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Tetrahedron Letters 47 (2006) 5561–5563
Tetrahedron Letters

Total synthesis of (*S*)-(−)-cyclooroidin

Jignesh Patel, Nadia Pelloux-Léon,* Frédéric Minassian* and Yannick Vallée

Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité, UMR 5616 CNRS/UJF, Institut de Chimie Moléculaire de Grenoble, FR-2607, Université Joseph Fourier, Grenoble I, 301 rue de la Chimie, BP 53, 38041 Grenoble cedex 9, France

Received 4 April 2006; revised 15 May 2006; accepted 19 May 2006
Available online 16 June 2006

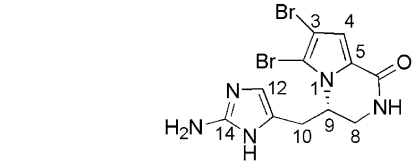
Abstract—The first total synthesis of enantiopure (*S*)-(−)-cyclooroidin is described. Absolute configuration of this natural product has been confirmed by comparison of the optical rotation value of our synthetic sample with the one measured on natural cyclooroidin.

Pyrrole alkaloids represent an important class of natural products that often display interesting biological activities.[1] Their isolation and preparation have been extensively reported.[2] Among them, pyrrole–imidazole alkaloids extracted from marine sponges are interesting targets,[3] such as cyclooroidin **1**. This compound was isolated in enantiopure form from Mediterranean sponge *Agelas oroides* by Taglialatela-Scafati and co-workers in 2000.[4] It exhibited a negative optical rotation $[\alpha]_D$ −12 (*c* 0.02, MeOH) and the absolute stereochemistry was established to be (*S*) by comparison of its CD spectrum with the one reported for dibromophakellin **2**.[5] This alkaloid was also detected in an extract obtained from the Okinawan marine sponge *Agelas* sp.[6]

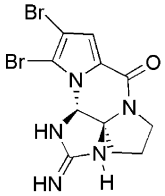
Very recently, two racemic syntheses of cyclooroidin have been described. The first one, published by Papeo et al.,[7] was achieved in nine steps with an overall yield of 10%. The second one, disclosed by Lindel and co-workers,[8] involved the intramolecular cyclization of oroidin formate in protic solvents. The authors suggested that the biosynthesis of optically active cyclooroidin from the major marine metabolite oroidin **3** may be an enzyme-assisted process.

During the course of our research on pyrrole alkaloids[9] we performed the total synthesis of enantiopure (*S*)-(−)-longamide B **4** from the commercially available L-aspartic acid β-methyl ester.[9c] We demonstrated that the previously postulated (*R*) stereochemistry[10] of the *laevorotary* enantiomer of longamide B **4** and of its ester **5** were incorrect (Scheme 1).

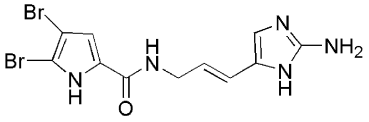
Pursuing this study, we decided to achieve the first synthesis of non-racemic (*S*)-(−)-cyclooroidin **1** in order to confirm the stereochemistry of the natural product. We



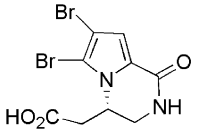
1 : (*S*)-(-)-Cyclooroidin



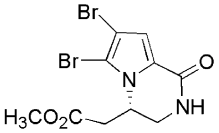
2 : (-)-Dibromophakellin



3 : Oroidin



4 : (*S*)-(-)-Longamide B



5 : (*S*)-(-)-Longamide B methyl ester

Scheme 1.

* Corresponding authors. Tel.: +33 476 514 908; fax: +33 476 635 983; e-mail addresses: nadia.pelloux-leon@ujf-grenoble.fr; frederic.minassian@ujf-grenoble.fr

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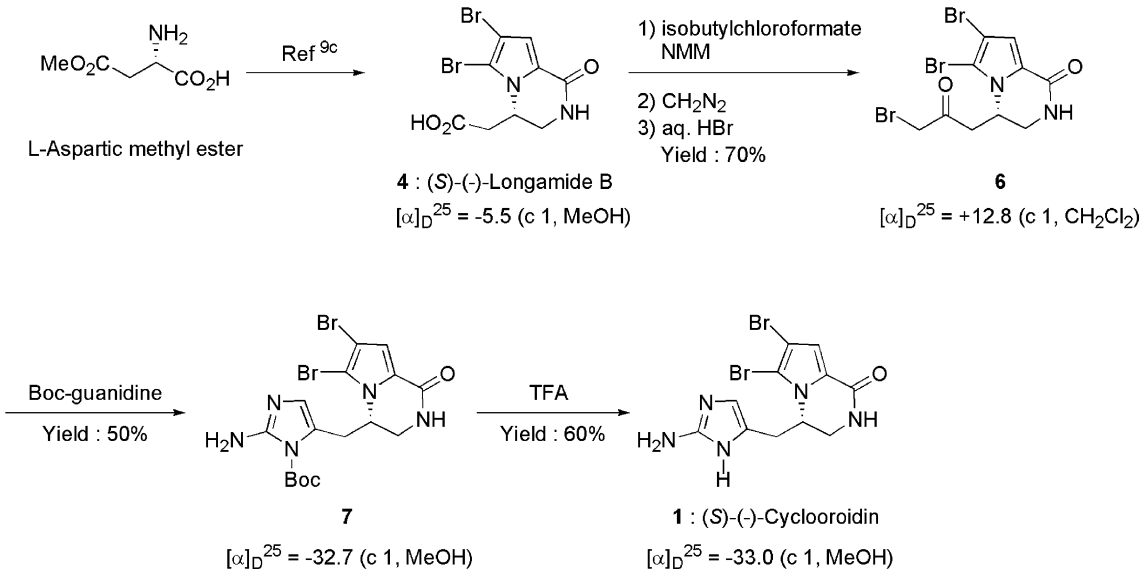
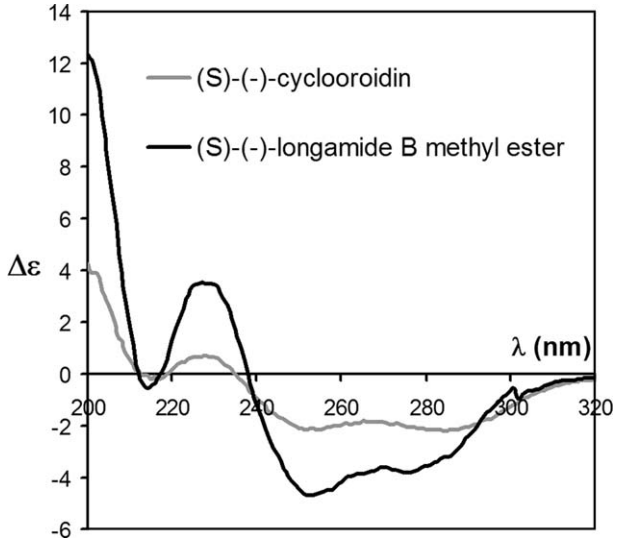
doi:10.1016/j.tetlet.2006.05.130



Scheme 2.

took advantage of our synthesis of (*S*)-(−)-longamide B **4**[9c] and of the one described for racemic cyclooroidin by Papeo et al.[7] (Scheme 2). Starting from our enantiopure sample of (*S*)-(−)-longamide B **4**,[9c] the carboxylic acid was transformed into a mixed anhydride with isobutylchloroformate.[11] The corresponding compound was then sequentially treated with CH_2N_2 and aqueous HBr[11] to give the optically active ($[\alpha]_D^{25}$ +12.8 (*c* 1, CH_2Cl_2)) bromoketone **6** (70% isolated yield), which was converted to 15-*N*-Boc protected cyclooroidin **7**. In our case, unreacted Boc-guanidine was eliminated by washing the organic layer with an acetate buffer solution (pH = 4.8). After chromatography, compound **7** was obtained in 60% yield. Its optical rotation was −32.7 (*c* 1, MeOH). The last step led to enantiopure (*S*)-(−)-cyclooroidin **1**. Spectroscopic data of our synthetic sample were then compared with those described in the literature.[4,7,8] The ^1H and ^{13}C NMR spectra[12] were in very good agreement with those mentioned by Papeo et al.[7] The 2D NMR spectrum (GHMBC) displayed the same correlations as those seen in the natural sample.[4] The UV spectrum, recorded in methanol solution, displayed strong absorptions at 224 nm ($\log\varepsilon = 3.1$) and 283 nm ($\log\varepsilon = 2.85$). These values were in agreement with those described by Lindel and co-workers.[8] CD spectra of synthetic cyclooroidin **1** and of (*S*)-Longamide B methyl ester **5** were compared. Almost no difference in the positive and negative Cotton effects was observed (Scheme 3). This result showed, without any doubt, that these two alkaloids have the same stereochemistry at C9.

Finally, specific rotation was measured. In the first experiment, we reproduced the conditions used for the natural product.[4] In that case, our synthetic sample exhibited the same value as the one described for natural cyclooroidin (−12.5 (*c* 0.02, MeOH)). The second measurement was performed using a more concentrated solution ($[\alpha]_D^{25}$ −33.0 (*c* 1, MeOH)). Those experiments enable the confirmation that natural cyclooroidin has



Scheme 3. CD spectra in methanol of (*S*)-(−)-cyclooroidin **1** and (*S*)-(−)-longamide B methyl ester **5**.

an (*S*) configuration at C-9 as it was postulated by Taglialatela-Scafati and co-workers.[4]

In conclusion, the first synthesis of enantiopure (*S*)-(−)-cyclooroidin is reported. The CD spectrum and the value of the optical rotation of our synthetic sample confirm that the *laevorotary* enantiomer of this natural alkaloid has the (*S*) configuration as postulated earlier on the natural sample.

Acknowledgments

We are grateful to the Université Joseph Fourier, the CNRS (UMR 5616, FR 2607) and MENR (ACI no. 02L0525, 'Molécules et Cibles Thérapeutiques') for financial support.

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12. (***S***)-(−)-**Cyclooroidin**: $[\alpha]_D^{25}$ −12.5 (*c* 0.02, MeOH) and $[\alpha]_D^{25}$ −33.0 (*c* 1, MeOH). CD (*c* 0.02, MeOH) 284 nm ($\Delta\varepsilon$ −2.2), 254 nm ($\Delta\varepsilon$ −2.16) and 215 nm ($\Delta\varepsilon$ −0.2). IR (film) *v* 3241, 2916, 2841, 1684, 1548, 1433, 1339, 1210, 1129, 756, 716 cm^{-1}. UV (MeOH): λ_{max} ($\log\varepsilon$) = 224 (3.1), 283 (2.85) nm. ^1H NMR (300 MHz, CD_3OD): δ (ppm) 6.94 (s, 1H, H_4), 6.30 (s, 1H, H_{12}), 4.60 (m, 1H, H_9), 3.79 (dd, J = 13.5, 4.2 Hz, 1H, H_{8a}), 3.54 (d, J = 13.5 Hz, 1H, H_{8b}), 2.85 (d, J = 7.2 Hz, 2H, H_{10}). ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 160.6, 149.9, 126.2, 125.7, 116.3, 112.1, 108.5, 100.9, 54.7, 43.4, 29.7. HRMS (ESI) *m*/*z* for $C_{11}H_{11}N_5O^{79}Br_2$: calcd 409.9228 $[M+Na]^+$; found 409.9223 and calcd 425.89674 $[M+K]^+$; found 425.8974.