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Total synthesis of (±)-cyclooroidin

Gianluca Papeo,* María Antonia Gómez-Zurita Frau,† Daniela Borghi and Mario Varasi

Department of Chemistry, BU-Oncology, Nerviano Medical Sciences, Viale Pasteur 10, 20014 Nerviano (MI), Italy

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Abstract—The first total synthesis of (±)-cyclooroidin, a member of the pyrrole–imidazole alkaloid family recently isolated from the sponge *Agelas oroides* in optically pure form, is described. The synthesis was achieved in nine linear steps, with an overall yield of 10%. Key step was a Wolff bromoketone synthesis performed on the intermediate longamide B.

Marine sponges represent a largely unexploited mine of natural products.[1] Their extremely diverse and challenging chemical architectures continue to entice the chemical community, both from an intellectual and a practical point of view.[2] Among them, pyrrole–imidazole alkaloids constitute a vast and fast-growing family of compounds, whose syntheses and biological activities have been recently reviewed.[3] Their biosynthetic pathways as well as the ecological functions, especially concerning the most complicated structures, still remain a partially unresolved task, although recent studies[4] help to cast some light on these subjects. In 2000, Fattorusso et al.[5] isolated a new alkaloid pertaining to this family, (−)-cyclooroidin (**1**, Fig. 1), from the Mediterranean sponge *Agelas oroides* collected in the bay of Naples. (−)-Cyclooroidin results from an unprecedented cyclization mode[3,5] of oroidin (**2**), the main secondary metabolite of pyrrole–imidazole alkaloids producing sponges. (−)-Cyclooroidin is not however an artifact due to the isolation conditions because it is enantiomerically pure. Interestingly, the absolute stereochemistry of (−)-cyclooroidin was established to be (*S*)- by the observation of superimposable Cotton effects in the CD spectra of (**1**) and (−)-dibromophakellin (**3**).

The natural (−)-cyclooroidin was tested for potential anticholinergic, antiserotonergic and antihistaminic activities on isolated guinea pig ileum, showing no activity.[5] No further biological investigations have been reported thus far. Moreover, to our knowledge, no total synthesis of either the racemic or optically pure (**1**) has been disclosed. These data prompted us to design a synthetic strategy towards this alkaloid, starting from (±)-longamide B (**4**), another marine natural product isolated, along with its corresponding methyl ester, each in their racemic form, from the Japanese sponge *Homaxinella*.[6] Thus, according to our retrosynthetic analysis (Scheme 1), (±)-cyclooroidin synthesis could be envisaged through the construction of the 2-aminoimidazole ring from the corresponding α-bromoketone (**5**)[7] that could, in turn, be derived from the previously prepared (±)-longamide B (**4**)[8a] through a Wolff bromoketone synthesis.[9]

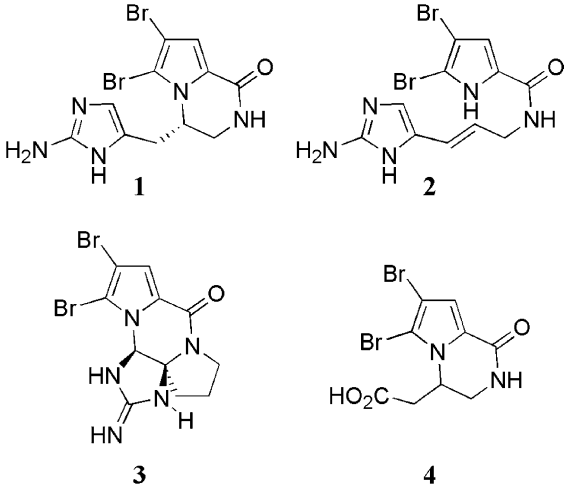

Figure 1.

Keywords: Pyrrole–imidazole alkaloids; Cyclooroidin; Wolff bromoketone synthesis.

* Corresponding author. Tel.: +39 0331581537; fax: +39 0331581757; e-mail: gianluca.papeo@nervianoms.com

† Present address: Centro de Investigación Biomolecular Aplicada—CIBASA, Edificio del Centro de Investigación del Cáncer, Campus Miguel de Unamuno, 37007 Salamanca, España.

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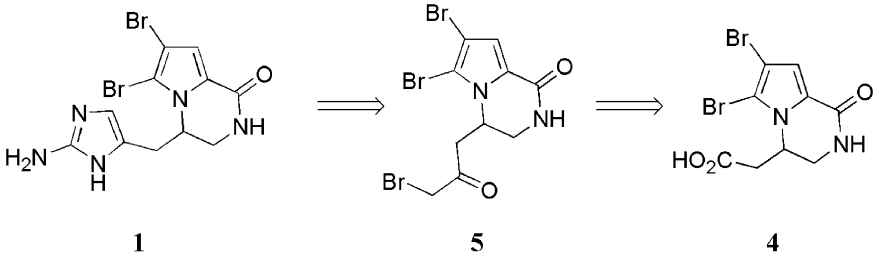
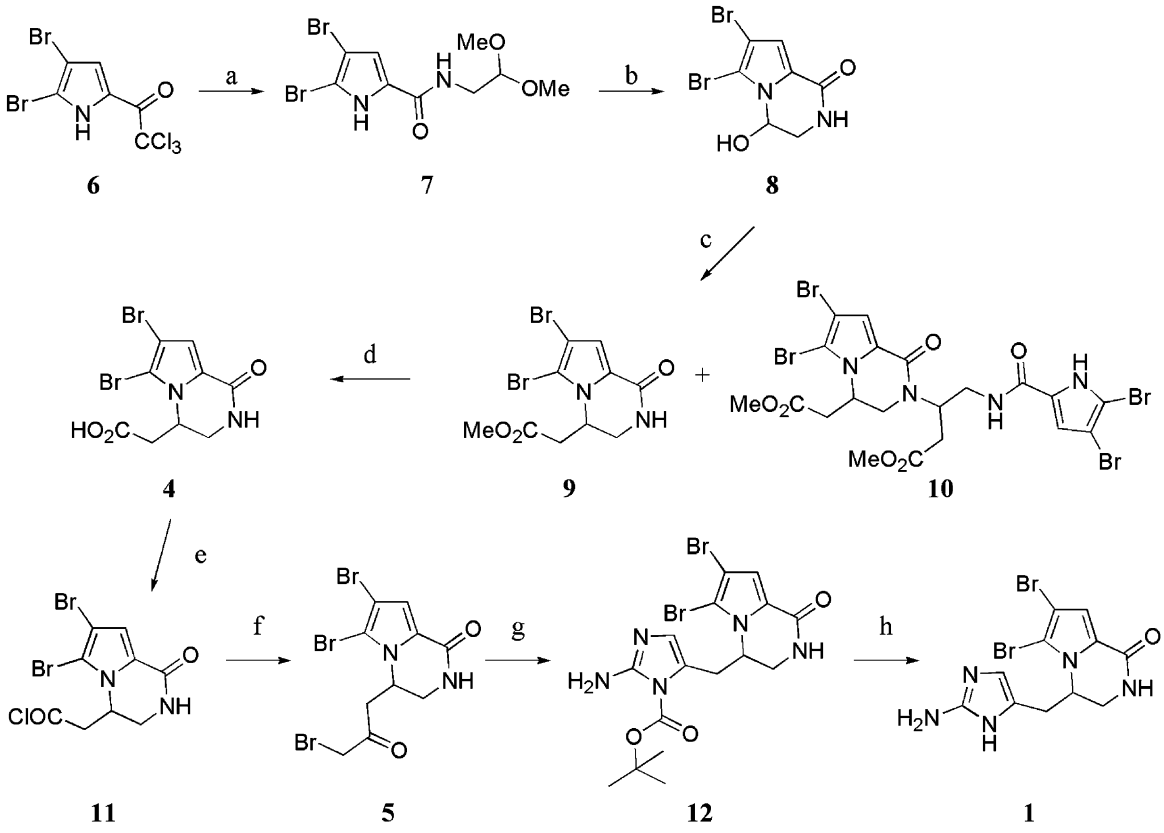


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) aminoacetaldehyde dimethyl acetal (1.1 equiv), acetonitrile, rt, 2 h, 99%; (b) 2 N aqueous HCl (2.5 equiv), acetone, rt, 16 h, 94%; (c) NaH (60% w/w dispersion in mineral oil, 3 equiv), trimethylphosphonoacetate (3 equiv), THF, 30 min at 0 °C then add (**8**), rt overnight, 82%; (d) LiOH (1.5 equiv), THF, water, rt, 24 h, 99%; (e) $SOCl_2$ (3 equiv), toluene, 90 °C, 6 h; (f) Me_3SiCHN_2 (3 equiv), THF, 0 °C, 5 h, then rt, overnight; then add 62% aqueous HBr (5 equiv) at −5 °C, 20 min; (g) Boc-guanidine[19b] (3 equiv), DMF, rt, 4 h, 30% (over four steps); (h) TFA, DCM, rt, 1 h, 45%.

Our synthetic efforts commenced (Scheme 2) by exploiting the previously disclosed protocol[8a] reported for the synthesis of (±)-longamide B (**4**). Starting from the readily accessible 4,5-dibromo-trichloroacetylpyrrole (**6**),[10] amidation with commercially available aminoacetaldehyde dimethyl acetal delivered amido-acetal (**7**). Exposure of (**7**) to 2 N HCl allowed the preparation of intermediate (±)-longamide (**8**), which was achieved in nearly quantitative yield.[8a,11]

^{1}H NMR (DMSO-d_6) of (±)-longamide (**8**) showed the compound being exclusively in the hemiaminal form. The stability of the pyrrolyl carbinols[12] could account for this observation. Naturally occurring (+)-longamide absolute stereochemistry had been originally described as (*S*)- again by comparison of its CD spectra with that of (−)-dibromophakellin (**3**).[13] It was later revised to (*R*)- by comparison of the circular dicroism spectra of optically active (**8**) with more closely related tricyclic analogues.[14] However, analytically separated enantiomers of (**8**) would racemize in a few minutes.[11a]

We then capitalized on the only published procedure[8a] (MeONa/MeOH/methyl diethylphosphonoacetate) reported for the synthesis of (±)-longamide B methyl ester. However, we obtained a complex reaction mixture, in which the amount of the desired product was overshadowed by a multitude of by-products, most of them arising from hydrolysis and competitive conjugate addition of methanol. In the event, longamide B methyl

ester (**9**) was then smoothly secured (82% isolated yield) by using NaH/trimethylphosphonoacetate in THF.

Along with the expected product, a diastereomeric mixture (15/85 ratio based on HPLC analysis) of dimers (**10**), arising from an intermolecular aza-Michael reaction, has been isolated (up to 15% yield, depending on reaction time and reactant concentration). Unfortunately, the relative stereochemistry of the major isomer could not be attributed by common NMR techniques.[15] Longamide B methyl ester (**9**) was then quantitatively converted into longamide B (**4**) in the presence of LiOH in a mixture of THF/water at room temperature.

We then focused on the construction of the aminoimidazole ring. Initially, we attempted to transform (**4**) into the corresponding mixed anhydride with isobutyl chloroformate,[16] however unsuccessfully. Longamide B (**4**) was then converted into the corresponding acyl chloride (**11**). Reaction of (**11**) with Me_3SiCHN_2,[17] followed by exposure of the resulting diazoketone solution to aqueous HBr at −5 °C delivered crude α-bromoketone (**5**).

As the above bromoketone (**5**) proved to be extremely reactive (washing with brine the organic phase gave a nearly 20% scrambling Br/Cl!), (**5**)[18] was immediately reacted with Boc-guanidine.[7,19] The isolated (30% over four steps) 15-Boc- protected[20] cyclooroidin (**12**) required extensive chromatography (AcOEt/MeOH) in order to remove unreacted Boc-guanidine. We postulated the migration of the *tert*-butoxycarbonyl group from the exo- to the endocyclic nitrogen atom[7] could occur during the purification step. Finally, removal of the protective group followed by column chromatography with a basic mobile phase (DCM/MeOH/NH_3 aq) delivered (±)-cyclooroidin (**1**) as the free base in 45% yield (80% based upon starting material consumed).

The spectral data of (**1**)[21] were in agreement with that of Fattorusso et al.,[5] except for the optical rotation.

In conclusion, the first total synthesis of (±)-cyclooroidin (**1**) has been achieved. Starting from 4,5-dibromotrichloroacetylpyrrole (**6**), a linear sequence of nine steps allowed us to secure (**1**) in 10% overall yield. The culminating step was represented by the application of a Wolff bromoketone synthesis protocol on the previously described (±)-longamide B (**4**).

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15. NMR spectra of (**10**), major isomer: ^{1}H NMR (DMSO-d_6): 2.50 (1H, m), 2.69 (2H, m), 2.76 (1H, dd, $J = 9.8$, 16.0 Hz), 3.38 (1H, m), 3.46 (1H, m), 3.56 (3H, s), 3.60 (3H, s), 3.62 (1H, d, $J = 14.0$ Hz), 3.99 (1H, dd, $J = 3.7$, 14.0 Hz), 4.73 (1H, m), 4.85 (1H, m), 6.83 (2H, s), 8.20 (1H, br s), 12.65 (1H, br s). ^{13}C NMR (DMSO-d_6): 33.2, 34.4, 39.3, 43.8, 39.4, 43.9, 49.8, 50.4, 51.6, 51.6, 98.0, 99.8, 104.9, 106.0, 126.1, 128.0, 157.5, 160.0, 170.7, 171.9. ^{15}N NMR (DMSO-d_6): 101.9, 103.5, 161.7, 167.0. MS (ES+): 728.9 $[M+H]^+$.
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18. An analytical sample was purified by column chromatography (AcOEt/toluene). NMR spectra of (**5**): ^{1}H NMR (DMSO-d_6): 2.80 (1H, d, $J = 17.1$ Hz), 3.26 (1H, m), 3.28 (1H, m), 3.80 (1H, dd, $J = 3.8$, 13.3 Hz), 4.39 (2H, s), 4.74 (1H, m), 6.86 (1H, s), 7.81 (1H, d, J = 5.0 Hz). ^{13}C NMR (DMSO-d_6): 36.2, 40.0, 41.8, 48.8, 99.5, 105.9, 114.1, 125.8, 157.3, 198.9.
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20. Numbering system according to Ref. 5. HRMS (ES+): *m/z*: calcd for $C_{16}H_{20}Br_2N_5O_3$: 487.9927 $[M+H]^+$; found: 487.9925. NMR spectra of (**12**): ^{1}H NMR (DMSO-d_6): 1.54 (9H, s), 2.48 (1H, m), 2.70 (1H, dd, $J = 10.9$, 14.0 Hz), 3.34 (1H, dd, $J = 5.5$, 13.2 Hz), 3.68 (1H, dd, $J = 4.1$, 13.2 Hz), 4.54 (1H, m), 6.53 (2H, br s), 6.65 (1H, s), 6.85 (1H, s), 7.80 (1H, d, $J = 5.2$ Hz). ^{13}C NMR (DMSO-d_6): 27.2, 29.9, 40.5, 52.2, 83.8, 98.4, 105.6, 107.4,

113.8, 125.5, 133.5, 149.7, 157.5. ^{15}N NMR (DMSO-d_6): 58.9, 94.7, 158.8, 171.0, 213.0.

21. Spectroscopic data of (**1**): HRMS (ES+): *m/z*: calcd for $C_{11}H_{12}Br_2N_5O$: 387.9403 $[M+H]^+$; found: 387.9406. ^{1}H NMR (CD_3OD): 2.83 (2H, d, $J = 7.2$ Hz), 3.53 (1H, d, $J = 13.5$ Hz), 3.78 (1H, dd, $J = 4.1$, 13.5 Hz), 4.59 (1H, m), 6.30 (1H, s), 6.93 (1H, s). ^{13}C NMR (CD_3OD): 30.1, 43.4, 55.0, 108.7, 112.2, 117.3, 125.6, 128.3, 150.6, 161.4.