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Synthesis of IB-01211, a Cyclic Peptide Containing 2,4-Concatenated Thia- and Oxazoles, via Hantzsch Macrocyclization†

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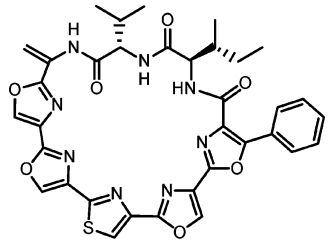
ABSTRACT



IB-01211

An efficient and versatile convergent synthesis of IB-01211 based on a combination of peptide and heterocyclic chemistry is described. The key step in the synthesis is macrocyclization through intramolecular Hantzsch formation of the thiazole ring. Dehydration of a free primary alcohol to furnish the exocyclic methylidene present in the natural product was applied during the macrocyclization.

Naturally occurring, directly linked 2,4-azoles possess fascinating structures and interesting biological activities. Numerous bis- and trisoxazoles as well as a few oxazole−thiazoles have been isolated from marine organisms, whereas linked thiazole-containing natural products have generally been obtained from marine microorganism cultures.[1]

Recently, a new cyclic peptide, IB-01211 (Figure 1), was isolated from the marine microorganism strain ES7-008, which is phylogenetically close to *Thermoactinomyces genus*.[2,3] This peptide is strongly cytotoxic to several tumor cell lines.[4] IB-01211, which has no precedent in natural products, contains four oxazoles, one thiazole, and a tripeptide that includes a didehydroamino acid residue. Herein,

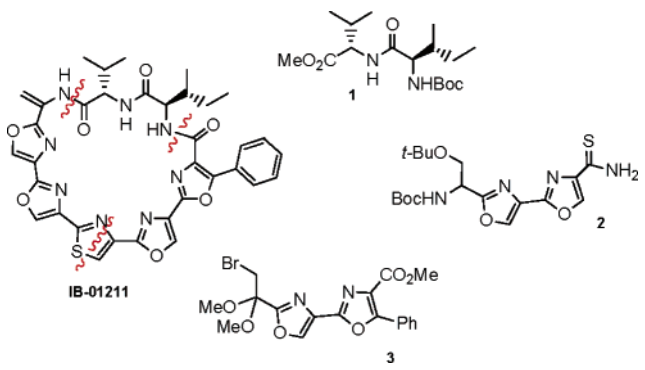


Figure 1. Structure of IB-01211 and synthons for its preparation.

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(1) Reviews of the chemistry can be found in: (a) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249. (b) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995.

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an efficient and versatile synthesis of IB-01211 based on a combination of peptide (dehydration of serine- and phenylserine-containing peptides) and heterocyclic chemistry (Hantzsch synthesis) is described.[5−7] The key step in the synthesis is a Hantzsch macrocyclization with concomitant dehydration of the deprotected hydroxy group to render the didehydro residue.

The synthesis of IB-01211 was designed, following a biomimetic pathway, through the bond-disconnection depicted in Figure 1, which provided three key synthetic precursors, the dipeptide **1** and the bis-oxazoles **2** and **3**.

Several approaches to the target compound could be followed depending on the order of precursor connection. Reaction between **2** and **3** with formation of the central thiazole could give a penta-azole, which could then be reacted with **1** to achieve macrocyclization. Alternatively, formation of two peptide bonds among **1**, **3**, and **2** could afford a peptide−heterocycle useful for macrocyclization, whereby concomitant formation of the thiazole ring would occur at the last step of the synthesis. We opted for this last approach, using a peptide−tetra-azole, for our synthesis of IB-01211.

Peptides **1**, **4** (precursor of **2**), and **5** (precursor of **3**) were prepared in excellent yields from the appropriate amino acids with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl)/1-hydroxybenzotriazole (HOBt) in the presence of diisopropylethylamine (DIEA) as coupling reagent (see the Supporting Information). Hydroxyl groups involved in oxazole formation were incorporated unprotected. When needed, *N*-Boc, methyl ester, and *O*-*t*-Bu were used as protecting groups. These groups were stable in the azole ring-formation conditions.

The bis-oxazoles **2** and **3** were prepared from Ser- or PhSer-containing peptides, respectively (Scheme 1). The procedure began with activation of the hydroxy group followed by cyclization under basic conditions to give an oxazoline. Finally, oxidation of the oxazoline furnished the corresponding oxazole. The bis-oxazole **2** was obtained from the tri-Ser peptide **4** by simultaneous construction of the two azole rings, using a cyclization−oxidation procedure, followed by final transformation of the methyl ester into the thioamide. Activation of the hydroxy group using (diethylamino)sulfur trifluoride (DAST) in CH_2Cl_2 at low temperature[8] followed by cyclization with K_2CO_3 afforded the bis-oxazoline **6**, which was oxidized with 1,8-azabicyclo[5.4.0]-undec-7-ene (DBU)−CCl_4 in a mixture of CH_3CN and pyridine (Pyr) to give the bis-oxazole **7**.[9] Last, reaction of **7** with NH_4OH and treatment of the resulting amide **8** with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) provided **2** in 73% yield for the two steps. To the best of our knowledge, this is the first report of the one-pot formation of two concatenated oxazoles by cyclodehydration−oxidation of amino acids.[10] The procedure is faster and higher yielding than sequential formation of the two rings.[11]

Preparation of the bis-oxazole **3** (Scheme 1) required more development because the presence of a PhSer favored β-elimination over cyclization. The DAST/K_2CO_3 protocol for cyclization of Boc-Ser(*t*-Bu)-PhSer-OMe **5** afforded a 1:2 mixture[12] of the desired oxazole **9** and the didehydropeptide **10**.[13] β-Elimination also occurred during the simultaneous formation of the two oxazoles when starting from the tripeptide Boc-Ser(*t*-Bu)-Ser-PhSer-OMe and using the DAST/K_2CO_3 protocol. However, **3** was obtained in 25% yield via sequential formation of the two oxazole rings starting from Boc-Ser(*t*-Bu)-PhSer-OMe **5** by changing the base to pyridine instead of K_2CO_3 for cyclization of the phenylazole ring.

Cyclization−oxidation of **5** using DAST−Pyr and DBU−CCl_4 gave oxazole **9**.[8,14] Deprotection of the hydroxy and amino groups of **9** with trifluoroacetic acid (TFA) and formation of the amide bond with the bromopyruvic acid dimethyl acetal[15]—the precursor of the Hantzsch synthesis—using EDC·HCl/HOBt in CH_2Cl_2 gave **11**, which was in turn used for the subsequent oxazole-ring formation to afford bis-

(2) Romero, F.; Malet, L.; Cañedo, M. L.; Cuevas, C.; Reyes, J. WO 2005/000880 A2, 2005.

(3) The same structure was proposed for mechercharmycin A, isolated from a marine-derived *Thermoactinomices* sp., by: Kanoh, K.; Matsuo, Y.; Adachi, K.; Imagawa, H.; Nishizawa, M.; Shizuri, Y. *J. Antibiot.* **2005**, *58*, 289.

(4) Cañedo, M. L.; Martínez, M.; Sánchez, J. M.; Fernández-Puentes, J. L.; Malet, L.; Pérez, J.; Romero, F.; García, L. F. *4th European Conference on Marine Natural Products*, Paris, 2005, poster 54.

(5) Recently, Pattenden and Deeley (Deeley, J.; Pattenden, G. *Chem. Commun.* **2005**, 797) and Takahashi et al. (Doi, T.; Yoshida, M.; Shin-ya, K.; Takahashi, T. *Org. Lett.* **2006**, *8*, 4165) have published syntheses of YM-216391 and telomestatin, respectively, which are other cyclopeptides containing concatenated azoles. Telomestatin was described in a patent by Yamada, S.; Shigeno, K.; Kitagawa, K.; Okajima, S.; Asao, T. (Taiho Pharmaceutical Co. Ltd., SoseiCo. Ltd.) WO2002248153, 2002; *Chem. Abstr.* **2002**, *137*, 47050.

(6) For a recent review, see: Riego, E.; Hernández, D.; Albericio, F.; Álvarez, M. *Synthesis* **2005**, 1907.

(7) (a) Raman, P.; Razavi, H.; Kelly, J. W. *Org. Lett.* **2000**, *2*, 3289. (b) You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 83. (c) Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908. (d) DeRoy, P. L.; Charette, A. B. *Org. Lett.* **2003**, *5*, 4163. (e) Knight, D. W.; Pattenden, G.; Rippon, D. E. *Synlett* **1990**, 36. (f) Chattopadhyay, S. K.; Kempson, J.; McNeil, A.; Pattenden, G.; Reader, M.; Rippon, D. E.; Waite, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2415. (g) Stankova, I. G.; Videnov, G. I.; Golovinsky, E. V.; Jung, G. *J. Peptide Sci.* **1999**, *5*, 392. (h) Muir, J. C.; Pattenden, G.; Thomas, R. M. *Synthesis* **1998**, 613. (i) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (j) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924.

(8) Temperature control is crucial in this step because dehydration was a severe side reaction favored by higher temperatures.

(9) Oxidation of the dioxazoline **6** with DBU−$BrCCl_3$ furnished a 1:1 mixture of **7** and a partially oxidized compound. Other reagents such as MnO_2 in CH_2Cl_2, NiO_2 in benzene at reflux, I_2, and KHDMS also gave mixtures of oxidized products. Further experiments were carried out to investigate if CCl_4 was required. Thus, DBU/CBr_4 in CH_3CN/Pyr, DBU/CBr_4 in CH_3CN, and DBU/$CBrCl_3$ in CH_3CN were assayed, but in all cases the partially oxidized system was the major product.

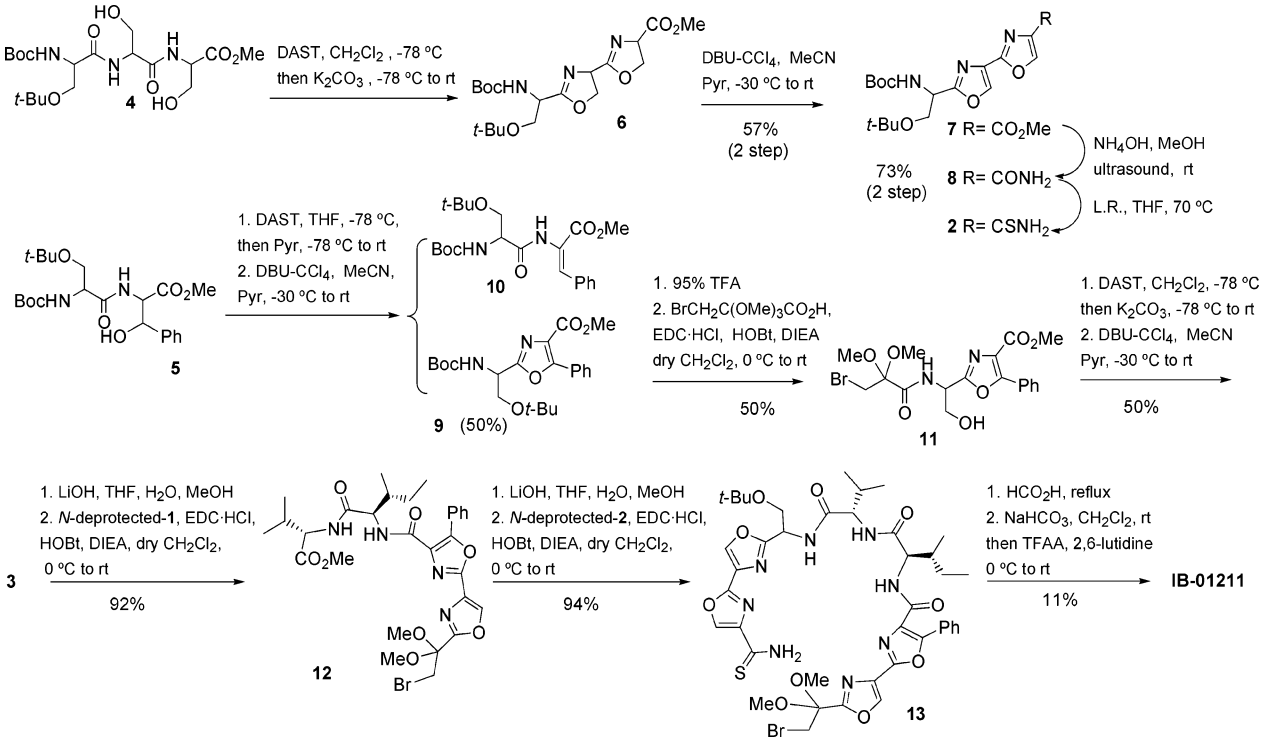
(10) This strategy was used only for the preparation of the tetrathiazoline/thiazole of (−)-mirabazole by Akaji, K.; Kuriyama, N.; Kiso, Y. *J. Org. Chem.* **1996**, *61*, 3350, and in the synthesis of tiangazole,which contains a tetrathiazoline/oxazole system by: Wipf, P.; Venkatraman, S. *Synlett* **1997**, 1.

(11) The global yield working on a 500 mg scale was 57%. However, with 2 g of tripeptides, it decreased to 32%, which is still superior to the 28% obtained by sequential formation of the oxazole rings.

(12) The proportion of each compound was evaluated by ^{1}H NMR by the relative integration of the methyl ester singlets of **9** (3.92 ppm) and **10** (3.84 ppm). A sign of the formation of **10** was the upfield shift of the phenyl protons as compared to those of **9**, which occurs as a result of their conjugation with the ester. For the ortho protons, the difference in chemical shift is 0.5 ppm.

(13) Other reagents, such as the Burgess reagent, did not improve the results.

Scheme 1. Total Synthesis of IB-01211



oxazole **3**. Compound **12** may be sequentially prepared in 92% yield from **3** by methyl ester hydrolysis with LiOH, followed by condensation with *N*-deprotected **1** using EDC·HCl/HOBt/DIEA as an activating reagent. Introduction of the bis-oxazole **2**, followed by selective *N*-deprotection of **2** with 25% TFA, and reaction of the resulting amine with the acid from the saponification of **12**, using the same conditions as before, gave the peptide−heterocycle **13** in 94% yield. As **13** has the open skeleton of the target natural compound, it possesses the proper functionalities to obtain the latter: the protected α-bromo ketone and the thioamide needed for the thiazole ring formation and the protected alcohol precursor of the exocyclic methylidene. Deprotection of **13** with formic acid afforded a peptide−heterocycle with the free hydroxyl and carbonyl group precursors of the exocyclic double bond and the thiazole ring, respectively. Treatment of a dilute solution of the resulting compound with $NaHCO_3$ followed by addition of trifluoroacetic anhydride (TFAA) and 2,6-lutidine gave IB-01211 in 11% yield (from **13**). Formation of the thiazole ring, macrocyclization, and dehydration were achieved in a one pot-reaction as the last step of the synthesis. The ^{1}H NMR spectrum of the product reveals singlets at 6.06 and 6.70 ppm, due to the two methylidene protons, and four singlets, corresponding to the protons of the azole rings—all indicative of formation of IB-01211. The IB-01211 obtained had the same spectroscopic data and HPLC retention time as the natural product.[16]

The total synthesis of the cyclic peptide IB-01211, which contains 2,4-concatenated thia- and oxazoles, using a convergent strategy is described. This strategy combines peptide chemistry approaches for the preparation of the backbone and the formation of the oxazole structures by dehydration−oxidation of Ser- containing peptides, and the Hantzsch synthesis for the elaboration of the thiazole unit.

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Supporting Information Available: Experimental details, characterization of products, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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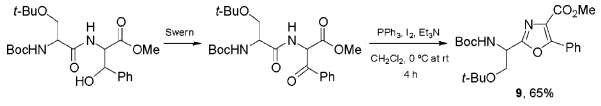
(14) Alternatively, and to avoid the elimination side reaction, the phenyloxazole was also obtained from a route that involves reaction of the ketoamide formed by Swern oxidation, as described by: Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.



(15) Obtained by saponification of the methyl bromopyruvate dimethyl acetal with LiOH as described by: Chari, R. V. J.; Kozarich, J. W. *J. Org. Chem.* **1982**, *47*, 23.

(16) Simultaneous injection of natural and synthetic compounds gave only one peak at t_r = 14.2 min (A = H_2O + 0.045% TFA, B = MeCN + 0.036% TFA, gradient = 0−100% B in 15 min) and identical shape and wavelength in the UV detector. A sample of IB01211 was kindly supplied by the fermentation department of PharmaMar.