

Synthesis of oxazole, oxazoline and isoxazoline derived marine natural products:

A Review

Supriya Tilvi,^{**} and Keisham S. Singh^a

^aBio-Organic Chemistry Laboratory, CSIR-National Institute of Oceanography,
Dona Paula Goa 403 004, India.

Correspondence

Dr. Supriya Tilvi,

Bio-Organic Chemistry Laboratory,

CSIR-National Institute of Oceanography, Dona Paula Goa 403 004, India.

E-mail: supriyatilvi@nio.org ;

Phone: + 91(0) 832-2450392 Fax: +91 (0) 832-2450 607

Abstract:

Naturally occurring secondary metabolites containing oxazole, oxazoline and isoxazoline subunits, commonly derived from amino acids, are widely distributed in nature, both in marine and terrestrial organisms. These natural compounds have diverse significant biological activities, including anti-tumor, anti-bacterial, anti-viral, anti-malarial and immunosuppressive. Due to their significant biological properties, complex molecular structure and different functionalities present, synthesis of these classes of compounds continue to pay attention for natural product researcher and synthetic chemists. However, their complex nature, multifunctional substituents and often existed in diastereomers pose a major challenge and obstacles in their synthesis. In recent years, retrosynthetic analysis and total synthesis of oxazole containing marine natural products namely bengazoles, phorboxazole, pseudopteroxazoles, hennoxazole and cyclopeptide were reported by several groups. Total synthesis of a less common marine natural products containing oxazoline and isoxazoline ring such as calafianin, bistratamide E and tyrosine derived marine sponge metabolites have also been described. This review describes the isolation, biological activities and recent development on total syntheses of oxazole, oxazoline and isoxazoline derived marine natural products reported till 2014.

Key words: oxazole, oxazoline, isoxazoline, marine natural products, synthesis

1. Introduction

Marine natural products containing oxazole, oxazoline and isoxazoline skeleton have been reported from numerous marine organisms [1]. They display various biological properties including antifungal properties [2], cytotoxicity [3]. Among them, prominent examples of these classes of compounds include bengazoles, helipeptins, phorboxazole, (+)-calafianin, several cyclodepsipeptide and bromotyrosine derivatives. The burgeoning family of polyoxazole-based secondary metabolites now includes the phorboxazoles, hennoxazoles, diazonamide A, several azole-based cyclic peptides, the tetraoxazole YM-216391, and the intriguing hepta-oxazole telomestatin. This five membered heterocyclic ring *viz.* oxazole, oxazoline and isoxazoline (**Figure 1**) were mainly isolated from marine sponges although a few of them have been obtained from associated microbes. Due to their interesting biological properties and diverse functional group derivatives, total synthesis of these class of compounds have paid attention for the past several years.

This review, present the compilation of the total synthesis reported for these three classes of compounds of marine origin. In some cases where several synthesis methods were available only the most convenient and recent syntheses are discussed. For easy reading, the content has been divided under three categories; oxazole, oxazoline and isoxazoline containing marine natural products.

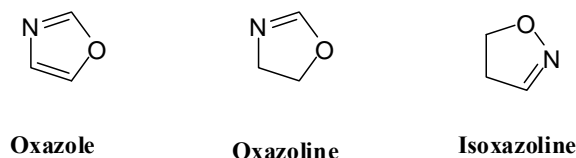


Figure 1. Chemical structures of oxazole, oxazoline and isoxazoline rings

2. Oxazole:

Marine natural products with oxazole skeleton are distributed in several marine organisms mainly sponges possessing a wide range of pharmacological activities. They are found as mono, bis, tris, tetra etc. oxazole ring containing compounds. Bengazoles and phorboxazole are the two widely distributed important marine natural products of this class. Bengazole A was isolated for the first time in 1988 by Crew and co-workers from a marine sponge of the genus *Jaspis* [4], and to date the bengazole family consists of 22 members [5]. Several marine natural products with 2,4-substituted azoles have been isolated and synthesized during the past few years[6]. Hennoxazoles (potent antiherpes virus agents and peripheral analgesics) [7] contain a bioxazole unit; muscoride A [8] (an antibacterial agent) features a bioxazole with methyl substituents at the 5-position of both oxazole rings; the macrolactams ulapualides,[9] kabiramides,[10] mycalolides,[11] and halichondramides [12] all contain a teroxazole unit; and the structurally complex diazonamides,[13] telomestatin,[14]

YM-216391,[15] and IB-01211 [16] all feature 2,4-substituted polyoxazoles linked to other heterocycles and/or peptidic fragments (**Figure 2**).

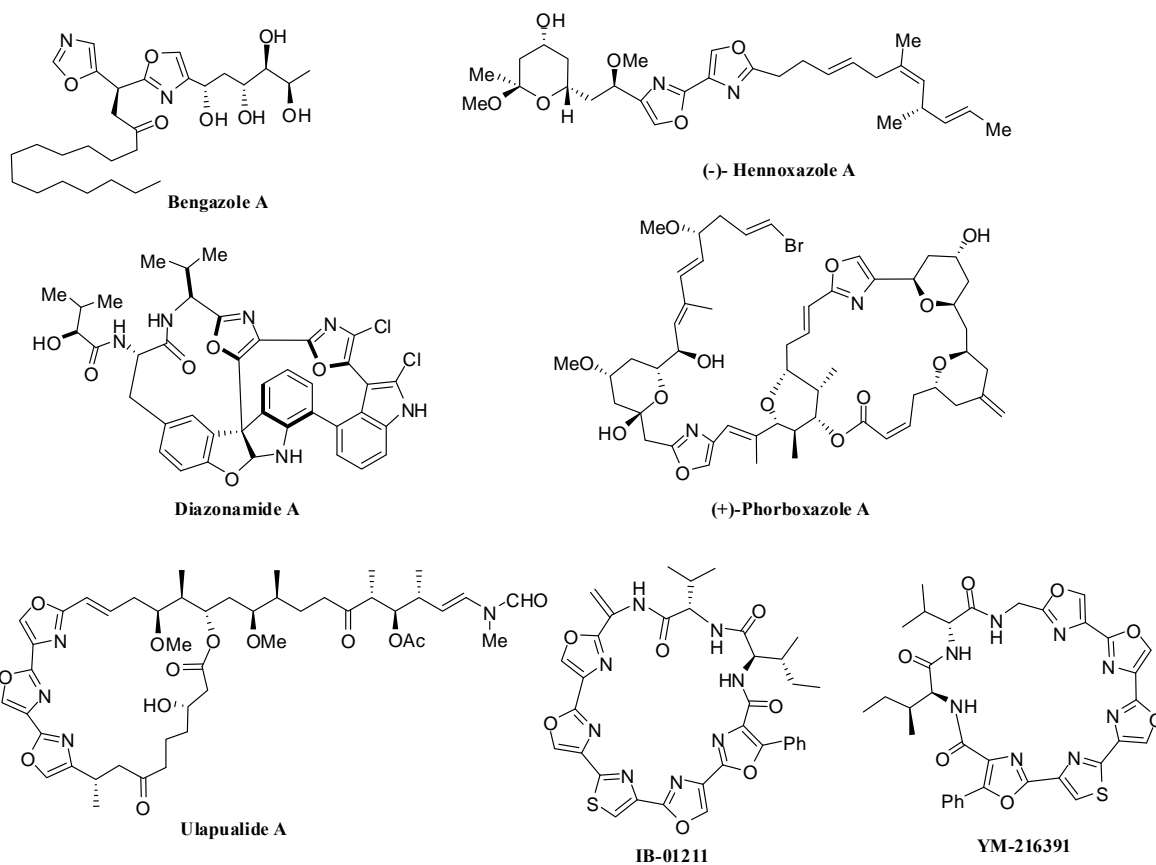


Figure 2. Structures of some oxazole containing marine natural products

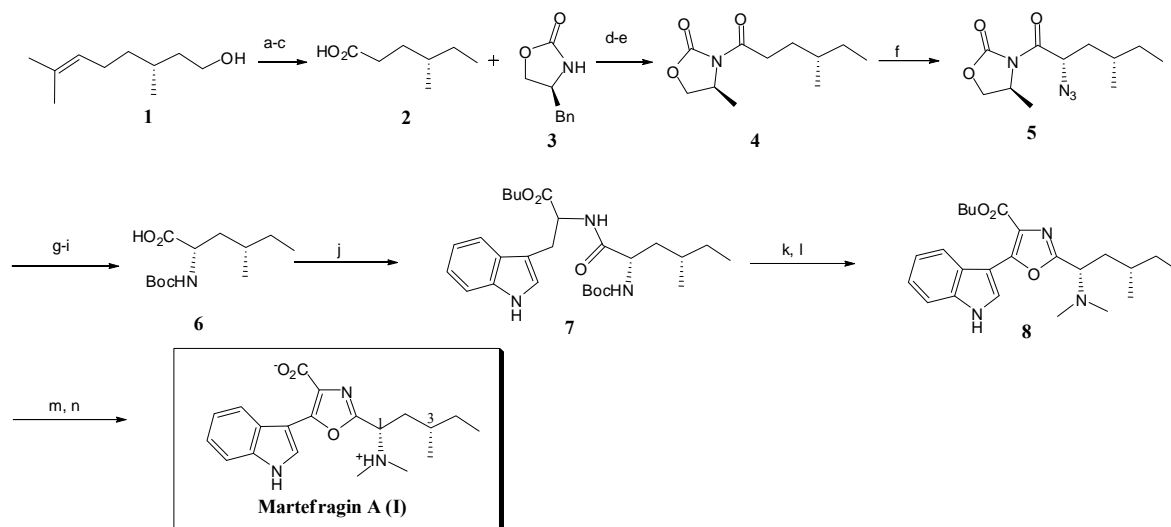
2.1 Monoxazole:

2.1.1 Martefragin A (I)

The sea alga *Martensia fragilis* produces a potent inhibitor of lipid peroxidation. The active metabolite has been identified as martefragin A (**I**) and its first synthesis has been reported starting with *R*-citronellol **1**[17] (**Scheme 1**). Removal of the hydroxy group was followed by oxidative cleavage of the double bond to produce carboxylic acid **2** which was condensed (*via* its acid chloride) with oxazolidine **3** to give **4**. Asymmetric azidation using the Evans procedure gave azide **5** in diastereomerically pure form. Conversion of this azide into the protected (2*S*,4*S*)-homoleucine **6** occurred in three steps whence it was condensed with *O*-benzyl-L-tryptophan hydrochloride to give dipeptide **7**. This dipeptide cyclised upon treatment with DDQ^[†] to give oxazole **8**. *N,N*-dimethylation and debenzylation resulted in (1*S*,3*S*)-martefragin A (**I**). The spectral properties of the

[†] A list of abbreviations can be found at the end of the Review

synthetic product were in good agreement with those of the natural product thus indicating that martefragin A has either the 1*S*,3*S* or 1*R*,3*R* absolute configuration.



Scheme 1. Total synthesis of Martefragin A. Reagents and conditions: (a) MsClEt_3N ; (b) LiAlH_4 , Et_2O , 77%; (c) KMnO_4 , NaIO_4 aq acetone, 74%; (d) SOCl_2 , benzene; (e) Li-(*S*)-4-benzyl-2-oxo-1,3-oxazolidine; (f) $\text{KN}(\text{TMS})_2$, THF, -78°C then 2,4,6-triisopropylbenzenesulfonyl azide, -78°C then HOAc, -78°C , 78%; (g) LiOH, aq THF; (h) H_2 , 10% Pd/C, EtOH; (i) $(\text{Boc})_2\text{O}$, NaOH, aq dioxane, 81%; (j) Benzyl-L-tryptophan HCl, diethyl phosphonocyanidate, Et_3N , THF, 0°C then rt, 97%; (k) DDQ, THF, reflux; (l) $\text{CF}_3\text{CO}_2\text{H}$, CH_2Cl_2 , 57%; (m) Formalin, AcOH dioxane, H_2 , 10% Pd/C; (n) H_2 , Pd/C, AcOEt, 47%.

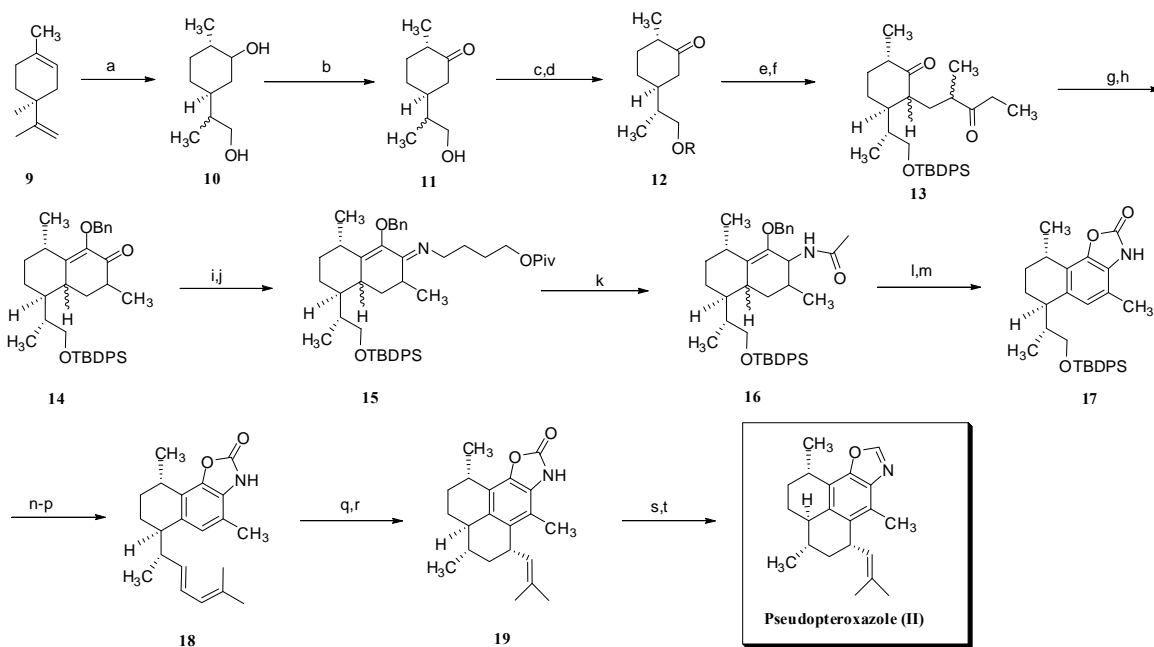
2.1.2 Pseudopteroxazole (II)

Pseudopteroxazole (**II**) was isolated along with homopseudopteroxazole, and *seco*-pseudopteroxazole by Rodrigues and coworkers from the sponge *Pseudopterogorgia elisabethae* which showed activity against *Mycobacterium tuberculosis* [18]. Several synthetic chemists paid attention on the synthesis of these classes of compounds mainly due to their biological activity, complex molecular structure, and functionalization of the compounds present in *P. elisabethae* [19].

Corey and Davidson reported a concise, enantiospecific synthesis of pseudopteroxazole (**II**), starting from *S*-(-)-limonene **9** [20] (**Scheme 2**). They have initiated their synthesis starting from the commercially available (*S*)-(-)-limonene **9** and after cyclic hydroboration and alkaline peroxide oxidation, the diol **10** was obtained which was on selective oxidation with sodium hypochlorite in aqueous acetic acid provided the diastereoisomeric mixtures of hydroxyl ketones **11**. Protection of the hydroxyl as the *tert*-butyl-diphenylsilyl ether (TBDPS) afforded the sython **12** in 96% yield.

The selective kinetic deprotonation of the intermediate was carried out using lithium diisopropylamide (LDA) and trapping chlorotrimethylsilane (TMSCl) furnishing the desired silyl enol ether, which on subsequent treatment with 1-benzyloxy-3-methyl-but-3-en-2-one and thionyl

chloride (SnCl_4), gave the Mukaiyama-Michael adduct **13** in 61%. The α,β -enone **14** was obtained as a mixture of diastereoisomers after cyclization of the 1,5-diketone in dilute solution of potassium hydroxide (KOH) in ethanol (83%) and elimination of the tertiary hydroxyl group in presence of SnCl_4 in pyridine. The oxime pivalate **15** was obtained in 96% yield after the oxime formation using hydroxylamine followed by acylation with pivaloyl chloride. The aromatization and *N*-acylation of the intermediate **16** was achieved using an acetyl chloride at 80°C giving **17** in 64% yield [20]. The hydrogenolysis of the benzyl ether and cyclization of the phenol with carbonyldiimidazole, followed by mildly basic aqueous workup using NaHCO_3 to remove the *N*-acyl group afforded the cyclic carbamate **18** in 94% yield. The diene **19** was obtained by deprotection of **18** in the presence of HF-pyridine followed by mild oxidation to the aldehyde with tetrapropylammonium perruthenate and *N*-methylmorpholine-*N*-oxide (TPAP-NMO, 82% yield) and *E*-selective olefination while the key intermediate was obtained in 80% yield by cationic cyclization in the presence of three equivalents of methanesulfonic acid and acetic acid as solvent at 19 °C. After *N*-protection using di-*tert*-butyl dicarbonate (Boc_2O) and excess of the methylmagnesium bromide (CH_3MgBr) followed by addition of the resulting dianion to a mixture of trifluoroacetic acid and triethylorthoformate lead to the formation of the natural product pseudopteroxazole (**II**) in 91% yield (**Scheme 2**).[20]

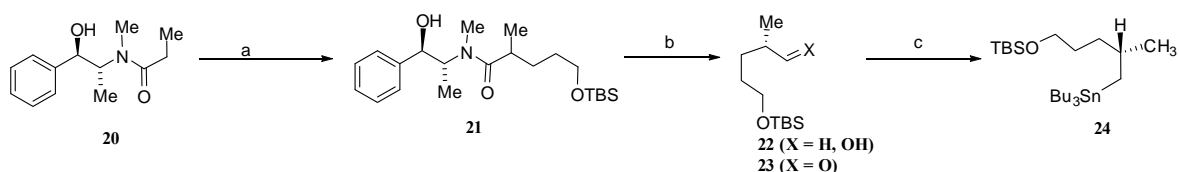


Scheme 2. Total synthesis of pseudopteroxazole A. Reagents and conditions: (a) T hexylboranes, alkaline peroxide oxidation, 92%; (b) NaOCl , 86%; (c) $\text{AcO-C}(\text{CH}_3)(\text{CH}_2)$, lipase; (d) TBDPSCl , imidazole, DMF, 96%; (e) LDA, TMSCl , -78 °C, 100%; (f) 1-benzyloxy-3-methyl-but-3-en-2-one, SnCl_4 , CH_2Cl_2 , -78 °C, 61%; (g) KOH , EtOH , -10 °C, 83%; (h) SOCl_2 , pyridine, 83%; (i) NH_2OHHCl , pyridine, 69%; (j) pivaloyl chloride, pyridine, 96%; (k) acetylchloride, toluene, 80 °C, 64%; (l) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, EtOH , 99%; (m) carbonyldiimidazole, Et_3N ; then, aqueous NaHCO_3 , 94%; (n) HF-pyridine, 95%; (o) TPAP, NMO, 82%; (p) Wittig olefination, 81%; (q) MeSO_3H , AcOH , 18 °C, 80%; (r) Boc_2O , DMAP, 96%; (s) MeMgBr , -78 to 23 °C, then (t) TFA, $\text{HC}(\text{OEt})_3$, 90%.

2.1.3 (+)-Ileabethoxazole (III)

Ileabethoxazole (**III**) was isolated in 2006 by Rodriguez and co-workers from the specimens of *Pseudopterogogia elisabethae* collected near the Island of Providencia Columbia [21]. Ileabethoxazole represent a rare example of a marine derived benzoxazole derived from serrulatane diterpenoid skeleton and the metabolite concentration in the sample is very low (yield 9.4×10^{-5} % based on dried gorgonian weight). The metabolite is structurally similar to that of pseudopteroxazole [18][22] and homoseudopteroxazole [23]. This metabolite show strong inhibition of *Mycobacterium tuberculosis* and represent a subsets of the family pseudopterrosins [24]. Total synthesis of pseudopterrosin A was reported by Broka [25], while pseudopterrosin E have been reported by Corey [26].

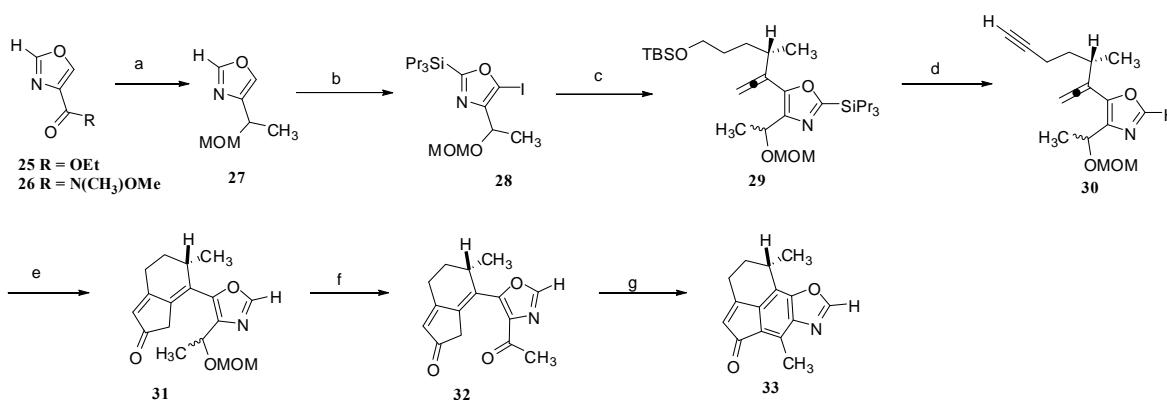
Recently, David *et. al.* described the total synthesis of (+)-ileabethoxazole *via* Iron-mediated Pauson-Khand [2+2+1] carbocyclization reaction [27]. They have carried out the total synthesis of (+)-ileabethoxazole by adopting three major strategy *viz.* i) preparation of allene **30** and ii) formation of enone **33** (**Scheme 4**); iii) reduction of enone **33** (**Scheme 5**) and iv) introduction of C₁₁ substitution to ketone and completion of synthesis of ileabethoxazole in a few efficient steps as shown in (**Scheme 6**). The preparation of stannane from **20** was initiated by introduction of asymmetric at C-1 by the Myers alkylation. A subsequent reduction of **21** followed by Dess-Martin oxidation lead to the nonracemic aldehyde **23**. The aldehyde was then transformed into propargylic stannane **24** in three steps by application of Corey-Fuchs procedure (**Scheme 3**).



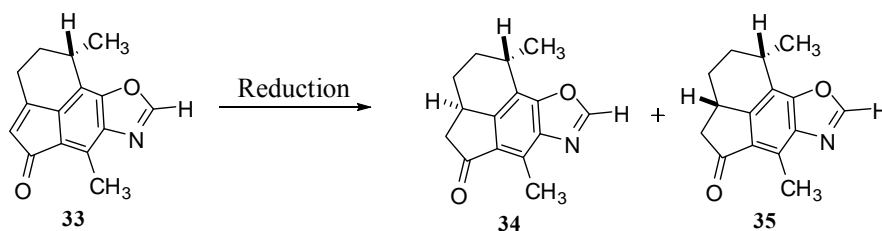
Scheme 3. Preparation of stannane 24: Reaction conditions. a) $i\text{Pr}_2\text{NH}$, $n\text{BuLi}$, $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$ then tert-butyl(3-iodopropoxy)dimethyl silane, 20 hrs, 0°C ; b) 1. $i\text{Pr}_2\text{NH}$, $n\text{BuLi}$, $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$ then: $\text{BH}_3 \cdot \text{NH}_3$, 2. Dess-Martin periodinane, dry CH_2Cl_2 (76% over 2 steps); c) 1. CBr_4 , PPh_3 (77%), 2. $n\text{BuLi}$, THF at -78°C then (HCHO)n (90%), 3. EtO_2CCl , pyridine (95%), 4. $\text{Ti}(\text{O}i\text{Pr})_4$, $i\text{PrMgCl}$, Et_2O then: $n\text{Bu}_3\text{SnCl}$ at -78°C (90%).

The required allene (**30**) has been prepared effectively by Stille cross coupling of propargylic stannanes (**Scheme 4**). The preparation of allene starts from commercially available ethyl-1,3-oxazole-4-carboxylate *via* conversion to the Weinreb amide **26** for addition of methyl magnesium bromide. The resulting C-4 methyl ketone was transformed into the corresponding methoxymethyl (MOM) ether **27**, and sequential ring metallations at C-2 and C-5 by regioselective deprotonations

with LDA in THF gave the desired iodide **28**. The stille cross coupling of **28** with the propargylic stannane **24** proceeds with allylic transposition to give allene **29** in 76% yield. Upon stirring in methanol with pyridinium tosylate (PPTs) at 22 °C lead to removal of silyl protecting groups and the alkyne of **30** had been introduced by oxidation and application of the Ohira-Bestmann procedure [28]. The expected dienone **31** was obtained in 61% yield by iron mediated [2+2+1] carbocyclization of **30** (Scheme 4) in THF warming from -50 °C to 5 °C. Employing Swern oxidation efficiently achieved cyclization and aromatization by cleavage of MOM acetal of **31** and subsequently treatment with potassium *tert*-butoxide (2.4 equiv) in dry toluene at -20 °C afforded enone **33**. They have studied stereoselectivity of 1,4-reduction of **33** in various conditions (Scheme 5) [27].



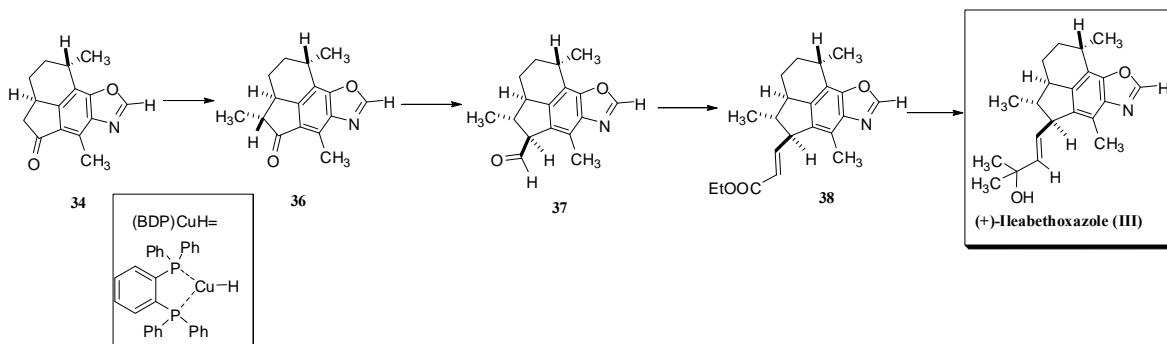
Scheme 4. Preparation of Allene 30 and Iron mediated [2+2+1] carbocyclization to enone 33: Reaction Conditions: a) 1. H₃CMgBr, THF (87%), 2. NaBH₄, MeOH (90%), 3. MOMCl, NaH, THF (61%); b) 1. TIPSOTf; LDA, -78 °C; THF (97%), 2. LDA; THF -78 °C, NIS (99%); c) Stannane 24, Pd₂(dba)₃ (20 mol%) Cs₂CO₃; AsPh₃, dry DMF 22 °C (76%); d) 1. PPTs, MeOH (78%), 2. IBX; DMSO (81%), 3. dimethyl 1-diazo-2-oxopropylphosphonate, K₂CO₃, MeOH (85%); e) Fe₂(CO)₉; NMO, THF: -50 °C->5 °C (61%); f) 1. 2-bromobenzo [d][1,3,2]dioxaborole, CH₂Cl₂; -78 °C (85%), 2. (COCl)₂; DMSO, Et₃N; CH₂Cl₂ (81%); g) *t*BuOK, dry toluene, -20 °C (93%).



Scheme 5. Reduction of enone 33

The optimized conversion of **34** was obtained by the use of (S)-H₈-BINAP (20 mol%) and Ph₂SiH₂ at 20 °C. A convenient transformation of **34** to the corresponding C-11 methyl ketone **101** was obtained by α -methylenation using *N,N,N,N*-tetramethyldiaminomethane and acetic anhydride (Ac₂O) and subsequent reduction as described by Lipshut and co-workers using in situ (BDP)CuH reagent [29]. Finally, the total synthesis of Ileabethoxazole was completed in three steps by treatment of **36** with

methylenedimethylsulfurane ($\text{Me}_2\text{S}=\text{CH}_2$) at $-20\text{ }^\circ\text{C}$ giving intermediated epoxide which undergoes facile rearrangement in the presence of anhydrous InCl_3 [30]. Application of Horner-Emmons reaction [31] to aldehyde **37** results in formation of the stable α,β -unsaturated ethyl ester **38** which on subsequent addition of methyl lithium gave to synthetic (+) ileabethoxazole (**III**) (Scheme 6).



Scheme 6. Introduction of C11 Substituion and Completion of the synthesis of (+)-Ileabethoxazole (III): Reaction conditions. a) N,N,N',N' -tetramethylmethanediamine, Ac_2O ; DMF, $95\text{ }^\circ\text{C}$, $(\text{BDP})\text{CuH}$, PMHS (3 equiv) $t\text{BuOH}$ (3 equiv) $22\text{ }^\circ\text{C}$ (76%); b) $\text{Me}_2\text{S}=\text{CH}_2$, THF, $-20\text{ }^\circ\text{C}$, then InCl_3 ; CH_2Cl_2 , $22\text{ }^\circ\text{C}$ (90%); c) ethyl 2-(diethoxyphosphoryl)acetate, LiCl ; ACN, $i\text{Pr}_2\text{NEt}$, $22\text{ }^\circ\text{C}$ (74%); d) MeLi (3 equiv) THF $-20\text{ }^\circ\text{C}$ (87%).

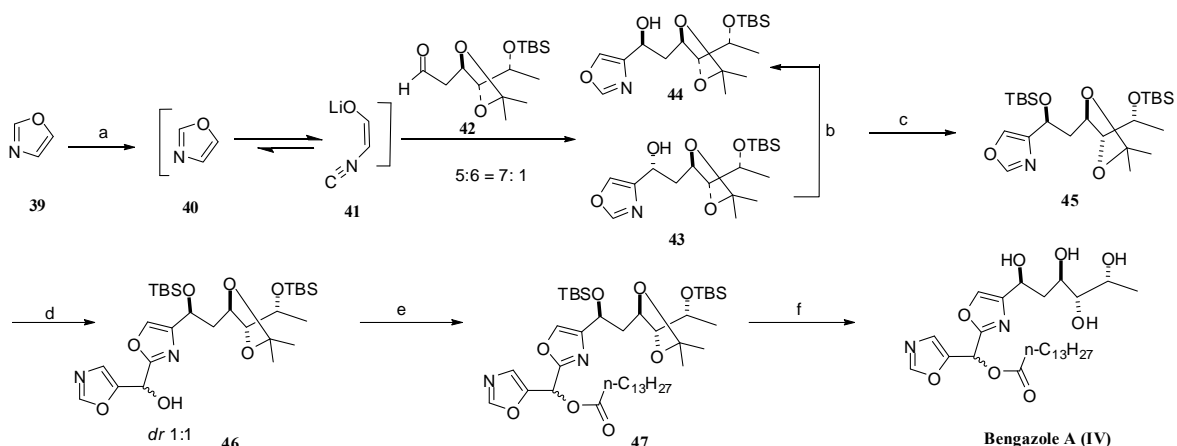
2.2 Bisoxazole

2.2.1 Bengazole A (IV)

Bengazoles are unusual bisoxazoline natural products originally isolated in 1988 from a *Jaspis* sponge of Fiji Island possessing anthelmintic activity against the nematode *Nippostrongylus braziliensis* [4,5a,32]. The family comprises of 22 bengazoles and many of them have been reported for anthelmintic and cytotoxicity [4]. Total synthesis of bengazoles and their analogs have been reported by several groups [3,33]. Molinski and coworkers reported synthesis of bengazole A (**IV**) using a regioselective metalation/addition strategy starting from 1,3-oxazole which gave a mixture of the C10 epimers that could not be isolated (Scheme 7) [34].

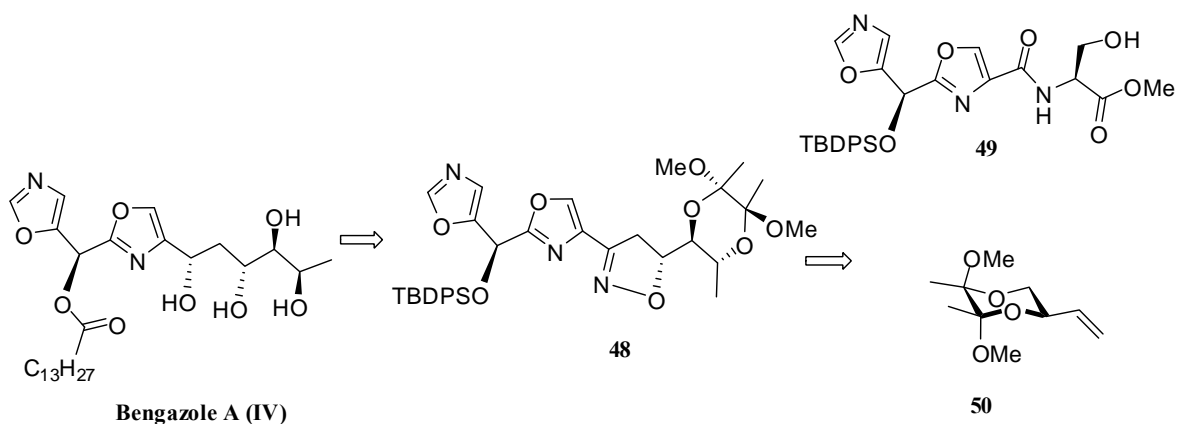
Molinski's Synthesis of Bengazole A: In their synthesis, the strategy was the deprotonation of oxazole (**39**) with $n\text{BuLi}$ followed by addition of aldehyde **42** leading to exclusive C4 addition, providing **43** and **44** as a mixture favouring the unwanted diastereomer **43** (Scheme 7). The unwanted diastereomer **43** were converted into **44** in two steps using procedure of Mitsunobu inversion followed by methanolysis. The alcohol **44** was protected as its TBS ether oxazole **45** which on deprotonation using $\text{BH}_3\cdot\text{THF}$, followed by addition of oxazole-5-carboxaldehyde led to formation of **46** as a mixture of inseparable diastereomers (*dr* 1:1). Acylation of **46** with myristoyl chloride followed by global protection gave bengazole A (**IV**) in good yield as an inseparable mixture of

epimers at C-10. Thus, in Molinski's method, bengazole A was obtained as C-10 epimers which could not be separated at any stage of the synthesis.[34]



Scheme 7. Molinski's synthesis of Bengazole A. Reagents and Conditions: a) *n*BuLi, THF/hexane (20:1) -78 °C; b) 1. PPh₃, DEDA, lutidine, *p*-NO₂C₆H₄CO₂H, C₆H₆; 2. K₂CO₃, MeOH; c) TBSOTf, lutidine, CH₂Cl₂; d) 1. BH₃, THF, THF, 25 °C; 2. *t*BuLi, -78 °C, 3. oxazole-5-carbaldehyde; e) *n*-C₁₃H₂₇COCl, Et₃N, DMAP, CH₂Cl₂ 84%; f) HF, MeCN, H₂O (94%).

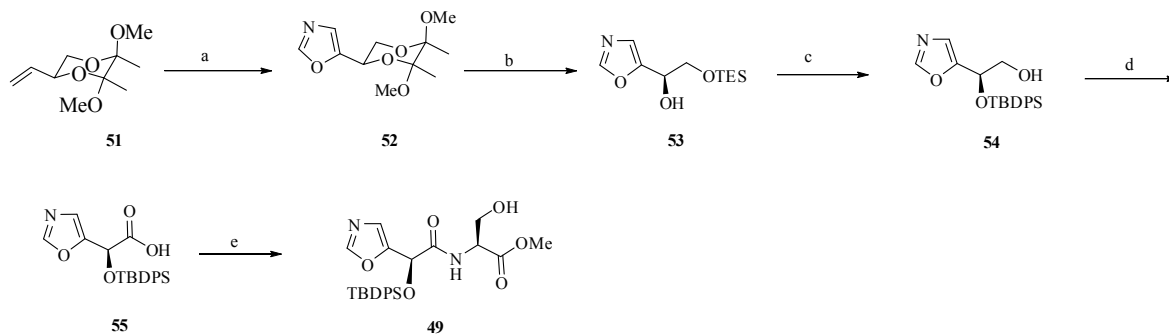
Bull's synthesis: Bull et. al. [3] have reported a stereocontrolled total synthesis of bengazole A by using an oxazole synthesis under mild conditions and a diastereoselective 1,3-dipolar cycloaddition providing a single stereoisomer of bengazole A (IV). Their retrosynthetic analysis revealed that the desired bisoxazole unit could be derived from the diastereomerically pure serine amide 49 which in turn could be converted into a suitable precursor for diastereoselective 1,3-dipolar cycloaddition of nitrile oxide with alkene 50 (Scheme 8).



Scheme 8. chemical structure and retrosynthetic analysis of bengazole A (IV). TBDPS = *tert*-butyldiphenylsilyl

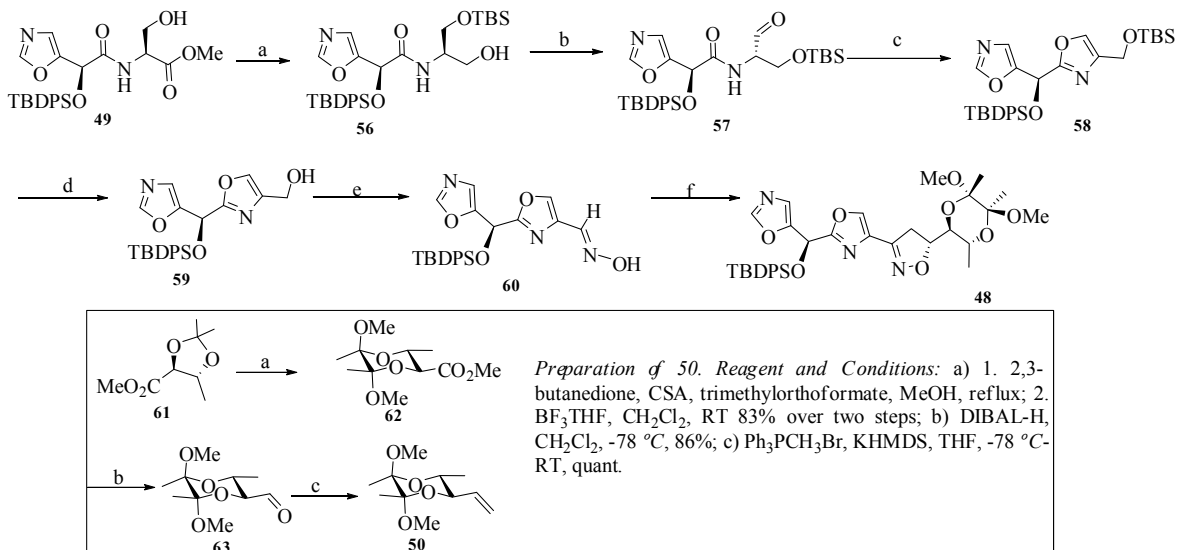
They synthesized amide 49 fragment using BDA-protected glyceraldehyde derivative 51 which was used as substrate for a Schöllkopf-type of oxazole synthesis [35]. Synthesis was initiated with the preparation of oxazole 52 by treating aldehyde 51 with TosMIC and K₂CO₃. Oxazole 52 was isolated

in excellent yield exclusively as the equatorially substituted diastereomer, hence establishing the desired stereochemistry at the C-10 centre for the natural product. Mono-TBDPS protected diol **54** was obtained after removal of BDA and insertion of silyl protecting group. Oxidation of diol **54** using Jones's reagent provided carboxylic acid **55** which on subsequently amide coupling in DMSO gave the desired amide **49** (Scheme 9).



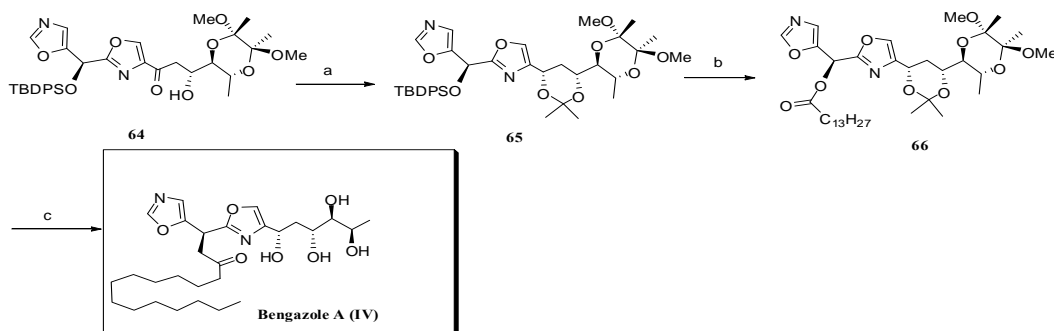
Scheme 9. Synthesis of amide fragment, Reagent and conditions: a) TosMIC, K_2CO_3 , MeOH, reflux, 82%; b) 1. TFA, H_2O , rt; 2. TESCl, iPr_2NEt , CH_2Cl_2 , $-78\text{ }^\circ C$, 94% over 2 steps; c) 1. TBDPSCI, Et_3N , DMAP, CH_2Cl_2 , rt; 2 PPTS, MeOH, rt, 96% over two steps; d) Jones reagent, acetone, $0\text{ }^\circ C$, 49%; e) TBTU, H-(L)-Ser-OMe-HCl, iPr_2NEt , DMSO, rt, 64%.

In order to construct the central 2,4-disubstituted oxazole ring under mild conditions in the presence of sensitive C10 stereogenic centre, the amide **49** was converted into primary alcohol **56** and further oxidized using buffered Dess-Martin periodinane [36] giving aldehyde **57** which was then subjected to Robinson-Gabriel-type oxazole formation under Panek and Beresis condition [37]. After which aldehyde **57** was treated with PPh_3 , 2,6-di-*tert*-butylpyridine and dibromotetrachloroethane gave intermediate bromoxazoline which on addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in elimination of HBr providing 2,4-disubstituted oxazole **58** in 72 % yield. However, the product obtained still displayed significant racemization (33-66% *ee*) at the crucial C10 centre. This problem of racemization was completely prevented by replacing DBU with Et_3N over two steps from alcohol **56** to an excellent 89% yield of bisoxazole **58** with greater than 98% *ee* (Scheme 10). Benzoxazole **58** was then converted into oxime **60** for the 1,3-dipolar cycloaddition which is proceeded in three steps under mild conditions giving average yield of 95% (Scheme 10). The oxime **60** was chlorinated by treatment with NCS and then added Cs_2CO_3 was added to a solution of the chlorooxamic acid in DME in the presence of alkene **50** which was prepared in 71 % yield over four steps from the commercially available acetonide **61** (Scheme 10). The 1,3-dipolar cycloaddition of resulting product provided isoxazoline **48**.



Scheme 10. Synthesis of bisoxazole and conversion into oxime 48. Reagent and conditions: a) 1. TBSCl, imidazole, DMAP, DMF, rt, 90%; 2. NaBH₄, LiCl, THF, MeOH, 0 °C, rt, 80%; b) Dess-Martine periodinanane, NaHCO₃, CH₂Cl₂, 2,6-Di-*tert*-butylpyridine, 0 °C, then Et₃N, MeCN, 0 °C, rt, 89% over 2 steps; c) PPh₃, C₂Br₂Cl₄, CH₂Cl₂, 2,6-Di-*tert*-butylpyridine, 0 °C then Et₃N, MeCN, 0 °C, rt, 89% over 2 steps; d) PPTS, MeOH, rt, 93%; e) 1. Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, 0 °C; 2. NH₂OH·HCl, K₂CO₃, MeOH, H₂O, rt, 93% over two steps; f) 1. NCS, CH₂Cl₂, pyridine, rt, 2. Alkene 50, Cs₂CO₃, DME; rt, 77% over two steps (dr 7:2).

In order to get the targeted natural product, the isoxazoline **48** was subjected to reductive cleavage using Raney nickel and boric acid in ethanol/water giving β -hydroxy ketone **64** in 61% yield, which was then subjected to a *syn*-selective reduction in the presence of diethylmethoxyborane and sodium borohydride giving acetonide **65** in 89% yield over two steps. Acetonide **65** was subjected for the deprotection of TBDPS group and installation of the myristoyl side chain which proceeded in excellent yield of acetal protected bengazole A **66**. Finally, acidic deprotection using TFA/water removed both the acetonide and the BDA groups from **66** and completed the total synthesis of bengazole A (**IV**) (Scheme 11).

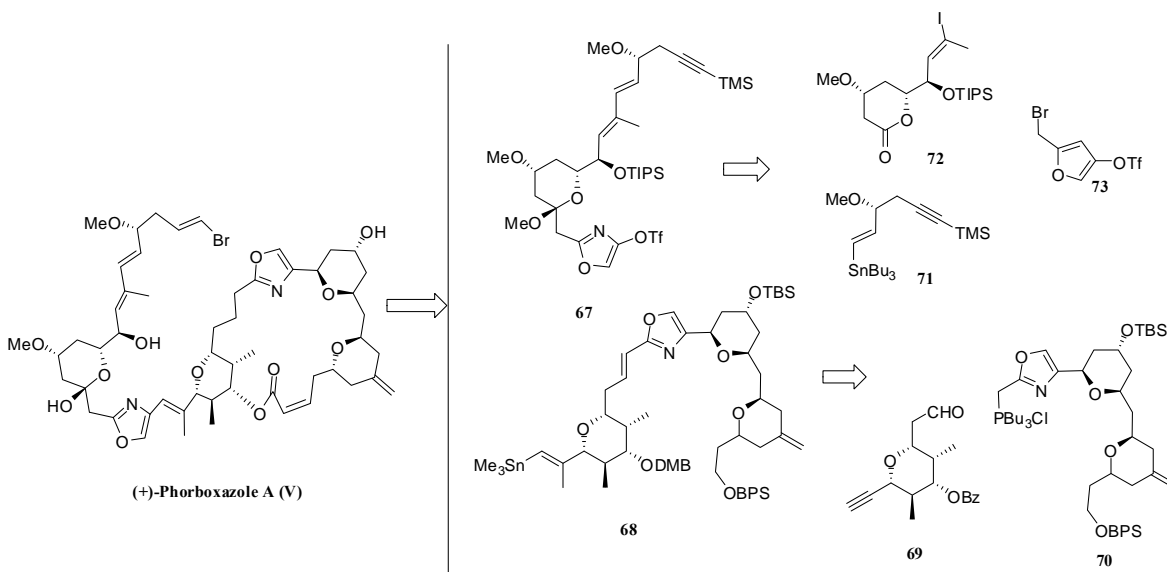


Scheme 11. Completion of total synthesis of bengazole A (IV). Reagent and conditions. a) Raney nickel, H₂, B(OH)₃, EtOH, H₂O, 61%; b) 1. Et₂BOMe, NaBH₄, THF, -78 °C, (*d:r* 14:1); 2. 2,2,-dimethoxypropane, TsOH 89% over 2 steps; c) 1. TBAF, THF, 0 °C, quant; 2. myristoyl chloride, NEt₃, CH₂Cl₂ 0 °C, 85%; d) TFA, H₂O, rt, 95%.

Phorboxazoles (V)

Phorboxazoles A and B were isolated by Searle and Molinski in 1995 from marine sponge *Phorbas sp.* [38]. Phorboxazoles displayed virtually unsurpassed cytotoxicity exhibiting a mean GI₅₀ of 1.58 x 10⁻⁹M and selected by the NCI for *in vivo* trials [39]. The first total synthesis of phorboxazole A was reported by Forsyth and coworkers in 1998 [40]. In the later years, Evans and Fitch reported the completed first total synthesis of phorboxazole B [41]. Their retrosynthetic analysis differs significantly from Forsyth's strategy in that only two fragments of equal complexity (C₁-C₁₉ and C₂₀-C₃₈) are employed and the C₃₉-C₄₆ side chain is added late in the synthesis. Smith and co-workers embarked on the total synthesis of these challenging marine natural products in 1997. Subsequently they disclosed assembly of two subtargets exploiting a modified Petasis-Ferrier union-rearrangement tactic for stereo-controlled construction of the two *cis* fused tetrahydropyrans [42].

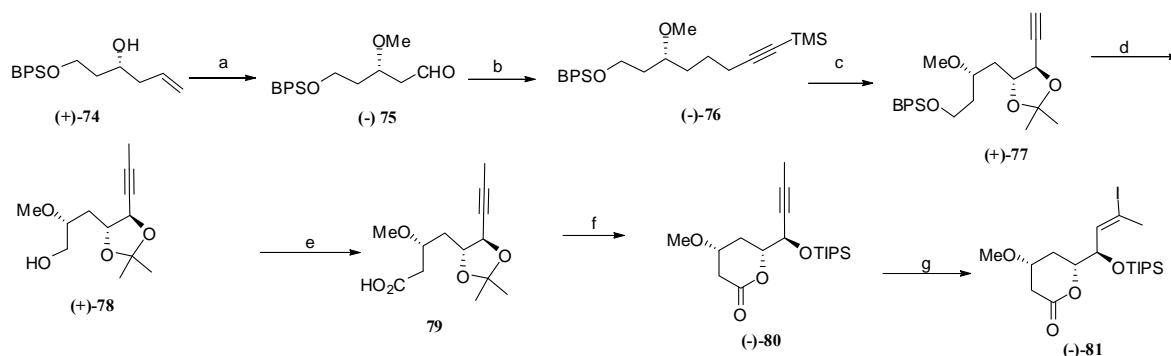
Smith *et. al.* [43] also described a highly convergent, stereocontrolled total synthesis of phorboxazole A (V) by use of modified Petasis-Ferrier rearrangements for the effective assembly of both the C11-15 and C22-26 tetrahydropyran rings. Smith retrosynthesis analysis of Phorbazole A lead to side chain subtarget 67 and macrolide precursor 68 which on further dissected into known aldehyde 69 and salt 70 (Scheme 12). Whereas disconnection of 67 lead to stannane 71, vinyl iodide 72 and bifunctional oxazole 73.



Scheme 12. Retrosynthesis analysis of Smith (+)-phorboxazole A (V)

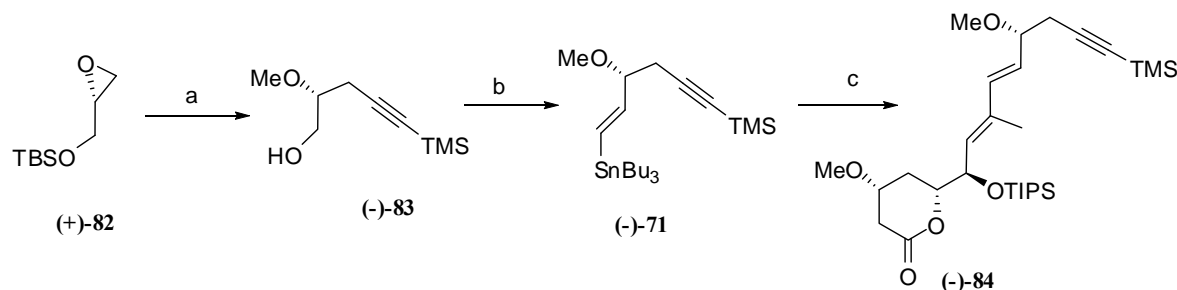
They assembled the side chain of phorboxazole with known Brown allylation adduct (+)-74 (Scheme 13) [44]. Aldehyde (-)-75 was obtained in two steps by methylation of the hydroxyl followed by ozonolysis. They observed that Wittig olifination of (-)-74 with methyl alkyne results a mixture of olefins (*E/Z* ca 2.2:1), however, condensation with the commercially available phosphate salt

afforded enyne (-)-76 in good yield. The removal of TMS followed by Sharpless dihydroxylation of the enyne and acetonide lead to (+)-77. Methylation of terminal alkyne followed by desilylation gave alcohol (+)-78 which upon TEMPO oxidation gave carboxylic acid 79. Immediate hydrolysis of the acetonide with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ followed by protection of the remaining secondary hydroxyl furnished (-)-80 that subsequently hydrostannylation/ iodination with palladium lead to the desired vinyl iodide (-)-81 (Scheme 13).



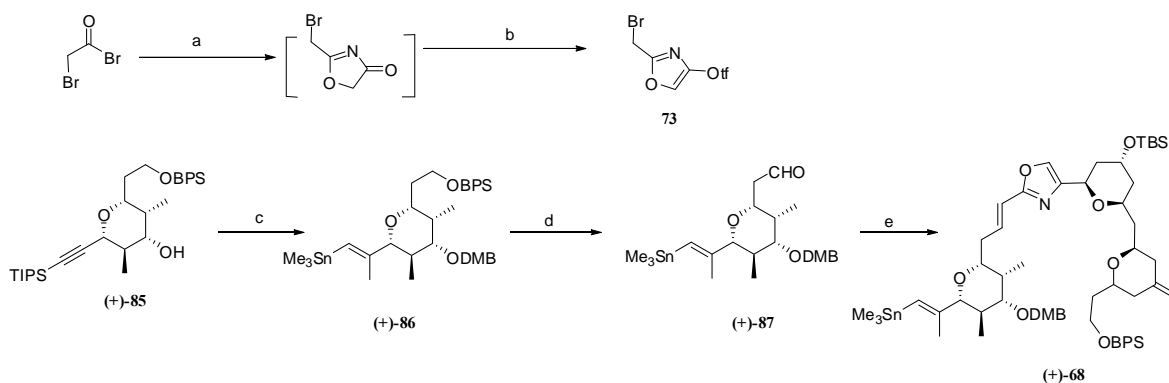
Scheme 13. Synthesis of vinyl iodide (-)-77. Reagent and condition: a) 1. DTBMP, MeOTf (84%), 2. O_3 , PPh_3 (96%); b) 1. $\text{BrPh}_3\text{PCH}_2\text{C}_2\text{TMS}$; 2. $n\text{BuLi}$, THF, 97%; c) 1. K_2CO_3 , MeOH (96%), 2. AD-mix β , 0 °C, 3. $\text{CH}_3\text{C}(\text{OMe})_2\text{CH}_3$ PPTS (78%); d) 1. $t\text{BuLi}$, MeI (100%) 2 steps; 2. TBAF (100% 2 steps); e) TEMPO, MeCN, pH = 8.7 buffer, NaOCl, NaClO_2 ; f) 1. $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, (72 % 2 steps), 2. TIPSCI Imid (88%); g) Bu_3SnH , $\text{PdCl}_2(\text{PPh}_3)_2$, I_2 (83%, 2 steps).

They prepared the Stille coupling partner (-)-71 from the known TBS-glycidol (-)-82 (Scheme 14) [45]. Exposure of (-)-82 to lithium TMS acetylide in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ followed by methylation with MeOTf/DTBMP and selective removal of the TBS group in the presence of TMS alkyne provide (-)-83 which gave corresponding aldehyde by Perikh-Doering [46] oxidation without epimerization. Hodgson homologation of aldehyde using with CrCl_2 , $\text{Bu}_3\text{SnCHBr}_2$, LiI in THF/DMF afforded vinyl stannane (-)-71 as single isomer. Then the stille coupling of (-)-81 and (-)-71 in the presence of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and $\text{Ph}_2\text{PO}_2\text{NBu}_4$ gave (-)-84 (Scheme 14).

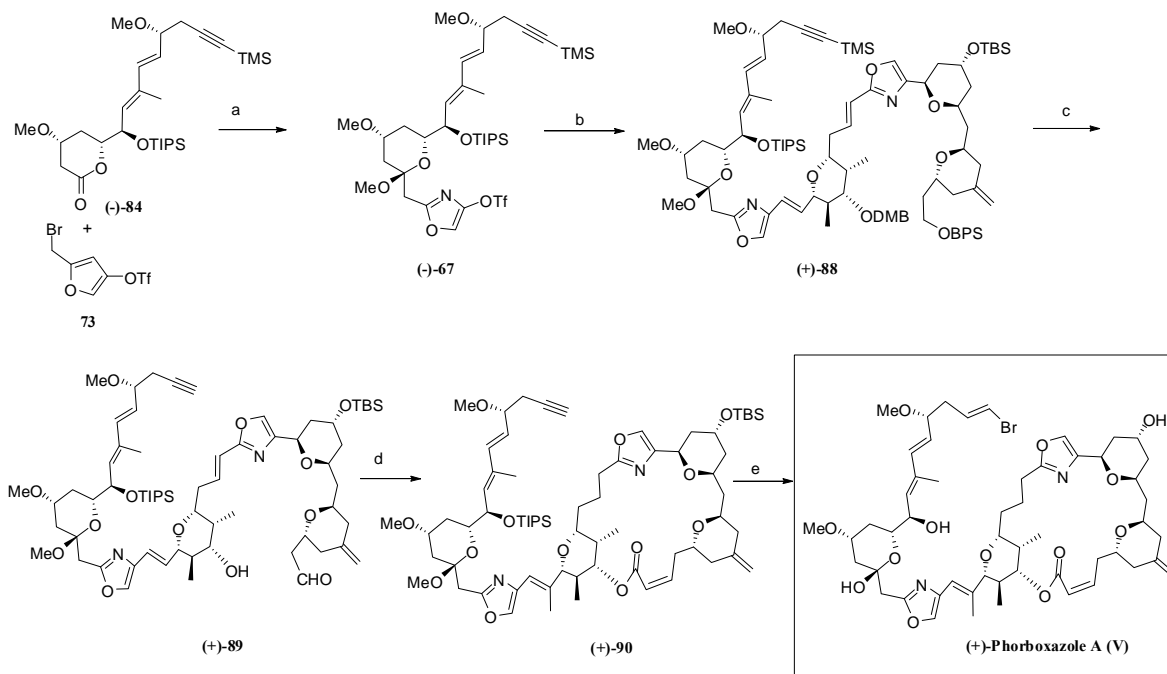


Scheme 14. Synthesis of lactone (-)-84. Reagent and conditions. a) 1. Acetylene trimethylsilane, $t\text{BuLi}$, $\text{BF}_3 \cdot \text{OEt}_2$; 2. MeOTf, DTBMP, 3. Cat HCl, MeOH (90%); b) 1. $\text{SO}_3 \cdot \text{Pyr}$, DMSO (92%), 2. CrCl_2 , $\text{Bu}_3\text{SnCHBr}_2$, LiI, THF/DMF (77%); c) (-)-81, $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, DMF, rt, 4h, $\text{Ph}_2\text{PO}_2\text{NBu}_4$ (99%).

In the next step, the required bromide **73** was prepared using a method developed by Sheehan for oxazole synthesis [47] (**Scheme 15**). Whereas, adduct (+)-**68** was prepared from the alcohol (+)-**85** which was then subjected to hydroxyl protection with DMBCl and desilylation with TBAF. Subsequent exposure to tin cuprate followed by methylation provided (+)-**86** in 71% yield which was then oxidized using SO₂Pyr followed by Wittig olefination of the resulting aldehyde (+)-**87** with (+)-**70** afforded the alkene (+)-**68** (**Scheme 15**). The lactone (-)-**84** was then coupled with the bromide **73** in the presence of *i*-PrMgCl to afford methyl hemi ketal **67** and thus completed the synthesis of the C(29-41) side chain trifalte (-)-**67** (**Scheme 16**). Stille coupling of (-)-**67** with vinyl stannane (+)-**68** provided (+)-**88** adduct which on subsequent removal of BPS group, Dess-Martin oxidation followed by removal of DMB group afforded hydroxyaldehyde (+)-**89**. Then addition of phosphonate moiety followed by a Still-modified Horner-Emmons macrocyclization provided (+)-**90**. Finally, a palladium mediated hydrostannylation with PdCl₂(PPh₃)₂, Bu₃SnH, NBS yielded predominantly the internal bromide which on deprotection with 6% HCl, THF gave (+)-phorboxazole A (**V**) (**Scheme 16**) [47].



Scheme 15. Synthesis of bromide 73 and alkene (+)-68. Reaction conditions: a) AgOCN, Et₂O, 30 min, CH₂N₂; b) Et₃N, Tf₂O, THF, - 78 °C to rt (48%); c) 1. KH, DMBCl (99%), 2. TABAF (67%), 3. BPS-Cl, EtN₃, DMF (93%), 4. Hexamethylditin, MeLi, CuCN, MeI, DMPU (80%); d) 1. TBAF (100%) 2. SO₃Pyr (92%); e) (+)-70 LHMDS, DMF 25 °C (99%).



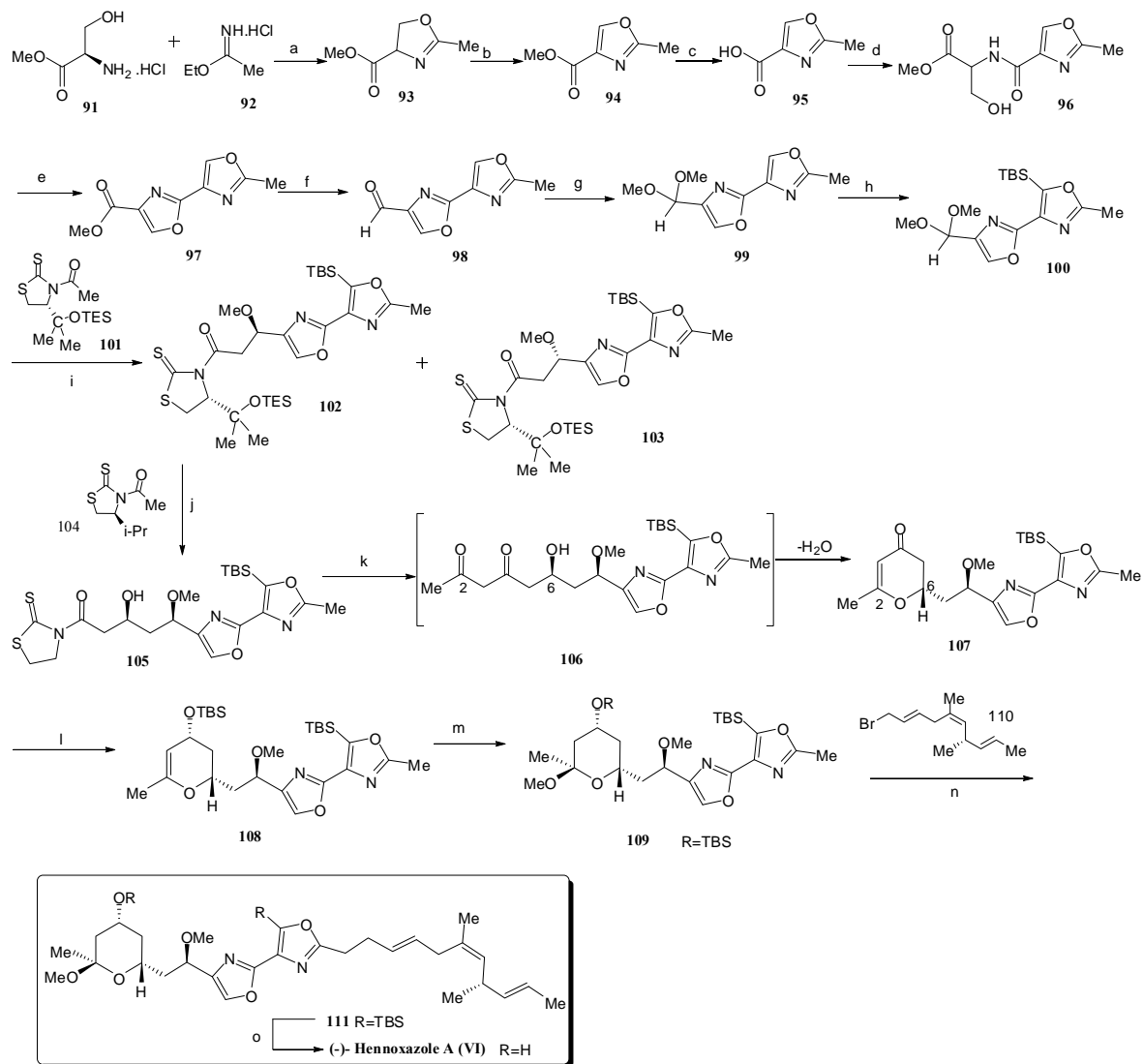
Scheme 16. Stille coupling of (-)-67 with (+)-68 and completion of total synthesis of Phorboxazole A. Reaction Conditions: a) 1. *i*PrMgCl -78 °C (76%), 2. PTSA MeOH (74%); b) (+)-68, Pd(Ph₃)₄, LiCl, 100 °C, dioxane, 24 h (72%); c) 1. KOH, 18-crown-6, THF, H₂O (83%), 2. Dess-Martin, NaHCO₃ (97%), 3. DDQ; d) 1. 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)acetic acid, EDCI-MeI, HOBT (94%), 2. K₂CO₃, 18-crown-6 PhCH₃ -78 °C (1:1 *Z/E*), -40 °C (2.5:1 *Z/E*), 0 °C (3.5:1 *Z/E*), rt (4:1 *Z/E*); e) 1a. NBS, AgBr, 1b. Bu₃SnH, PdCl₂(PPh₃)₂ 1c. NBS (82%), 2. 6% HCl, THF 72 h (70%).

2.2.2 (-)-Hennoxazole A (VI):

In 1991, a research team led by Paul Scheuer at the University of Hawaii reported the isolation and structural elucidation of hennoxazoles A (VI) from a species of *Polyfibrospongia* sponge off the coast of Miyako island in Okinawa, Japan [7]. It displays antiviral activity against herpes simplex 1 (IC₅₀ 0.6 μg/mL) and peripheral analgesic activity comparable to that of indomethacin [48]. Structurally, the hennoxazole contain a bisoxazole ring (2,4-disubstituted oxazoles) system, functionalized pyranyl ring and the nonconjugated triene side chain containing a trisubstituted *Z*-double bond and a remote stereogenic center. Although the assignment of relative stereochemistry about the C2-C6 pyran ring was secure, the relative stereochemistry of the distant C8 and C22 stereogenic centers and the absolute configuration remained unknown. Pioneering synthetic work by Wipf led to the total synthesis of the unnatural antipode of hennoxazole A and solved the stereochemical puzzle [49]. This landmark synthesis proceeded in a 28-step longest linear sequence (LLS) from mercaptoimidazole. They also discovered that hennoxazole A and its C22 epimer are chromatographically and spectroscopically indistinguishable except by optical rotation. The second total synthesis, by Williams and co-workers, proceeded in a 20-step and took advantage of a directed

allylborane addition to an aldehyde to form the C7-C8 bond in the key fragment coupling step) [50]. The third total synthesis, by Shioiri and co-workers, shared Wipf's strategy for late-stage oxazole formation as the key coupling step accomplished by 25-step [51]. Here, we detail total synthesis of (-)-hennoxazole A (**VI**) which have culminated in a 14-step (**Scheme 17**) by Smith and co-workers [52].

Commercially available (\pm)-serine methyl ester hydrochloride (**91**) was condensed with ethyl acetimidate (**92**) to give oxazoline **93**, which was then oxidized to oxazole **94**. It was then saponified to carboxylic acid **95**, which was activated as its acid chloride and combined with another equivalent of serine methyl ester to give amide **96**. The one-pot cyclodehydration/oxidation method of Wipf and Williams [53] was used to generate bisoxazole methyl ester **97** in 82% yield. Partial reduction with DIBAL-H gave aldehyde **98** in quantitative yield. Finally, Noyori conditions were used to generate dimethyl acetal **99** in 96% yield. Treatment of **9** with *n*-BuLi followed by addition of TBSOTf led to C13-protected bisoxazole **100** in 88% yield. Several chiral auxiliaries and soft enolization conditions were surveyed to find suitable reaction conditions to get pyran/bisoxazole fragment. Overall, the direct pathway of using $-\text{CMe}_2(\text{OTES})$ -substituted auxiliaries (**101**) with enolization condition (PhBCl_2 , sparteine) yielded **102** and **103** (86:14) with major diastereomer in 53% yield. This appeared to be the best compromise of increased structural complexity and yield and was appropriated to advance material to the forefront of the synthesis. The thione auxiliary was reductively cleaved from **102** using DIBAL-H. The resulting β -methoxy aldehyde was prone to β -elimination and was immediately subjected to an auxiliary-directed acetate aldol reaction using *ent*-**104**. Further, Tin enolate conditions gave aldol adduct **105**. Treatment with magnesium acetoacetate and imidazole led to the desired transacylation reactions and upon quenching with aqueous acid, provided cyclodehydrated pyrone **107**. Luche reduction gave an unstable allylic alcohol, which was immediately protected as its TBS ether (**108**) in a combined yield of 61%. Mixed methyl acetal formation, in accordance with Wipf's pioneering work, finalized the synthesis of C1-C15 pyran/bisoxazole coupling fragment **109**. With both coupling partners in hand, they endeavored to unite them in the pivotal transformation of the synthesis. Using the same conditions that had been successful for model fragment couplings, treatment of bisoxazole **109** with LiNEt_2 and allylic bromide **110** [52] led to the anticipated union in 77% yield along with 7% unalkylated **109**, thus securing the entire carbon framework of the natural product. Double TBS deprotection of **111** provided (-)-hennoxazole A (**VI**).



Scheme 17: Synthesis of (-)-hennoxazole A (VI). Reagents and conditions: a) Et₃N, CH₂Cl₂ (80%); b) CuBr, DBU HMTA, CH₂Cl₂ (85%); c) NaOH, H₂O, MeOH (99%); d) (1) SOCl₂, reflux (2) Ser-OMe.HCl, Et₃N, CH₂Cl₂ (77%); e) (1) Deoxo-Fluor, CH₂Cl₂, -20 °C, (2) DBU, BrCCl₃, 0 °C (82%); f) DIBAL-H, CH₂Cl₂, -78 °C (100%); g) TMSOMe, TMSOTf, CHCl₃, -30°C (96%); h) (1) *n*BuLi, THF, -78 °C, (2) TBSOTf (88%); i) 101, PhBCl₂, Sparteine, add dimethyl acetal, BF₃.OEt₂, -78°C to rt; j) (1) DIBAL-H, CH₂Cl₂, -78 °C, (2) 104, Sn(OTf)₂, *N*-Et-piperidine, CH₂Cl₂, -50 °C then add aldehyde, -110 to -78 °C (dr 3:1; 46% isolated diastereomer); k) Magnesium acetoacetate imidazole, DMF, then add 2M HCl, 0 °C (65%); l) (1) NaBH₄, CeCl₃, THF/MeOH, -78 °C to -30 °C, (2) TBS-Cl, imidazole, Cat. DMF (61%, two steps); m) HC(OMe)₃, MeOH, PPTS, benzene (80%); n) LiNEt₂, THF, -78 °C then add 110, 77%; o) TBAF, THF (99%)

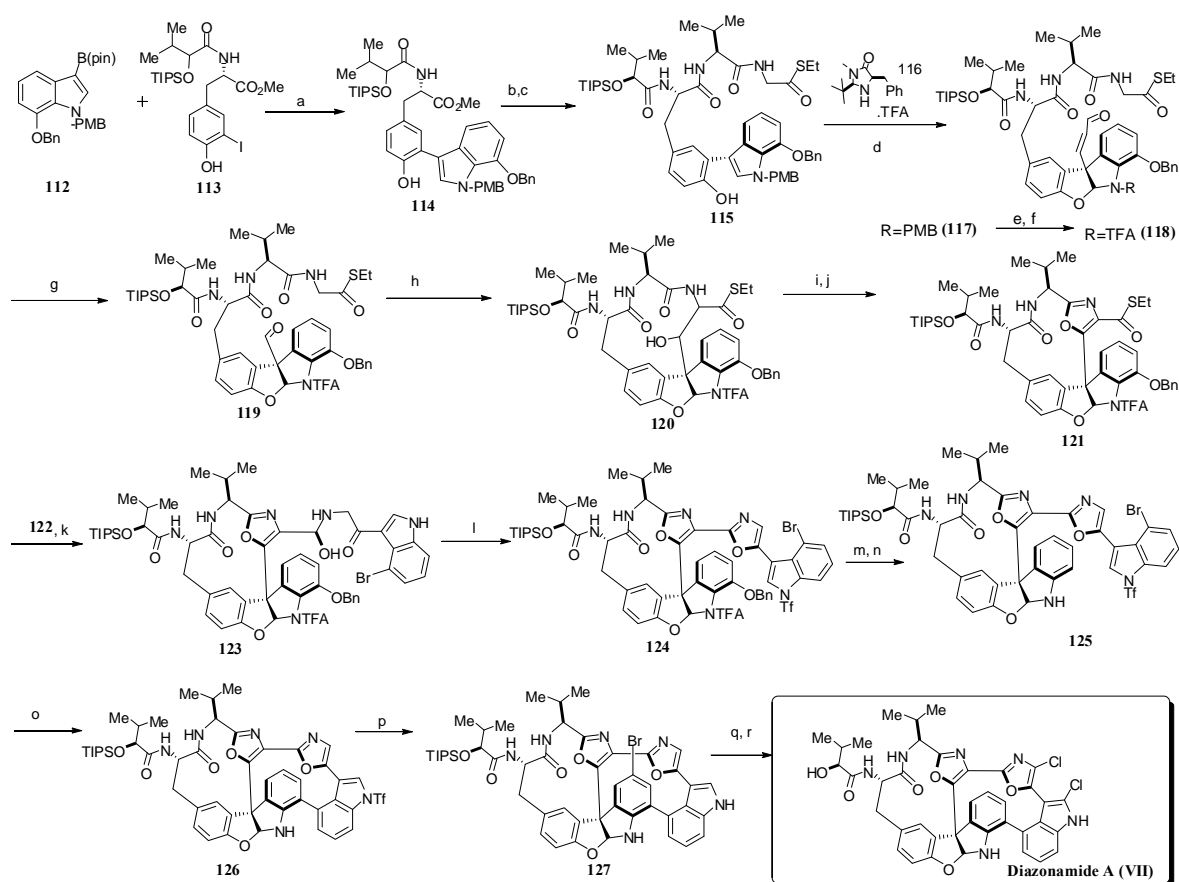
2.2.4 Diazonamide A (VII):

The diazonamides are a structurally unique class of secondary metabolites first isolated by Fenical and coworkers from the colonial marine ascidian *Diazona angulata* [13,54]. Within this family, diazonamide A (VII) was found to be a potent antimetabolic agent, exhibiting low nanomolar GI₅₀ values towards a diverse panel of human cancer cell lines [13,55]. The structure of diazonamide A (VII) was misassigned in the original isolation report, but was later corrected by Harran and

coworkers in 2001 following a seminal synthesis of the nominal structure [56]. The correct structure of diazonamide A (**VII**) is characterized by two 12-membered macrocycles that are conjoined through a triarylsubstituted quaternary carbon stereocenter embedded in an unusual furanoindoline core. Together with a large degree of unsaturation, these structural elements comprise an exceptionally compact and rigid framework whose inner atoms possess almost no rotational degrees of freedom.

Many groups have reported partial syntheses of diazonamide A (**VII**) over the past decade, Nicolaou [57] and Haran [58] have reported the only three completed total syntheses of diazonamide A (**VII**) to date, while Magnus [59] and Sammakia [60] have recently outlined formal syntheses. However, here we have outlined latest synthesis described by Robert Knowles and co-workers [61]. This synthesis involves 20 steps in its longest linear sequence and proceeds in 1.8% overall yield. The principal challenge associated with the synthesis of diazonamide A (**VII**) is the stereoselective installation of the C(10) quaternary carbon stereocenter. The first step involved Suzuki coupling of boronic ester **112** and iodophenol **113** under the action of catalytic Pd(dppf)Cl₂ to yield biaryl **4** in 82% yield (**Scheme 18**). The methyl ester of **114** was then hydrolyzed with aqueous lithium hydroxide and the resulting carboxylic acid was coupled to an N-TFA salt of valine-glycine dipeptide thioester, providing access to **115**. Further, treatment of **115** with 30 mol% of imidazolidinone catalyst **116**TFA and excess propynal in dichloromethane and methanol at -70 °C resulted in full conversion to **117**, though as a modest 4.2 : 1 mixture of diastereomers at the critical C(10) position. Interestingly, the use of a ternary solvent mixture comprised of toluene, chloroform and methanol ultimately proved superior, to deliver **117** in 86% isolated yield and >20 : 1 dr after 24 h at -50 °C. With the diazonamide core in hand, the indoline protecting group was exchanged to ensure the stability of the nascent aminal towards a subsequent ozonolysis, which cleanly furnished aldehyde **119** in 84% yield. Aldehyde **119** was specifically targeted as the substrate for a proposed intramolecular aldol reaction to furnish a 13-membered, ring-opened form of the left-hand macrocycle. A careful evaluation of Lewis acids, amine bases and solvents led to the discovery that treatment of thioester **119** with MgBr₂.Et₂O, TMSCl and triethylamine in THF at room temperature readily effected soft enolization, allowing an efficient, intramolecular macroaldolization to deliver **120** as a single diastereomer in 67% yield. Alcohol **120** was readily oxidized with the Dess–Martin periodinane to its corresponding ketone which on direct treatment with an excess of diethylamino sulphur trifluoride (DAST) in benzene led to a highly efficient cyclodehydration, furnishing central oxazole ring to get **121** in 61% yield over two steps. The thioester functionality of **121** was activated with AgTFA and displaced by amine **122** to yield ketoamide **123** in 88% yield. Furanoindoline **123** was in turn subjected to the Wipf conditions for oxazole cyclodehydration, furnishing bisoxazole **124**

in 86% isolated yield (**Scheme 18**). Deprotection of the benzyloxy and trifluoroacetamide groups of **124** with BBr_3 , followed by treatment of the crude product with excess PhNTf_2 provided bromo-bistriflate **125** in 80% yield over two steps. After extensive optimization, there was a successful tandem borylation/annulation, as treatment of **125** with $(\text{Bpin})_2$, KF , and $\text{Pd}(\text{PPh}_3)_4$ in a 5% aqueous solution of dioxane under microwave heating at $120\text{ }^\circ\text{C}$ yielded the desired biaryl bond of macrocycle **126** in 50% yield. selective introduction of the aryl chlorides was accomplished by first brominating the activated indoline *E*-ring, followed by in situ hydrolysis of the indolyl triflate to yield **127** in 83% isolated yield. Subsequent chlorination of the desired oxazole and indole functionalities of **127** was achieved upon exposure to NCS , and the aryl bromide was selectively excised by hydrogenolysis over Pearlman's catalyst in a two-step, one-pot procedure. Finally, treatment with TASF removed the remaining silyl ether to furnish synthetic diazonamide **A** (**VII**).



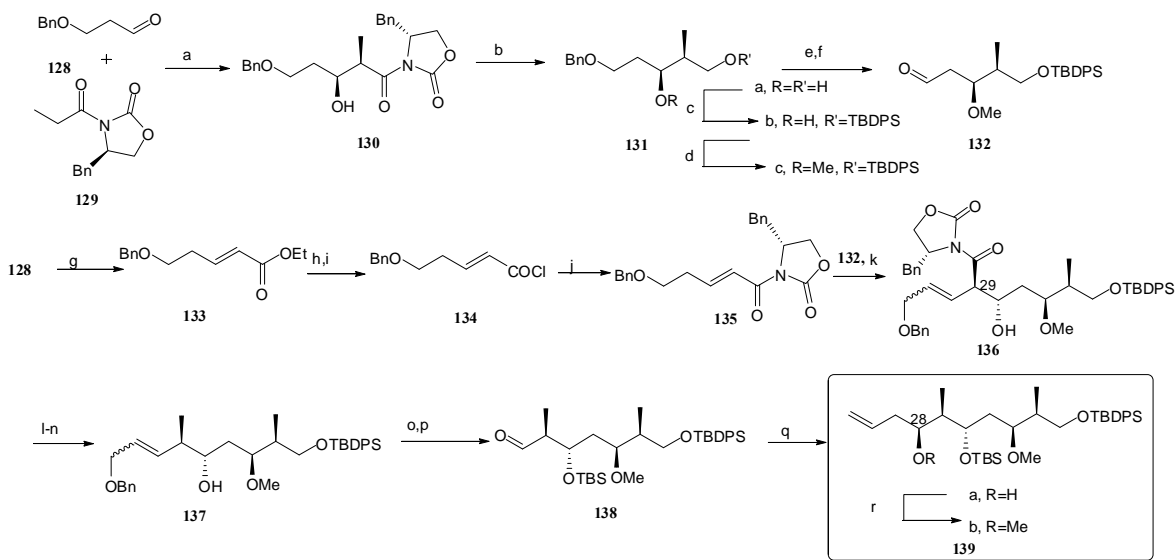
Scheme 18: Synthesis of bisoxazole diazonamide A (VII). Reagents and conditions: (a) 5 mol% $\text{Pd}(\text{dppf})\text{Cl}_2$, K_3PO_4 , dioxane, $40\text{ }^\circ\text{C}$, 82%; (b) LiOH , THF, MeOH, H_2O , rt; (c) EDC, HOBT, (*S,S*-Ethyl 2-(2-amino-3-methylbutanamido) ethanethioate).TFA, NaHCO_3 , DMF, rt, 95%; (d) 30 mol% **116**, $\equiv\text{CHO}$, CHCl_3 :PhMe (10:1), 86% >20:1 dr (e) DDQ, CH_2Cl_2 , pH 7 buffer, $0\text{ }^\circ\text{C}$ (f) TFAA, DMAP, CH_2Cl_2 , $0\text{ }^\circ\text{C}$ (g) O_3 , CH_2Cl_2 , MeOH, $-78\text{ }^\circ\text{C}$ (h) $\text{MgBr}_2\cdot\text{Et}_2\text{O}$, TMSCl, NEt_3 , THF, rt (i) Dess–Martin, CH_2Cl_2 , rt (j) DAST, C_6H_6 , rt. (k) 2-amino-1-(4-bromo-1H-indol-3-yl)ethanone.TFA (**122**), AgTFA , NaHCO_3 , DMF, $40\text{ }^\circ\text{C}$, 88% (l) PPh_3 , C_2Cl_6 , NEt_3 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 86% (m) BBr_3 , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ (n) PhNTf_2 , NEt_3 , CH_2Cl_2 , rt, 80% (o) $(\text{Bpin})_2$, KF , 70 mol% $\text{Pd}(\text{PPh}_3)_4$, dioxane: H_2O (20 : 1), MW120 $^\circ\text{C}$ (p) NBS , THF; then LiOH , THF, MeOH, H_2O , 50% (q) NCS , THF, $40\text{ }^\circ\text{C}$; then H_2 , $\text{Pd}(\text{OH})_2$, THF, $40\text{ }^\circ\text{C}$ (r) TASF , DMF, rt, 80%.

2.3 Trisoxazole

2.3.1 Ulapualide A (VIII)

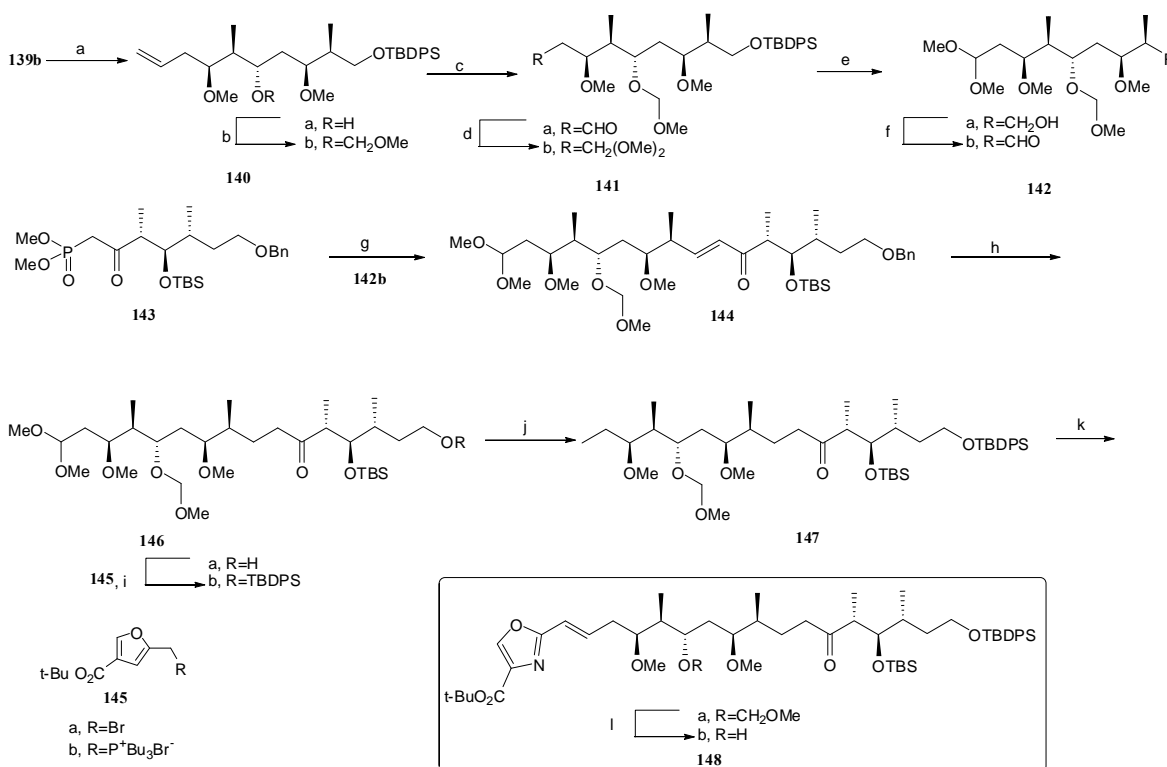
The “ulapualides” are a unique family of macrolides isolated from sponges and nudibranchs (sea slugs). Ulapualide A (**VIII**) was the first of their number to be characterised, [62] and the family now includes the mycalolides, kabiramides, halishigamides and halichondramides, together with a number of congeners [63]. The ulapualides show antifungal activity and ichthyotoxic properties, together with modest activity against L1210 leukemia cells. Gerald Pattenden and coworkers approached total synthesis of (-)-ulapualide A based on some biosynthesis speculation [64].

In the first, the side chain **139** (C25–C34) was synthesized starting from 3-benzyloxypropanal **128**, (*R*)-2-benzyl-3-propionyl-2-oxazolidinone **129** and (*R*)-pentenyloxazolidin-2-one **135** using conventional Evans aldol chemistry [65] (**Scheme 19**). This introduced the *syn* stereochemistry at side chain C32–C33 (**129** to **130**) and the *anti*-stereochemistry at C29–C30 (**135** to **136**). The β -orientated hydroxyl group at C28 (**138** to **139a**) was introduced by applying Brown’s allylboration chemistry [66]. Further, protection of the hydroxyl group in **139a** as its methyl ether gave **139b**.



Scheme 19: Preparation of 139. Reagents and conditions: a) Bu_2BOTf , Et_3N , DCM, -78°C , 72%; b) LiBH_4 –MeOH, THF; c) TBDPS-Cl, imidazole, DMF, 94%; d) NaHMDS, MeI, THF, 0°C , 90%; e) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , EtOAc, 92%, f) DMSO, $(\text{COCl})_2$, DCM, Et_3N , -78°C , 96%; g) ethoxy carbonyl methylene triphenyl phosphorane, DCM, 68%; h) LiOH, THF, H_2O , 95%; i) $(\text{COCl})_2$, DMF, DCM, 99%; j) *n*BuLi, 4-phenylmethyl-2-oxazolidone, -78°C , 95%; k) **132**, Bu_2BOTf , Et_3N , DCM, -78°C , 58%; l) LiBH_4 –MeOH, THF, 99%; m) MsCl, DIPEA, DCM, -40°C ; n) LiBH_4 –MeOH, THF, 85%; o) TBSOTf, 2,6-lutidine, DCM, 85%; p) O_3 , DCM, PPh_3 , -78°C , 93%; q) allylmagnesium bromide, Et_2O , -78°C , (-)- β -chlorodiisopinocampheylborane, 91%; r) NaHMDS, MeI, THF, -15°C , 91%;

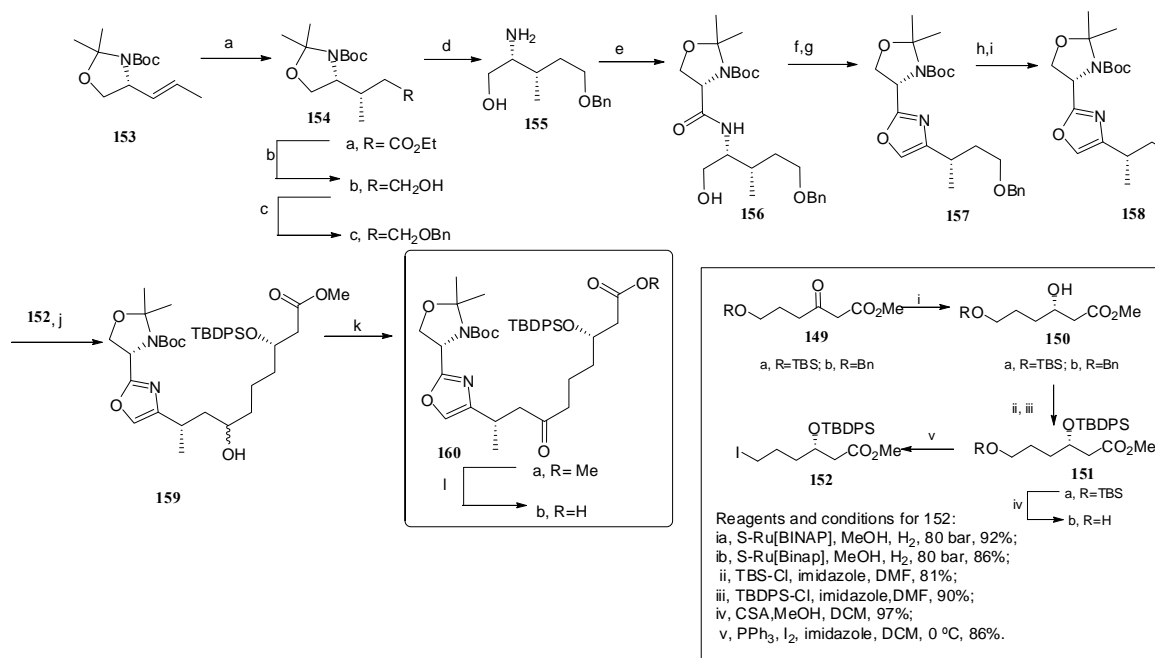
Further, the oxazole-substituted compound **148b**, containing the entire C25–C41 top chain in ulapualide A, was synthesised from **139b** following exchange of TBS for MOM. Oxidative cleavage of the alkene bond in **140b** and protection gave corresponding dimethylacetal **141b** (Scheme 20). Deprotection followed by oxidation yielded aldehyde **142b**. A Wadsworth–Emmons reaction between the aldehyde **142** and the phosphonate ester **143** [67] resulted in **144**, which, was converted to the alcohol **146a** [68] Further, the primary alcohol in **146a** was protected as its TBDPS ether **146b**, and the dimethylacetal group was then unmasked selectively using Me_2BBr at -78°C [69] to give the aldehyde **147** in excellent yield. Finally, Wittig reaction between **147** and the phosphonium salt **145b**, led to the *E*-2-alkenyloxazole **148a**, followed by deprotection using Me_2BBr in CH_2Cl_2 at -78°C to provide C30-alcohol **148b**.



Scheme 20. Preparation of C30 alcohol 148b. Reagents and conditions for: a) PPTS, EtOH, reflux, 77%; b) MOM-Cl, DIPEA, DCM, reflux, 95%; c) O_3 , DCM, PPh_3 , -78°C , 99%; d) trimethylorthoformate, MeOH, *p*TSA, 89%; e) TBAF, THF 99%; f) TPAP, NMO, DCM, 78%; g) **142b**, $\text{Ba}(\text{OH})_2$, THF, H_2O , 68%; h) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , EtOAc, 96%; i) TBDPS-Cl, imidazole, DMF, 93%; j) Me_2BBr , DCM, -78°C , 98%; k) **145a**, PBu_3 , then **147**, DBU, DMF, 75%; l) Me_2BBr , Et_2O , -78°C , 79%.

Asymmetric reduction of the known β -keto ester **149a** [70] using (*S*)-Ru[BINAP] [71] gave (*S*)-hydroxy ester **150a** (97% ee), which was selectively protected as its C6-TBS, C3-TBDPS *bis*-silyl ether **151a**. Selective deprotection of the TBS group in **151a**, using camphorsulfonic acid in MeOH, followed by iodination gave the (*S*)-iodide **152** in 83% overall yield (Scheme 21a). The substituted aldehyde **158** was prepared from Garner's aldehyde starting with an *E*-selective Wittig reaction,

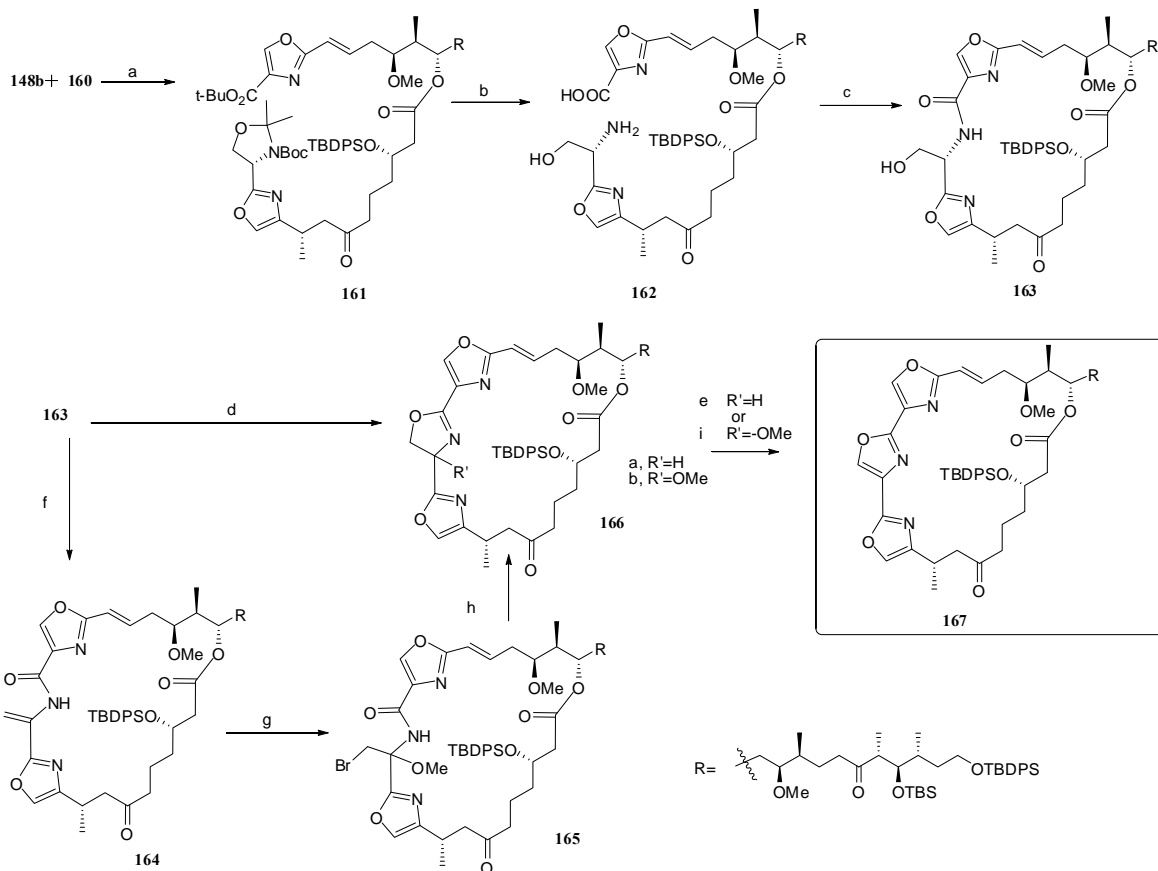
leading to the α,β -unsaturated ester **153**, followed by chelation-controlled *syn*-addition of lithium dimethylcuprate producing the adduct **154a** (9:1 *syn* selectivity) [72]. Successive functional group inter-conversions led to the amino alcohol **155**, which was then reacted with Garner's acid [73] to deliver the corresponding amide **156** (Scheme 21). Oxidation of the primary OH group in **156** followed by a Robinson–Gabriel cyclisation gave the substituted oxazole **157**, which was then elaborated to the C7-aldehyde **158** in two straightforward steps. The oxazole-substituted aldehyde **158** was coupled to the iodide **152** in degassed DMF in the presence of chromium chloride and vitamin B₁₂ to give a 1:1 mixture of C7 epimers of the alcohol **159** in 88% yield. Finally, oxidation of the alcohol **159** using Swern conditions, followed by saponification of the ester group in the resulting 6-ketoester **160a**, using LiOH/MeOH, gave the carboxylic acid **160b**.



Scheme 21. Preparation of carboxylic acid 160b. Reagents and conditions: a) Me₂CuLi, TMS-Cl, THF, 81%; b) DIBAL-H, THF, 100%; c) NaH, BnBr, TBAL, THF, 78%; d) HCl, dioxane; e) Garner's acid, EDC, 4-methylmorpholine, THF, HOBt, 79%; f) DMSO, (COCl)₂, Et₃N, DCM, -78 °C, 97%; g) PPh₃, 1,2-dibromotetrachloroethane, 2,6-di-*t*-butylpyridine, DCM, DBU, MeCN, 72%; h) Pd/C, EtOAc, H₂, 81%; i) DMSO, (COCl)₂, Et₃N, DCM, -78 °C, 87%; j) **152**, vitamin B₁₂, CrCl₂, DMF, 88%; k) DMSO, (COCl)₂, Et₃N, DCM, -78 °C, 85%; l) LiOH, MeOH, H₂O, 88%.

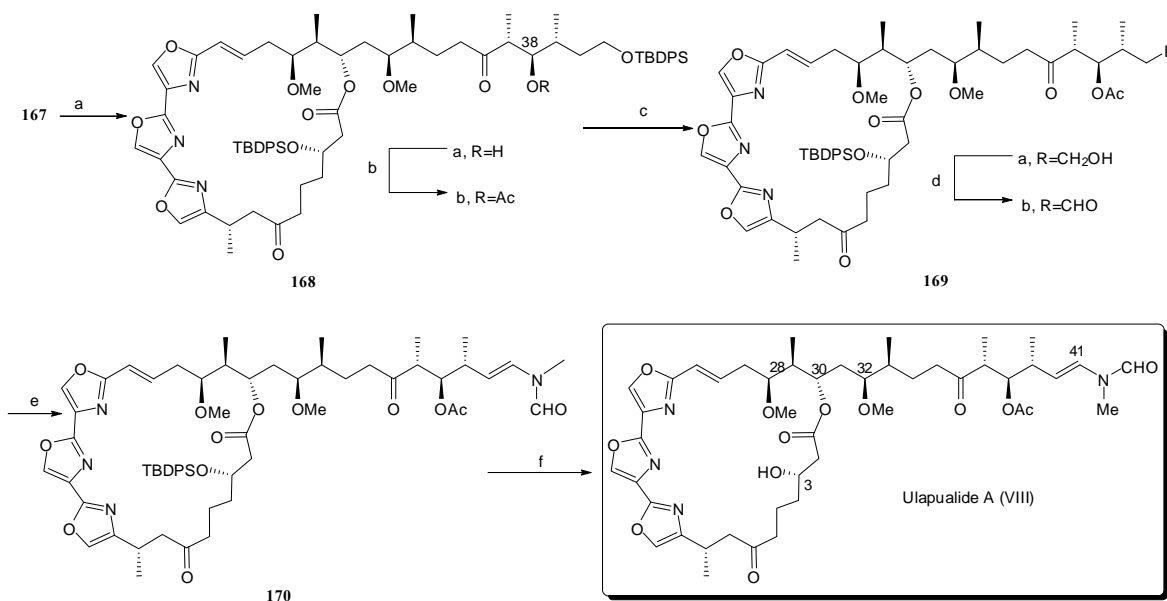
Esterification of the carboxylic acid **160b** with the alcohol **148b**, followed by removal of the *t*-butyl ester and *N*-Boc protecting groups in the product **161**, gave **162** (Scheme 22). Treatment of **162a** with HATU [74] at 0 °C, resulted in macrolactamisation to give **163** (over 2 steps). Further treatment with DAST at -78 °C gave the oxazoline **166a** (89%), but the subsequent oxidation of **166a** to the corresponding *tris*-oxazole **167**, using NiO₂ in benzene under reflux, was unreliable and seldom gave yields above 25%. A more reliable route to **167** from **163** was *via* the enamide formation (Scheme

22). Thus, mesylation of **163** followed by elimination of MeSO₂H gave the enamide which on treatment with NBS in MeOH led to the methoxybromide. Further, dehydrobromination in the presence of Cs₂CO₃²² produced methoxyoxazoline **166b**. Finally, treatment of **166b** with camphor sulfonic acid in benzene, heated under reflux, gave the same *tris*-oxazolemacrolide **167** to that obtained using the NiO₂ oxidation route.



Scheme 22. Preparation of *tris*-oxazolemacrolide. Reagents and condition: a) 2,4,6-trichlorobenzoyl chloride, Et₃N, toluene, DMAP, 0 °C, 93%; b) TMSOTf, Et₃N, DCM, 0 °C; c) HATU, Et₃N, DCM, 0 °C, 67%; d) DAST, DCM, -78 °C, 89%; e) NiO₂, benzene, reflux, 25%; f) MsCl, DIPEA, DCM, DBU, 0 °C, 75%; g) NBS, MeOH, DCM, 92%; h) Cs₂CO₃, dioxane, 60 °C, 92%; i) CSA, benzene, 5Å mol. sieves, reflux, 58%.

The selective deprotection of the TBS group in **167** followed by acetylation led to the C₃₈-acetate **168b** (Scheme 23). A second, selective deprotection using HF–pyridine (1.5 h only) gave the alcohol **169a**, which on oxidation gave aldehyde **169b**. Further, aldehyde **169b** in benzene was heated under reflux with *N*-methylformamide) (22 equiv.) in the presence of PPTS (0.25 equiv) for 6-10 h to give *E*-alkenyl formamide **170** which was isolated as a 3:2 mixture of rotamers, in 25-40% yield. Finally, removal of the TBDPS protection at C₃ in **170**, using HF–pyridine in THF (12 h), gave (-)-ulapualide A (**VIII**) as a colourless viscous oil, in 60% yield.

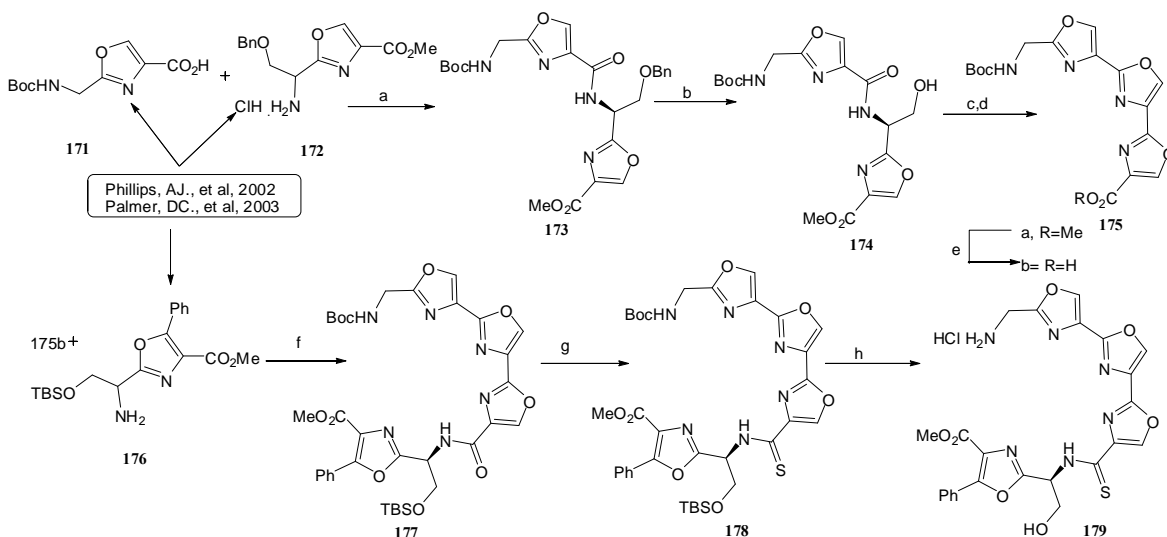


Scheme 23. Synthesis of Ulapualide A (VIII). Reagents and conditions: a) TMSOTf, DCM, $-78\text{ }^{\circ}\text{C}$, 85%; b) acetic anhydride, DMAP, DCM, pyridine, 84%; c) HF–pyridine, DCM, pyridine, 61%; d) Dess–Martin periodinane, DCM, 80%; e) *N*-methylformamide, PPTS, benzene, reflux, 40%; f) HF–pyridine, THF, 60%.

2.4 Tetraoxazole

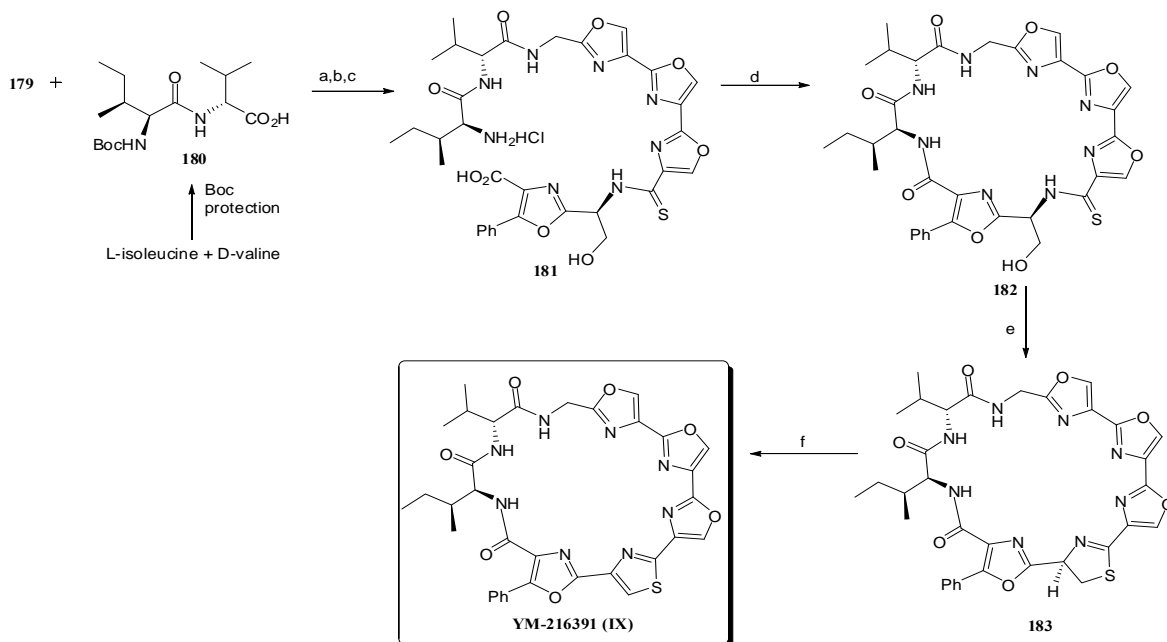
2.4.1 Cyclopeptide YM 216391(IX)

The unusual polyoxazole–thiazole-based cyclopeptide, designated as YM-216391 (**IX**), was recently isolated from *Streptomyces nobilis*. YM-216391 dose-dependently inhibited the growth of human cervical cancer HeLa S3 cells with an IC_{50} value of 14 nM. YM-216391 also showed potent cytotoxic activity against a human cancer cell line panel [75]. The structure of YM-216391 comprises a continuum of five azoles which have their origins in serine, cysteine and phenylalanine, linked via a glycine–valine–isoleucine tripeptide tether. The complete stereochemical assignment of YM-216391 has not been established. Jon Deeley and Gerald Pattenden in 2005 [76] described a concise total synthesis of this cyclopeptide, which not only confirms its unique structure but also allows the assignment of its stereochemistry. A coupling reaction between 2,4-disubstituted oxazoles **171** and **172** [77] in the presence of EDC, HOBt and NMM led to the amide **173** which was then converted into the trisoxazole **175a** via **174**, in three straightforward steps (**Scheme 24**). Next, saponification of **175a**, followed by coupling the resulting carboxylic acid **175b** with the oxazole substituted amine **176** (EDC, HOBt, NMM; 87%) led to the tetraoxazole amide **177**. The amide **177** was then converted into the corresponding thioamide **178**, using Lawesson’s reagent, which was deprotected leading to the amine hydrochloride salt **179**.



Scheme 24. Preparation of carboxylic acid 175b and amine hydrochloride salt 179. Reagents and conditions: a) EDC, HOBT, NMM, CH₂Cl₂, 0 °C A rt, 24 h, 56%; b) H₂, 20% Pd(OH)₂/C, MeOH–THF (2 : 1), rt, 81%; c) DAST, CH₂Cl₂, 278 °C, 1.5 h; d) BrCCl₃, DBU, CH₂Cl₂, 0 °C - rt, 24 h, 57% over two steps; e) NaOH, THF, H₂O, rt, 24 h, 88%; f) EDC, HOBT, NMM, CH₂Cl₂, 0 °C- rt, 24 h, 87%; g) Lawesson's reagent, THF, reflux, 18 h, 50%; h) 4.0M HCl solution in dioxane, rt, 24 h, 91%.

Next, amine **179** was condensed with the protected dipeptide **180** which is derived from D-valine and L-isoleucine (**Scheme 25**). Using sequence of reactions produced the cyclopeptide intermediate **182**. Conversion of the intermediate **182** into the thiazoline **183**, followed by oxidation with MnO₂ in CH₂Cl₂ gave the cyclopeptide **IX**.



Scheme 25. Complete synthesis of YM-216391 (IX). Reagents and conditions: a) EDC, HOBT, NMM, CH₂Cl₂, 0 °C - rt, 48 h, 82%; b) NaOH, THF, H₂O, rt, 24 h; c) 4.0 M HCl solution in dioxane, rt, 18 h, 70% over two steps; d) HATU, NMM, CH₂Cl₂–DMF (2:1), 0 °C - rt, 72 h, 75%; e) DAST, CH₂Cl₂, 278 °C, 2 h, 89%; f) MnO₂, CH₂Cl₂, rt, 48 h, 55%.

2.4.2 Cyclic peptide IB-01211 (X)

Cyclic peptide IB-01211 (**X**) was reported from the marine microorganism strain ES7-008 which is phylogenetically close to *Thermoactinomyces* genus [78,79]. Mechercharmycin A isolated from marine derived *Thermoactinomyces* sp. by Kanoh has same structure as IB-01211 [80]. This peptide is strongly cytotoxic to several tumor cell lines [81], structurally it contains four oxazoles, one thiazole, and a tripeptide that includes a didehydroamino acid residue. Delia *et. al.* [82], reported the total synthesis of IB-01211. The key step in their synthesis is a Hantzsch macrocyclization with concomitant dehydration of the deprotected hydroxyl group. They have designed the synthesis of IB-01211 through the bond-disconnection depicted in **Figure 3**, providing three key precursors, the dipeptide **184**, bis-oxazoles **185** and **186**.

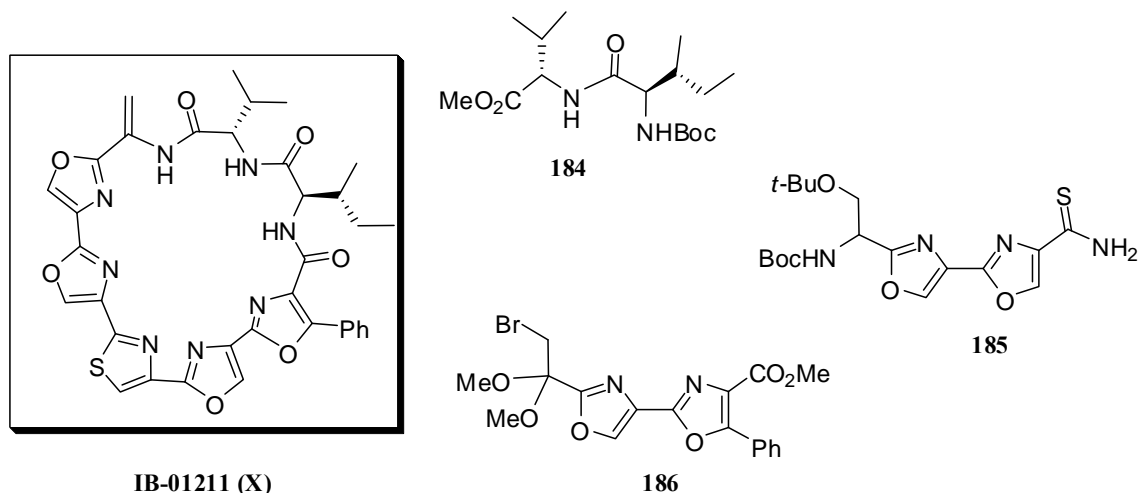
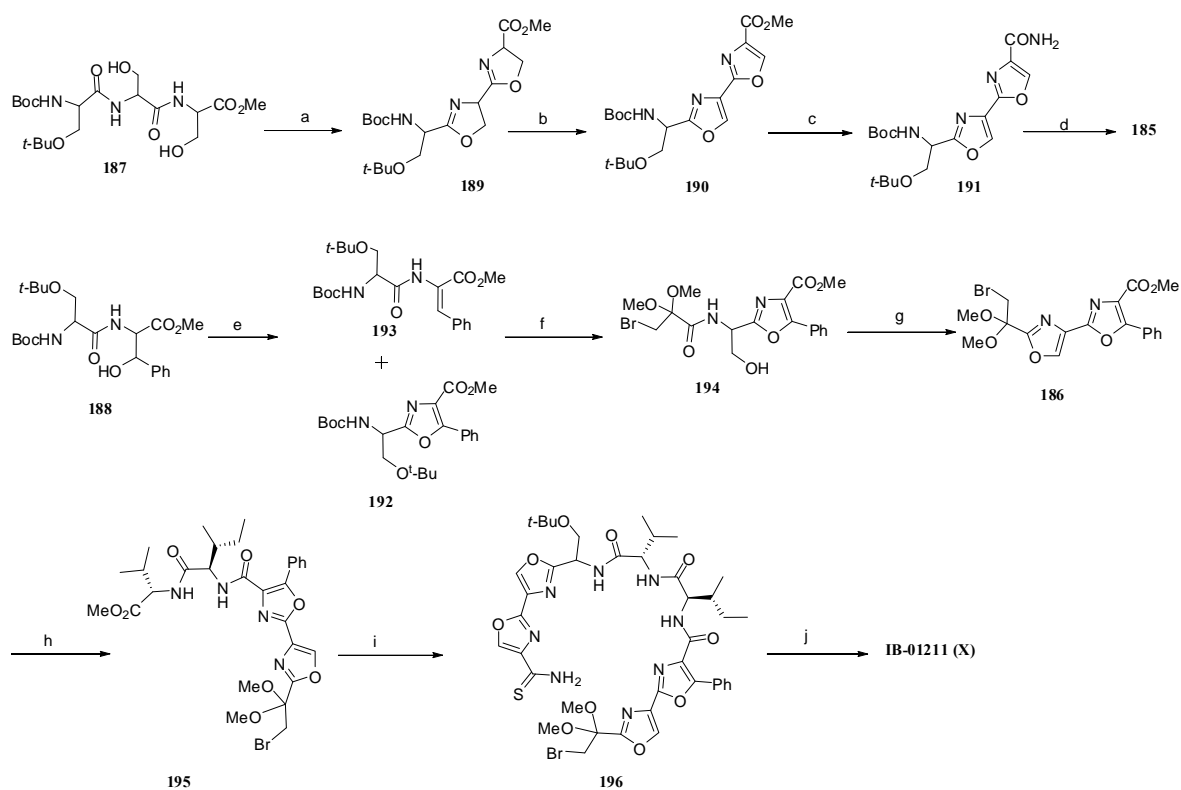


Figure 3. Chemical structure of IB-01211 (**X**) and synthons for its preparation

They prepared the precursor of **185** from peptide **184** and **187** while the precursor of **186** was prepared from peptide **188**, in excellent yields from the appropriate amino acids with EDC.HCl, HOBT in the presence of diisopropylethylamine (DIEA) as coupling reagent. In their method, the bisoxazoline **185** was prepared from tri-Ser peptide **187** by simultaneous construction of the two oxazole rings, using cyclization-oxidation procedure followed by final transformation of the methyl ester into the thioamide. Hydroxyl group was activated using diethylamino sulphur trifluoride (DAST) at low temperature followed by cyclization with K₂CO₃ provided bisoxazoline **189**. Upon oxidation with 1,8-azabicyclo [5.4.0]-undec-7-ene (DBU)-CCl₄ in a mixture of CH₃CN and pyridine afforded the bis oxazole **190**, which on reacting with NH₄OH and then treating the resulting amide **191** with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) provided **185** in 73% yield in two steps.

The cyclization-oxidation of **188** using DAST-pyr and DBU-CCl₄ gave oxazole **192** which upon deprotection of the hydroxyl and amino groups with TFA and formation of the amide bond with the bromopyruvic acid dimethyl acetal using EDC.HCl/HOBt in CH₂Cl₂ afforded **194**. Further reaction with DAST then K₂CO₃ followed by DBU-CCl₄ pyridine gave bis-oxazole **186**. Compound **195** was prepared by hydrolysis of **186** with LiOH followed by condensation with *N*-deprotected **184** using EDC.HCl/HOBt/DIEA as an activating reagent. Bis-oxazole was introduced followed by selective *N*-deprotection of **185** with 25% TFA and reaction of **195** in the same condition as before afforded the peptide heterocyclic **13** (**Scheme 26**). The compound **196** was deprotected with formic acid giving peptide-heterocyclic with the free hydroxyl and carbonyl group precursors of the exocyclic double bond and thiazole ring, respectively. The resulting compound upon treatment with NaHCO₃ followed by addition of TFAA and 2,6-lutidine afforded IB-01211(**X**) in 11% yield [83].



Scheme 26. Total synthesis of IB-01211 (X). Reagent and conditions: a) DAST, CH₂Cl₂, -78 °C then K₂CO₃, -78 °C to rt; b) DBU-CCl₄, MeCN, Pyridine, -30 °C to rt, 57% (2 steps); c) NH₄OH, MeOH, ultrasound, rt; d) 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane (Lawesson's reagent), THF, 70 °C; e) 1. DAST, THF, -78 °C, then pyridine, -78 °C to rt, 2. DBU-CCl₄, MeCN, pyridine, -30 °C to rt; f) 1. 95% TFA, 2. BrCH₂C(OMe)₂CO₂H, EDC.HCl, HOBt, DIEA dry CH₂Cl₂, 0 °C to rt; g) 1. DAST, CH₂Cl₂, -78 °C then K₂CO₃, -78 °C to rt 2. DBU-CCl₄, MeCN, pyridine, -30 °C to rt (50%); h) 1. LiOH, THF, H₂O, MeOH, 2. *N*-deprotected- Boc-D-allo-Ile-L-Val-OMe, EDC.HCl, HOBt, DIEA, dry CH₂Cl₂, 0 °C to rt (92%); i) 1. LiOH, THF, H₂O, MeOH, 2. *N*-protected-2'-(2-*tert*-Butoxy-1-*tert*-butoxycarbonylaminoethyl)-[2,4']bis-oxazolyl-4-carboxythyamide, EDC. HCl, HOBt, DIEA, dry CH₂Cl₂, 0 °C to rt (94%); j) 1. HCO₂H, reflux, 2. NaHCO₃, CH₂Cl₂, rt then TFAA, 2,6-lutidine 0 °C to rt. (11%).

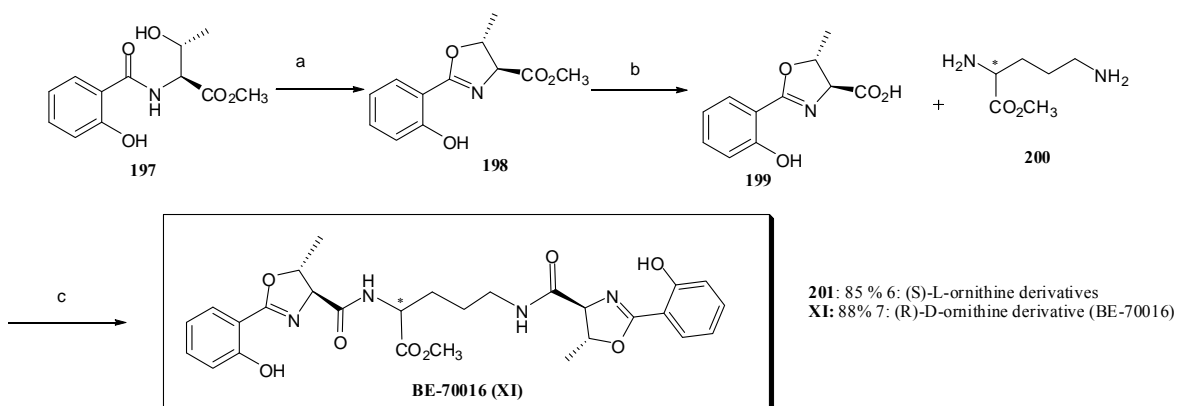
3. Oxazoline

Since the late 1980s, many oxazoline-containing natural products have been isolated from marine organisms [84]. The biosynthesis of these oxazolines appears to involve the dehydrative cyclization of serine and threonine residues [84c]. Among these oxazoline-containing natural compounds, 2-(*o*-hydroxyphenyl)oxazoline structures are often found. For example, BE-70016 is

an antitumour substance that was isolated from *Actinoplanes sp* [85]. This compound appears to be useful in the control of human and mouse tumours.

3.1 BE-70016 (XI)

The first total synthesis of the antitumour substance BE-70016 (**XI**) was achieved by Akira Sakakura, et al, 2008 [86] using the catalytic dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine derivative (**197**) as a key reaction. 2-(*o*-hydroxyphenyl)oxazoline containing BE-70016 was isolated from marine sponge *Actinoplanes sp*. In the presence of (NH₄)₂MoO₄ (10 mol%) and C₆F₅CO₂H (10 mol%), a solution of **197** was heated under azeotropic reflux conditions with the removal of water for 12h. After aqueous work-up (washing with a 1M aqueous solution of citric acid), oxazoline **198** was obtained in 76% yield. Hydrolysis of **198** with lithium hydroxide gave carboxylic acid **199** in quantitative yield. The condensation of ornithine methyl esters **200** was conducted with **199** (3.0 mol equivs.) using WSCI-HCl (3.0 mol equivs.) and HOBt (2.0 mol equivs.) in CH₂Cl₂, to give (*S*)-L-ornithine derivative **201** and (*R*)-D-ornithine derivative (**XI**) in respective yields of 85 and 88% (**Scheme 27**).



Scheme 27. Preparation of BE-70016 (XI). Reagents and conditions: (a) (NH₄)₂MoO₄ (10 mol%), C₆F₅CO₂H (10 mole %, toluene-DMF (9:1 v/v), azeotropic reflux 12 hr; (b) LiOH, MeOH-H₂O (1:1 v/v), 0 °C, 2.5 h, 99%; (c) WSCLHCl, HOBt, Et₃N, CH₂Cl₂, 6 °C, 15h; **6**: 85%, **7**: 88%

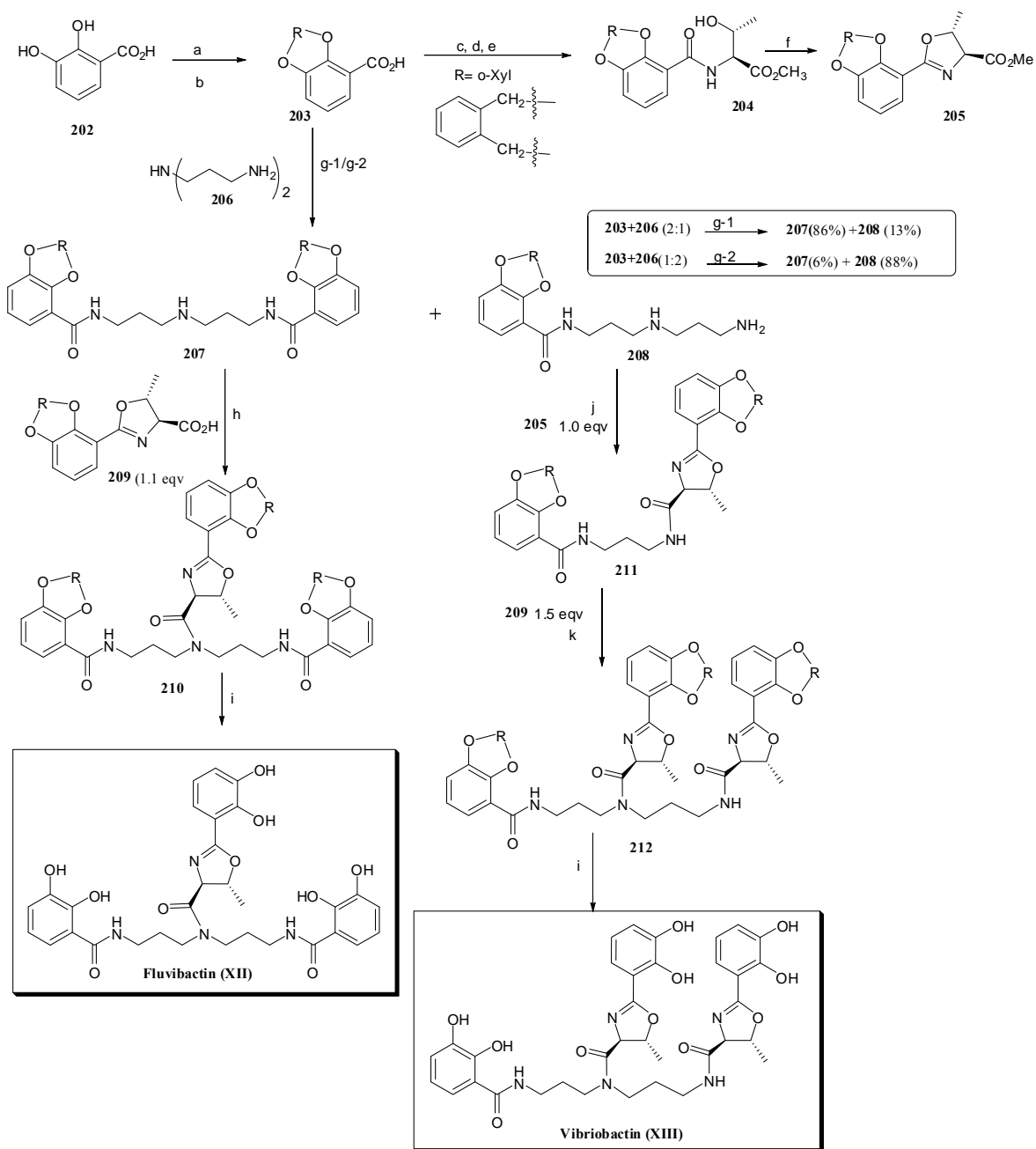
3.2 Fluvibactin (XII) and vibriobactin (XIII)

Fluvibactin (**XII**) [85] and vibriobactin (**XIII**) [87] are representative catechol siderophores that have been isolated from low-iron cultures of *Vibrio fluvialis* and *Vibrio cholerae*, respectively. These compounds consist of a norspermidine backbone with 2-(*o,m*-dihydroxyphenyl)oxazoline-4-carboxylate and 2,3-dihydroxybenzoate moieties. They serve as Fe(III) ion-specific chelators and facilitate Fe(III) ion uptake [88]. The first total syntheses of (**XII**) [89] and (**XIII**) [90] were reported by Bergeron et al. [91]. According to their reports, synthesis of the 2-(*o,m*-dihydroxyphenyl)oxazoline structure is one of the most problematic steps. However, the yields of the products were moderate (65% of **XII** and 58% of **XIII**).

Akira Sakakura and coworkers [92] reported efficient total syntheses of (**XII**) and (**XIII**), construction of the 2-(*o,m*-dihydroxyphenyl)oxazoline moiety at an early stage. They reported that molybdenum (VI) oxides were highly effective dehydrative cyclization catalysts for the synthesis of oxazolines and thiazolines. Compound **204** was prepared from commercially available 2,3-dihydroxybenzoic acid **202** by a five-step transformation *via* compound **203** (72% overall yield). The synthesis involved conversion of 2-(*o,m*-dialkoxyphenyl)oxazoline **205** at an early stage from *N*-(*o,m*-dialkoxybenzoyl)-L-threonine **204** *via* the Mo(VI)=O-catalyzed method. Further investigation of the protecting groups for the hydroxyl groups of the catechol moiety revealed that compound **204** protected by a cyclic *o*-xylylene group (*o*-Xyl) showed excellent reactivity. When the reaction of **204** was conducted with 10 mol% of (NH₄)₂MoO₄, oxazoline **205** was obtained in 96% yield. When the reaction of a 2 : 1 mixture of **203** and norspermidine **206** was conducted in the presence of Sb(OEt)₃ (1.0 equiv) under solvent-free conditions at 80 °C, the desired diamide **207** was obtained in 86% yield along with monoamide **208** (13%). To synthesis fluvibactin, the dehydrative condensation of **207** which was obtained in 86% with carboxylic acid **209** was prepared from **205** in 97% yield [CsOH (2 equiv), acetone–MeOH–H₂O (2:1:1 v/v/v), 0 °C, 1 h]. It showed that the intensive examination of dehydrative condensation of **207** with **209**, we found that WSCI.HCl and HOAt (1.5 equiv) showed high activity for the condensation of **207** with **209** (1.1 equiv) and gave the desired triamide **210** in 98% yield. Finally, the three *o*-xylylene groups in **210** were easily removed by hydrogenolysis using 10% Pd/C to give fluvibactin (**XII**) in 99% yield.

Vibriobactin (**XIII**) was synthesized from **208**, **205** and **209** *via* a strategy similar to that for fluvibactin (**XII**) (**Scheme 28**). Selective monoamide formation between **206** and **203** was performed using Sb(OEt)₃. When the reaction of a 1 : 2 mixture of **206** and **203** was conducted in the presence of Sb(OEt)₃ (1.0 equiv) under solvent-free conditions at 80 °C, monoamide **208** was obtained in 88% yield along with diamide **207** (6%). Monoamide **208** was then subjected to the second ester-amide

transformation with an equimolar amount of **205** using $\text{Sb}(\text{OEt})_3$ (1.0 equiv), and gave diamide **211** in 90% yield. As in the case of fluvibactin, condensation of **211** with **209** (1.5 equiv) using WSCI.HCl and HOAt (1.5 equiv) successfully gave triamide **212** in 82% yield. The final removal of the *o*-xylylene groups in **212** gave vibriobactin (**XIII**) in 99% yield.

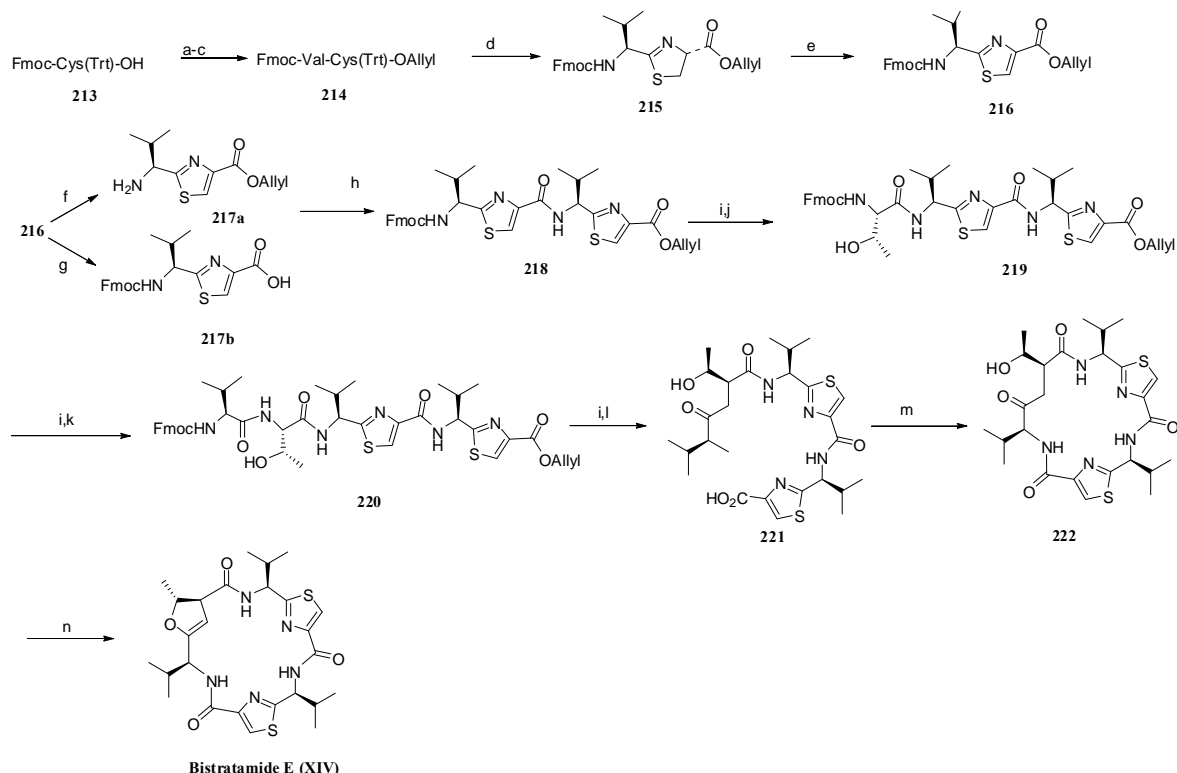


Scheme 28. Total synthesis of Fluvibactin (XII) and Vibriobactin (XIII). Reagents and conditions: (a) H_2SO_4 , MeOH, Reflux 5h; (b) *o*-(BrCH_2) $_2\text{C}_6\text{H}_4$, K_2CO_3 , DMF, 120 °C, 8h, 77% (2 steps); (c) NaOH, acetone-MeOH- H_2O , 50 °C, 1h; (d) SOCl_2 , DMF, CHCl_3 reflux, 1h; (e) H-L-Thr-OMe, DMAP (10 mol %) Et_3N (2 eqv), CH_2Cl_2 , 0 °C to rt, 2h, 93% (3 steps); (f) $\text{Mo}(\text{VI})=\text{O}$ cat., toluene, 5h, azeotropic reflux, 96%; (g-1) 7+5 (2:1); $\text{Sb}(\text{OEt})_3$, 1 eqv, solvent free, 80 °C, 3h; (g-2) $\text{Sb}(\text{OEt})_3$ 1 eqv, solvent free, 80 °C, 3h; (h) WSCI.HCl (1.5eqv), HPAt (1.5 eqv), THF-DMF, rt, 12h, 98%; (i) H_2 , 10% Pd-C, EtOH, 60 °C, 2h, 99%; (j) $\text{Sb}(\text{OEt})_3$ 1.0eqv, no solvent, 80 °C, 5h, 90%; (k) WSCI.HCl (1.5 eqv), Et_3N (1.5 eqv), THF-DMF, rt, 12h, 82%

3.3 Bistratamide E (XIV)

Bistratamides A-D and K are bioactive cyclic polyether isolated from *Lissoclinum bistratum*. Recently, bistratamide E a thiazole-oxazoline and bistratamide J a bis-thiazole containing peptide-derived macrocycles were isolated from the same source *Lissoclinum bistratum* and they were found to be exhibited cytotoxic activity against a human colon tumor cell line [93]. Bistratamides A-D lack oxazoline ring and their total synthesis have been reported by several groups [94]. Kelly *et. al.* described the total synthesis of Bistratamide E and J using common starting material and similar strategy. We discussed here only the total synthesis bistratamide E which contain an oxazoline ring.

They have prepared the required starting material **218** with allyl and Fmoc protecting group on the C- and N- terminal starting with protecting carboxylic acid in two steps (**Scheme 29**). Deprotection of Fmoc allowed the resulting amine coupled with ester of *N*-Fmoc-*L*-valine affording the fully protected dipeptide in three steps (84%). Conversion of triethyl protected cysteine residue in **214** to a thiazoline **215** was achieved by utilizing Bis(triphenyl)oxodiphosphonium trifluoromethane sulfonate. Thiazoline **215** was subsequently oxidized to thiazole **216** using activated manganese oxide. The carboxylic acid compound **217b** was obtained from **216** by removing the allyl protecting group of **216** using a solid phase palladium catalyst generated from Pd(OAc)₂ and polymer supported triphenylphosphine in the presence of phenylsilane [95]. While the amine donor compound **217a** was obtained by removing the protecting group Fmoc of **216** using diethylamine. Coupling of **217a** and **217b** employing HBTU, HOBt and DIEA afforded tetrapeptide-derived bisheterocycle **218** in 91% yield. Subsequently, deprotection and coupling of **218** to *N*-Fmoc-*O*-*allo*-threonine afforded **219** which on further deprotection and coupling with *N*-Fmoc-*L*-valine afforded **220**. Removal of the Fmoc and allyl protecting group of **220** using DEA and solid phase palladium catalyst provided macrocyclic precursor **221** in quantitative yield. Cyclodehydration of **221** to **222** was achieved in 81% yield by adding **221** into a solution of PyBOP and DMAP over a period of 16 h with syringe pump. Finally, the Val-Thr substructure was converted to an oxazoline using Burgess reagent [(methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt] in THF provided the natural product bistratamide E (**XIV**) in 63% yield.



Scheme 29. Total synthesis of bistratamide E. Reagents and reaction conditions: a) HOBt, HBTU, DIEA, allyl alcohol, DMF; b) DEA, CH₃CN; c) HOBt, HBTU, DIEA, *N*-Fmoc-L-valine, DMF, 84%; d) Ph₃PO, Tf₂O, CH₂Cl₂, -20 °C, 89%; e) activated MnO₂, CH₂Cl₂, 94%; f) DEA, CH₃CN; g) Pd(OAc)₂, PS-triphenylphosphine, PhSiH₃, CH₂Cl₂; h) HOBt, HBTU, DIEA, DMF, 91%; i) DEA, CH₃CN; j) HOBt, HBTU, DIEA, *N*-Fmoc-*allo*-threonine, DMF, 95%; k) HOBt, HBTU, DIEA, *N*-Fmoc-L-valine, DMF, 86%; l) Pd(OAc)₂, PS-triphenylphosphine, PhSiH₃, CH₂Cl₂; m) PyBOP, DMAP, CH₂Cl₂, DMF, 81%; n) Burgess reagent, THF, reflux, 63%.

4. Isoxazoline alkaloids: Bromotyrosine alkaloids

Marine sponges, especially belonging to the order Verongidae, are a rich source of highly oxidative secondary metabolites derived from bromotyrosine. These widespread spiroisoxazoline natural products can easily be distinguished by three major structure categories in which the brominated spiroisoxazoline core contains a cyclohexadiene, a bromo epoxy ketone, or a bromohydrin moiety (**Figure 4**). The structural diversity arising from the unique spiro linkage between a brominated cyclohexadiene, an isoxazoline, and a wide range of amine and diamine linkages brings about a broad spectrum of pharmacological activities including antiviral [96], antimicrobial [97], anti-HIV [98], antifungal [99], antifouling [100], Na⁺/K⁺ ATPase inhibition [101], histone deacetylase (HDAC) inhibition [102], histamine H3 antagonism [103], mycothiol *S*-conjugate amidase inhibition [104], isoprenylcysteine carboxy methyltransferase (Icmt) inhibition, [105] and antineoplastic properties [106]. It is very clear that constructing the unique and synthetically challenging spiro

skeleton has been of great interest to many chemists. Continuous efforts have been made to construct spiroisoxazoline skeleton, some of which are represented below.

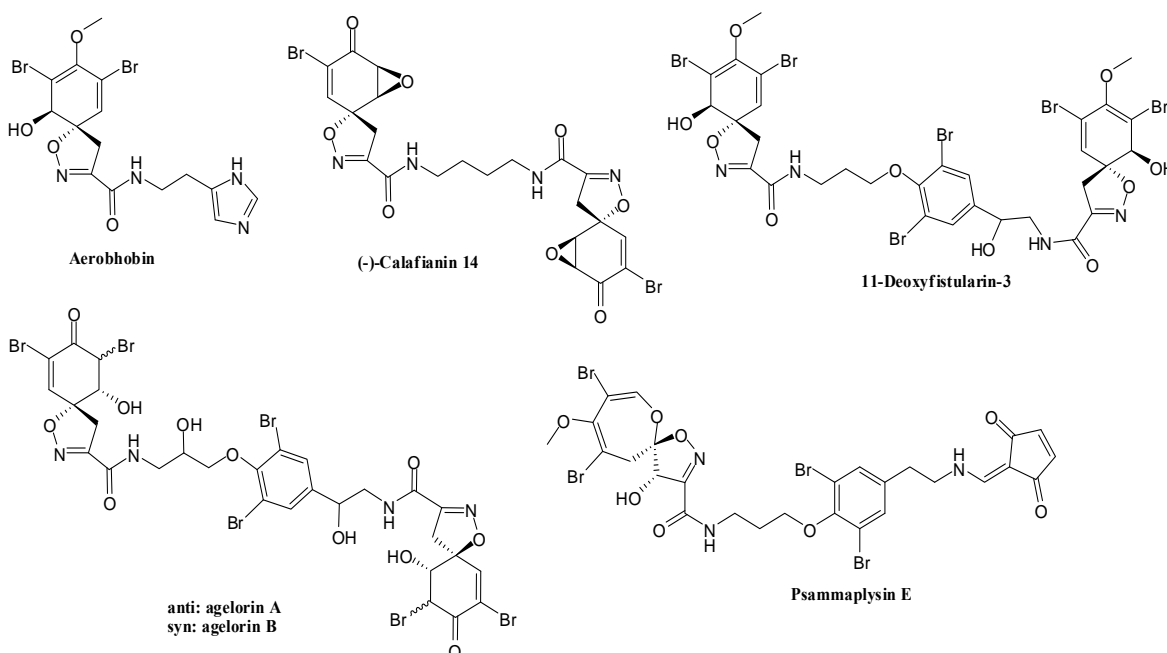
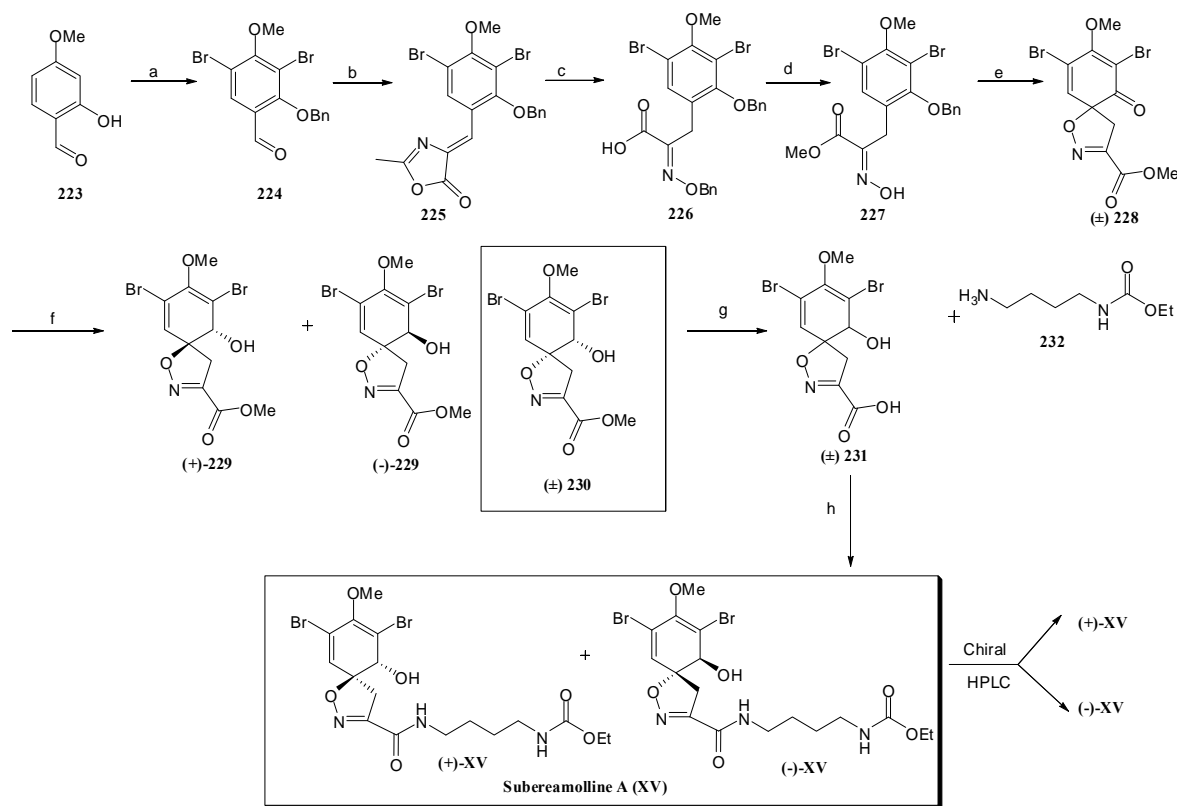


Figure 4: Structures of marine natural products containing spiroisoxazoline moiety

4.1 Subreamolline A (XV)

A bioactive dibrominated metabolite, (+)-subreamolline A (**XV**) has been reported from the sponge *Suberea mollis*. It potently inhibits the migration and invasion of metastatic human breast cancer cells i.e. MDA-MB-231 at the nanomolar dose level [107]. Shearman et al. reported the first total synthesis of (+)-subreamolline A (**XV**) and (-)-subreamolline A (**XV**) by using preparative chiral HPLC separation of the corresponding racemates [108]. In this approach, 2-hydroxy-4-methoxybenzaldehyde **223** reacted with *N*-bromosuccinimide (NBS) followed by benzyl protection of the phenolic oxygen to obtain aldehyde **224** in 92% yield. It was further converted into the azlactone **225** by treating **224** with *N*-acetylglycine and sodium acetate in the presence of acetic anhydride. Further saponification with barium hydroxide and condensation with *O*-benzylhydroxylamine yielded carboxylic acid **226** with 49% yield along with an oxime (22% yield) as a side product. The treatment of **226** with trimethylsilyldiazomethane gave corresponding methyl ester which on subsequent hydrogenolysis over palladium black gave oxime methyl ester **227** as a cyclization precursor. Oxidative cyclization of **227** with iodobenzene diacetate using acetonitrile as a solvent gave (\pm)-**228** which underwent diastereoselective reduction with $\text{Zn}(\text{BH}_4)_2$ to produce *trans* isomer (\pm)-**229** as the major product along with *cis* isomer (\pm)-**230** as the minor one. Alkaline hydrolysis of methyl ester (\pm)-**230** with lithium hydroxide gave spiroacid (\pm)-**231** in an overall yield

of 11% starting from aldehyde **223**. The coupling of spiroacid (\pm)-**231** with amine **232** in the presence of DCC and HOBT afforded (\pm)-(**XV**) with 91% yield. However, improved yield (96%) of (\pm)-(**XV**) was obtained by using propylphosphonic anhydride as a coupling agent. The resolution of (\pm)-subereamolline A (**XV**) was carried out by using preparative chiral HPLC which gave (+)-**XV** having absolute configuration *R* and *S* at C-1 and C-6 chiral centre, respectively and (-)-**XV**, having *S* and *R* configuration at C-1 and C-6 chiral centre, respectively (**Scheme 30**).

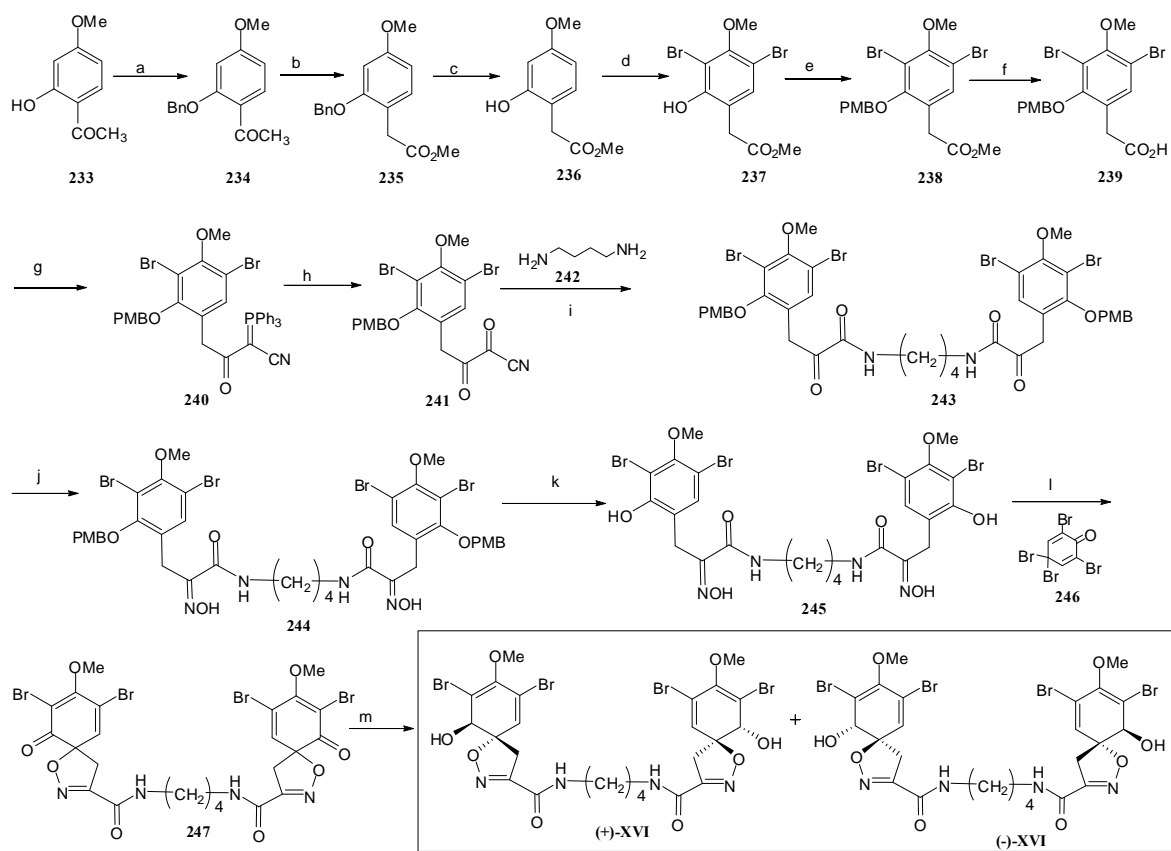


Scheme 30. Reagents and conditions: (a) (i) NBS/DMF, 0 °C, 50 min, (ii) BnCl, NaI, K₂CO₃/DMF, rt, 13h; (b) *N*-acetylglycine, NaOAc, Ac₂O, 120 °C, 6h; (c) (i) Ba(OH)₂·8H₂O, 1,4-dioxane/H₂O (1:1), 60 °C, 1h, (ii) *O*-benzylhydroxylamine; (d) (i) TMSCHN₂, PhMe/MeOH (3:1), 0 °C, 1h, (ii) Pd-Black, H₂, dioxane/AcOH, rt., 3h; (e) PhI(OAc)₂, MeCN, 0 °C, 1h; (f) Zn(BH₄)₂, CH₂Cl₂, rt; (g) LiOH, H₂O, MeOH/H₂O (3:1), rt, 1h; (h) DCC, HOBT, *i*Pr₂EtN, CH₂Cl₂, rt, 0 °C, 2h

4.2 Aerothionin (XVI)

(+)-Aerothionin (**XVI**), a tetra bromo compound having spirohexadienylisoxazoline pharmacore was isolated from the marine sponges, *Aplysina aerophoba* and *Verongia thiona* [109]. It was found that (+)-*trans-trans* aerothionin (*trans*-vicinal relationship between hydroxyl group and oxygen atom in the spiroisoxazoline unit) having *S*-configuration at both spirocentres exhibited moderate cytotoxicity with EC₅₀ value 42 μM against the benchmark HeLa cell line [110]. Several efforts have been made to synthesis aerothionin (**XVI**) which have been represented here.

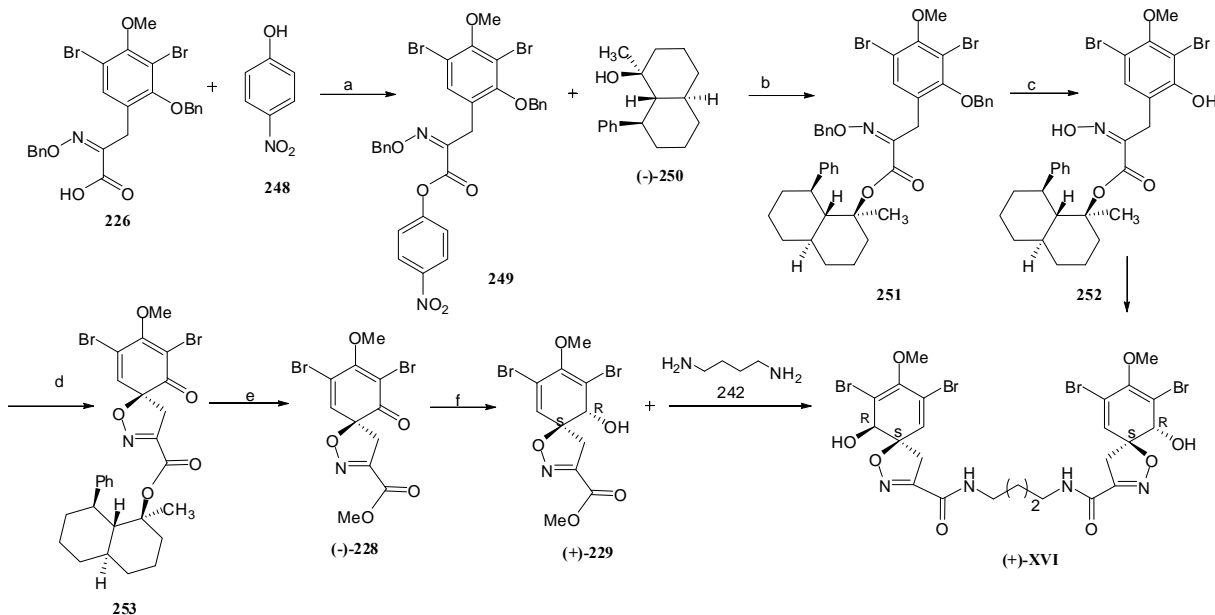
a) The synthesis of (\pm)-*trans-trans* arothionins using the cyano ylide coupling methodology has been reported by Wasserman et al. (**Scheme 31**) [111]. In this approach, protection of phenolic hydroxyl was achieved by treating 2-hydroxy-4-methoxyacetophenone **233** with a mixture of benzyl bromide (BnBr), 18-crown-6 and K₂CO₃ using acetone as a solvent to obtain benzyl ether **234** (97% yield). The rearrangement of **234** in the presence of thallium nitrate trihydrate afforded methyl[2-(benzyloxy)-4-methoxyphenyl]acetate **235** in 76% yield which underwent deprotection on treatment with Pd/C catalyst under hydrogen atmosphere to furnish methyl-(2-hydroxy-4-methoxyphenyl)acetate **236**. Dibromo derivative **237** was formed in 90% yield by the treatment of compound **236** with bromine using pyridine. This on further reaction with *p*-methoxybenzyl chloride (PMBCl) in the presence of K₂CO₃, 18-crown-6 and tetra butyl ammonium iodide (TBAI) using acetone as a solvent gave methyl-[3,5-dibromo-2-(*p*-methoxybenzyloxy)-4-methoxyphenyl]acetate **238**. Hydrolysis of ester **238** to obtain **239** was readily achieved by treatment with sodium hydroxide in methanol. The coupling of compound **239** with (triphenylphosphoranylidene)acetonitrile using 1-ethyl-3-(3-dimethyl-aminopropyl) carbodimide (EDCI) afforded ylide **240** which was further transformed to diketonitrile **241** by reacting it with ozone in dichloromethane at a very low temperature. Bis- α -ketoamide **243** obtained by treating **241** with 1,4-diaminobutane **242** was further converted into bis-*E*-oxime **244** in 95% yield using hydroxylamine hydrochloride in the presence of sodium acetate. Deprotection of **244** with trifluoroacetic acid yielded substrate **245** which underwent intramolecular ring closure to form bis-spiro isoxazolidine **247** by the reaction of **245** with 2,4,4,6-tetrabromo-2,5-cyclohexadienone **246** in acetonitrile. The reduction of cyclohexadienone ketonic centres of **247** underwent in a stereospecific manner in order to generate both the hydroxyl groups particularly in *trans* relationship with respect to the corresponding spiroisoxazoline rings to form racemic mixture of (\pm)-*trans-trans* arothionins in 25% yield was achieved by using sodium cyanoborohydride in trifluoroacetic acid.



Scheme 31. Total synthesis of (±)-trans-trans aerothionins. Reagent and conditions: a) BnBr, K₂CO₃, 18-crown-6, acetone, reflux, 5h; (b) Ti(NO₃)₃·3H₂O, MeOH, Stir, rt, 18h; (c) H₂, Pd/C, MeOH, Stir, rt, 7h; (d) Br₂/Pyridine, stir, 0 °C - rt, 1h; (e) PMBCl, K₂CO₃, 18-crown-6, (*n*Bu)₄NI, acetone, reflux, 3h; (f) 2N NaOH, MeOH, stir, rt, 1.5h; (g) Ph₃P=CHCN, EDCI, CH₂Cl₂, Stir, rt, 4h; (h) O₃/CH₂Cl₂, Stir, -78 °C, 5min; (i) CH₂Cl₂, Stir, -78 °C, 5 min, then stir, rt, 1h; (j) NH₂OH.HCl, NaOAc, EtOH/THF (1:2), heat, 50-60 °C; (k) TFA, CH₂Cl₂, stir; (l) CH₃CN, heat; (m) NaCNBH₃, TFA, Stir, 0 °C, 20 min

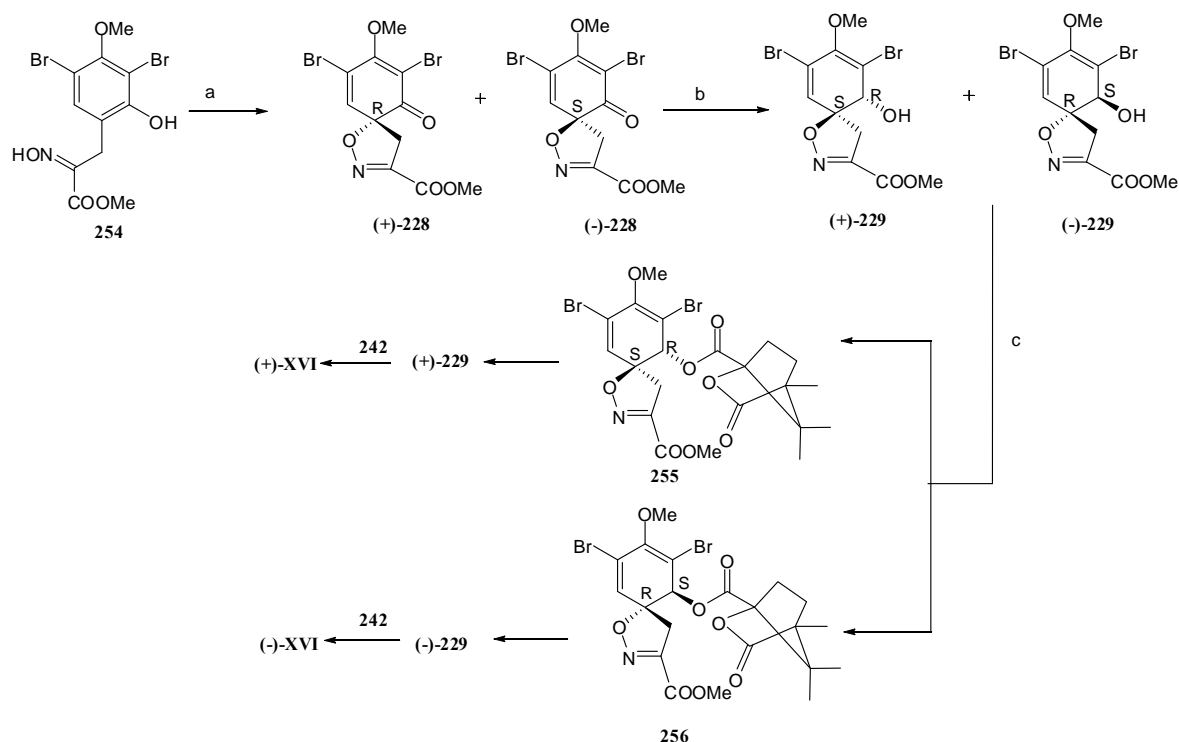
b) Asymmetric synthesis of (+)-aerothionin *via* the synthesis of enantiomerically enriched cyclohexadienone spiroisoxazoline (-)-**228** has been reported by Murakata et al. (**Scheme 32**) [112]. In this method, 2-[(benzyloxy)imino]-3-[2-(benzyloxy)-3,5-dibromo-4-methoxyphenyl]-propanoic acid **226** was treated with *p*-nitrophenol **248** in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) using a mixture of dichloromethane/methanol as solvent to produce *p*-nitrophenyl ester **249** in 91% yield. The transesterification of **249** with lithiated (-)-**250** as a chiral auxiliary gave 1-methyl-1-decyl ester **251** in 85% yield which underwent hydrogenolysis in the presence of palladium catalyst using a mixture of acetic acid-dioxane (1:1) solvent system to produce *o*-phenolic oxime ester **252** in 91% yield. The compound **252** so obtained was further reacted with iodobenzene (PhIO) in the presence of camphor-sulfonic acid (CSA) using dichloromethane to obtain spiroisoxazoline **253** in 83% yield. Chiral auxiliary was easily removed by treating **253** with trifluoroacetic acid at room

temperature for 1 h followed by the formation of methyl ester (-)-**228** in 71% yield with 74% enantiomeric excess by the use of combination of *N,N'*-Dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in the mixture of methanol and dichloromethane. The reduction of (-)-**228** with $\text{Zn}(\text{BH}_4)_2$ in ether furnished cyclohexadienylisoxazoline (+)-**229**, which on amidation with butanediamine **242** afforded (+)-**XVI** with *S*-configuration at both the spirocentres [113]



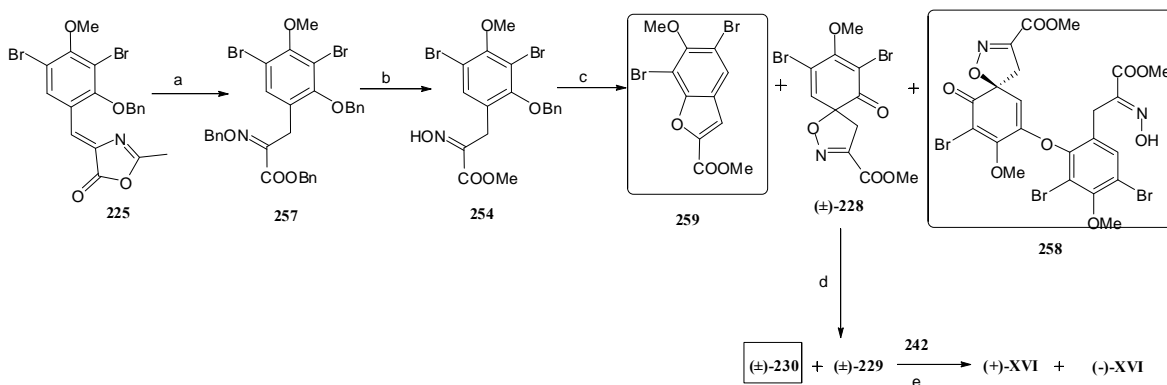
Scheme 32. Asymmetric synthesis of (+)-aerothionin. Reagents and conditions: (a) DCC/ CH_2Cl_2 , stir, 0°C -rt, 30 min-4h; (b) MeLi, HMPA, toluene, 0°C ; (c) H_2 /Pd black, AcOH/dioxane, rt, 7h; (d) PhIO, CSA, CH_2Cl_2 , -78°C ; (e) (i)TFA/ CH_2Cl_2 , stir, 0°C -rt, 1h, (ii) CH_2Cl_2 , MeOH, DCC, DMAP; (f) $\text{Zn}(\text{BH}_4)_2$ /ether, Yamamura's method

c) Ogamino *et al.* reported a highly efficient synthesis of optically pure (+)-**XVI** and (-)-**XVI** from the racemic spiroisoxazoline derivative (\pm)-**229** [114]. In this approach, synthesis of compound (\pm)-**229** was efficiently achieved by electrochemical oxidation of **254** using constant potential electrolysis (CPE) to produce (\pm)-**228** followed by its reduction with $\text{Zn}(\text{BH}_4)_2$ [115]. The treatment of (\pm)-**229** with (-)-camphanic chloride resulted in the formation of camphanic acid esters **255** and **256** as two diastereomers in 46% and 47% yield, respectively which were easily separated by silica gel chromatography. The solvolysis of **255** and **256** using K_2CO_3 as a base furnished optically active spiroisoxazoline (+)-**229** and (-)-**229**, respectively. Finally, condensation of (+)-**229** and (-)-**229** with 1,4-diaminobutane produced optically pure (+)-**XVI** and (-)-**XVI** in 28% and 33% yield, respectively (**Scheme 33**).



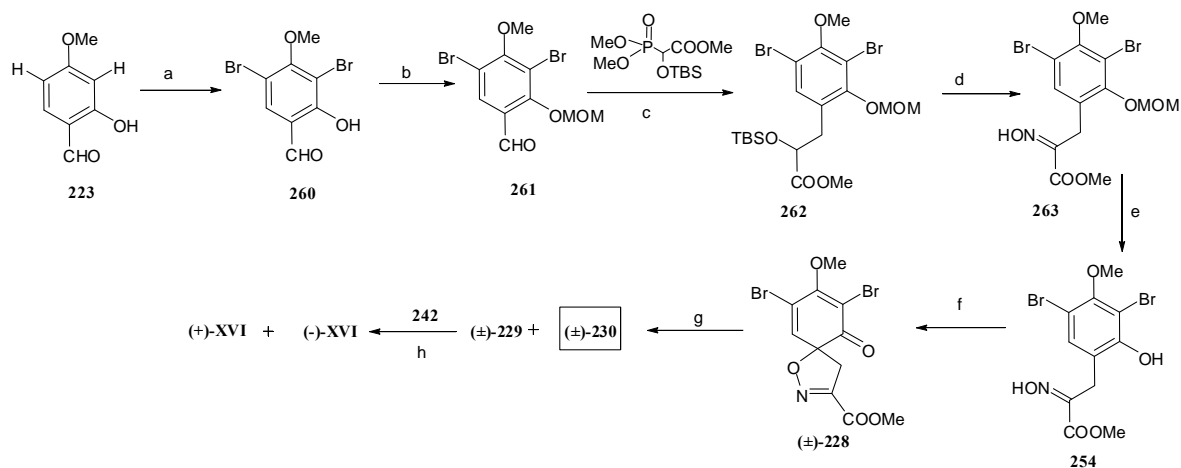
Scheme 33. Total synthesis of optically pure aerothionins. Reagents and conditions: (a) CPE, $n\text{Bu}_4\text{NClO}_4$, MeCN; (b) $\text{Zn}(\text{BH}_4)_2$; (c) (-)-Camphanic chloride

d) Another approach for the synthesis of (\pm)-*trans-trans* aerothionins (**XVI**) via phenolic oxidation of methyl pyruvate **254** with thallium (III) trifluoroacetate as a key step has been reported by Yamamura *et al.* [116]. Alkaline hydrolysis of azalactone **225** with KOH in a mixture of dioxane-water followed by the oximation with hydroxylamine hydrochloride and benzylation using potassium carbonate (K_2CO_3) in *N,N*-dimethylformamide (DMF) afforded tribenzyl derivative **257** in 31% yield. Transesterification of **257** in methanol containing K_2CO_3 base furnished the corresponding methyl ester which further on hydrogenolysis in the presence of catalytic palladium-carbon (10%) using a mixture of dioxane-acetic acid gave the desired dihydroxy derivative **254** in moderate yield. The compound so obtained was further oxidized by thallium (III) trifluoroacetate in TFA to afford compounds **258**, (\pm)-**228** and **259** in 21, 27 and 3% yield, respectively. The reduction of racemate (\pm)-**228** by excess of $\text{Zn}(\text{BH}_4)_2$ in a mixture of chloroform and ether yielded a mixture of (\pm)-**229** *trans-trans* and (\pm)-**230** *cis-cis* products in ratio (1.3:1) with 70% yield. Finally, amidation of (\pm)-**229** with 1,4-butanediamine **242** furnished (\pm)-*trans-trans* aerothionins (**XVI**) in 18% yield (**Scheme 34**).



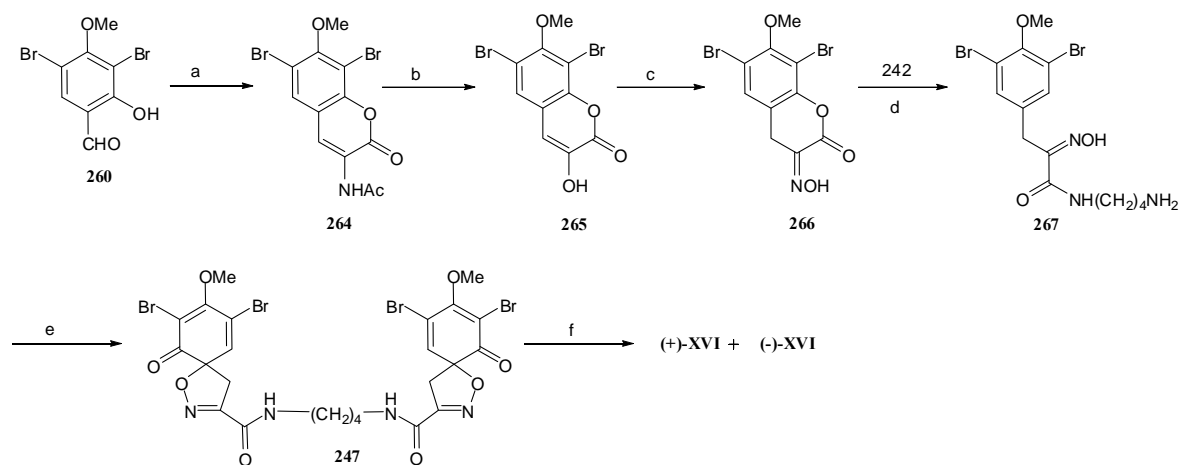
Scheme 34. Total synthesis of (±)-trans-trans aerotherionins. Reagents and conditions: (a) i) KOH/dioxane- H₂O, 100 °C, 9h (ii) NH₂OH.HCl, rt, overnight, (iii) BnCl, K₂CO₃/DMF, rt, overnight; (b) (i) K₂CO₃/dioxane-MeOH, rt, 40 min; (ii) H₂/Pd/C, dioxane-AcOH, rt, overnight (c) Ti(CF₃COO)₃/TFA, rt, 4h; (d) Zn(BH₄)₂, excess; (e) rt, overnight

e) An efficient method for the synthesis of (±)-*trans-trans* aerotherionins (**XVI**) by adopting a new route for oxidative spirocyclization of phenolic oxime ester has been developed by Boehlow *et al.* [117]. The bromination of 2-hydroxy-4-methoxybenzaldehyde **223** with NBS in DMF resulted in the formation of dibromoaldehyde **260** in 97% yield. The compound **260** so obtained was further treated with methyl chloromethyl ether (MOMCl) in the presence of EtNi-Pr₂ using THF to afford the protected aldehyde **261** in 99% yield which on further reaction with 2-(*tert*-butyldimethylsilyloxy)-2-(dimethylphosphono)acetate using LDA and THF yielded silyl enol ether **262** in 92% yield. Deprotection of **262** by Et₃N.HF in methanol followed by immediate addition of hydroxylamine hydrochloride furnished oxime **263** in 90% yield. The treatment of **263** with catalytic amount of TsOH in methanol resulted in removal of MOM group to produce phenolic oxime **254** in 100% yield. The oxidative cyclization of oxime ether **254** using polymer-supported (diacetoxyiodo)benzene (PSDIB) reagent in acetonitrile afforded spiroisoxazoline (±)-**228** with high yield and purity. Spiroisoxazoline (±)-**228** so obtained was easily transformed into (±)-**XVI** by the same procedure as adopted by Yamamura *et al.* [116] (**Scheme 35**).



Scheme 35. Total synthesis of (±)-trans-trans aerothionins. Reagents and conditions: (a) NBS/DMF, 0 °C; (b) MOMCl, Et₃Ni-Pr₂/THF; (c) LDA/THF; (d) Et₃N.HF/MeOH, NH₂OH.HCl; (e) TsOH, MeOH; (f) PSDIB, MeCN, rt; (g) Zn(BH₄)₂ excess, CH₂Cl₂-Et₂O, rt, overnight

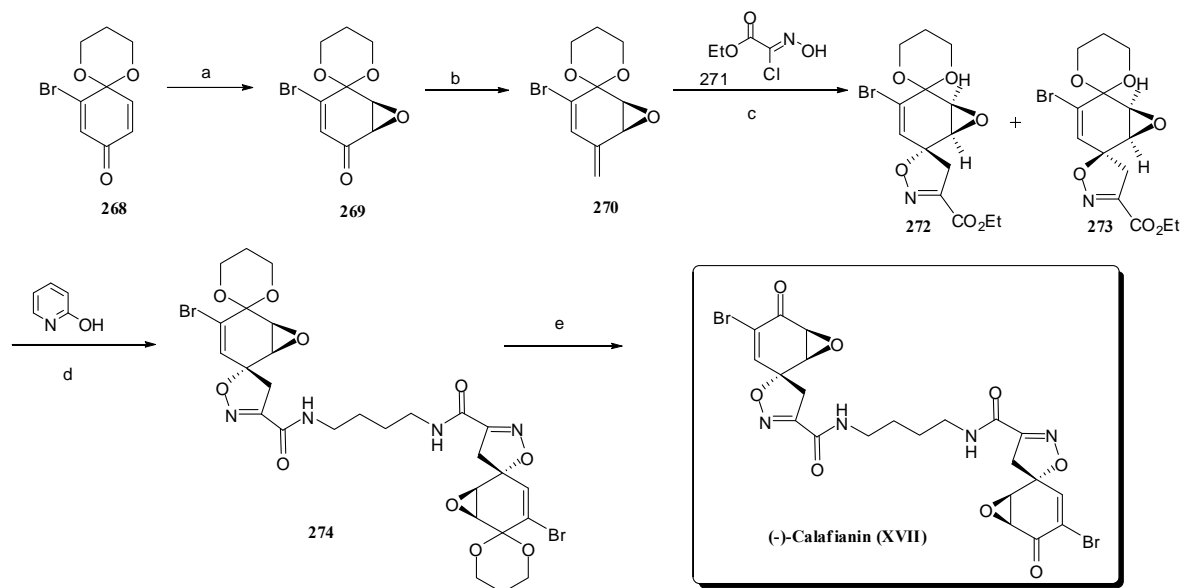
f) Harburn *et al.* have developed a novel synthetic approach to (±)-**XVI** through acylation of amine with coumarin as a key step [118]. In this method, dibromosalicylaldehyde **260** was treated with *N*-acetylglycine in the presence of sodium acetate using acetic anhydride to afford acetamido coumarin **264** in 53-90% yield. Hydrolysis of **264** with an ethanolic solution of sulfuric acid gave enol **265** in 90% yield which on reaction with 8.5 equivalent of hydroxylamine hydrochloride in 80% ethanol under reflux produced oximino coumarin **266** in 69% yield. The compound **266** was reacted with 1,4-butanediamine **242** using triethylamine as a base in methanol at 60 °C under reflux to afford amide **267** derivative in 68% yield. The treatment of **267** with PSDIB using acetonitrile resulted in the oxidative spirocyclization which led to the formation of aerothionin precursor **247** and further converted into (±)-**XVI** by the same procedure as adopted by Wasserman *et al.* [111] (**Scheme 36**).



Scheme 36. Reagents and conditions: a) AcNHCH₂COOH, AcONa/Ac₂O, reflux, overnight; b) H₂SO₄/EtOH, reflux, overnight; c) NH₂OH.HCl, EtOH/H₂O, reflux, 1-2hr; (d) Et₃N/MeOH, reflux; (e) PSDIB, MeCN, Stir, rt, 1h; (f) NaCNBH₃/TFA, stir, 0 °C, 20 min

4.3 (-)-calafianin (XVII)

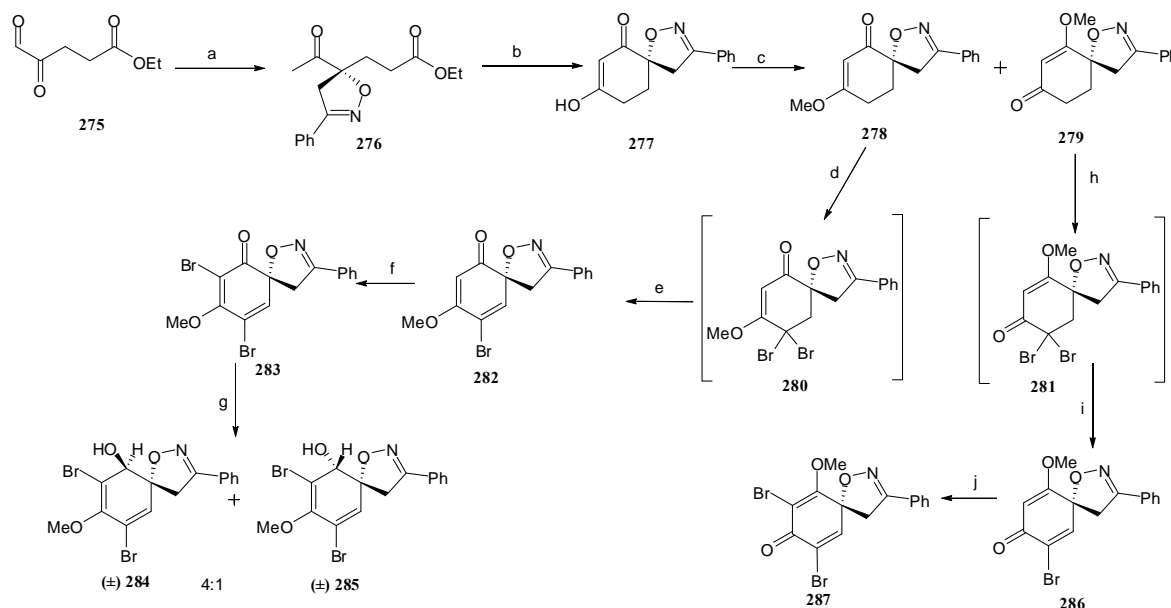
The synthesis of a (-)-calafianin (XVII) core precursor was initiated by enantioselective tartrate-mediated nucleophilic epoxidation of the readily available quinone monoketal **268** (Scheme 37) [119]. Methylenation of epoxy ketone **269** to prepare the exocyclic vinyl epoxide **270** was found by olefination employing *t*BuOK as base and CH₃PPh₃Br (THF, 0.03 M, -40 °C). Further, 1, 3-dipolar cycloaddition of vinyl epoxide **270** for spiroisoxazoline construction was explored. Dipolar cycloaddition using a nitrile oxide generated *in situ* from ethyl chloro oximinoacetate **271** and Zr(O-*t*Bu)₄ led to optimal conversion, affording a moderate to high yield (85-93%) of **272/273** (dr = 1.0:1.8) and minimal formation of the furoxan dimer. Key *NOE* enhancements were observed between diagnostic protons to enable assignment of the *syn* and *anti* spiroisoxazoline diastereomers. The synthesis of calafianin commenced with an extrapolation of the ester–amide exchange methodology. Gratifyingly, after extensive screening of metal additives, it was found that addition of Zn(OTf)₂ (20 mol %) in addition to Zr(IV)-2-hydroxypyridine afforded increased yields of acetal-protected calafianin **274**. Late stage acetal deprotection was performed by using 48% aqueous HF in a binary solvent mixture of CH₃CN and CH₂Cl₂ effecting clean hydrolysis of both cyclic ketals to afford (-)-calafianin (XVII) in high yield and purity with negligible hydrolysis and side reactions observed. Similar synthetic route was extended for the synthesis of natural (+)-calafianin and stereochemical determination.



Scheme 37. *Reagent and conditions:* (a) L-DIPT, NaHMDS (1M), TrOOH, toluene, -50 °C, 15 h, 80%, 95% ee; (b) CH₃PPh₃Br, *t*BuOK, THF, -40 °C, 95%; (c) Zr(O-*t*Bu)₄, Zn(OTf)₂, 1,4 diaminobutane, toluene; (d) Zr(O-*t*Bu)₄, toluene, rt; 85-93% of **272/273** (dr = 1.0:1.8); (e) 48% aq HF, CH₃CN/CH₂Cl₂, rt, 12h, 90%

Prasanta Das, 2014 approach for synthesis of spiroisoxazoline analogue core: In another approach Prasanta Das *et al.*, 2014 [120] (**Scheme 38**) were successful in accomplishing the synthesis of a core skeleton that is very similar to naturally available spiroisoxazolines, such as 11-deoxyfistularin-3 and also synthesized an isomeric spiroisoxazoline core in which the isoxazoline moiety and the carbonyl group are positioned in a fashion similar to that found in agelorin A and B.

In this synthesis, acyclic isoxazole derivative **276** [121] obtained from **275** was used as a key precursor for this model study. After treating **276** with sodium hydride, diketone spiroisoxazoline **277** was isolated in 80% yield. Further, the best reaction condition was determined by using TiCl_4 (5 mol-%) in methanol with triethylamine, to obtain both spiroisoxazolines **278** and **279** from **277** that was isolated in 97% yield in a 2.5:1 ratio in favor of spiroisoxazoline **278** after 15 min. On treatment of **278** with an excess amount (2.5 equiv.) of LHMDS and excess amount of bromine provided allylic geminal dibromo compound **280** through bromination. Crude allylic geminal dibromo compound **280** was further treated with 1,4-diazabicyclo[2.2.2]-octane (DABCO) *in situ* to afford **282** in 76% yield over two steps in one reaction vessel. Bromination of **282** adjacent to the carbonyl was achieved in 76% yield with NBS in the dark. Diastereoselective reduction of **283** with $\text{Zn}(\text{BH}_4)_2$ afforded desired spiroisoxazoline core structures (\pm)-**284** and (\pm)-**285** in a 4:1 diastereomeric ratio. Similarly, compound **279** on treating with excess amount of LHMDS and Br_2 provided desired monobromo derivative **286** in 78% yield. Further bromination of **286** by using PTB/ K_2CO_3 provided desired α -dibromo derivative **287** in 80% yield.



Scheme 38. Reagent and conditions: (a) Reference [119]; (b) NaH, toluene; (c) 5 mol-% $\text{TiCl}_4/\text{MeOH}/\text{Et}_3\text{N}$, reflux, 6 h (d) LHMDS, THF -78°C , then Br_2 ; (e) DABCO, reflux, 3h, 76% in 2 steps; (f) NBS, CH_2Cl_2 , dark, 24h, 76%, (g) $\text{Zn}(\text{BH}_4)_2$, CH_2Cl_2 , 80%; (h) LHMDS, THF -78°C , then Br_2 ; (i) DABCO, reflux, 3h, 78% in 2 steps; (j) PTB, K_2CO_3 , CH_2Cl_2 , 24h, 80%

Conclusion:

The present review focuses on the total synthesis of marine natural products (MNPs) containing oxazole, oxazoline and isoxazoline subunits. In addition, their isolation from the marine sources along with relevant biological activities is also provided. The synthetic strategies directed towards most biologically active 17 MNPs containing different azole units have been described. In the oxazole containing MNPs, the recent development in the total synthesis and the earlier attempts made by different chemists has been discussed. The total synthesis of MNPs containing oxazole section have been arranged according to the number of oxazole ring present *viz.*, monoxazoles, e.g. martefragin A, pseudopteroxazole and (+)-ileabethoxazole are described. Further, total synthesis of bisoxazoles (bengazoles, Phorboxazoles, (-)-hennoxazole A, diazonamide A; trisoxazole (ulapualide A) and tetraoxazoles, cyclopeptide (YM 216391, IB-01211) has been described in detail. Molinski's synthesis and Bull's stereoselective controlled synthesis of bengazole have been explained in detail. Synthesis of four oxazoline compounds, *viz.* BE-70016, fluvibactin, vibriobactin and bistratamide E has been provided. Among these, synthesis of BE-70016, fluvibactin and vibriobactin have used dehydrative cyclization by utilizing molybdenum (VI) oxide-catalyst as the key reaction. There are different approaches as far as synthesis of bromotyrosine is concerned. However here, we have detailed 7 different approaches used towards the synthesis of aerothionin. We believe that, the detailed synthetic explanations discussed in this review will provide a reader with a wealth of additional knowledge and might be of great interest to those working in branches of pharmaceutical, chemical and medical biosciences.

Appendix

List of abbreviations

AcOEt	Ethyl acetate
AcOC(CH ₃)(CH ₂)	Prop-1-en-2-yl-acetate
AsPh ₃	Triphenylarsine
Ac ₂ O	Acetic anhydride
AD MIX beta	Asymmetric dihydroxylation
AgTFA	Silver trifluoroacetate
BH ₃ .NH ₃	Ammonia borane
B(OH) ₃	Boric Acid
BPS-Cl	Bis(4-chlorophenyl) sulfide
<i>n</i> -Bu ₃ SnCl	Tributyltin chloride
Bu ₃ SnH	Tributyltin hydride
Bu ₂ BOTf	Trifluoromethanesulfonate
Ba(OH) ₂	Barium hydroxide
<i>n</i> BuLi	<i>n</i> -Butyl lithium
BnBr	Benzyl bromide
Br ₂	Bromine

<i>t</i> BuLi	<i>tert</i> -Butyllithium
(Boc) ₂ O	Di- <i>tert</i> -butyl-dicarbonate
(BDP)CuH	1,2-Bis(diphenylphosphino)benzenecopper Hydride
<i>t</i> BuOH	<i>tert</i> -Butyl alcohol
(<i>n</i> Bu) ₄ NI	Tetra butyl ammonium iodide
BF ₃ .OEt ₃	Boron trifluoride diethyl etherate
NBu ₄ NCIO ₄	<i>tetra-n</i> -butylammonium perchlorate
BrCCl ₃	Bromotrichloromethane
BnCl	Benzyl chloride
CH ₂ Cl ₂	Dichloromethane
CH ₃ PPh ₃ Br	Methyltriphenylphosphonium bromide
CeCl ₃	Cerium(III) chloride
CCl ₄	Carbon tetrachloride
Cs ₂ CO ₃	Caesium carbonate
CrCl ₂	Chromium(II) chloride
(COCl) ₂	Oxalyl chloride
CuBr	Copper bromide
CSA	Camphorsulfonic acid
DMAP	4-Dimethyl amino -pyridine
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DAST	Diethylaminosulfur trifluoride
DMBCl	3,4-Dimethoxybenzyl chloride
DMF	Dimethyl formamide
DME	1,2-dimethoxy-ethane
DMSO	dimethyl sulfoxide.
DABCO	1,4-Diazabicyclo[2.2.2]octane
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
DEDA	<i>N,N</i> -Diethylethylenediamine
DIBAL-H	Diisobutylaluminium hydride
DTBMP	2,6-Di- <i>tert</i> -butyl-4-methylpyridine
DIPEA	<i>N,N</i> -Diisopropylethylamine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEA	Diethylamine
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Et ₃ N	Triethyl amine
EtO ₂ CCl	Diethoxycarbonyl chloride
Et ₂ O	Diethyl ether
Et ₂ BOMe	Methoxydiethylborane
FeCl ₃ .6H ₂ O	Iron(III) chloride hexahydrate
HF	Hydrofluoric acid
H ₂ SO ₄	Sulphuric acid
HOBt	1-hydroxybenzotriazole
HMTA	Hexamethylenetetramine
HATU	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
HBTU	<i>N,N,N',N'</i> -Tetramethyl- <i>O</i> -(1H-benzotriazol-1-yl)uranium hexafluorophosphate

HCl	Hydrochloric acid
InCl ₃	Indium trichloride
IBX	2-iodoxybenzoic acid i
KMnO ₄	potassium permanganate
KN(TMS) ₂	Potassium bis(trimethylsilyl)amide
<i>t</i> BuOK	Potassium- <i>tert</i> -butoxide
K ₂ CO ₃	Potassium carbonate
K ₃ PO ₄	<i>Tripotassium phosphate</i>
KHMDS	Potassium hexamethyldisilazide
KH	Potassium hydride
KOH	Potassium hydroxide
LiOH	Lithium hydroxide
LDA	Lithium diisopropylamide
LiAlH ₄	Lithium Aluminium hydride
LiCl	Lithium chloride
LiI	Lithium iodide
LiBH ₄	Lithium borohydride
LHMDS	Lithium HexaMethylDiSilazide
L-DIPT	L(+)-DIISOPROPYL TARTRATE
MsCl	Mesyl chloride
MOMCl	Methyl chloromethyl ether
MeOH	Methanol
MeLi	Methyl lithium
MeI	Methyl iodide
MeOTf	Methyl trifluoromethanesulfonate
MnO ₂	Manganese dioxide
NaIO ₄	Sodium Periodate
NaClO	Sodium hypochlorite
NaClO ₂	Sodium chlorite
NaHMDS	Sodium Hexamethyldisilazane
NaBH ₄	Sodium borohydride
NaH	Sodium hydride
NaHCO ₃	Sodium bicarbonate
NaOH	Sodium hydroxide
NIS	N-Iodosuccinimide
NiO ₂	Nickel oxide
NCS	<i>N</i> -Chlorosuccinimide
NBS	<i>N</i> -Bromosuccinimide
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -Oxide
NaI	Sodium iodide
(NH ₄) ₂ MoO ₄	Ammonium Monomolybdate
NMM	<i>N</i> -methylmorpholine
NaCN.BH ₃	Sodium Cyanoborohydride
NaOAc	Sodium acetate
PPTS	Pyridinium- <i>p</i> -toluenesulfonate
PSDIB	polymer-supported (diacetoxyiodo)benzene
PTSA	<i>p</i> -Toluenesulfonic acid
PPh ₃	Triphenylphosphine
Pbu ₃	Tributylphosphine

Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium
PdCl ₂ (PPh ₃) ₂	Bis(triphenylphosphine)palladium(II) dichloride
Pd(Ph ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
Pd(DPPF)Cl ₂	1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) Dichloride
Ph ₃ PO	Triphenylphosphine oxide
PMHS	Polymethylhydrosiloxane
PhNTf ₂	N-Phenyl-bis(trifluoromethanesulfonimide)
Pd(OH) ₂	Palladium hydroxide
PhSiH	Phenylsilane
PhIO	Iodosylbenzene
PMBCl	4-methoxybenzyl chloride
SOCl ₂	Thionyl Chloride
SnCl ₄	stannic chloride
Sn(OTf) ₂	Tin(II) trifluoromethanesulfonate
Sb(OEt) ₃	<i>Tris</i> -ethoxyantimony
T ₃ OH	Toluene-4-sulfonic acid
TBAF	Tetrabutyl ammonium fluoride
TosMIC	toluene-4-sulfonyl-methylisocyanide
TFA	Trifluoroacetic acid
TES	Triethylsilyl
TBDPS	<i>tert</i> -butyl-diphenylsilyl ether
TPAP-NMO	Tetrapropylammonium perruthenate- N-methylmorpholine N-oxide
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TBSCl	<i>tert</i> -Butyldimethylsilyl chloride
THF	Tetrahydrofuran
TMSCl	Chlorotrimethylsilane
Ti(O- <i>i</i> Pr) ₄	Titanium isopropoxide
TIPSOTf	Triisopropylsilyl trifluoromethanesulfonate
TBSOTf	<i>tert</i> -butyldimethylsilyl triflate
TiCl ₄	Titanium tetrachloride
TIPSCl	Triisopropylchlorosilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TFAA	Trifluoroaceticacid anhydride
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TPAP	Tetrapropylammonium perruthenate
Tl(NO ₃) ₃ .3H ₂ O	Thallium(III) Nitrate Trihydrate
Tl(CF ₃ COO) ₃	Thallium(III) trifluoroacetate
TrOOH	Triphenylmethyl hydroperoxide
Tf ₂ O	Trifluoromethanesulfonic anhydride
WSCl.HCl	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
Zn(BH ₄) ₂	Zinc borohydride
Zn(OTf) ₂	Zinc trifluoromethanesulfonate
Zr(O- <i>t</i> Bu) ₄	Zirconium(IV) <i>tert</i> -butoxide

Acknowledgements:

The authors thank the Director, CSIR-National Institute of Oceanography for constant encouragement. Financial assistance provided by the CSIR (Project OLP 1201) and EU-FP7-KBBE-2009-3-245137 MAREX are highly acknowledged.

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