,[7] as well as the related dysinosin A have been achieved. Interestingly, in three of these syntheses there has been a revision of the proposed structure and a reassignment of the real structure (Fig. 1).[11]

As part of our work on the total synthesis of aeruginosins, we were interested in studying an approach to aeruginosins 205 (Fig. 2),[12,13] which have been found to be potent inhibitors of trypsin and thrombin. For this purpose it was necessary to synthesize the core of these peptides, which consists of the new bicyclic amino acid (2*S*,3a*S*,6*R*,7a*S*)-2-carboxy-6-chlorooctahydroindole (L-Ccoi). We report here the synthesis of this new amino acid and demonstrate that it is different from the one reported to be in the core of these natural products, thus opening up the need for a revision of the claimed structure of aeruginosins 205.

The synthesis of L-Ccoi was carried out as outlined in Scheme 1 and takes advantage of our previously reported stereocontrolled synthesis of the bicyclic ketone **1**.[4] Starting from *O*-methyl-L-tyrosine, the bicyclic ketone **1** was obtained in 40% yield by a five-step sequence consisting of: (i) Birch reduction; (ii) aminocyclization of the dihydroanisole formed by treat-

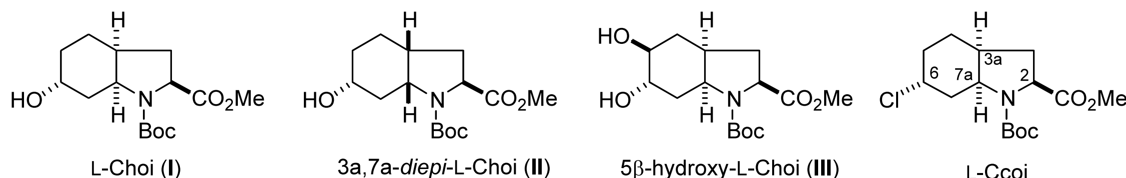

Figure 1.

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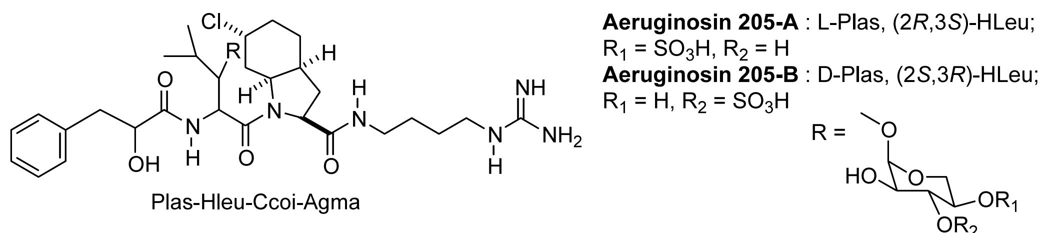
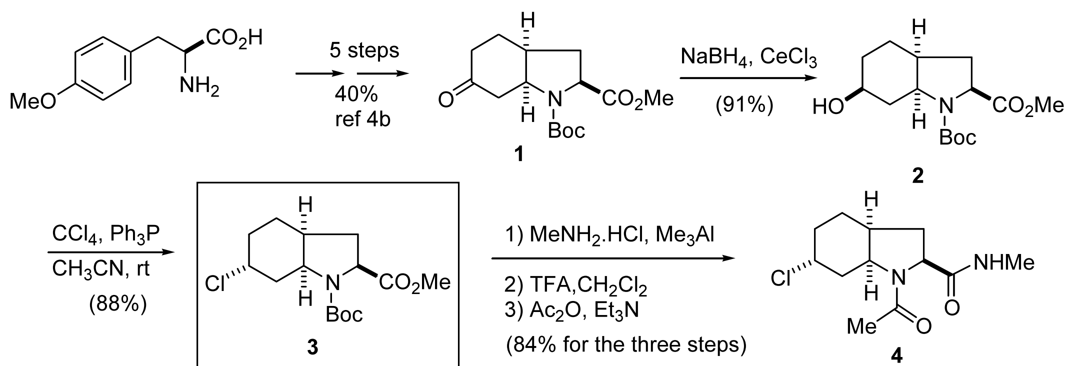


Figure 2. Proposed structures for aeruginosins 205.



Scheme 1. Synthesis of orthogonally diprotected L-Ccoi.

equilibration process of the mixture of β-amino ketones *endo–exo*; (v) exchange of the *N*-protecting group of the *endo* isomer by debenzylation in the presence of Boc_2O. Reduction of ketone **1** with $NaBH_4$ at −78°C in MeOH in the presence of $CeCl_3$ stereoselectively gave alcohol **2**, in which the hydroxyl group is equatorially located according to the preferred conformation of this azabicyclic compound. Next, alcohol **2** was converted into its α-chloro analogue **3** in a stereospecific manner by PPh_3–CCl_4 in acetonitrile under mild conditions[14] (Scheme 1).

Compound **3** adopts the preferred ring conformation that avoids the $A^{(1,3)}$ strain between the carbamate and the C(7) methylene group. In this conformation, which was assigned unequivocally by 2D NMR experiments, the chlorine atom is located axially. The stereostructure of azabicyclic compound **3** was confirmed by X-ray diffraction analysis (Fig. 3).[15] Table 1 shows the NMR data of **3**, recorded above the coalescence temperature of the *cis–trans* rotamers (50°C), which clearly disagree with those reported for the Ccoi core of aeruginosins 205. Comparison of the NMR values of protons and carbons in the domain C(5)–C(6)–C(7) reveals significant differences (Table 1). Most notably, the methine proton H-6 of the Ccoi resonates at δ 4.60, whereas that of aeruginosin 205-A appears at δ 3.83. Moreover, significant differences in the ^{13}C NMR spectra of **3** and aeruginosin 205-A were observed for the carbons (C-5, C-6, C-7), which resonate in **3** at δ 27.2, 59.1, and 33.8, respectively, whereas those in the natural compound appear at δ 24.7, 68.7, and 28.6, respectively. Therefore, the substituent at C-6 in aeruginosins 205 does not seem to be a chlorine atom. In order to reinforce this point of view and to obtain additional information we have prepared the *N*(Ac)-Ccoi(CONHMe) **4**[16] and its NMR data were again very different from the values reported for the azabicyclic α-amino acid found in aeruginosins 205.

In conclusion, we have reported an efficient and stereoselective route to the new α amino acid (−)-**3**, which is the proposed core of aeruginosins 205. When the spectral data of these aeruginosins and synthetic **3** are compared it is clear that the azabicyclic rings differ

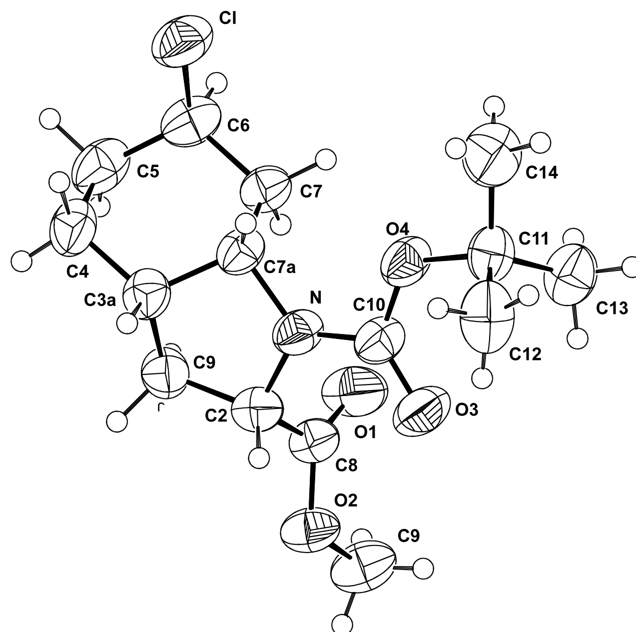


Figure 3. X-Ray diffraction structure (ORTEP) of **3**.

Table 1. NMR data of octahydroindole core of aeruginosin 205-A, Ccoi **3** and **4**[a]

	Core of aeruginosin 205-A		Ccoi **3**[b]		N(Ac)-Ccoi(NHMe) **4**[c]	
	^{1}H mult, *J* (Hz)	^{13}C	^{1}H mult, *J* (Hz)	^{13}C	^{1}H *trans*/*cis* rotamer	^{13}C
C-2	4.21 dd (9.7, 8.0)	59.8	4.17 dd (9.6, 7.8)	58.5	4.14 dd/4.26 dd (10, 8)/(10, 8)	59.6/60.6
C-3 α	2.02 ddd (13.1, 8.0, 6.8)	30.7	2.13 ddd (12.6, 8, 7.2)	31.6	2.01 m	31.3/33.3
C-3 β	1.85 ddd (12, 6)		1.90 m		1.77 ddd/1.85 m (12.5, 12, 11)	
C-3a	2.24 dddd (13.1, 6.8, 6.4, 5.8)	35.9	2.34 ddddd (12, 6, 6, 6, 0.5)	35.0	2.32 ddddd/2.21 (12, 6,6,6, 0.5)	36.1/34.5
C-4 eq	2.13 m	19.4	2.03 dddd (13.5, 6, 5.5, 2.5)	19.7	2.01 m	19.9/20.1
C-4 ax	1.48 m		1.55 m		1.59 m	
C-5 eq	1.53 m	24.7	1.90 m	27.2	1.85 m	27.1/27.6
C-5 ax	1.53 m		1.65 m		1.59 m	
C-6	3.83 dddd (2.4, 2.4, 2.4, 2.4)	68.7	4.60 dddd (3, 3, 3, 3)	59.1	4.70 dddd/4.60 (3, 3, 3, 3)	60.0/60.0
C-7 eq	2.28 ddd (14.0, 6.4, 2.4)	28.6	2.24 br d (14.4)	33.8	2.11 m/ 1.85 m	34.4/33.7
C-7 ax	1.59 ddd (14.0, 11.9, 2.4)		1.90 m		2.11 m/1.85 m (15, 11, 4)	
C-7a	4.33 ddd (11.9, 6.4, 6.4)	54.3	4.02 ddd (10.5, 6, 6)	52.9	4.04 ddd/4.30 (10.5, 6, 6)	54.6/53.0

[a] All spectra were recorded in DMSO-d_6 and the peak assignments are derived from COSY, HMBC/HSQC and NOESY experiments.
[b] Recorded at 50°C. Other signals: δ 27.9, 78.9, 153.0 (Boc); 51.7, 173.1 (CO_2Me).
[c] Other signals: for *trans* rotamer δ 22.1, 167.9 (Ac); 25.9, 172.4 (CONHMe); for *cis* rotamer δ 21.9, 168.8 (Ac); 26.0, 172.4 (CONHMe).

and hence the assigned constitution of aeruginosins 205 must be revised. The elucidation of the structure of aeruginosins 205 remains an unsolved puzzle.

Acknowledgements

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14. Triphenylphosphine (332 mg, 1.26 mmol) was added at 0°C to a solution of alcohol **2** (252 mg, 0.84 mmol) in CH_3CN (2.5 mL) and CCl_4 (2.5 mL). The mixture was allowed to reach rt and was stirred for 18 h. Silica gel (2 g) was added and the solvents were removed. Flash chromatography of the residue with EtOAc furnished compound **3** (235 mg, 88%) as colorless needles, $R_f = 0.68$ (EtOAc); mp 95–97°C; $[\alpha]_D^{22} = -29$ (*c* 0.3, $CHCl_3$); IR (neat) 1751, 1698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, COSY, NOESY) and ^{13}C NMR (75 MHz, HSQC) see Table 1 for spectra recorded at 50°C. At 22°C the NMR showed duplicate signals (*cis–trans* rotamer ratio 2:1). Anal. calcd for $C_{15}H_{24}ClNO_4 \cdot 1/2H_2O$: C, 61.07; H, 9.51; N, 3.39; Cl, 8.58. Found: C, 61.19; H, 9.21; N, 3.41; Cl, 8.46.
15. Crystallographic data for the structure **3** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 201530. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44) 1223-336-033; e-mail deposit@ccdc.ca.ac.uk).

16. Compound **4** was synthesized in 84% yield by treatment of methyl ester **3** in CH_2Cl_2 with a solution of methylamine hydrochloride and trimethylaluminium in benzene, followed by solvolysis of the Boc group with trifluoroacetic acid and subsequent *N*-acetylation with acetic anhydride and triethylamine. For this protocol in the proline series, see: Beausoleil, E.; Lubell, W. D. *J. Am. Chem. Soc*. **1996**, *118*, 12902–12908. For compound **4**: $R_f=0.49$ (EtOAc/MeOH 1:1); mp 201–202°C; $[\alpha]_D^{22}=-97.6$ (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3452, 3329, 1670–1620 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, COSY, NOESY) and ^{13}C NMR (75 MHz, HSQC) see Table 1. The NMR showed duplicate signals, (*trans–cis* rotamer ratio 2:1). Anal. calcd for $C_{12}H_{19}ClN_2O_2$: C, 55.70; H, 7.40; N, 3.39; Cl, 13.70. Found: C, 55.79; H, 7.35; N, 10.58; Cl, 13.56.