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Total synthesis of cyclotripeptidic natural products anacine, aurantiomide C, polonimides A and C, and verrucine F

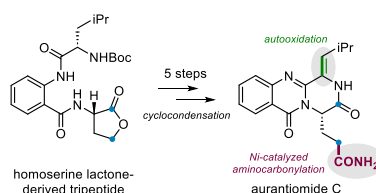
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ABSTRACT

The total synthesis of cyclotripeptidic natural products possessing a central piperazino[2,1-b]quinazolin-3,6-dione core is described, through an original strategy involving the pivotal cyclocondensation of an electrophilic homoserine lactone intermediate. The alkylidene group was spontaneously installed by autooxidation during the cyclocondensation process, while the propionamide side-chain was introduced through the nickel-catalyzed aminocarbonylation of a bromoethyl intermediate. This last reaction is unprecedented on such highly functionalized intermediates. Finally, we explored structural modifications and interconversions of the natural products. Overall, this work led to anacine, aurantiomide C, polonimide A and C, and verrucine F.



Numerous studies have documented the synthesis of the 4-quinazolinone framework, with the Niementowski reaction¹ standing out as a leading approach.^{2–4} This reaction proceeds under heating through the acid-catalyzed condensation of anthranilic acid with an amide. As a privileged structure, the 4-quinazolinone template holds an important medicinal value.^{5,6} Synthetic studies have thus been reported towards more functionalized and complex structures.^{7–10} In natural products, the fused piperazino[2,1-b]quinazolin-3,6-dione core is found in tripeptide derivatives predominantly found in marine fungi.^{8,11,12} They exhibit a diverse array of biological activities, encompassing antibacterial, anticancer, antifungal, anti-HIV, anti-inflammatory, and antimalarial properties. In particular, anacine (1),^{13,14} aurantiomide C (4) and derivatives (Figure 1),¹⁵ isolated from a marine sponge-associated fungus, *Penicillium aurantiogriseum*, have demonstrated a significant inhibitory potential against chitinase enzymes and cytotoxicity towards various cell lines.¹⁶ Biosynthetic studies demonstrated the involvement of a non-ribosomal peptide synthetase in the assembly of fumiquinazolines from anthranilic acid and amino acids.¹⁷ Notably, this route undergoes an important oxidative metabolism leading to structure functionalization, and more specifically to oxepin derivatives.¹⁸ Incidentally, we recently reported the total synthesis of some of those oxepin natural products.^{19,20}

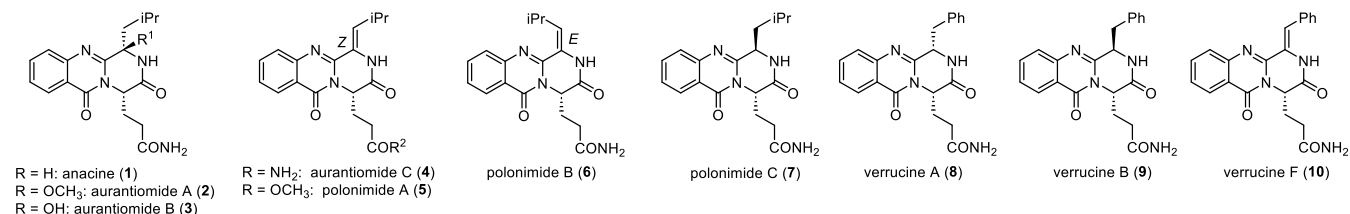
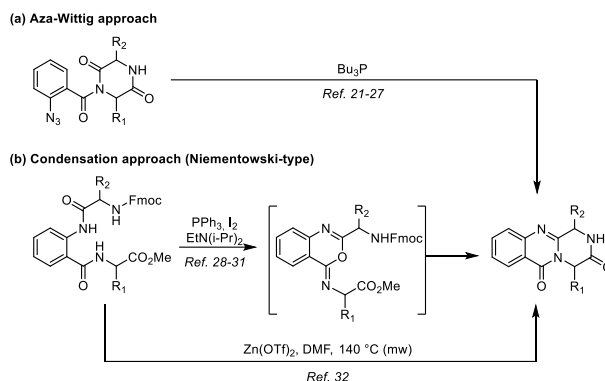


Figure 1. Examples of cyclotripeptidic natural products featuring a glutamate-derived piperazino[2,1-b]quinazolin-3,6-dione.

In 1994, Danishefsky reported the first total synthesis on *N*-acetylardeemin,^{21–23} a compound that reverses the multidrug resistance of cancer cells.²⁴ It featured a pivotal aza-Wittig reaction for the closure of the central ring, forging the C=N bond of the piperazino[2,1-b]quinazolin-3,6-dione core (Scheme 1a). This reaction was also adopted by Snider and co-workers for the total synthesis of fumiquinazolines.^{25–27} Alternatively, the Niementowski condensation approach (Scheme 1b) was used by Wang

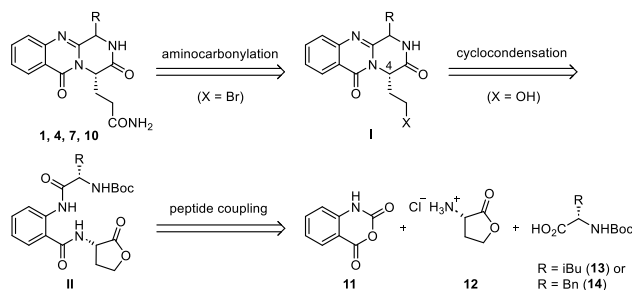
and Ganesan during the liquid and solid phase syntheses of fumiquinazolines and fiscalin B from tripeptide precursors.^{28–30} The solid-phase method was also applied by Wang and Sim to the total synthesis of anacine (**1**), and verrucines A (**8**) and B (**9**).³¹ Finally, Tseng and Chu devised a microwave-assisted synthesis in presence of Zn(OTf)₂ to facilitate a condensation process.³²

Scheme 1. Strategies on the synthesis of piperazino[2,1-b]quinazolin-3,6-diones.



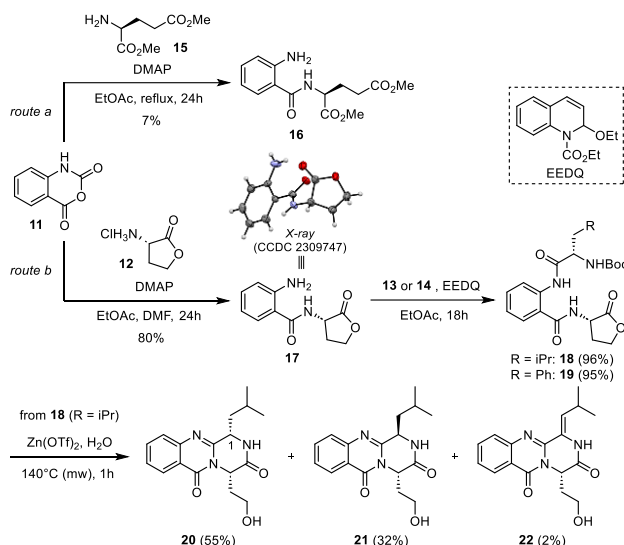
Herein, we report an alternative cyclocondensation strategy towards piperazino[2,1-b]quinazolin-3,6-diones **I** (Scheme 2), and its application to the total synthesis of anacine (**1**), aurantiomide C (**4**), polonimides A and C (**7**), and verrucine F (**10**). During the cyclocondensation step, we took benefit of the electrophilicity of an L-homoserine lactone residue on tripeptide intermediate **II** (made from isatoic anhydride **11**, homoserine lactone **12** and Boc-protected L-leucine **13** or L-phenylalanine **14**), allowing the release of a 2-hydroxyethyl substituent in position 4 (**I**, X = OH). From here, after bromination (**I**, X = Br), a rare nickel-catalyzed aminocarbonylation installed the propionamide side-chain of the natural products.

Scheme 2. Synthetic strategy towards glutamate-derived piperazino[2,1-b]quinazolin-3,6-diones.



The choice of L-homoserine lactone (**12**) as a starting material in this study came from our initial difficulties encountered during coupling attempts between **11** and dimethyl L-glutamate **15**, only resulting in a poor 7% yield of dipeptide **16** (Scheme 3, route a). Conversely, the reaction of **11** with L-homoserine lactone hydrochloride (**12**), which is easily accessible from L-methionine (see the supporting information), was successfully performed in presence of 4-dimethylaminopyridine (DMAP) to provide anthranilic amide **17** in a 80% yield (route b). Then, tripeptide intermediates **18** and **19** were obtained through the reaction of **17** with *N*-Boc-L-leucine (**13**) or *N*-Boc-L-phenylalanine (**14**), respectively, in presence of the coupling reagent 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ).³³

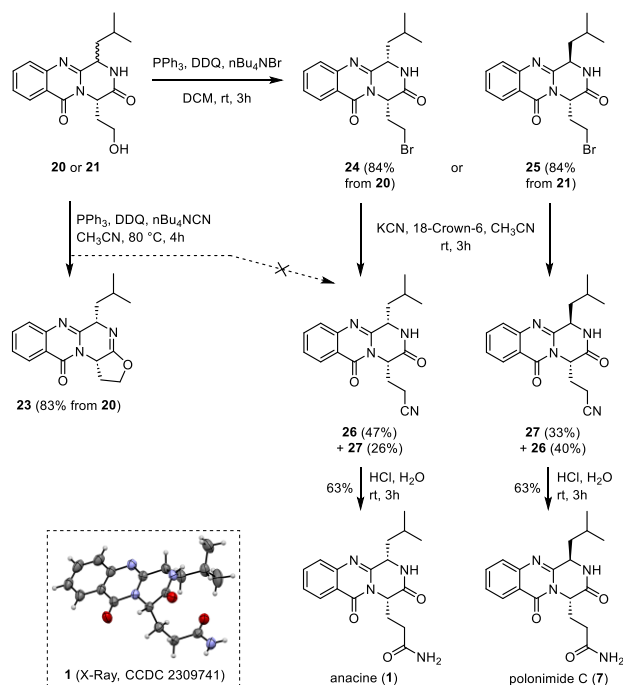
Scheme 3. Synthesis of cyclotripeptides: a three-step route from L-homoserine lactone.



After screening several cyclocondensation conditions, including temperature, reaction time, and solvent selection, we found that microwave heating at 140 °C in water in presence of $\text{Zn}(\text{OTf})_2$ (1.0 equiv), as inspired by Tseng and Chu,³² afforded *cis*-cyclotripeptide **20** in a 55% yield. The whole process was accompanied by the Boc deprotection. Unfortunately, an epimerization at position 1 could not be avoided and gave a substantial amount of *trans* isomer **21** in 35% yield (this amount could vary depending on the reaction conditions used). From the literature, the epimerization was known to occur regioselectively at position 1 under these acidic conditions, or at position 4 under basic conditions.^{28–32} Most importantly for the following discussion, isopropylidene byproduct **22** was also formed in minute amounts (2%), presumably resulting from an autooxidation process in presence of oxygen and favored by the rigorous condition used. The formation of this product (**22**) was magnified by prolonged heating, or minimized at higher concentration of reactants or by using DMF as a co-solvent.

To achieve the synthesis of anacine **1**, the primary alcohol of tricyclic compound **20** was planned to be converted into an amide group, with subsequent homologation (Scheme 4). Firstly, a modified Mitsunobu protocol in presence of PPh_3 , 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and tetra-*n*-butylammonium cyanide,³⁴ was attempted to directly substitute the hydroxyl with a cyanide group toward intermediate **26**. However, under these conditions at 80 °C, an intramolecular substitution of the activated hydroxyl group by the adjacent ketopiperazine amide occurred, leading to cyclic imidate **23** and precluding the cyanation. A two-step route was thus used from **20**, involving a bromination to **24**³⁴ followed by the substitution of the bromide by a cyanide in presence of KCN and 18-crown-6 ether. This step inevitably yielded a separable mixture of *cis*-isomer **26** (47%) and of *trans*-isomer **27** (26%). Finally, the hydrolysis of the nitrile group of isomer **26** under aqueous HCl condition yielded anacine (**1**) in a 63% yield. The same sequence was applied to alcohol intermediate **21**, giving polonimide C (**7**) in comparable yields through isomer **27**. Fortunately, crystals of **1** were obtained (CCDC 2309741) and allowed confirmation of the relative configuration (Scheme 4). However, the compounds turned out to crystallize as a racemate. Quasi complete racemization of **1** and **7** was confirmed by measuring their respective optical rotations: for **1**, $[\alpha]_D^{25} = +5.0$ (c 0.26, MeOH) [lit.¹⁵: $[\alpha]_D^{24} = +233.3$ (c 0.21, MeOH)], resulting in an optical purity of 2%; for **7**, $[\alpha]_D^{25} = +53.9$ (c 0.33, MeOH) [lit.¹⁶: $[\alpha]_D^{20} = +171.0$ (c 0.3, MeOH)], resulting in an optical purity of 32%. This short sequence of reaction highlights the difficulties of this stepwise approach to anacine **1**, and the need to explore alternative strategies not only for the introduction of the amide group, but also the synthesis of other natural product congeners.

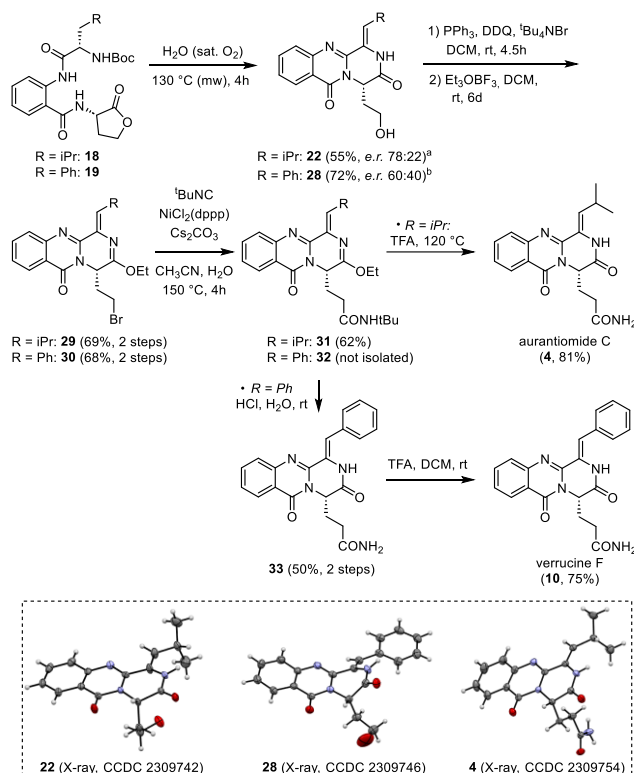
Scheme 4. First synthetic route to anacine and polonimide, showing an X-ray crystallographic structure of anacine.



As mentioned before, prolonged reaction times for the cyclocondensation of tripeptide **18** enhanced the production of autooxidation product **22**. Considering this side-product could be a good entry to the synthesis of aurantiomide C, further optimization was performed by conducting the reaction under microwave, in a solution saturated with oxygen. We observed that the presence of $\text{Zn}(\text{OTf})_2$ catalyst significantly reduced the yields of **22**. Ultimately, the optimal yield for this reaction was achieved at a concentration of 0.1M of tripeptide **18** in water and in the absence of $\text{Zn}(\text{OTf})_2$ at 130 °C (microwave) during 4 hours, resulting in a 55% yield of **22** (Scheme 5). Subsequently, following an acylation reaction with the Mosher reagents (Figure S1 in the supporting information),³⁵ NMR analysis allowed to determine an enantiomeric ratio (*e.r.*) of 78:22 for **22** ($[\alpha]_D^{25} = -23.4$, *c* 0.72, MeOH). Compound **22**, as all those of this series, crystallized as a racemate (CCDC 2309742).

After successful bromination of the primary alcohol **22** (see compound **S5** in the supporting information), the formation of cyclic imidate by-product **S6** similar to **23** (see supporting information) could not be avoided upon a cyanation attempt. The amide function was thus protected as an ethyl imidate (**29**), in presence of Meerwein's reagent (80% yield).³⁶ Furthermore, inspired by a recent report of Zhou and co-workers,^{37,38} the alkyl bromide on **29** was straightforwardly converted into homologated amide **31** through an aminocarbonylation. The reaction was catalyzed by $\text{NiCl}_2(\text{dppp})$ (20 mol%) in presence of *t*-butylisocyanide (1.0 equiv) and Cs_2CO_3 (1.0 equiv) in a mixture of acetonitrile and water at 150 °C (sealed tube). This step generated *t*-butyl amide **31** in 62% yield. Notably, this isocyanide coupling is unique with such a functionalized substrate, since the related literature only reported poorly functionalized alkyl bromide substrates.^{37,38} Finally, convergent deprotection of the two protecting groups (ethyl imidate and *t*-butyl amide) by acidolysis in trifluoroacetic acid (TFA) at the needed temperature of 120 °C was performed in 81% yield, thus achieving the total synthesis of aurantiomide C (**4**) with a global yield of 15%. This compound, crystallizing as a racemate, showed a marked reduction of the optical rotation compared to the literature ($[\alpha]_D^{25} = +5.2$, *c* 0.25, CHCl_3 ; Lit.¹⁵: $[\alpha]_D^{24} = +25.8$, *c* 0.1, CHCl_3) corresponding to an optical purity of 20%.

Scheme 5. Total synthesis of aurantiomide C and verrucine F.

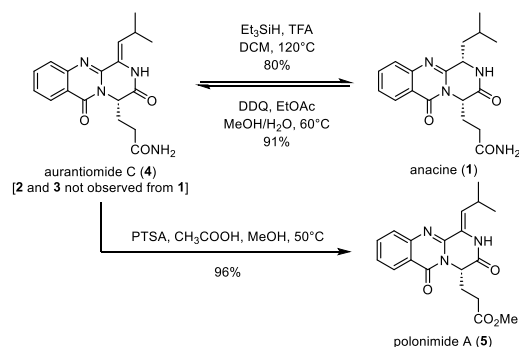


Notes: ^a Ratio obtained by NMR analysis of the (*R*)-Mosher esters (**S1** and **S2**, see Figure S1); ^b Since the NMR analysis could not distinguish the diastereomeric Mosher esters of **28** (**S3** and **S4**, see Figure S2), the enantiomeric ratio was obtained by HPLC analysis (see the supporting information).

In a very similar sequence from tripeptide **19**, verrucine F (**10**) was obtained in a global yield of 15% (Scheme 5). Notably, the autooxidation step occurring during the tripeptide condensation was more efficient, supposedly due to the stabilizing conjugation with the phenyl group. It gave cyclotripeptide **28** in 72% yield ($[\alpha]_D^{25} = -139.1$, c 0.34, MeOH; also crystallizing as a racemate, CCDC 2309746), with an *e.r.* of 60:40 measured by HPLC analysis of Mosher esters **S3** and **S4** (Figure S2). Furthermore, the final deprotection step necessitated two separated steps under acidic conditions to remove the *t*-butyl group (aqueous HCl) and the ethyl imidate (TFA), to afford natural product **10** in 75% yield ($[\alpha]_D^{25} = -29$, c 0.1, MeOH). The optical purity could not be evaluated in that case, due to the absence of data in the literature.

To complete this work, the reactivity of aurantiomide C (**4**) was investigated (Scheme 6), as an attempt to reach other natural products (**1-3**, **5**, **6**). Compound **4** turned out to be particularly stable. Although aurantiomides A (**2**) and B (**3**) were unreachable by the acid-catalyzed methoxylation and hydration of **4**, respectively, the reduction of the isopropylidene double bond could be efficiently performed in presence of triethylsilane and TFA in dichloromethane, to give diastereomerically pure anacine (**1**) in 80% yield. The optical rotation of this new sample of **1** ($[\alpha]_D^{25} = +20.3$, c 0.23, MeOH; lit.¹⁵: $[\alpha]_D^{24} = +233.3$, c 0.21, MeOH) suggested an optical purity of 8.7%. Furthermore, during our methoxylation attempts, polonimide A (**5**) was inadvertently obtained in 96% yield in presence of *para*-toluenesulfonic acid (PTSA) and acetic acid ($[\alpha]_D^{20} = -1.4$, c 0.22, MeOH; lit.¹⁶: $[\alpha]_D^{20} = +14$, c 0.3, MeOH). Finally, while an attempt of oxygen-mediated autooxidation of anacine (**1**) was inefficient, its oxidation in presence of DDQ in a methanol/water mixture successfully led to aurantiomide C (**4**) in 91% yield, with no formation of **2** or **3**.

Scheme 6. Conversion of aurantiomide C into anacine and polonimide A.



In summary, we successfully achieved the total synthesis of several cyclotripeptide natural products possessing a central piperazino[2,1-*b*]quinazolin-3,6-dione structure: anacine (**1**), aurantiomide C (**4**), and verrucine F (**10**). The tricyclic core was

constructed by a Niementowski-type cyclocondensation method involving a key homoserine lactone residue. Furthermore, relying on a nickel-catalyzed isonitrile coupling, it was possible to perform the aminocarbonylation of a bromoethyl side-chain to install the amide function of these natural products. Some of these steps had to be performed under drastic conditions that led to the epimerization or partial racemization of products, mostly resulting in a complex mixture of the final natural products. During this work, we took advantage of this epimerization to synthesize polonimide C (**7**), diastereoisomer of anacine (**1**), while the ester polonimide A (**5**) could be generated by the acid-catalyzed methanolysis of amide **4**. Finally, it is interesting to mention that both **1** and **4** can be interconverted under specific redox conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Detailed experimental procedures, spectroscopic and crystallographic data, and ¹H and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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