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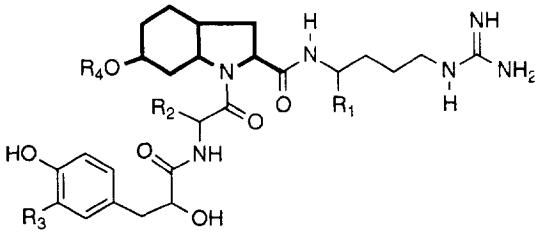
Synthesis of the Octahydroindole Core of Aeruginosins: a New Bicyclic α-Amino Acid

Josep Bonjoch*, Juanlo Catena, Esther Isábal, Meritxell López-Canet, and Nativitat Valls

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

Abstract: The first synthesis of 6-hydroxyoctahydroindole-2-carboxylic acid derivatives with a *cis* fusion in the azabicyclic nucleus is described. The synthesis involves a Birch reduction of *O*-methyl-L-tyrosine followed by an aminocyclization in acid medium to give a mixture of 6-oxo-octahydroindole-2-carboxylic acids **3** and **4**, which could be separated after dibenzylation. Transesterification, hydrogenolysis in the presence of acetic anhydride and reduction of the amido ketones **9** and **10** provides the four stereoisomeric alcohols from which alcohol **14** showed nmr data very close to the aeruginosin 298-A core.

Aeruginosins are new thrombin and trypsin inhibitors isolated from the blue-green alga *Microcystis aeruginosa*.[1,2] Structurally, these compounds are linear peptides which incorporate a nucleus of the new amino acid, 6-hydroxyoctahydroindole-2-carboxylic acid.

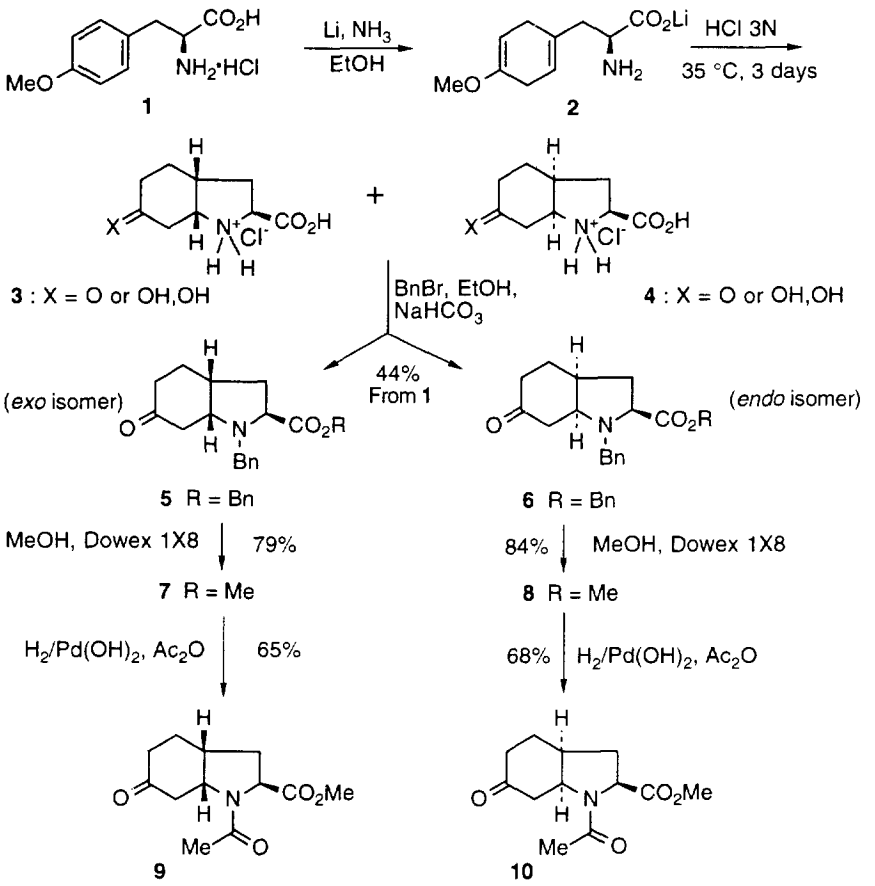


Aeruginosin	R_1	R_2	R_3	R_4
298-A	CH_2OH	$CH_2CH(CH_3)_2$	H	H
98-A	H	$CH(CH_3)CH_2CH_3$	Cl	SO_3H
98-B	H	$CH(CH_3)CH_2CH_3$	H	SO_3H

Here we describe the first synthesis of 6-hydroxyoctahydroindole-2-carboxylic acid derivatives, which was carried out for two reasons: a) to obtain a building block for the synthesis of the above marine products and b) to obtain spectroscopic data on several diastereomers, which would allow the assignment of the stereochemistry of this nucleus in the natural products. Taking into account that the stereochemistry of the aeruginosin 298-A bicyclic nucleus has not been described so far, we decided to synthesize four diastereomers with the constitution of the aeruginosin core in which the fusion is *cis* and the configuration at C-2 is *S* in all compounds.[3]

The synthesis was started from L-tyrosine, which was converted into the corresponding *O*-methyl derivative.[4] Birch reduction of **1** followed by acid treatment of the resulting dihydroanisole **2** led to the diastereomeric α-amino acids **3** and **4**, each as a mixture of the keto and hydrate forms.[5] These compounds

Scheme 1. Synthesis of *cis*-octahydroindolones from *O*-methyl-L-tyrosine



were converted into the benzylderivatives **5** and **6**, which were then separated.[6,7] The overall yield for the three step-sequence was 44%.

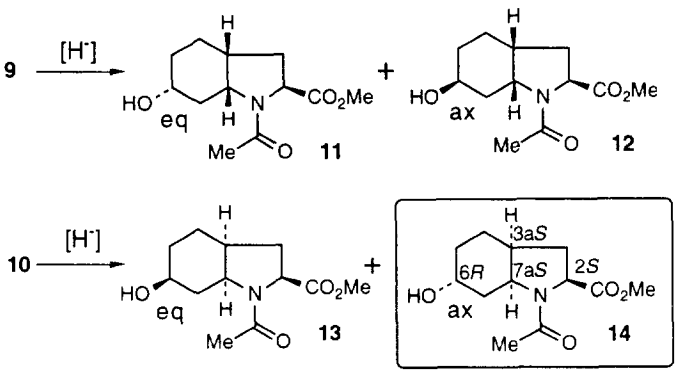
The absolute configuration of compounds **5** and **6** was assigned taking into account their nmr data. The *cis* fusion for the azabicyclic nucleus was evident from ROESY data as well as for coupling constants for the methine protons at H-7a. The multiplicity of the H-2 is diagnostic for the relation *endo*/*exo* of the ester group towards the octahydroindole moiety: in the *exo* isomers, for instance **5**, H-2 appears as a doublet whereas in the *endo* series, for instance **6**, H-2 shows a virtual triplet.

The next steps involves transesterification, followed by debenzylation of the resulting compounds **7** and **8** with simultaneous acetylation protection to give azabicyclic derivatives **9** and **10**.[8,9] These derivatives incorporate an amide bond, making them excellent structural mimics for the azabicyclic core of aeruginosins.

Finally, reduction of ketones **9** and **10** with both $NaBH_4$ and L-selectride® produced the corresponding four diastereomeric alcohols. Among these, compound **14** (2*S*, 3a*S*, 6*R*, 7a*S* configuration), with the hydroxyl axially located and the methoxycarbonyl at C-2 with *endo* relationship with the azabicyclic nucleus, shows nmr spectra data very similar to aeruginosin 298-A.[1] Consequently, we have assigned the same relative configuration to the natural product. In preliminary attempts to enhance the diastereoselectivity in the reduction

step to obtain the alcohol **14** we used the more bulky LS-Selectride® as reducing agent. In this manner the ratio in favour of the axial alcohol increases to 6:1.[10] It is noteworthy that from synthetic standpoint in the field of aeruginosins the equilibration of *exo* isomers to *endo* derivatives can be carried out at the stage of β-amino ketone to obtain only the appropriate derivatives of the *endo* series.[11]

Scheme 2. Synthesis of methyl 6-hydroxy-*cis*-octahydroindole-2-carboxylate derivatives



Method[a]	Yield[b]	Ratio[c] (**11**/**12**)
A	73	6 : 1
B	40	1 : 8

Method[a]	Yield[b]	Ratio[c] (**13**/**14**)
A	93	24 : 1
B	40	1 : 3
C	65	1 : 6

[a] Method A: $NaBH_4$, MeOH, -23 °C. Method B: L-Selectride, THF, -78 °C. Method C: LS-Selectride, THF, -78 °C.
[b] Processes not optimized. Yields determined by column chromatography. [c] Ratio determined by gas chromatography.

Table 1. ^{13}C-Nmr data of 6-hydroxyoctahydroindole-2-carboxylic acid derivatives 11-14[a]

Compound	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	N-subst	CO_2Me
11	57.8	30.2	34.8	22.6	29.3	67.8	37.2	57.8	168.9 / 21.5	172.6 / 52.1
12	57.8	30.2	35.2	18.8	26.2	65.3	34.1	54.5	169.5 / 21.3	172.9 / 50.5
13	58.2	30.5	36.4	22.7	29.0	67.9	36.7	58.7	169.5 / 21.3	172.9 / 50.5
14	58.7	30.6	36.9	19.0	26.3	65.9	33.4	54.8	168.7 / 21.5	172.9 / 52.2

[a] In ppm at 50 MHz in $CDCl_3$. Assignments were aided by HMQC and ^{1}H-^{1}H COSY spectra

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6. Enantiomeric purity of **5** and **6** was confirmed by registration of the nmr spectra of their salts with both enantiomers of Mosher's acid . For the procedure, see: Villani, Jr. F. J.; Costanzo, M. J.; Inners, R. R.; Mutter, M. S.; McClure, D. E. *J. Org. Chem.* **1986**, *51*, 3715.
7. To a solution of *O*-methyl-L-tyrosine hydrochloride (**1**, 20.3 g, 87.6 mmol) in dry EtOH (125 mL) maintained at -78 °C, ammonia (450 ml) was added. Small chips of lithium (3.5 g, 0.5 g-atom) were added (*ca* 3 h) until the solution was a persistent deep blue for 1 h. Then, the cooling bath was removed, the ammonia was allowed to evaporate overnight, and the reaction mixture was evaporated. The dried extract was dissolved in HCl 3N (900 ml) and the solution was stirred for 3 days at 35 °C. After removal of the water the residue was dried and halved. Each half was dissolved in ethanol (430 ml) and treated with benzyl bromide 12.6 ml, 108 mmol) in the presence of sodium bicarbonate (18.2 g, 215 mmol). The mixture was refluxed for 6 h. After work-up and chromatography (1:1, hexane-methylene chloride) ketones **5** (3.4 g) and **6** (3.4 g) were isolated in a pure form (44% overall yield).
   Compound **5** (*exo* isomer): $[\alpha]_D$ = -44.3 (*c* 1.1, $CHCl_3$); IR (film): 1743, 1717 cm^{-1}; ^1H nmr (COSY, 500 MHz, $CDCl_3$) δ 1.71 (dq, *J*= 14, 6 Hz, H-4_{eq}), 1.85 (dt, *J*= 13, 8.5 Hz, H-3α), 2.01-2.04 (m, H-4_{ax}), 2.04-2.08 (m, H-3β), 2.22 (ddd, *J*= 18.5, 6, 5 Hz, H-5_{eq}), 2.41 (ddd, *J*= 18.5, 10.5, 5 Hz, H-5_{ax}), 2.55 (d, *J*= 5 Hz, 2H, H-7), 2.76 (m, H-3a), 3.53 (d, *J*= 13,5 Hz, 1H, C*H*$_2$N), 3.58 (d, *J*= 7,5 Hz, H-2), 3.74 (dt, *J*= 9, 5 Hz, H-7a), 3.84 (d, *J*= 13.5 Hz, 1H, C*H*$_2$N), 5.07 (d, *J*= 12 Hz, 1H, C*H*$_2$O), 5.18 (d, *J*= 12.5 Hz, 1H, C*H*$_2$O), 7.10-7.40 (m, 10H, Ar). Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.13; H, 6.95; N, 3.80.
   Compound **6** (*endo* isomer): mp 69-70 °C (Et_2O); $[\alpha]_D$ = -58.1 (*c* 1, $CHCl_3$); IR (KBr): 1737, 1706 cm^{-1}; ^1H nmr (COSY, 500 MHz, $CDCl_3$) δ 1.74 (ddd, *J*= 13, 8.5, 6 Hz, H-3α), 1.84-1.93 (m, 2H, H-4), 2.16 (ddd, *J*= 18, 8.5, 5 Hz, H-5), 2.32 (ddd, *J*= 13, 8.5, 8 Hz, 1H, H-3β), 2.42 (dd, *J*= 16, 4.5 Hz, H-7_{ax}), 2.43 (m, H-3a), 2.52 (ddd, *J*= 18, 8, 4.5 Hz, 1H, H-5), 2.56 (dd, *J*= 16, 4.5 Hz, 1H, H-7_{eq}), 3.07 (dt, *J*= 8.5, 5 Hz, 1H, H-7a), 3.32 (t, *J*= 8.5 Hz, H-2), 3,61 (d, *J*= 14 Hz, 1H, C*H*$_2$N), 3.82 (d, *J*= 14 Hz, 1H, C*H*$_2$N), 4.84 (s, 2H, C*H*$_2$O), 7.16-7.32 (m, 10H, Ar). Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.02; H, 7.10; N, 3.83.
8. Additionally, the spectroscopical data of the *N*-acylderivatives **9** and **10** corroborate the stereochemical assignment *endo*/*exo* because they allow the comparison of their ^1H nmr data (500 MHz) with those of racemic **10** of which the X-ray data are available: Souchet, M.; Guilhem, J.; Le Goffic, F. *Tetrahedron Lett.* **1987**, *28*, 2371.
9. The stereochemical integrity of **7**, **8**, and **10** was confirmed by ^1H nmr. The spectra of these compounds and of the corresponding racemic derivatives were recorded on fairly concentrated samples (*ca* 0.15 M in $CDCl_3$) in the presence of 15 mg of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.
10. To a solution of ketone **10** (80 mg, 0.33 mmol) in THF (2.5 ml) at -78 °C was added a solution of *LS*-Selectride (1M in THF, 0.5 ml) diluted with THF (2.5 ml). The reaction mixture was stirred at -78 °C for 2 h and then treated with THF (28 ml), H_2O (28 ml), and acetic acid (6 ml). The resultant mixture was warmed to room temperature for 20 min. The aqueous phase was then extracted with Et_2O and then with (4:1) $CHCl_3$-*i*PrOH. Flash chromatography (SiO_2, 5% MeOH in CH_2Cl_2) of the dried combined organic extracts afforded 51 mg (65%) of a mixture of alcohols **14** and **13** in a 6:1 ratio, respectively (GS). Separation by preparative HPLC was performed on a Nucleosil 120 column with water-methanol (70:30) as mobile phase. Compound **14**: $[\alpha]_D$ = -20.7 (*c* 0.9, MeOH); IR (film) 3405, 1743, 1623, 1016 cm^{-1};^1H nmr (500 MHz, CD_3OD, COSY, *Z* rotamer) δ 1.52-1.62 (m, 3H, H-4 and H-5), 1.72 (ddd, *J* = 14, 11.5, 3 Hz, H-7_{ax}), 1.97 (ddd, *J* = 12.5, 12.5, 10.5 Hz, H-3β), 2.08 (s, $COCH_3$), 2.09 (ddd, *J* = 14, 3, 1 Hz, H-7_{eq}), 2.15 (m, H-4), 2.20 (ddd, *J* = 12, 8.5, 6 Hz, H3α), 2.45 (m, H-3a), 3.70 (s, OCH_3), 4.08 (br s, H-6_{eq}), 4.19 (ddd, *J* = 11.5, 6, 6 Hz, H-7a), 4.36 (dd, *J* = 10, 8.5 Hz, H-2); ^{13}C nmr, see table 1; HRMS calcd for $C_{12}H_{19}NO_4$ 241.1314, found 241.1320.
11. For instance, treatment of β-amino ketone **7**, *exo* compound, with MeOH-HCl(g) at reflux affords the corresponding methyl ester **8** of the *endo* series.

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