



First total synthesis of versicotide A, B and C†

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1. Introduction

In the past years, a significant number of macrocyclic peptides, with very interesting biological activities, have been described in the literature.¹ They are known to be promising candidates in the search for new drugs as they show enhanced metabolic stability in comparison with their corresponding linear peptides, and could bind to receptors with high selectivity.² Moreover, chemoinformatic exploratory analyses of synthetic peptide combinatorial data sets have suggested that *N*-methylation and cyclization shifts their position toward the chemical space defined by sets of FDA approved drugs. Therefore, these modifications could result in compounds with biological activity and suitable physicochemical properties.³ In addition, it was demonstrated that multiple backbone *N*-methylation of cyclic peptides remarkably improves their cell permeability and therefore can be utilized in the design of new orally available drugs.⁴ Recent studies suggest that because of their conformational flexibility, cyclopeptides behave as molecular chameleons as they adjust their conformations and polar surface areas according with the properties of surrounding environment.⁵ On the other hand, constrained structures are expected to present a minor loss of conformational entropy upon binding, resulting in higher target affinity.⁶ Thus, many groups investigate the addition of further constraints to cyclopeptides in order to obtain a potential bioactive conformer.⁷

Natural products are a continuous source of inspiration for the discovery and development of new drug candidates.⁸ Those proceeding from marine environments, have been attracting special interest for their unexplored structural diversity.⁹

The syntheses of versicotides A–C, natural products containing anthranilic acid and NMe-Ala, were achieved by solid phase peptide synthesis on 2-chlorotrityl resin followed by solution phase macrocyclization. Using an oxyma additive, the difficult coupling reactions to the deactivated aromatic amine of *o*-aminobenzoic acid, were performed in high yield, avoiding anthranilic rearrangements or side reactions.

Particularly, marine fungi are subjected to many factors that contribute to gene modifications and to adaptive processes producing unique secondary metabolites. *Aspergillus* genus is an important source of bioactive secondary metabolites with high structural diversity.¹⁰ Versicotides are natural products produced by fungi of the *Aspergillus* family. Versicotides A (1) and B (2), Fig. 1, were first isolated by Li and co-workers from *Aspergillus versicolor* ZLN-60 extracts of the Yellow Sea sediment.¹¹ Later, the same group employed the OSMAC (one strain many compounds) approach on this fungus, resulting in the isolation and characterization of a new compound with structural similarities named versicotide C (3),¹² the first natural cyclic hexapeptide containing two anthranilic acids (Anth). Further on, three new cyclopeptides were isolated from *Aspergillus versicolor* LZD-14-1 namely versicotides D–F,¹³ along with the previously known versicotides A and B.

The presence of two rigid β -amino acids, Anth units, and two *N*-methyl-alanine (NMe-Ala) in 1–3 add further constraints to these cyclopeptides. In the case of the reported isolation of versicotide C (3), the authors stated that, in DMSO- d_6 , it presents one *trans* amide bond and one *cis* amide bond on its structure.¹²

Regarding their biological activity, 1 and 2 showed no cytotoxicity against murine leukemia P388, human hepatoma cell line BEL-7402 and human leukemia cell HL-60; versicotides A–C showed no activity against cancer cell lines A-549, HeLa and SMMC-7721. In addition, versicotides D–F exerted lipid lowering effects through the regulation of cholesterol efflux to HDL in RAW264.7 macrophages, while 1–3 do not exhibit this effect.

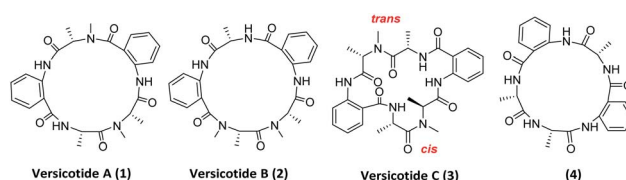


Fig. 1 Versicotides A–C and analogue 4.

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Recently, as part of a general program to obtain anti-plasmodial candidates,¹⁴ our group reported the synthesis of versicotide D and analogues and their evaluation as antimalarials against the chloroquine sensitive strain *P. falciparum* 3D7, where versicotide D showed $EC_{50} = 1.5 \mu\text{M}$.¹⁵

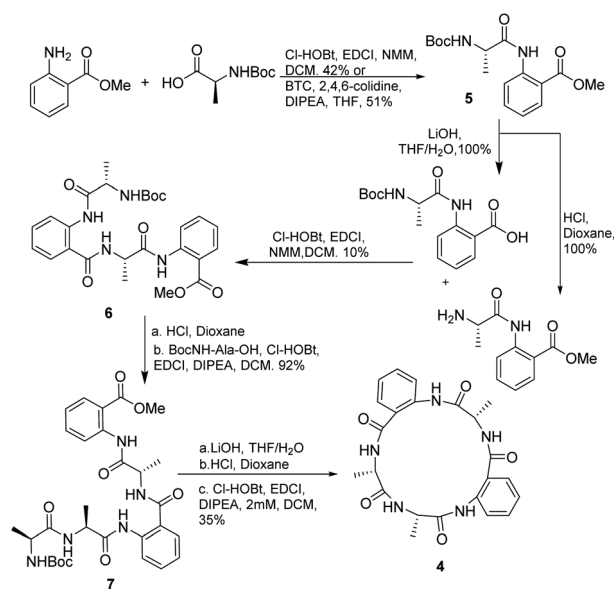
There are few examples in the literature related to the synthesis of cyclopeptide natural products containing anthranilic acid,¹⁶ and they are all broadly in line to the fact that amide bond formation involving the amine of Anth is a challenge not only because of the deactivation of the aromatic amine *via* resonance, but also due to rearrangements in which the Anth motif can be involved.¹⁷ Frequently, long, complicated, multi-stage and low yielding routes have been used to achieve the synthesis of natural products containing this motif. An example is the total synthesis of deoxo-solomonamide B in which Anth motif was masked with an indole group that is cleaved by ozonolysis in the last steps of the synthetic route.¹⁸ Therefore, a simpler methodology to obtain compounds with Anth in good yield is a chemical challenge. In addition, as many cyclopeptides containing Anth, present diverse bioactivities such as increasing blood pressure,^{16b} lipid lowering effect,¹² anti-proliferative,^{16a,16d} anti-inflammatory,¹⁸ insecticide,^{16e} the interest on this issue is enhanced. Here, we report the total synthesis of versicotides A–C and analogue 4. The structures of the obtained compounds were confirmed by MS, NMR and, in the case of versicotide A (1), by X-ray analysis. A deep analysis of NMR data (¹H, ¹³C, COSY, HSQC and HMBC) was done in order to determine the adopted conformations in the used solvents, along with temperature variation studies.

2. Results and discussion

2.1. Solution phase approach

First, we decided to prepare the *cyclo*[Ala-Anth-Ala-Anth-Ala] (4), analogue of 1 and 2, and to investigate the solution phase synthesis of the peptide precursor containing only Ala and Anth. The *in situ* acyl chloride formation using triphosgene¹⁹ made it possible to couple Ala to the amine of methyl anthranilate in 51% yield, Scheme 1. No racemization was observed by ¹H-NMR analysis. However, advanced intermediates could not be prepared using triphosgene. In an attempt to circumvent this, we tried to apply the methodology described by Xin and Burgess,²⁰ which employed a combination of EDCI and HOBt. As HOBt and HOAt present restrictions for their overseas shipment, we decided to substitute HOBt by Cl-HOBt.

Dipeptide 5 and tetrapeptide 6 were obtained in 42% and 10% yield, respectively. No racemization during the coupling reaction steps was detected according with the NMR spectra of 6. However, in the case of the synthesis of 6 many by-products, as fragments of the desired compound, were observed. Two of the detected by-products were methyl anthranilate and the tripeptide NH₂-Anth-Ala-Anth-OMe, derived from fragmentation of the labile Anth amide bond according with Hamada *et al.* results.^{17b} The preparation of pentapeptide 7 from 6 resulted in a high yielding process (92%). Finally, deprotection and cyclization in diluted conditions (2 mM) rendered analogue 4 in 35% yield.



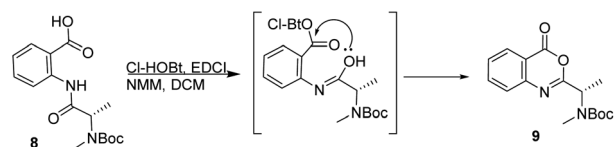
Scheme 1 Solution synthesis of cyclopentapeptide analogue 4.

Attempts to apply this strategy for the synthesis of versicotide A were not successful. The coupling reaction between BocNHMeAla-Anth (8) and Ala-Anth(OMe) using EDCI and Cl-HOBt rendered the corresponding tetrapeptide intermediate in very low yield along with the benzoxazinone 9, Scheme 2. According with previous results,²¹ this heterocycle is derived from the cyclodehydration reaction of 8.

2.2. SPPS synthesis of linear precursors and solution phase cyclization

In view of the limited achievements of the solution phase synthetic methodology, we decided to explore the synthesis of the linear precursors of versicotides A–C on solid phase and cyclize them on solution phase. The linear sequence of each one was chosen taking into account the characteristics of Anth explained before. Based on this, Anth amine was not chosen as the N-terminal in any case. Furthermore, we realized in early steps of this work that using Anth as the C terminal on solid phase peptide synthesis (SPPS) was not a good choice either, as it leads to very low resin loadings and it could give a great steric hindrance for the first coupling to occur. Because of this, the linear sequences chosen were: NHMeAla-Anth-NMeAla-Anth-Ala-OH for 1, NHMe-Ala-Anth-Ala-Anth-NMeAla-OH for 2 and NMeAla-Anth-Ala-NMeAla-Anth-Ala for 3.

Our first efforts to obtain the linear precursor of versicotide A, 10, by SPPS on 2-chlorotrityl chloride resin (2-CTC), were not successful. The use of HBTU, HATU, or DIC/Cl-HOBt for the



Scheme 2 Synthesis of benzoxazinone 9 from BocNHMeAla-Anth.



their proportion at higher temperatures. This fact allowed us to discard epimerization and to conclude that both samples contain a mixture of conformers of **2**; in one of them both NMe-amides are in *trans* configuration, Scheme 3, and in the other conformer, one amide is in *cis* and the other in *trans* configuration, (see ESI†) according with the literature.²⁴

In a similar way, the synthesis of the linear precursor of versicotide C (**12**), Scheme 4, was successfully achieved employing Oxyma + DIC in key steps, leading to 98% overall yield (based on the determination of the resin loading).

Then, macrocyclization in solution phase, using HATU in DCM (5 mM), rendered versicotide C (**3**) in 49% yield after purification and no dimer formation was observed. NMR spectra of synthetic versicotide C in DMSO-*d*₆, match those of the isolated natural product, even though the authors informed a single conformer with one NMe amide bond in *cis* and the other one in *trans* configuration.¹² A deep analysis of NMR spectra, with special regard to signal integrations, lead us to conclude that two conformers of **3**, in a 1 : 0.2 ratio, are present in both acetone-*d*₆ and DMSO-*d*₆. The conformers, which present symmetrical structure, were easily distinguished by the NMR signals of the two *N*-Me groups. The two corresponding *N*-methyl amide bonds of one conformer are in *trans* configuration, Scheme 4, and of the other conformer, in *cis* configuration. The presence of these two conformers were further confirmed

by a ¹H-NMR experiment of **3** at 80 °C which showed that the peaks assignable to the (*cis*, *cis*) conformer at 25 °C, disappeared at this temperature (see ESI†).

3. Experimental section

3.1. General procedure. Solid phase peptide synthesis

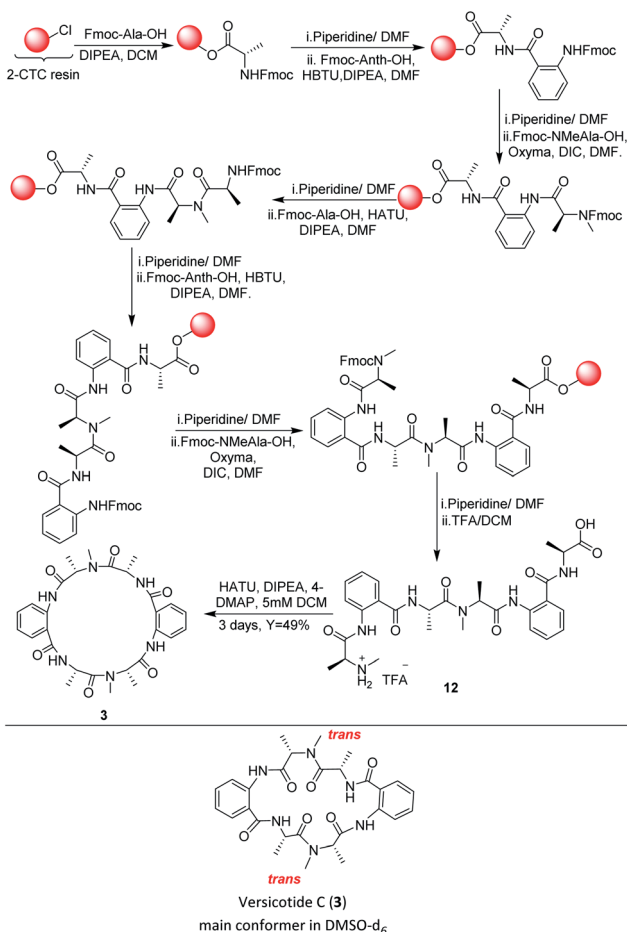
2-Chlorotrityl chloride resin (2-CTC) (100–300 mesh, 1.20 mmol g⁻¹) was added to a syringe peptide synthesis vessel. The resin was swelled in CH₂Cl₂ (3 × 5 min). A solution of first protected amino acid Fmoc-AA-OH (1 eq. for 0.8 mmol g⁻¹ loading) and DIPEA (3 eq.) in CH₂Cl₂ was added and the resin was shaken 10 minutes. Then, an extra 7.0 eq. of DIPEA were added and shaking was continued for 50 min. MeOH (0.8 mLg⁻¹ of resin) was added to the previous mixture in order to cap unreacted functional groups on the resin, and shaken for 10 min. After filtering, the resin was washed with CH₂Cl₂ (×3), MeOH (×3), CH₂Cl₂ (×3), DMF (×3). The resin was washed with DMF (×3) and Fmoc protecting group was removed by treating the resin with piperidine–DMF solution (1 : 4) for 1, 5 and 5 minutes successively. In exceptional cases deprotection step was accomplish by a single treatment with piperidine–DMF solution for 5 minutes, in order to prevent side reactions. Then, the resin was washed with DMF (×3), CH₂Cl₂ (×3) and DMF (×3). A solution of Fmoc-AA-OH or Fmoc-Anth-OH (3 eq.) and DIPEA (6 eq.) in DMF was added to the resin, followed by a solution of HBTU, for coupling to primary amines, or HATU (2.9 eq.) in DMF, in case of coupling to an *N*-methylated amino acid. The mixture was stirred for 60 min. After the coupling was completed, the resin was washed with DMF (×3) and CH₂Cl₂ (×3). Completion of the coupling was monitored by colorimetric assays; Kaiser test in case of primary amines and Chloranil test for secondary amines. Coupling procedure was repeated in case of positive results. For the coupling of subsequent Fmoc-AA to anthranilic acid, a solution of Fmoc-AA-OH (5 eq.), Oxyma Pure (5 eq.), and DIC (5 eq.) was added to the vessel. The mixture was stirred for 60 min. Then, the resin was washed with DMF (×3) and CH₂Cl₂ (×3). Deprotection and coupling cycles were repeated with the appropriate amino acids or Anth to provide the desired compound. The peptide was cleaved from the resin by treatment with 1% TFA in CH₂Cl₂ for 2–3 minutes at room temperature followed by filtration and collection of the filtrate in MeOH. The treatment was repeated three times and then the resin washed with CH₂Cl₂ (×5) and MeOH (×3). Solvents were removed *in vacuo* to obtain the crude peptide. LC-MS was used to identify the product.

3.2. Solution phase synthesis

3.2.1. General procedures for coupling reaction

3.2.1.1. Method 1. EDC·HCl (1.5 eq.), Cl-HOBT (1.5 eq.) and DIPEA (2.0 eq.) were added to a solution of Boc protected amino acid (Boc-AA-OH, 1.0 eq.) in DCM at 0 °C under N₂ atmosphere. *N*-Terminus deprotected linear peptide or amino acid ester (NH₂-AA-COOEt) was added and the reaction mixture was stirred at 0 °C for 10 min and then at room temperature, overnight.

DCM was removed under vacuum and AcOEt was added. The organic phase was washed with 0.1 M HCl aqueous solution



Scheme 4 SPPS and solution macrocyclization of versicotide C (**3**)



employing H₂O : MeCN and 0.1% formic acid in a 90 : 10 to 0 : 100 linear gradient in 15 min showed two peaks *tr* = 7.5 and 7.8 min in a 1.4 : 1 ratio. Collection of the peaks at the end of the column and LC-MS analysis revealed both peaks have the same mass as the natural product versicotide B. Thermal analysis by NMR proved them to be conformers. 91% total purity.

3.3.2.4. Cyclo-[NMeAla-Anth-Ala-Anth-NMeAla] (2). Yellow solid (*Y* = 54%). ESI-MS *m/z* calc. for C₂₅H₃₀N₅O₆ ([M + H]⁺) 480.2, found 480.6. ¹H NMR (400 MHz, DMSO-d₆) two conformers A : B in 1 : 1.3 ratio. δ 1.13 (d, *J* = 6.6 Hz, 3H_a), 1.26 (d, *J* = 6.7 Hz, 3H_b), 1.40–1.44 (m, 6H_a, 3H_b), 1.47 (d, *J* = 6.5 Hz, 3H_b), 2.24 (s, 3H_a), 2.96 (s, 3H_b), 2.99 (s, 3H_b), 3.06 (s, 3H_a), 4.14–4.25 (m, 1H_a), 4.52–4.68 (m, 1H_b), 4.70–4.87 (m, 1H_a), 5.08–5.17 (m, 1H_b), 5.17–5.26 (m, 1H_a), 5.30–5.41 (m, 1H_b), 7.12–7.22 (m, 1H_a + 1H_b), 7.23–7.31 (m, 1H_a), 7.34 (d, *J* = 6.7 Hz, 1H_b), 7.39–7.58 (m, 2H_a, 2H_b), 7.60 (m, 2H_a), 7.81 (d, *J* = 6.1 Hz, 1H_b), 8.07 (d, *J* = 7.6 Hz, 1H_b), 8.16 (d, *J* = 8.2 Hz, 1H_a), 8.44–8.5 (m, 2H_a + 2H_b), 9.07–9.20 (m, 2H_a), 9.24 (s, 1H_b), 9.36 (s, 1H_b), 10.58 (s, 1H_a), 10.92 (s, 1H_b). ¹³C NMR (100 MHz, DMSO-d₆) δ 13.5 (C_a), 13.8 (C_b), 14.8 (C_a), 16.7 (C_a), 17.1 (C_b), 17.5 (C_b), 28.7 (C_a), 30.3 (C_b), 30.8 (C_a), 34.3 (C_b), 49.8 (C_b), 50.3 (C_b), 52.1 (C_a), 52.5 (C_a), 52.6 (C_b), 54.5 (C_a), 120.3, 120.6, 122.1, 123.1, 123.7, 124.3, 124.6, 125.6, 126.1, 127.3, 128.6, 129.2, 129.4 (C_a), 130.2, 130.6, 132.1 (C_a), 132.9, 135.3, 136.2, 137.4 (C_a), 139.8, 141.6, 145.7, 168.4 (C_b), 168.6 (C_a), 169.6 (2C_{a,b}), 169.8 (C_a), 170.3 (C_b), 170.9 (C_b), 171.3 (C_a), 171.9 (C_a), 172.3 (C_b).

3.3.2.5. Cyclo-[NHMe-Ala-Anth-Ala-NMe-Ala-Anth-Ala] (versicotide C) (3). The trifluoroacetate salt of NHMe-Ala-Anth-Ala-NMe-Ala-Anth-Ala-OH was obtained as a white solid following the general SPPS procedure. The global yield, based on the determination of the resin loading, was 98% (240 mg, 0.35 mmol). ESI-MS *m/z* calc. for C₂₈H₃₇N₆O₇ ([M + H]⁺) 569.3, found 569.3. Macrocyclization reaction was performed following the general procedure method I (dilution 5 mM, 3 days), starting from the trifluoroacetate salt of linear peptide NHMe-Ala-Anth-Ala-NMe-Ala-Anth-Ala-OH (200 mg, 0.30 mmol), using HATU as coupling agent. Further purification by flash chromatography using AcOEt as mobile phase, rendered the desired macrocycle in 49% yield (77 mg, 0.15 mmol). HPLC analysis employing H₂O : MeCN and 0.1% formic acid in a 90 : 10 to 0 : 100 linear gradient showed 93% purity, *tr* = 6.88 min.

3.3.2.6. Cyclo-[NMeAla-Anth-Ala-NMeAla-Anth-Ala] (3). White solid (*Y* = 49%). *R_f* = 0.25 (AcOEt). [α]_D²⁵ = −35.83 (c 0.25, MeOH). ¹H NMR (400 MHz, (CD₃)₂CO) two conformers were present: A (*trans, trans*)-conformer and B (*cis, cis*)-conformer in 1 : 0.2 ratio. (*trans, trans*) Conformer: δ 1.43 (d, *J* = 7.0 Hz, 3H), 1.50 (d, *J* = 6.8 Hz, 3H), 3.53 (s, 3H), 3.93 (q, *J* = 6.8 Hz, 1H), 5.26–5.36 (m, 1H), 6.91–6.99 (m, 1H), 7.34–7.41 (m, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.75 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.69 (dd, *J* = 8.4, 0.9 Hz, 1H), 11.88 (s, 1H). (*cis, cis*) Conformer: δ 1.34 (d, *J* = 6.6 Hz, 1H), 1.67 (d, *J* = 7.2 Hz, 1H), 2.73 (s, 3H), 4.69 (q, *J* = 7.2 Hz, 1H), 5.26–5.36 (m, 1H), 6.86–6.91 (m, 1H), 7.05–7.11 (m, 1H), 7.88 (dd, *J* = 8.1, 1.2 Hz, 1H), 8.07 (dd, *J* = 8.4, 0.8 Hz, 1H), 8.15 (d, *J* = 9.5 Hz, 1H), 12.29 (s, 1H). ¹³C NMR (100 MHz, (CD₃)₂CO) (*trans, trans*) conformer: δ 12.7(2C), 18.1(2C), 38.4(2C), 46.7(2C), 63.1(2C), 119.5(2C), 119.9(2C), 122.6(2C),

128.6(2C), 133.2(2C), 141.6(2C), 168.3(2C), 169.8(2C), 172.3(2C). (*cis, cis*) Conformer: δ 17.1(2C), 18.1(2C), 28.4(2C), 46.1(2C), 56.4(2C), 119.8(2C), 120.1(2C), 128.1(2C), 133.3(2C), 141.6(2C), 142.9(2C), 169.7(2C), 170.7(2C), 171.1(2C). ESI-MS *m/z* calc. for C₂₈H₃₅N₆O₆ ([M + H]⁺) 551.3, found 551.3.

3.3.2.7. Cyclo-[NH₂Ala-Ala-Anth-Ala-Anth] (4). Compound 5 was prepared by solution phase synthesis, either by coupling method I or II (yield 42% and 51% respectively). Half of dipeptide 5 was deprotected on the C terminal following the general ester hydrolysis procedure. The other half was deprotected on the N terminal by Boc deprotection procedure. The resulting dipeptides were coupled following coupling method I to obtain 6 in a 10% yield. 6 was subjected to Boc deprotection conditions and then Boc-Ala-OH was coupled with coupling method I to obtain 7. 7 was deprotected first on the C terminal with ester hydrolysis procedure, and then at the N terminal with Boc deprotection procedure. The resulting peptide was cyclized following macrocyclization method II to render cyclopeptide 4 in 35% yield.

3.3.2.8. Cyclo-[Ala-Ala-Antr-Ala-Antr] (4). Yellow solid *R_f* = 0.41 (AcOEt : EP, 4 : 1). ¹H-NMR (400 MHz, (CD₃)₂CO) δ 1.27–1.36 (m, 3H), 1.53–1.62 (m, 6H), 4.46–4.58 (m, 1H), 4.63–4.75 (m, 1H), 4.80–4.95 (m, 1H), 7.08–7.19 (m, 2H), 7.72 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.48 (m, 2H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.98–8.06 (m, 1H), 8.10–8.19 (m, 1H), 8.20–8.26 (m, 1H), 8.35 (d, *J* = 8.3 Hz, 1H), 8.62 (d, *J* = 8.7 Hz, 1H), 11.05 (s, 1H), 11.31 (s, 1H). ¹³C NMR (100 MHz, (CD₃)₂CO) δ (ppm) 15.5, 17.1, 17.4, 49.6, 50.4, 51.2, 121.1, 121.2, 121.4, 121.5, 122.6, 122.8, 123.7, 125.3, 127.4, 128.6, 131.4, 132.1, 168.3, 170.2, 171.2, 173.0, 173.1. MS *m/z* calc. for C₂₃H₂₅N₅O₅ ([M + H]⁺) 452.19, found 452.2.

See ESI† for HPLC chromatograms, MS and NMR spectra data of the cyclopeptides.

4. Conclusions

In conclusion, the syntheses of three natural products, versicotides A–C, containing Anth, were accomplished in very good yields and purity after searching for the most adequate methodology and coupling reagents. The combination of oxyma and DIC, provided a simple methodology to achieve difficult couplings involving the aromatic amine of Anth, in short times, to avoid possible rearrangements or side reactions, and with very good yields. This methodology could be applied to the synthesis of interesting compounds containing this motif.

Macrocyclization of versicotides A and C was achieved with HATU and no epimerization was detected. For macrocyclization of versicotide B (2), Oxyma and EDCI provided higher yield. In the versicotides A–C NMR spectra, the presence of well-defined peaks for each conformer shows that these molecules are rigid enough for the conversion from one conformer into another to be slower than NMR time scale. A deep analysis of versicotide C NMR spectra led us to conclude that a mixture of (*cis, cis*) and (*trans, trans*) symmetrical conformers is present in DMSO-d₆ rather than a single (*cis, trans*) conformer as previously reported for the natural product. Biological evaluation against *P. falciparum* of compounds 1–4 will be performed and reported in the due course.



Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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