Efficient Construction of the Carbon Skeleton of the Novel Polyoxazole-Based Cyclopeptide IB-01211 via a Biomimetic Macrocyclisation

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This paper is respectfully dedicated to Professor Gerald Pattenden in celebration of his 70th birthday

Abstract: An efficient construction of the entire carbon skeleton of the novel polyoxazole-based natural product IB-01211 was developed which featured a biomimetic macrocyclisation of an ω-amino acid tethered through two bisoxazole units as the key step.

Key words: heterocycles, biomimetic, macrocyclisation, peptides, oxazoles

Several contiguously linked macrocyclic oxazole/thiazole-based natural products, isolated mainly from marine sources and/or microorganisms, have shown interesting and useful levels of biological activity.[1] This, in turn, has generated considerable interest not only in the synthesis of these challenging natural products but also in the design and synthesis of their simpler analogues with a view to obtaining compounds of desired properties.[2] YM-216391[3] (**1**, Figure 1), IB-01211[4] (**2**), and telomestatin[5] (**4**) are good examples in these regards.

A major hurdle in the synthesis of such complex targets has often been the crucial macrocyclisation step. Synthetic efforts by several groups towards these and related cyclic peptides have revealed interesting developments of several macrolactamisation protocols and problems associated with such cyclisations, but development of alternate macrocyclisation protocols have also been rewarding in some instances.[6] Several years ago, during the course of their synthetic studies on the novel trisoxazole-based marine metabolite ulapualide, Pattenden speculated[7] that perhaps one of the oxazole or thiazole rings is formed at the late stage of their biogenesis through a macrolactamisation reaction involving the NH_2 functionality of a serine–threonine–cysteine residue linked to an oxazole/thiazole ring and a CO_2H group linked to another such heterocyclic unit, for example, the conversion of **5** into **7** (Scheme 1). This biogenetically patterned macrocyclisation proposal has found important applications in the second-generation synthesis[8] of the important lectin-binding agent ulapualide A and in the synthesis of the important telomerase inhibitor telomestatin.[9] Herein, we wish to report another fruitful application of this concept in continuation of our ongoing work on the synthesis of polyazole-based bioactive natural products.[10]

IB-01211 (**2**), isolated[4] from the microorganism strain ES7-008, is strongly cytotoxic[11] to several cell lines. It has a unique and unprecedented structure accommodating four oxazole rings and one thiazole ring tethered with a tripeptide containing a dehydroamino acid residue. The total synthesis of IB-01211 as well as problems associated with the construction of the macrocyclic ring of this natural product has been recently reported.[12] We became interested in developing a general synthetic route to its all-oxazole analogue **3** based on Pattenden's biomimetic proposal. The retrosynthetic strategy we adopted for the compound **3** is depicted in Scheme 2, which left the key fragments to be the bisoxazole amino alcohol **10**, the dipeptide **11**, and the phenyl-substituted bisoxazole derivative **12**. A convergent union of these fragments following the synthetic direction was therefore pursued.

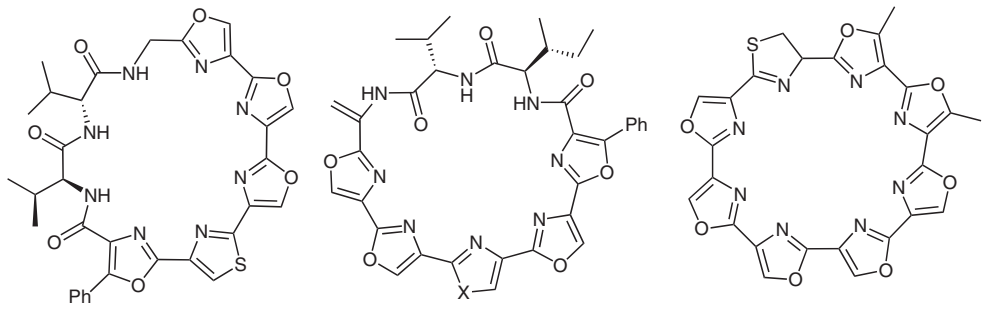

Figure 1

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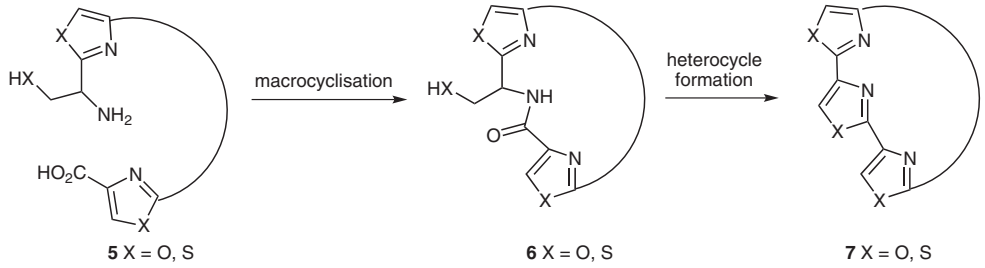
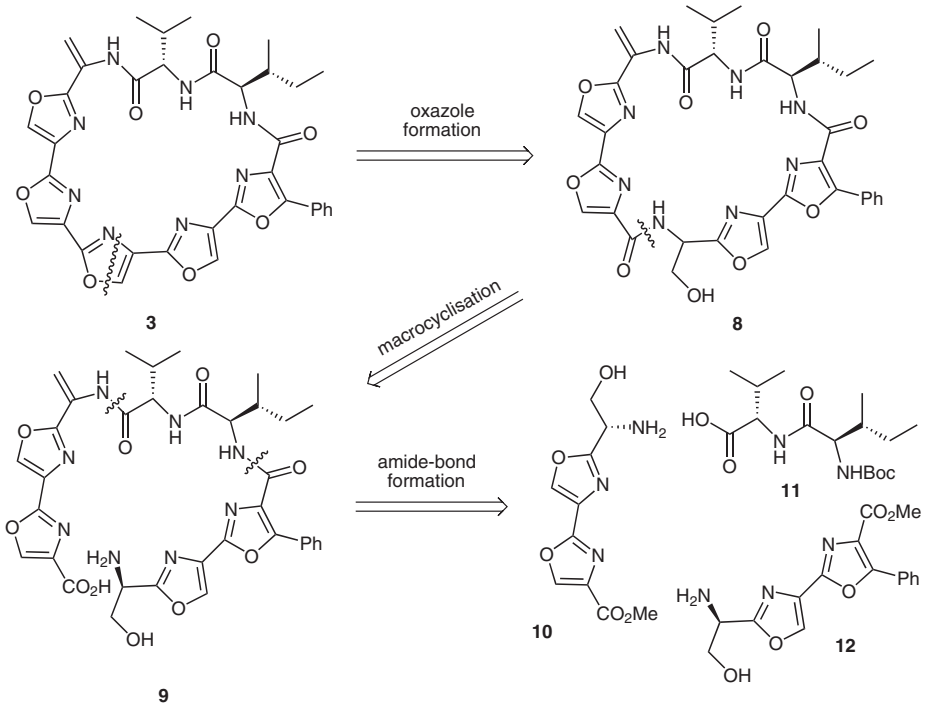


Scheme 1



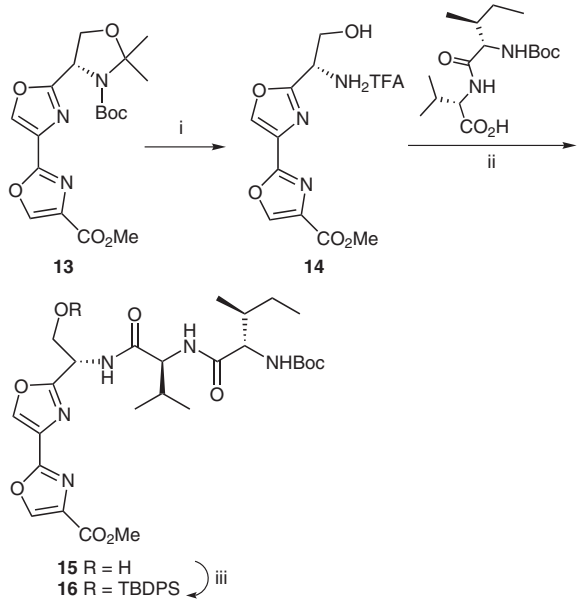
Scheme 2

Fragment **10** was easily prepared by trifluoroacetic acid mediated global deprotection of the bisoxazole-oxazolidine derivative **13** previously described by us.[13] The crude TFA salt **14** thus obtained was used as such in the next step. Although the natural dipeptide residue **11** contained D-allo-isoleucine as the N-terminal amino acid, we opted to use the cheaper L-isoleucine as a replacement in our explorative studies. Thus, the bisoxazole amine **14** was coupled with easily obtainable Boc-L-Ile-L-Val-OH using the *N*-methylmorpholine–EDC–HOBt combination to deliver the coupled product **15** (Scheme 3) in good yield and as a colourless solid. The free OH group in the latter was then protected as its TBDPS ether under standard conditions to provide **16**, $[\alpha]_D$ –37.5 (*c* 0.5, MeOH), also as a colourless solid, mp 178–179 °C.

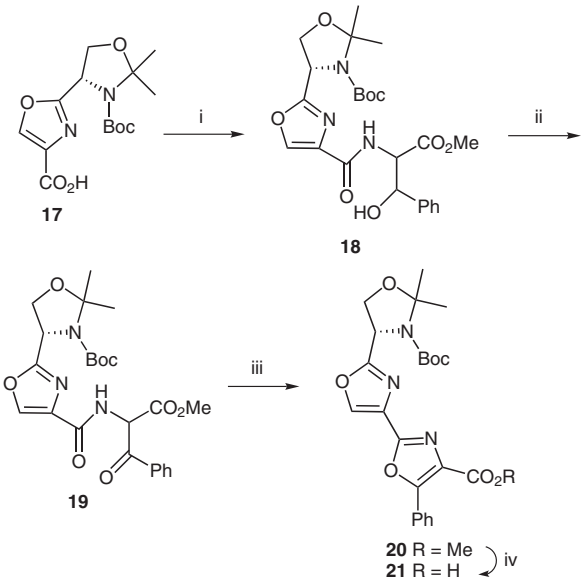
The preparation of the second bisoxazole fragment **12** followed from the monooxazole acid **17** (Scheme 4), also previously reported by us.[14] Thus, amide bond formation between **17** and racemic phenylserine methyl ester hydrochloride using dicyclohexylcarbodiimide (DCC) as the activating agent led to the β-hydroxy amide **18** as the expected diastereomeric mixture but in very good yield. The latter was then cleanly oxidized to the corresponding ketoamide **19** using pyridinium chlorochromate (PCC) as the oxidant. The survival of the sensitive oxazolidine ring during this transformation was a fortunate outcome; however, this has not been documented previously, to the best of our knowledge. The construction of the second oxazole ring from the latter was then attempted under Wipf's protocol[15] using triphenylphosphine–iodine combination.

Pleasingly, the reaction proceeded smoothly to provide the desired bisoxazole derivative **20**, $[\alpha]_D$ –72.6 (*c* 0.56, MeOH), as a colourless solid, mp 118–119 °C, in an overall yield of 51% from **16** over three steps. The ester functionality in compound **20** was then smoothly hydrolysed to the corresponding carboxylic acid **21**.

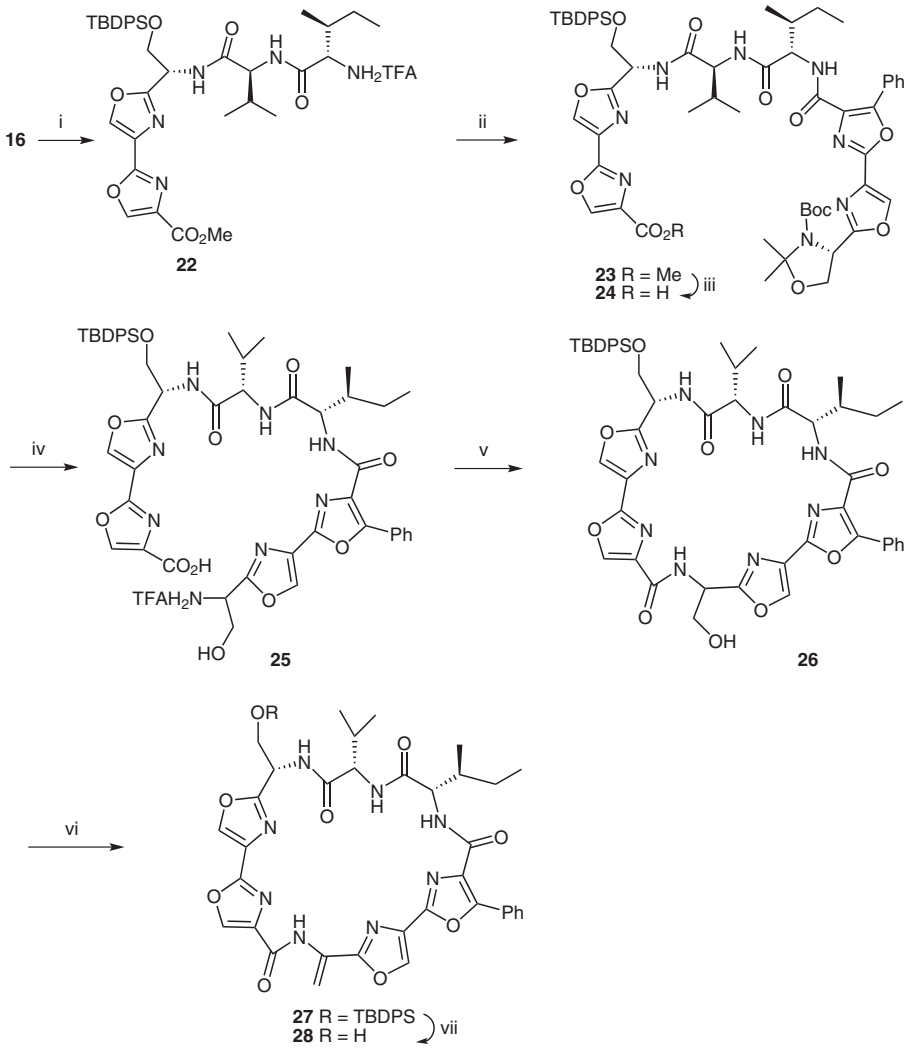
Having access to the desired key fragments, we then focused on their convergent union. Thus, the NBoc group in the dipeptide-linked bisoxazole derivative **16** was deprotected using trifluoroacetic acid to give the corresponding crude amine as its TFA salt **22** (Scheme 5) in readiness for peptide coupling with the bisoxazole acid **21** using the *N*-methylmorpholine–EDC–HOBt combination. The coupled product **23** was obtained as a colourless solid, mp



Scheme 3 *Reagents and conditions*: (i) 50% TFA in CH_2Cl_2, 0 °C to r.t., 1.5 h; (ii) EDC·HCl, HOBt, NMM, CH_2Cl_2, 0 °C to r.t., 18 h, 76%; (iii) TBDPSCl, Et_3N, DMAP (cat.), CH_2Cl_2, r.t., 18 h, 77%.



Scheme 4 *Reagents and conditions*: (i) PhSer-OMe·HCl, DCC, HOBt, Et_3N, CH_2Cl_2, 0 °C to r.t., 18 h, 84%; (ii)PCC, powdered MS 4 Å, CH_2Cl_2, r.t., 45 min, 82%; (iii) Ph_3P, I_2, Et_3N, THF, –78 °C, 3 h, 75%; (iv) LiOH, THF–H_2O (4:1), r.t., 1.5 h, 86%.



Scheme 5 *Reagents and conditions*: (i) 50% TFA in CH_2Cl_2, 0 °C to r.t., 1.5 h; (ii) 21, EDC·HCl, HOBt, NMM, CH_2Cl_2, 0 °C to r.t., 24 h, 70%; (iii) LiOH, THF–H_2O (4:1), r.t., 1.5 h, 90%; (iv) 50% TFA in CH_2Cl_2, 0 °C to r.t., 1.5 h; (v) DPPA, HOBt, DIEA, DMAP (cat.), DMF–CH_2Cl_2 (1:1) (2.5 mmol), r.t., 36 h, 39% over two steps; (vi) MsCl, DBU, 0 °C to r.t., 4 h, 74%; (vii) *n*-$Bu_4N^+F^-$, THF, 0 °C to r.t., 2 h, 89%.

96 °C, in 70% yield. The latter was then sequentially deprotected at the two bisoxazole termini, that is, hydrolysis of the methyl ester leading to the carboxylic acid **24** followed by TFA-mediated simultaneous removel of the Boc group and cleavage of the oxazolidine ring in a one-pot manner to provide the macrocyclisation precursor **25**, which was used as such in the next step. After some experimentation, it was found that macrocyclisation of **25** proceeded well using diphenylphosphoryl azide (DPPA) and 1-hydroxybenzotriazole (HOBt) as activating agents in the presence of diisopropylethylamine under high dilution (2.5 mmol) in a 1:1 mixture of DMF and dichloromethane at room temperature. The cyclised product **26**, $[\alpha]_D$ –17.6 (*c* 0.5, MeOH), was obtained as a colourless solid, mp 118–119 °C, in an overall yield of 39% over two steps from the carboxylic acid **24**. The macrocyclic β-hydroxy amide **26** was then subjected to a two-step, one-pot dehydration involving formation of the corresponding mesylate followed by elimination to the corresponding enamide **27** in good yield. Removal of the pendant TBDPS group from the latter was effected smoothly in the presence of fluoride ion to provide compound **28** in very good yield.[16]

In conclusion, we have developed, following Pattenden's biomimetic proposal, a concise synthetic route to the macrocyclic core of a proposed analogue of the important anticancer natural product IB-01211 with built-in functionalities for further synthetic manipulations. The β-hydroxy amide **26** and the enamide **27** may serve as appropriate handles to install the fifth oxazole ring in view of ample precedence[17] of such transformations.

The macrocyclic products **26**–**28** may also prove to be biologically relevant. The methodology developed may find use in the synthesis of related compounds and/or design and synthesis of modified IB-01211. Work will be continued in this laboratory along some of these directions.

Acknowledgment

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(16) All new compounds reported here gave satisfactory spectroscopic and/or analytical data.
Data for 27
Mp 144–146 °C. IR (KBr): 3367, 2927, 1683, 1652, 1515, 1259, 1114, 766 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.46 (s, 1 H), 8.61 (d, *J* = 8.4 Hz, 1 H), 8.35 (s, 1 H), 8.27 (s, 1 H), 8.14 (s, 1 H), 8.13 (d, *J* = 7.2 Hz, 1 H), 7.64–7.62 (m, 2 H), 7.49–7.43 (m, 6 H), 7.40–7.38 (m, 4 H), 7.36–7.33 (m, 3 H), 6.88 (s, 1 H), 6.01 (dd, *J* = 6.8 Hz, 1 H), 5.97 (s, 1 H), 5.34–5.28 (m, 1 H), 4.63 (dd, *J* = 8.0, 4.8 Hz, 1 H), 4.10 (dd *J* = 9.2, 5.6 Hz, 1 H), 3.97–3.92 (m, 1 H), 3.73 (t *J* = 9.2 Hz, 1 H), 2.42–2.37 (m, 1 H), 1.90–1.87 (m, 1 H), 1.03–0.99 (m, 15 H), 0.90–0.86 (m, 2 H), 0.80 (d, *J* = 6.8 Hz, 3 H), 0.65 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (s), 169.9 (s), 164.5 (s), 160.3 (s), 159.1 (s), 158.6 (s), 154.6 (s), 152.1 (s), 151.6 (s), 141.8 (d), 139.3 (d), 139.1 (d), 137.3 (s), 135.0 (d), 134.9 (d), 132.7 (s), 132.6 (s), 132.2 (s), 131.8 (s), 130.4 (d), 130.3 (s), 129.9 (d), 129.8 (d), 129.5 (s), 128.5 (d), 128.3 (d), 127.8 (d), 127.7 (d), 126.0 (s), 105.2 (t), 64.7 (t), 59.8 (d), 56.4 (d), 49.3 (d), 38.2 (d), 29.2 (d), 26.3 (q), 24.7 (t), 19.8 (q), 18.7 (q), 18.3 (s), 14.9 (q), 11.1 (q). HRMS (TOFMS ES^+): *m/z* $[M^+ + Na]$ calcd for $C_{51}H_{54}N_8NaO_9Si$: 973.3681; found: 973.3682

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