Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Synthesis and biological activity of natural thiazoles: An important class of heterocyclic compounds

Marcus Vinícius Nora de Souza[a]
[a] FioCruz-Fundação Oswaldo Cruz, Instituto de Tecnologia em Fármacos-Far Manguinhos, Manguinhos, , Rio de Janeiro, Brazil

To cite this Article de Souza, Marcus Vinícius Nora(2005) 'Synthesis and biological activity of natural thiazoles: An important class of heterocyclic compounds', Journal of Sulfur Chemistry, 26: 4, 429 — 449
To link to this Article: DOI: 10.1080/17415990500322792
URL: http://dx.doi.org/10.1080/17415990500322792

Journal of Sulfur Chemistry
Vol. 26, No. 4–5, August–October 2005, 429–449

Taylor & Francis
Taylor & Francis Group

Synthesis and biological activity of natural thiazoles: An important class of heterocyclic compounds

MARCUS VINÍCIUS NORA DE SOUZA*

FioCruz-Fundação Oswaldo Cruz, Instituto de Tecnologia em Fármacos-Far Manguinhos.
Rua Sizenando Nabuco, 100, Manguinhos, 21041-250, Rio de Janeiro, Brazil

(Received 1 April 2005; in final form 6 August 2005)

The class of heterocyclic compounds known as thiazole is found in many natural and synthetic products with a wide range of pharmacological activities, such as antiviral, anticancer, antibacterial, antifungal, anticonvulsant, antiparkinsonian and anti-inflammatory activities that can be well illustrated by the large number of drugs in the market containing this function group. Due to its importance, the aim of this review is to highlight the synthesis and biological activity of the thiazole natural products reported between 2000 and 2004.

Keywords: Thiazole; Natural products; Biological activity

1. Introduction

Molecules that possess sulfur atoms are present and very important in living organisms [1]. In this context, one important class of heterocycle compound that contains one sulfur atom is known as thiazole (figure 1). This class is present in many natural and synthetic products with a wide range of pharmacological activities, such as antiviral, anticancer, antibacterial, antifungal, anticonvulsant, antiparkinsonian and anti-inflammatory activities that can be well illustrated by the large number of drugs in the market containing this function group [2]. As examples, the anticonvulsivant riluzole, the antiparkinsonian talipexole, the antischistosomal miridazole, the anthelmintic tiabendazole, the anti-ulcer alizatidine, the vitamin B_1, the antibacterial sulfathiazole, and the antiviral ritonavir can be cited (figure 2) [2]. Thiazole ring also finds applications in other fields, such as polymers [3], liquid crystals [4], photonucleases [5], fluorescent dyes [6, 7], insecticides [8] and antioxidant [9]. In the case of natural products, thiazole is present as a subunit in a large number of terrestrial and marine compounds, with different biological activities that represent a very important field in drug discovery. Due to the importance of this nucleus, the aim of this review is to highlight the synthesis and biological activity of the thiazole natural products reported between 2000 and 2004.

*Email: marcos_souza@far.fiocruz.br

Journal of Sulfur Chemistry
ISSN 1741-5993 print/ISSN 1741-6000 online © 2005 Taylor & Francis
http://www.tandf.co.uk/journals
DOI: 10.1080/17415990500322792

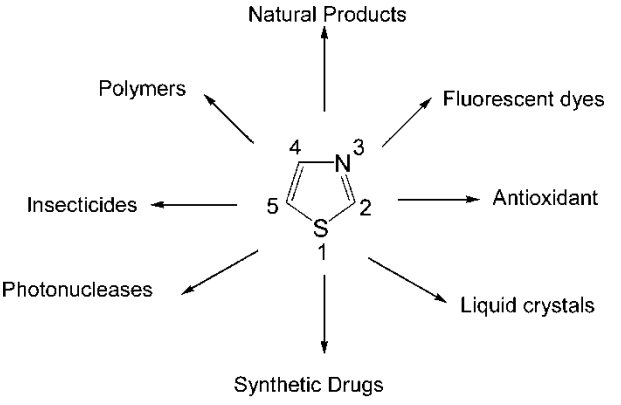


Figure 1. Thiazole.

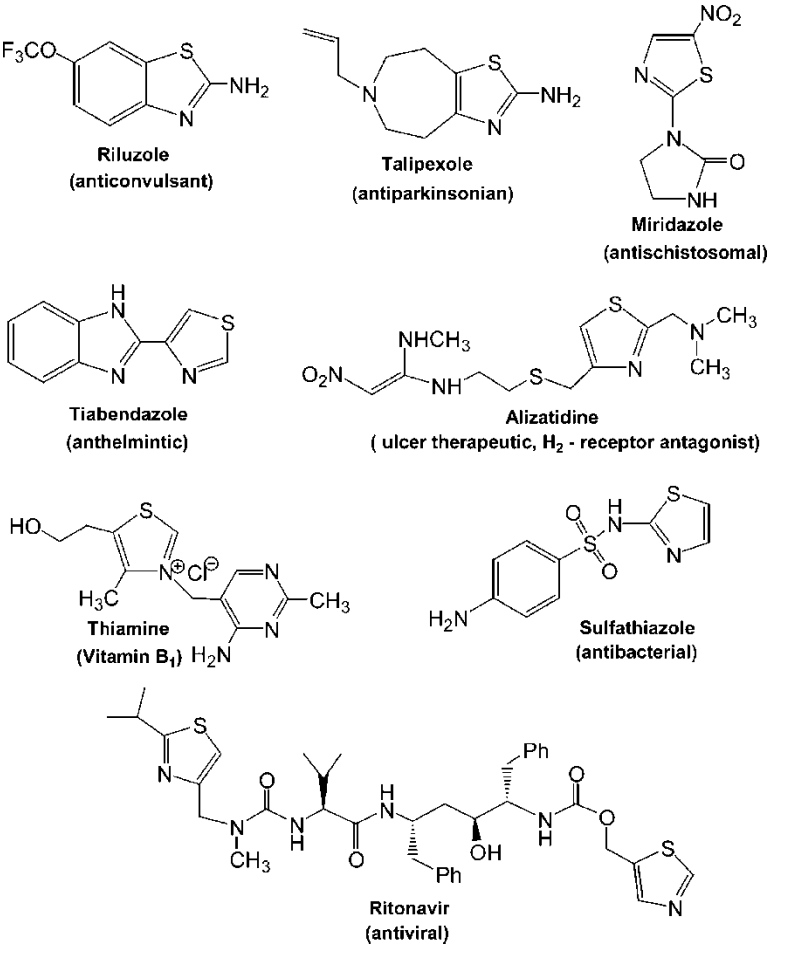


Figure 2. Natural and synthetic products containing thiazole.

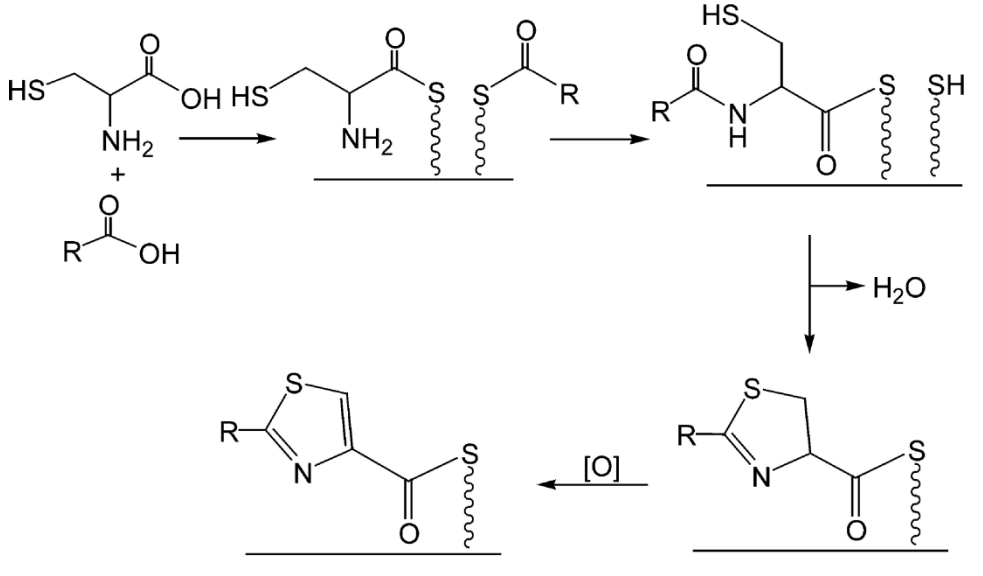
2. Natural thiazoles

The biosynthesis of thiazole-containing natural products is basically derived from cysteine peptide precursors, followed by coupling, cyclization and oxidation reactions that furnished the thiazole subunit (scheme 1) [10].

2.1 *Cystothiazole A*

The antibiotic cystothiazole A was isolated for the first time in 1998 by Sakagami and co-workers from the myxobacterium culture broth of *Cystobacter fuscus* with other five secondary metabolites named cystothiazoles B–F [11, 12] which are structurally similar to the myxothiazoles [13–15] and melithiazoles [12] (figure 3). Cystothiazole A possesses potent activity against a large range of fungi, including *Candida albicans* (AJ-5682, MIC 0.4 μg/mL), with no effect on bacterial growth. When compared with myxothiazole A [13–15], cytothiazole A was more active and less cytotoxic against fungi. Studies *in vitro* also demonstrated that cytothiazole A possesses citotoxicity activity against colon carcinoma HCT-116 and Leukaemia K 562 with an IC_{50} value of 130 and 110 ng/mL, respectively.

The total synthesis of cystothiazole A was accomplished by Williams in 2001 [16], Akita in 2002 [17] and Charette in 2003 [18] with their respective groups. In the Charette synthesis of cystothiazole A [18], the retrosynthetic strategy was based in the two key fragments **1** and **2** that could be accomplished by start materials **3** and **4** (scheme 2). The synthesis of the fragment **1** (scheme 3) started with the formation of the (*Z*)-silyketene thioacetal **3** from **5** in a 89% (91:9–*Z*:*E*). After aldol reaction between this intermediate and (benzyloxy)acetaldehyde led to the *syn* aldol adduct **6** in a 93% with a 98% ee. After methylation with the Meerwein reagent the thioester was reduced to the respective aldehyde in presence of triethylsilane as a source of hydride with 10% palladium on carbon. The crude product was then homologated with methyldiazoacetate **8** in presence of $SnCl_2$ to produce the β-ketoester (−)-**9** in 85% (two steps). This intermediate was deprotonated, followed by methylation using dimethyl sulfate that after benzyl deprotection and oxidation led the β-methoxyacrylate **1**.



SCHEME 1

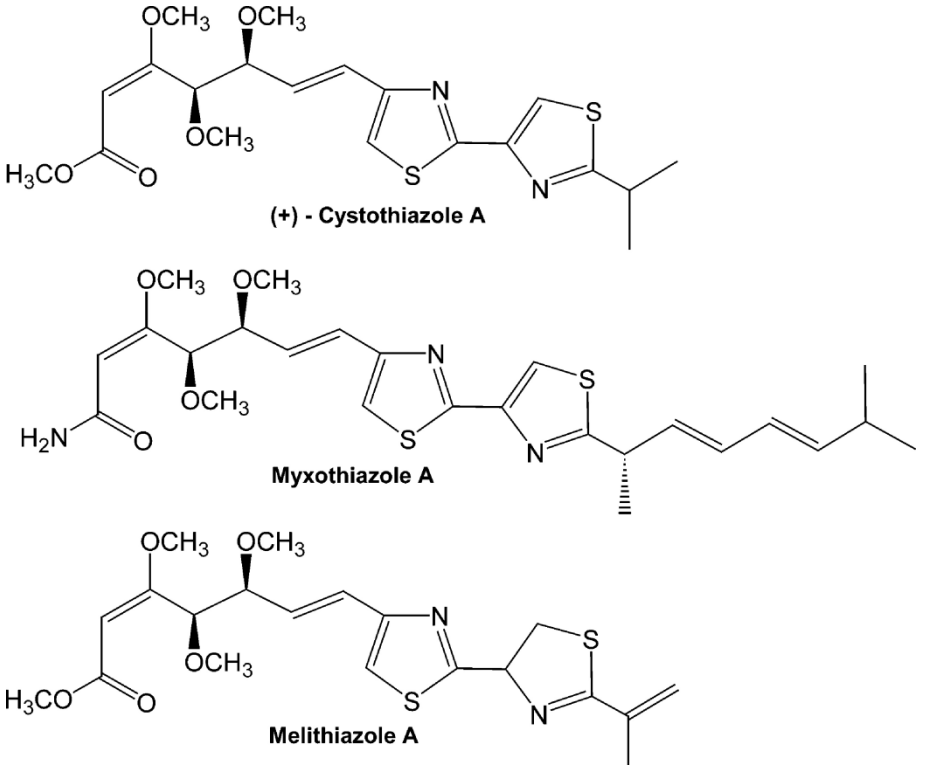
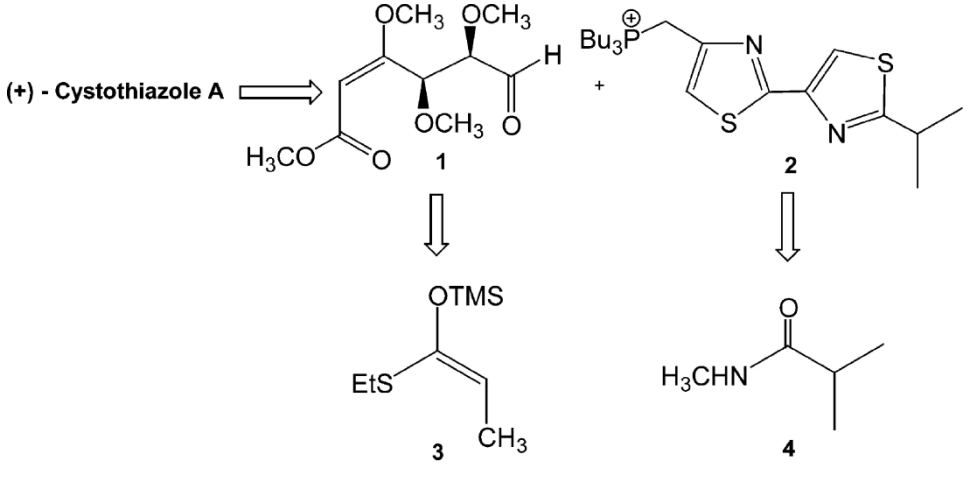
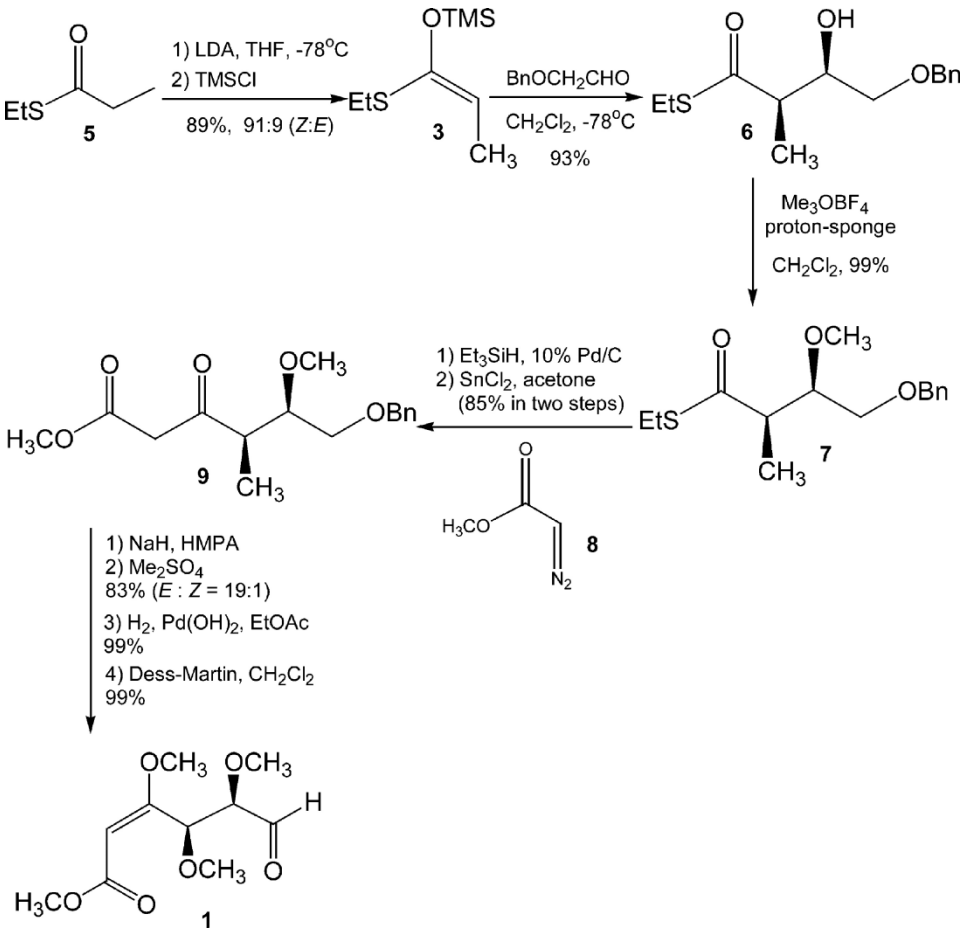


Figure 3. Cystothiazole A and variants.

The construction of the [2, 4′]-bis(thiazole) fragment **2** (scheme 4) began with isopropylamide **4** in presence of Tf_2O and pyridine, followed by addition of L-cysteine.HCl, which led to the thiazoline (+)-**10** in 90% yield. The oxidation of this intermediate followed by transformation of ester group in the respective amide produced the thiazol **11**. The same steps



SCHEME 2

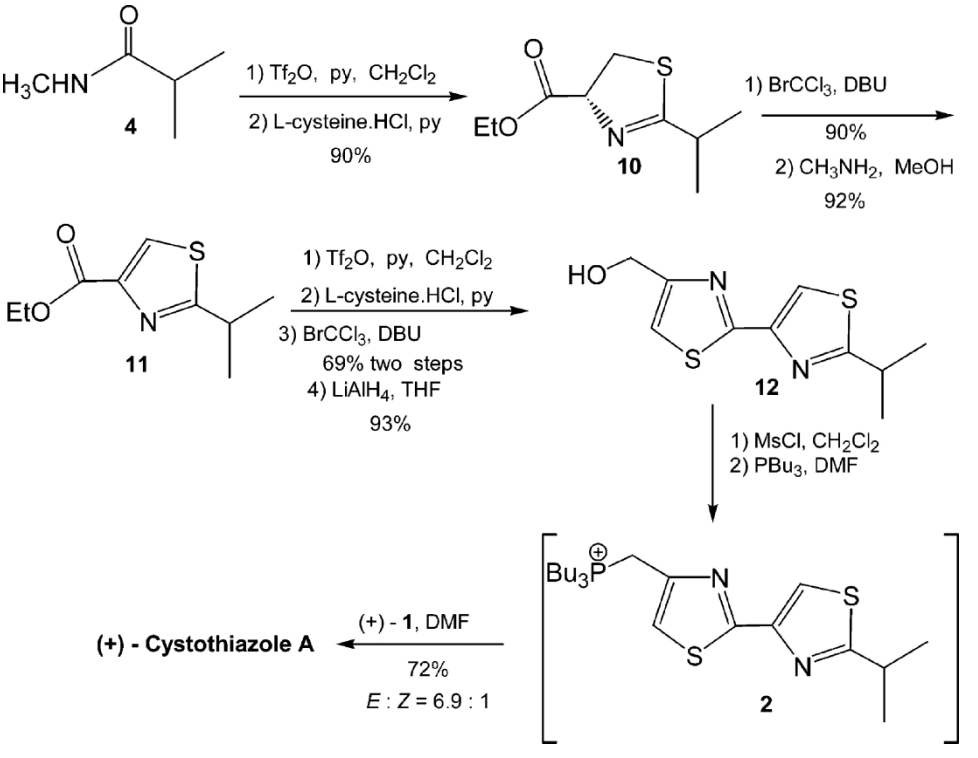


SCHEME 3

mentioned above were again employed to furnish bis(thiazole) **12**. After reduction, mesylation and addition of tributylphosphine (Bu_3P) the phosphonium salt **2** was produced and coupled with the key β-methoxyacrylate **1** by the Witting reaction that led the natural product cytothiazole A in 72% yield.

2.2 *Mycothiazole*

Mycothiazole, a polyketide thiazole (figure 4) is a natural marine product isolated from the Indo-Pacific sponge *Spongia mycofijiensis*, which was collected in 1988 by Crews and co-workers [19], as well as from a marine sponge of the genus *Dactylospongia* in 2001 by Cutignano and co-workers both of the Vanuatu islands [20]. This natural product showed anthelminthic activity as well as selectivity activity against lung cancer in the NCI *in vitro* 60-cell line panel [19]. The first asymmetric synthesis of (−)-mycothiazole was achieved by Shioiri and co-workers [21] and was based in the fragments described in the retrosynthetic analysis (scheme 5). The construction of the fragment **13** (scheme 6) was started with the ester **17** that after three steps furnished the aldehyde **18**, which was coupled with L-cysteine methyl ester in 71% yield (four steps) and after three steps the thiazole **20** was obtained.



SCHEME 4

This thiazole was coupled with the stannane derivatives **21** and **23** by Stille reaction to produce the intermediate **24**. The (R)-aldol adduct **26** was achieved by Nagao acetate aldol reaction of the aldehyde **15** with the chiral *N*-acetylthiazolidinethione **16** in a highly diastereoselective fashion >10:1 dr in a 75% yield. Following silyl protection, reduction and Witting reaction the key intermediate **13** was achieved. The other key fragment **14** was achieved by using the 3-butyn-1-ol **27**, which, after regioselective addition of HI under Ishii conditions followed by tosylation led to the iodine **28** in 55% yield (two steps). This intermediate, after three additional steps, furnished the desired intermediate **14**, which was coupled *via* Stille reaction with the fragment **13** and after deprotection produced the natural marine product (−)-mycothiazole (schemes 7 & 8).

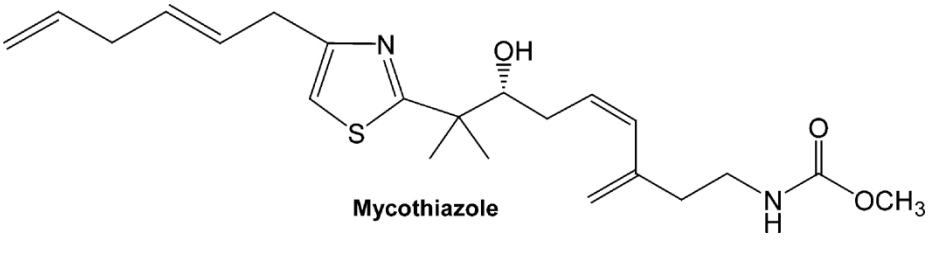
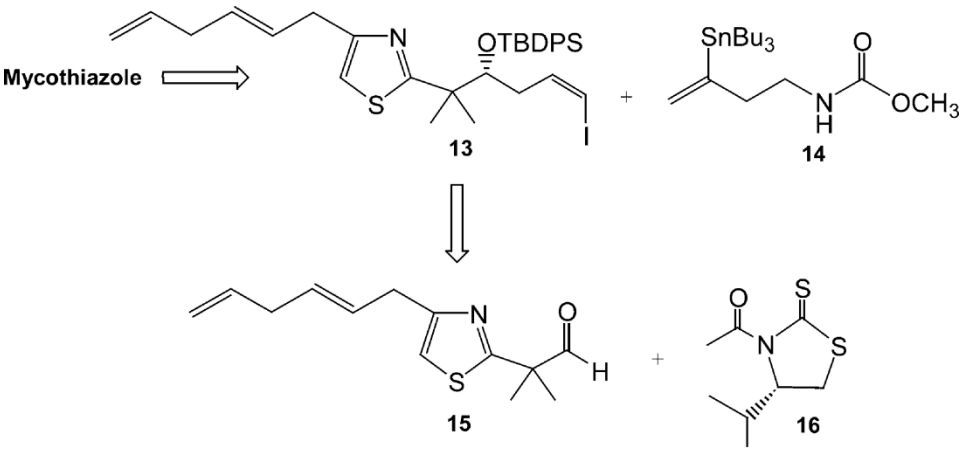
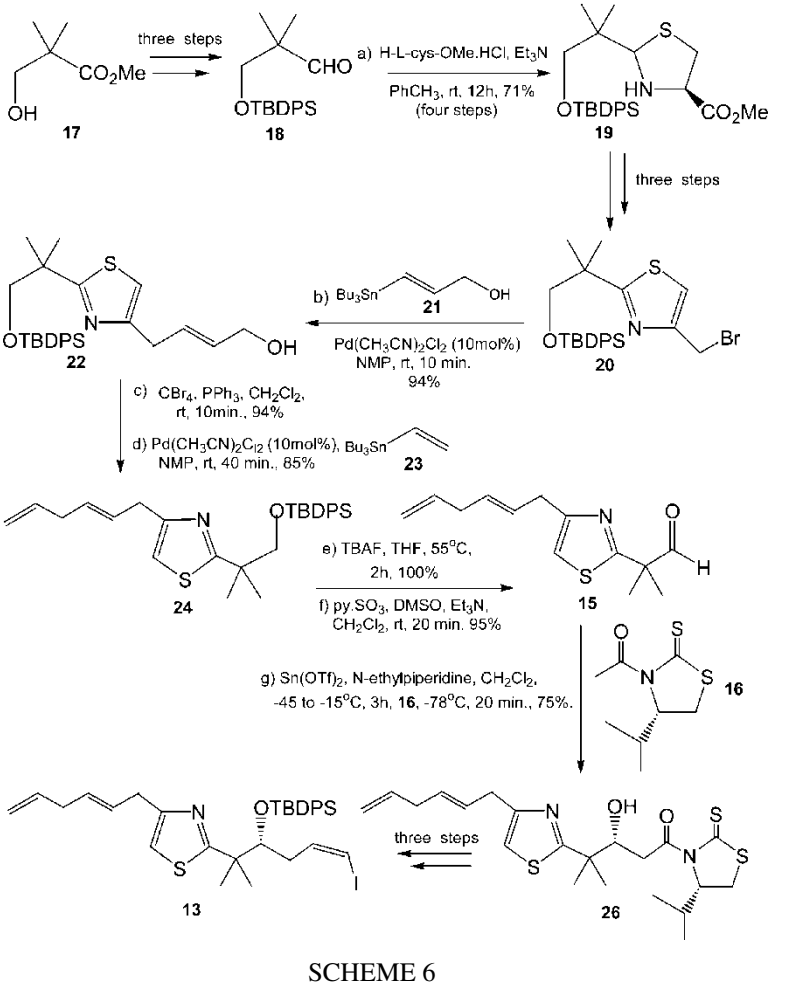


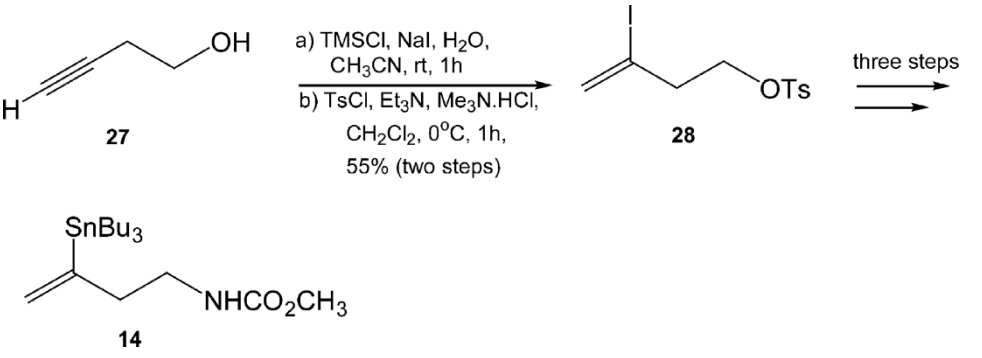
Figure 4.



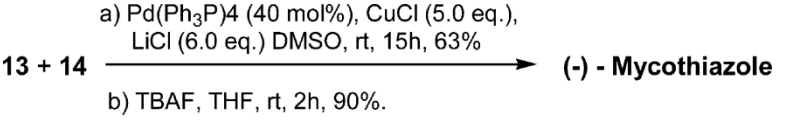
SCHEME 5



SCHEME 6



SCHEME 7



SCHEME 8

2.3 *WS75624 B*

The pyridine-thiazole WS75624 A and B (figure 5) were isolated from the fermentation broth of *Scharothrix* sp. No. 75624 [22] and are found to be potent hypertensive agents [23]. The total synthesis of WS75624 B was accomplished by Patt and Massa [24, 25], Huang and Gordon [26] and Sammakia and Stangeland [27]. In the synthesis of WS75624 B made by Sammakia and Stangeland [27] the retrosynthetic analyses (scheme 9) was based in the disconnection between the thiazole and the pyridine with the two key fragments **29** and **30**. The synthesis of fragment **30** (scheme 10) was made by using 2-picolinic acid **31** as material, that after two steps furnished the 4-chloro amide **32** in 93% yield. The 4-methoxypyridine derivative **33** was obtained with sodium methoxide followed by *ortho*-metalation with *n*-BuLi. This intermediate in presence of LDA induced the 1,3-migration of the iodine from the 3- to the 5-position. This reaction is known as the "halogen dance" [28], a methodology that rearranges the position of the iodine on the arene ring and produced the 5-iodopyridine **34** in 88% yield. Methoxypyridine **35** was produced with sodium methoxide and CuI in DMF in 92% yield,

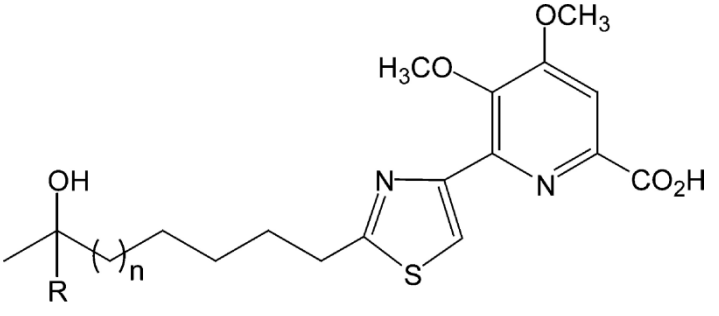
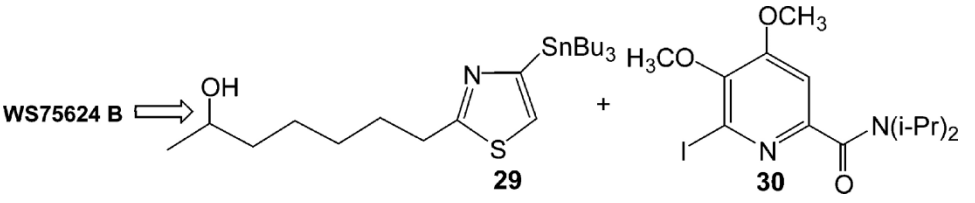


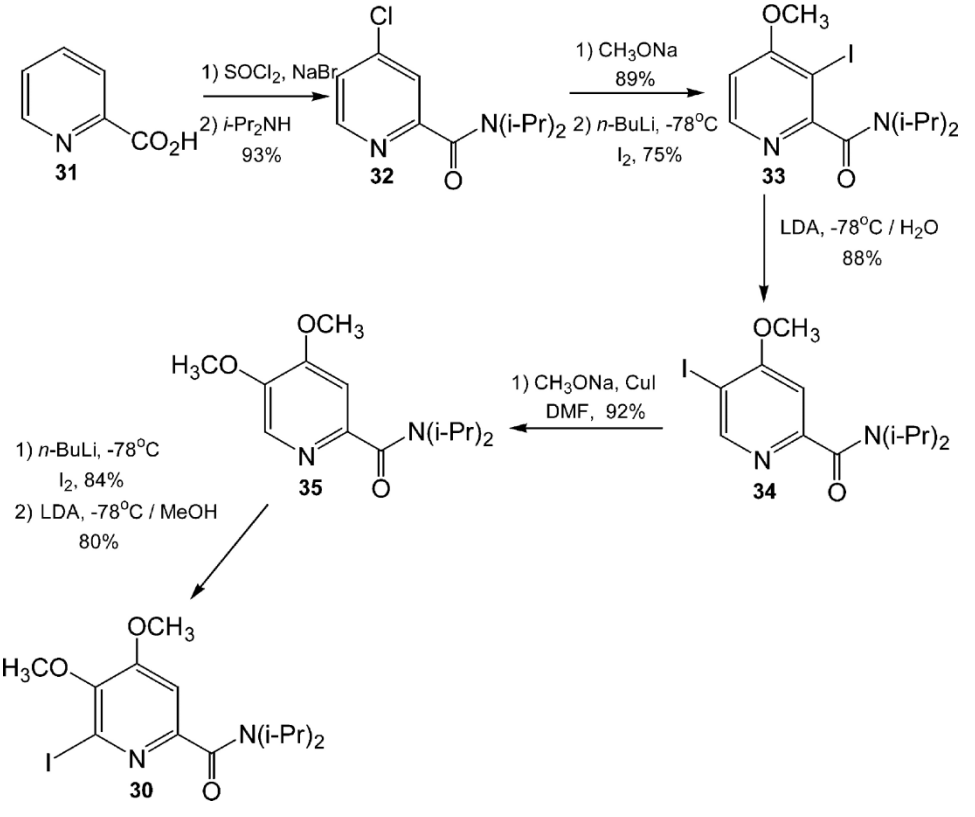
Figure 5. Pyridine-thiazole WS75624 A and B.



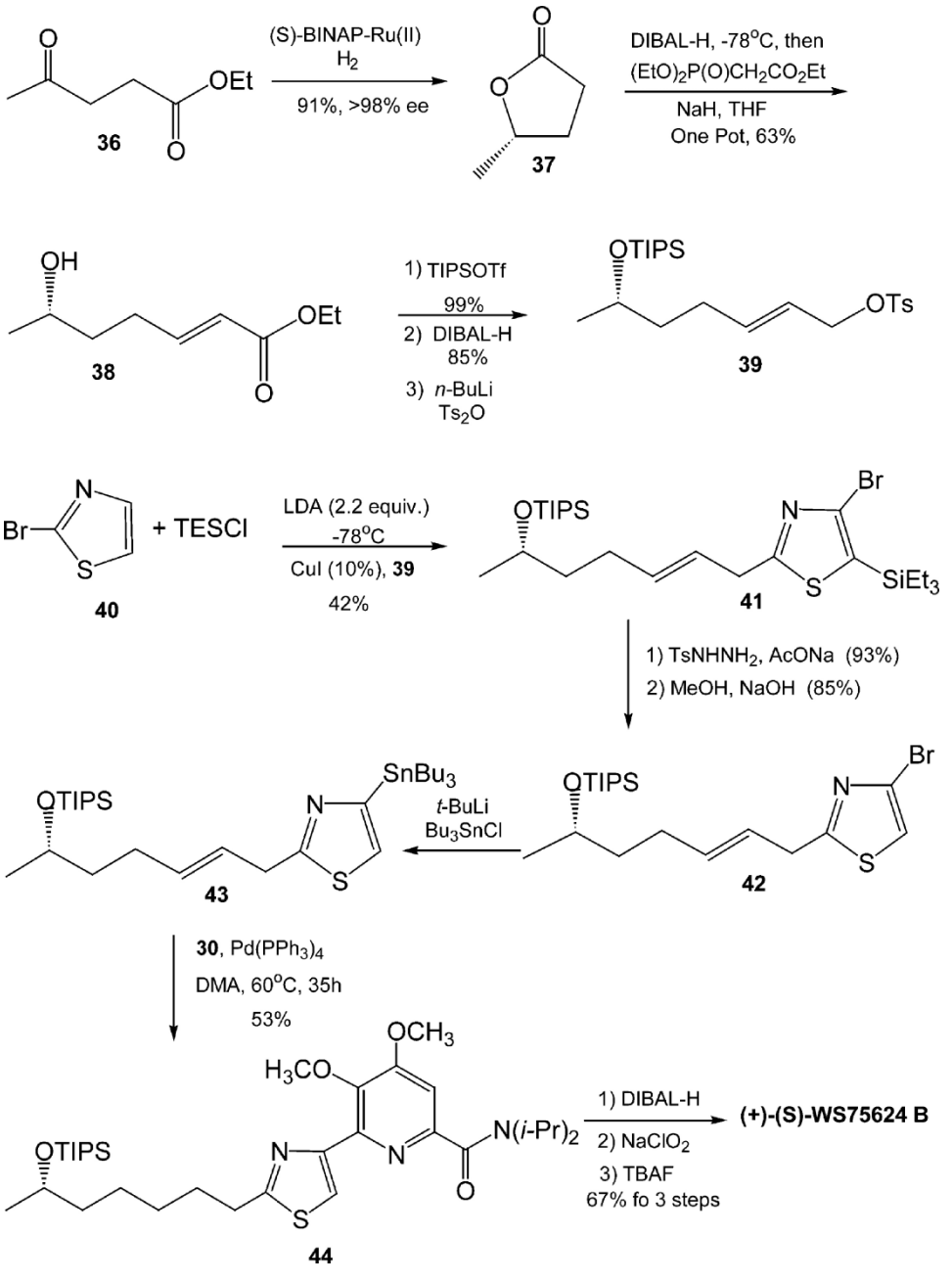
SCHEME 9

however without the presence of CuI or polar solvents only the reduced byproduct **34** was detected. Finally, the key intermediate **30** produced after *ortho*-metalation and halogen dance in 84 and 80% yield, respectively.

The synthesis of the thiazole **29** (scheme 11) began with the ethyl levulinate **36** as the starting material and after Noyori hydrogenation furnished the lactone **37** in 91% yield and >98% ee. This lactone was reduced without further purification followed by Horner-Emmons olefination to produced the enoate **38** in 63% yield (two steps). This enoate **38** after alcohol protection, reduction of ester group to alcohol and introduction of tosylate group led to intermediate **39**. This intermediate was employed in an elegant reaction to produce intermediate **41** by using the halogen dance. This reaction was achieved by using 2-bromothiazole **40** and triethylsilyl chloride (TES) in presence of LDA followed by addition of the compound **39**, which produced the intermediate **41** in 42% yield. After reduction of the double bond and TES deprotection,



SCHEME 10



SCHEME 11

compound **42** was converted to the tributylstannyl derivative **43**. Coupling with the pyridine intermediate **30** using Stille conditions, led to the key intermediate **44**. Finally, the natural product (+)-(*S*)-WS75624 B was achieved after reduction of amide to an aldehyde group followed by transformation to the carboxylic acid by deprotection of the silyl group in a 67% yield (three steps).

3. Natural macrocyclic contaning thiazole subunit

3.1 *Bistratamides*

There are a large number of natural macrolactam products containing heterocyclic amino acids composed of thiazole, oxazole, thiazolines and oxazolines with a wide range of biological activities [29, 30]. In this context, bistratamides are a family of macrolactams isolated from *Lissoclinum bistratum* in the southern Philippines that possess moderate cytotoxic activity against a human colon tumor (HCT-116) (figure 6) [31–33]. The total synthesis of bistratamides F-I

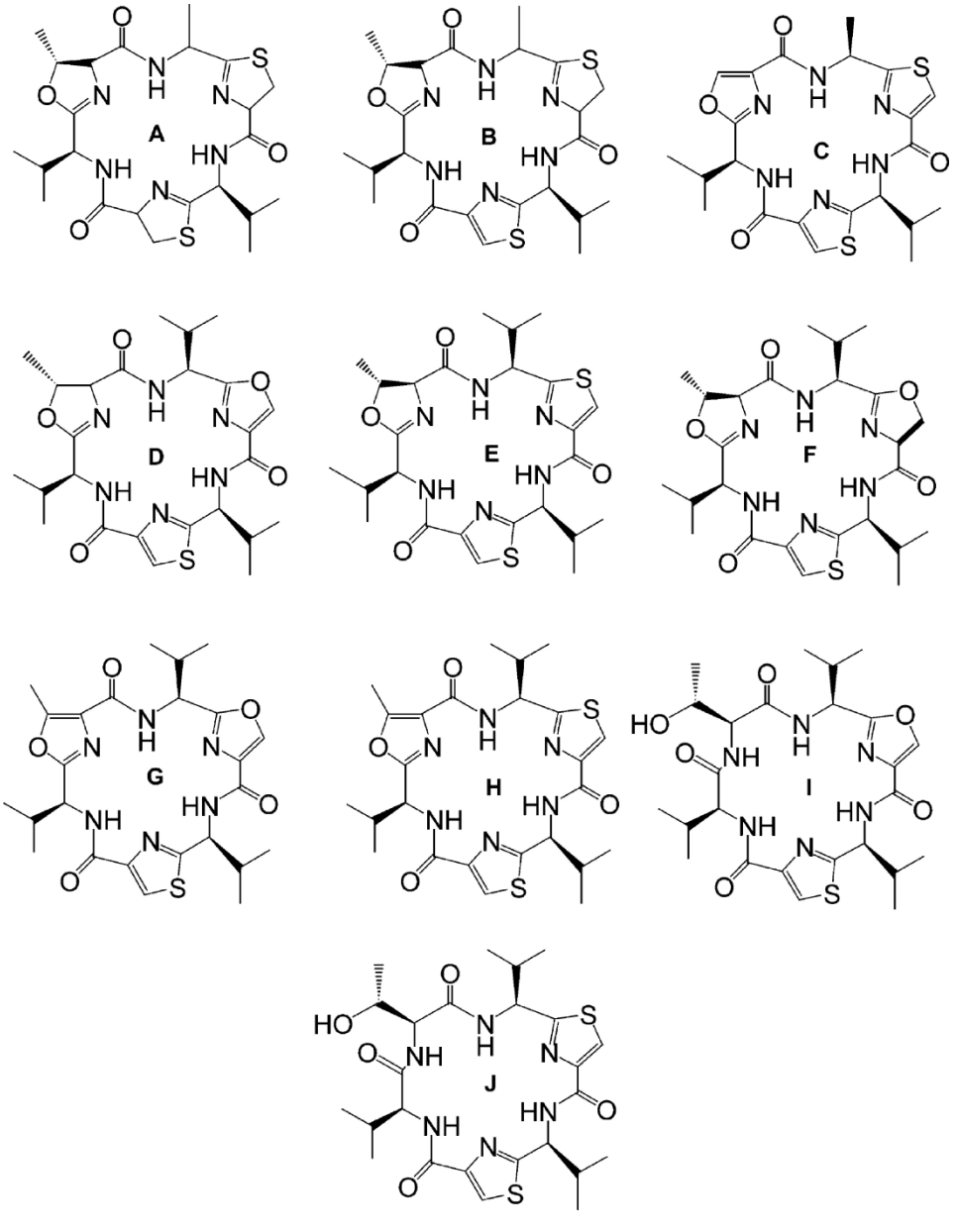
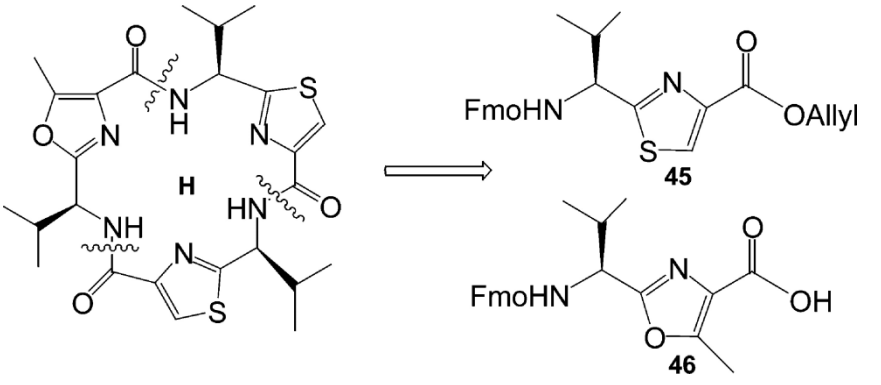


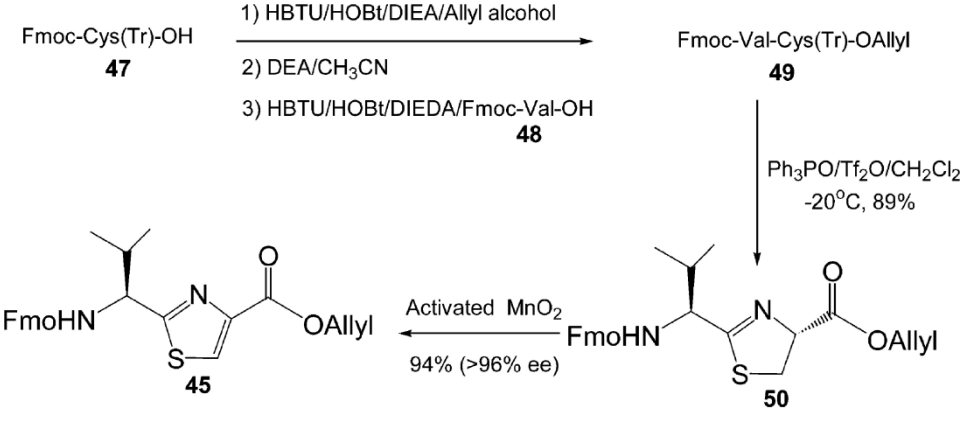
Figure 6. Bistratamides.



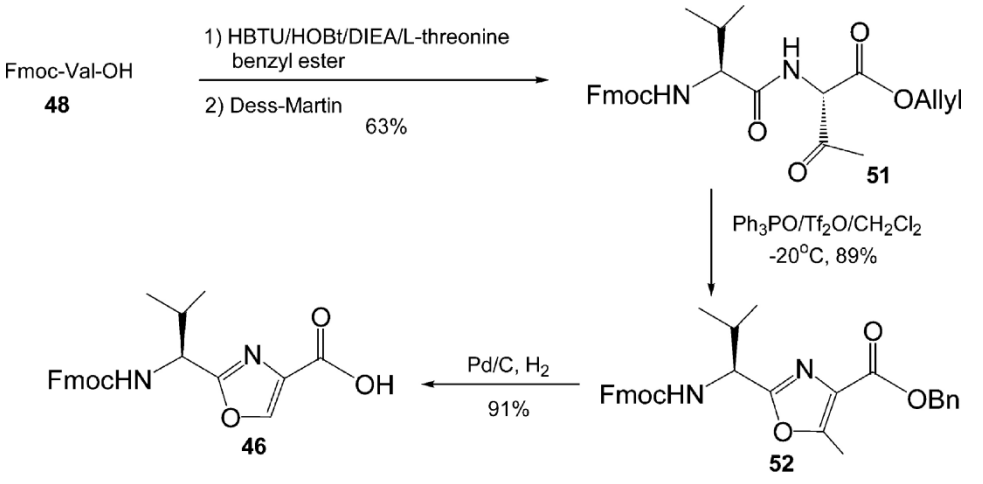
SCHEME 12

were synthesized by Kelly and You with similar strategies (scheme 12) [34]. For example, the synthesis of the bistratamides-H was based in two key fragments **45** and **46**. The construction of thiazole **45** (scheme 13) begun with the protection of the carboxylic acid of *N*-Fmoc-*S*-trityl-L-cysteine **47** as an allyl ester. After Fmoc deprotection followed by coupling with the *N*-Fmoc-L-valine **48** led to the protected dipeptide **49** in 84% yield (three steps). This dipeptide was converted into thiazoline **50** that was further oxidized to produce the thiazole **45** in 94% yield (>96% ee). The synthesis of the oxazole amino acid **46** (scheme 14) was achieved by coupling between *N*-Fmoc-L-valine **48** and L-threonine benzyl ester followed by oxidation to furnished the dipeptide that after oxidation furnished the ketone **51** in 63% yield (two steps). This β-ketodipeptide in the presence of bis (triphenyl)oxodiphosphonium trifluoro-methanesulfonate was converted in oxazole amino acid fragment **52** in 65% yield. Benzyl deprotection the second key fragment **46** was produced in a 91% yield. Finally, a series of coupling reactions between the fragments **45** and **46** (scheme 15) were made to produce the bistratamides-H.

Kelly and co-workers have also synthesized macrolactams to the tenuecyclamides family using solid-phase synthesis [35]. The tenuecyclamides A-D (figure 7) were isolated from the cyanobacterium *Nostoc spongiaforme* var. *tenue*, which inhibit the division of sea urchin embryos with an ED_{100} between 9.0–19.1 μM. The synthesis, as well the stereochemical



SCHEME 13

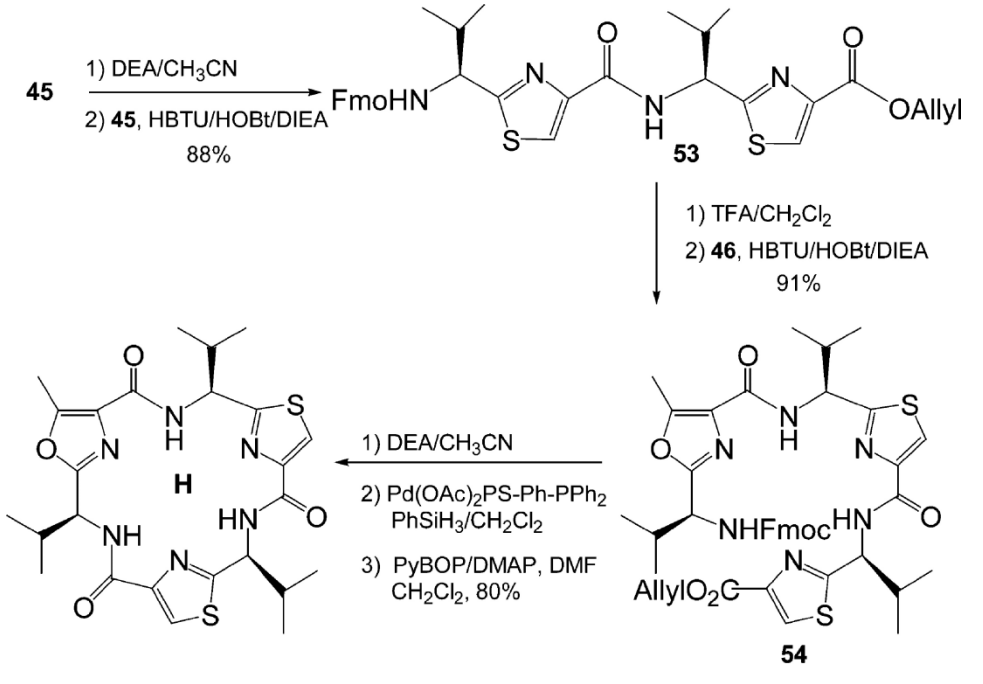


SCHEME 14

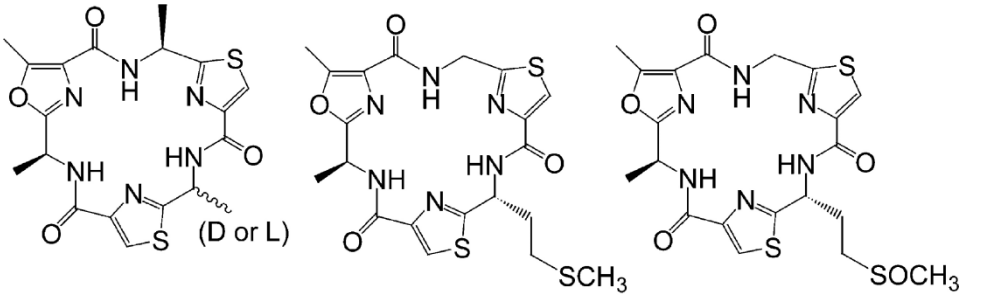
assignments of tenuecyclamides A-D was accomplished by Kelly and co-workers using similar strategy employed in the bistratamide macrolactams [34].

3.2 *Hectochlorin*

Hectochlorin (figure 8) is a marine natural fungicide isolated from *Lynbya majuscula*, a cyanobacteria collected in Hector Bay, Jamaica by Gerwick and co-workers who have also reported the structure elucidation, absolute stereochemistry and biological activities [36].



SCHEME 15



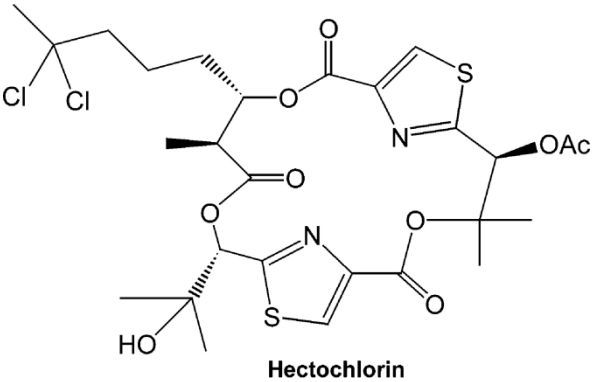
Tenuecyclamide A (D)
39% yield
Tenuecyclamide B (L)
71% yield

Tenuecyclamide C
54% yield

Tenuecyclamide D
67% yield from C

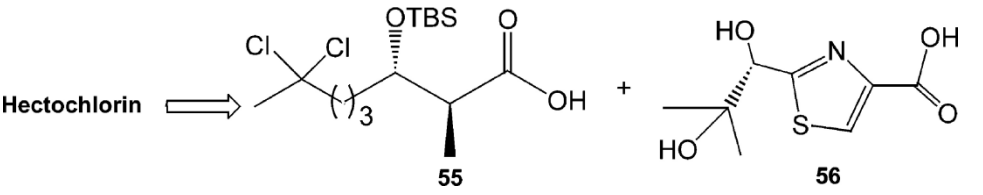
Figure 7. Tenuecyclamides.

Hectochlorin possesses potent antifungal activity against *Candida albicans*, antiproliferative activity in the NCI 60-cell line assay and it is a strong promoter of actin polymerization. The total synthesis of this natural product was accomplished by Cetusic and co-workers [36] and was based two key fragments: the aldol product **55** and thiazole **56** (scheme 16). The aldol fragment **55** was made (scheme 17) by using the procedure described by Yamada and co-workers [37] that uses the Evans aldol reaction with the imide **57** and the 5,5-dichlorohexanal **58** to produced the aldol product **59** with diastereoselectivity of 95:5 in 69% yield. The 5,5-dichlorohexanal **58** could be obtained by alkylation of lithiodichloromethane with 6-bromo-1-hexene, followed by ozonolysis. The intermediate **55** was furnished after inversion of the configuration of the hydroxyl group **59** *via* Mitsonobu reaction and removal of the chiral auxiliary in 57 and 72% yield, respectively. The synthesis of thiazole fragment **56** (scheme 18) started with the condensation of thiourea **60** and ethyl bromopyruvate **61** that produced the thiazole **62** that was then converted to bromothiazole **63**. The isobutylene **64** group was introduced to the thiazole ring by using Negishi reaction in 89% yield. Sharpless catalytic asymmetric dihydroxylation (90% yield, 90% ee), protection of the diol group with isopropylidene acetal (85% yield) and saponification of the ester group produced the carboylic acid **67** in 89% yield. The intermediate **66** also was used to produce compound **68** after transesterification to the allyl ester and selective acetylation of the secondary alcohol.



Hectochlorin

Figure 8.

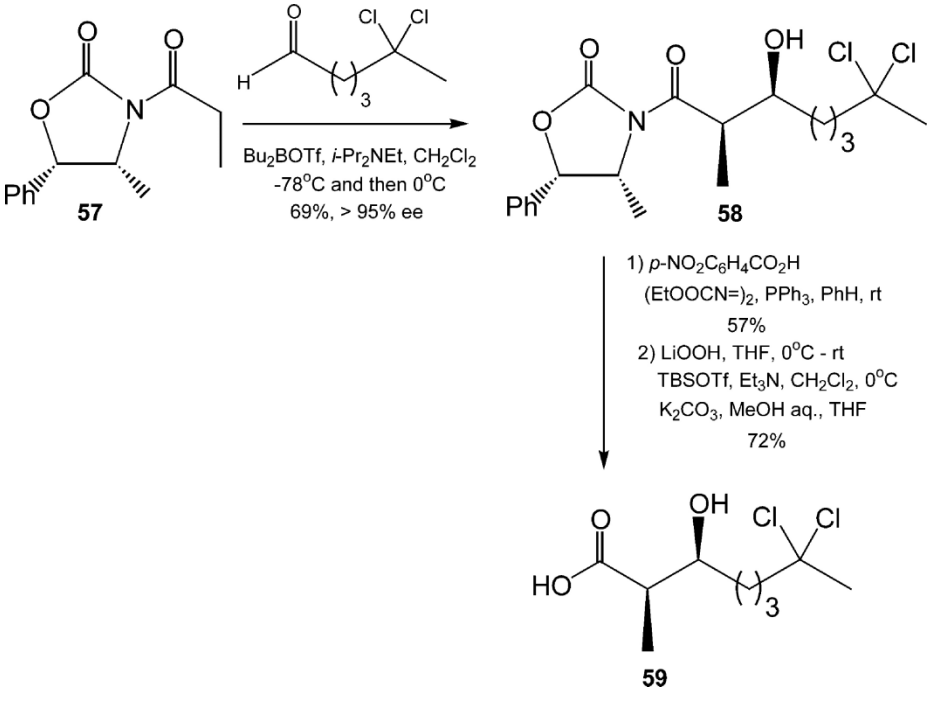


SCHEME 16

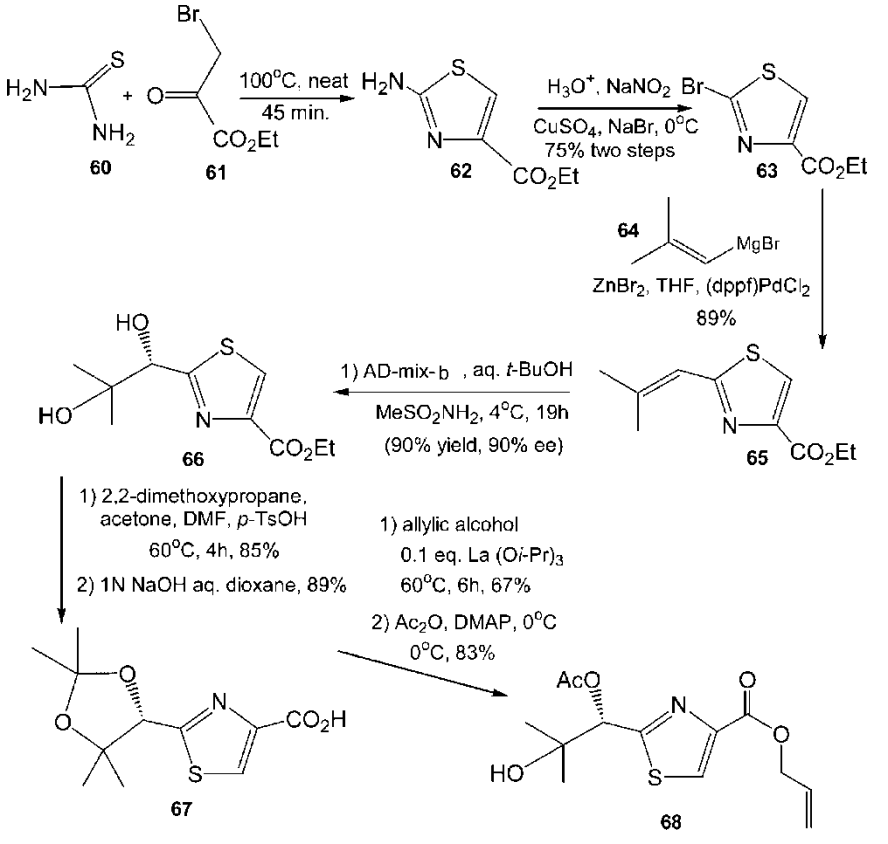
The allyl ester was chosen because it can be removed in mild conditions without affecting the other esters present in the molecule. The two fragments **67** and **68** were coupled (scheme 19) using dicyclohexylcarbodiimide (DCC) with a catalytic amount of 4-(dimethylamino)pyridine (DMAP). Deprotection of the acetal group and coupling with the aldol fragment **55** produced the intermediate key **69**. Finally, the synthesis of the natural product hectochlorin was accomplished by removing the ally ester group, deprotection of the silyl group and cyclization.

3.3 *Leinamycin*

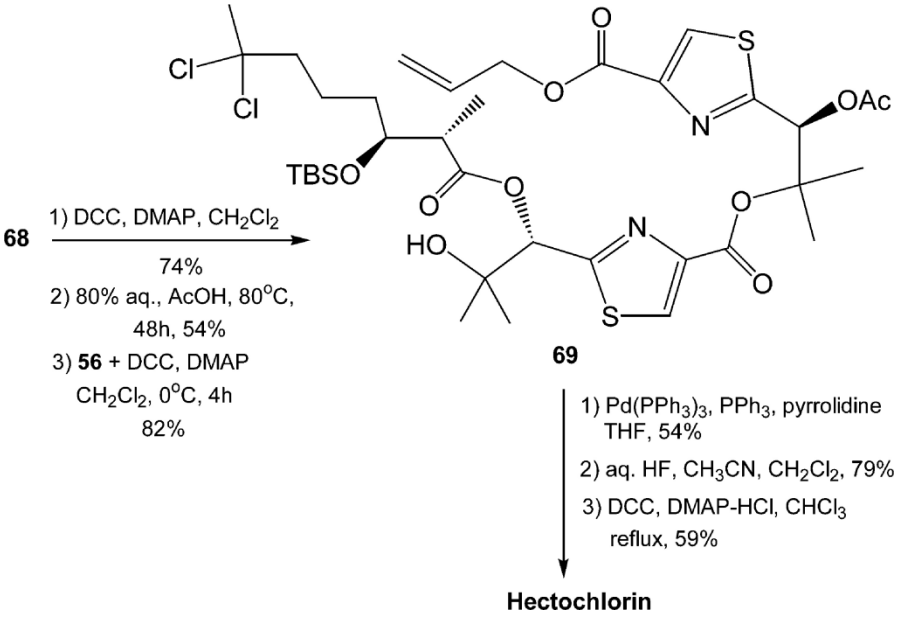
Leinamycin (figure 9) is a natural antibiotic isolated from *Streptomyces* by Hara and coworkers at Kyowa Hakko Ltd in 1989 [38, 39]. Its structure was elucidated by spectroscopic analysis and X-ray crystallography [40] with the total synthesis accomplished in 1993 by Kanda and Fukuyama [41]. Leinamycin possesses an unusual 1,3 dioso-1,2-dithiolane group, which is connected to the 18-membered lactam ring through a spiro linkage and represents a novel type of noncovalent DNA-binding structure. This natural product is DNA-damaging, and



SCHEME 17



SCHEME 18



SCHEME 19

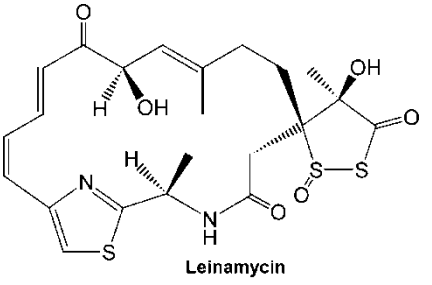
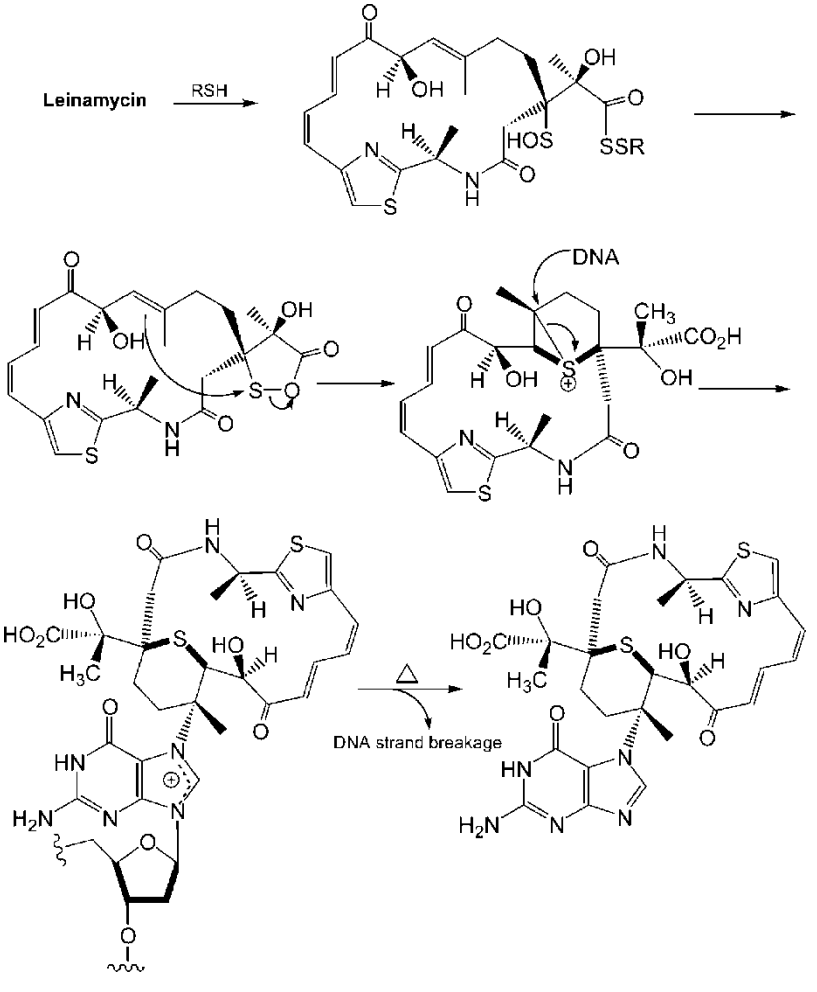


Figure 9.

exhibited potent antitumor activity against murine experimental tumor cells, leukemia P388, sarcoma 180 and HeLa S3. It is activity against gram-positive bacteria [42]. The detailed chemistry of thiol-activation and DNA-cleavage induced by leinamycin were well reported by Asai [43] and Gates [44–49] with their respective co-workers and are described in the scheme 20.



SCHEME 20

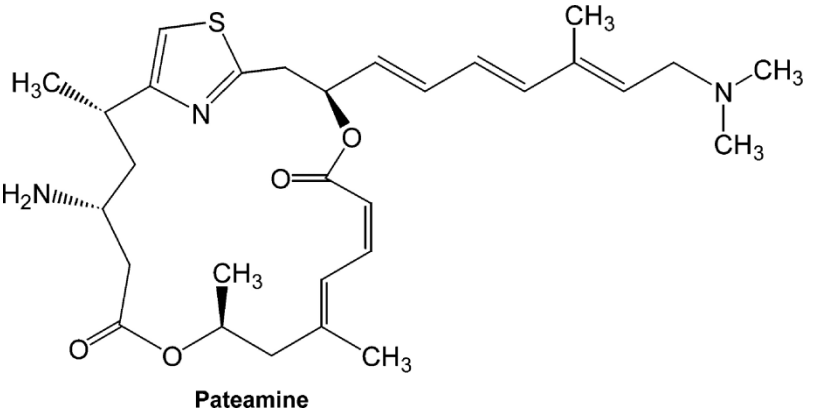
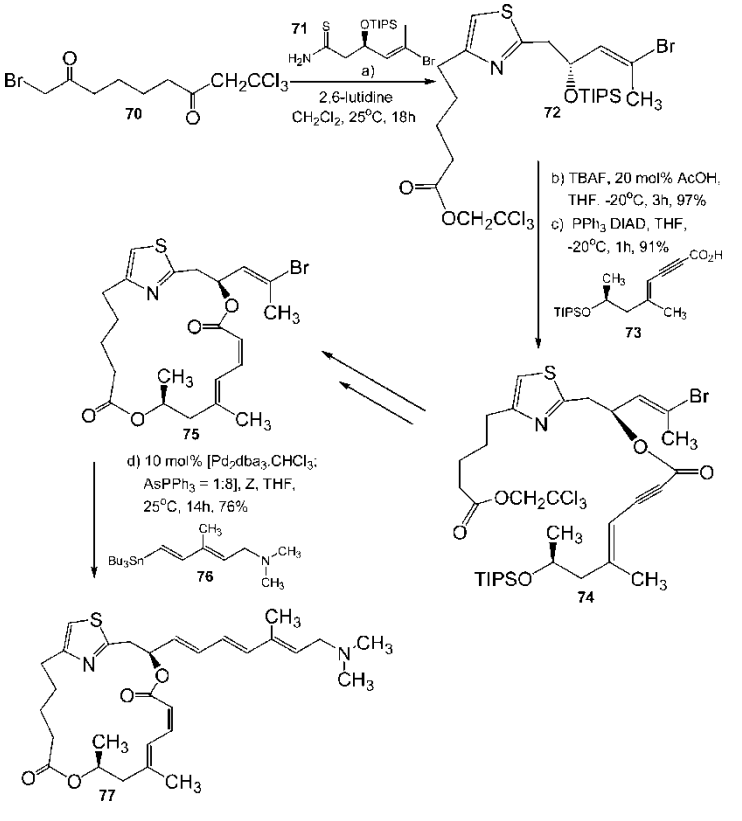


Figure 10.

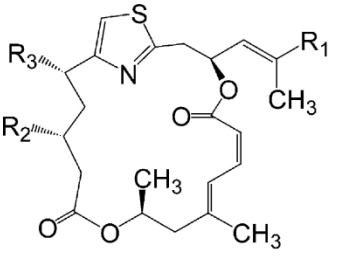
3.4 *Pateamine A*

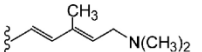
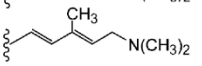
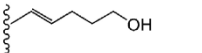
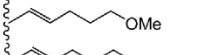
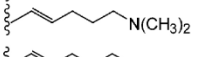
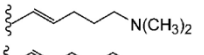
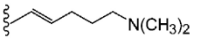
Pateamine A (figure 10) is a thiazole-containing dilactone macrolide isolated from the New Zealand marine sponge *Mycale sp* in 1991 by Munro and co-workers with potent cytotoxin activity (P388 cell line: $IC_{50} = 0.15$ nM) [50, 51]. This natural product also displays potent immunosuppressive activity ($IC_{50} = 2.6$ nM) with low citotoxicity, first discovered by

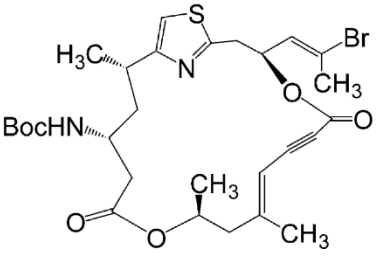


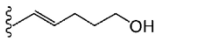
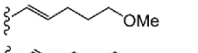
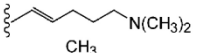
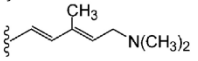
SCHEME 21

Table 1. IL-2-Reporter gene assay (transfected Jurkat cells) activity of panteamine A and derivatives.



Comp.	R_1	R_2	R_3	$IC_{50\ (nM)}$
77		H	H	0.81 ± 0.27
78		NH_2	Me	4.0 ± 0.94
79		NHBoc	Me	>1000
80		NHBoc	Me	>1000
81		NHBoc	Me	330 ± 120
82		NHC(O)OPh	Me	4.0 ± 0.94
83		$NHC(O)CF_3$	Me	330 ± 93



Comp.	R_1	$IC_{50\ (nM)}$
84		340 ± 180
85		55 ± 16
86		NA
87		NA

Dr. Glynn Faircloth, PharmaMar Inc. [52]. Due the promising proprieties of pateamine A, its first total synthesis was investigated by Romo, Liu and their respective co-workers in 1998 [53] followed by Pattenden and his group in 2000 [54]. Romo and Liu also reported in 2004 important biological activity studies providing new potent simplified analogues [55]. An example is the synthesis of the simplified analogue **77** (scheme 21) that was made by using the intermediate **70** prepared by esterification and bromination of 6-oxo-heptanoic acid. Hantzsch coupling reaction between **70** and **71** produced the thiazole **72**. This thiazole intermediate, after silyl deprotection and Mitsonobu coupling with the enyne acid **73** produced the intermediate **74** in 97% and 91% yield respectively. Yamagushi macrocyclization and Lindar reduction reduction furnished the key intermediate **75**. Finally, the simplified analogue of pateamine A **77** was achieved after Stille reaction with the fragments **75** and **76** in 76% yield. Using similar strategy Romo, Liu and their respective co-workers made and tested several different analogues of pateamine A (table 1). The IL-2-gene assay (transfected Jurkat cells) activity of the analogues synthesized has demonstrated that the desmethyl, desamino pateamine A **77**, prepared in ten steps, possesses greater potency (IC50 0.81 ± 0.27 nM) than pateamine A (IC_{50} 4.01 ± 0.94 nM). This work has provided important information about the stability and structure-activity relationship.

4. Conclusion

The heterocyclic class known as thiazole is an important subunit with a wide range of applications in many fields. In this context, natural products containing this nucleus represent an outstanding source of compounds with a wide range of biological activities, which can play an important role in the development of new drugs in the treatment of human diseases.

Abbreviations

Ac – acetyl; **AIBN** – 2,2′-azobisisobutyronitrile; **9-BBN** – 9-borabicyclo[3.3.1]nonane; **BINAP** – phosphine oxide, [2′-(diphenylphosphino)[1,1′-binaphthalen]-2-yl]diphenyl; **Bu** – butyl; **Bz** – benzyl; **Cys** – cysteine; **dba** – dibenzylideneacetone; **DBU** – 1,8-diazabicyclo [5.4.0]undec-7-ene; **DCC** – 1,3-dicyclohexylcarbodiimide; **DIAD** – diisopropyl azodicarboxylate; **DIBAL-H** – diisobutylaluminum hydride; **DEA** – diethylamine; **DIEA** – *N*, *N*-diisopropylethylamine; DIEDA – *N*, *N*′diisopropylethane-1,2-diamine; **DIPT** – diisopropyl tartrate; D**MA** – dimethyl amine; **DMAP** – 4-dimethylaminopyridine; **DMF** – *N*, *N*-dimethylformamide; **DMSO** – dimethylsulfoxide; **dppf** – 1,1′-bis(diphenylphosphino)ferrocene); **Et** – ethyl; **Fmoc** – *N*-(9-fluorenylmethoxycarbonyl); **HBTU** – *O*-benzotriazole-*N*,*N*, *N*′,*N*′-tetramthyl-uronium-hexafluoro-phosphate; **LDA** – lithium diisopropyl amide; **HMPA** – hexametylphosphoramide; **HOBt** – *N*-Hydroxybenzotriazole; **Ms** – mesyl; **NBS** – *N*-bromosuccinimide; **NMP** – 1-methyl-2-pyrrolidinone; **Ph** – phenyl; **PPTS** – pyridinium *p*-toluenesulfonate; **py** – pyridine; **PyBOP** – benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; **TBA** – *n*-tetrabutylammonium; **TBS** – *tert*-butyldimethylsilyl; **TBDPS** – *tert*-butyldiphenylsilyl; **TEMPO** – 2,2,6,6-tetramethylpiperidine-*N*-oxyl; **TFA** – trifluoroacetic acid; **TIPS** – triisopropylsilyl; **TC** – thiophene-2-carboxylate; **Tf** – triflate; **THF** – tetrahydrofuran; **TMS** – trimethylsilyl; **TMSE** – trimethylsilylethyl; ***t*-Bu** – *tert*-butyl; **Ts** – tosyl; **Val** – valine.

References

[1] M. Fontecave, S. Ollagnier-de-Choudens, E. Mulliez. *Chem. Rev.*, **12**, 2149 (2003).
[2] A. Kleemann, J. Engel. *Pharmaceutical Substances*, 4th Edition (2001).
[3] L.Y. Wang, C.X. Zhang, Z.Q. Liu, D.Z. Lio, Z.H. Jang, S.P. Yan. *Inorg. Chem. Comm.*, **6**, 1255 (2003).
[4] A.H. Al-Dujali, A.T. Atto, A.M. Al-Kurde. *European Polymer Journal*, **37**, 927 (2001).
[5] Y. Li, Y. Xu, X. Qian, B. Qu. *Tetrahedron Lett.*, **45**, 1247 (2004).
[6] I. Tintcheva, V. Maximova, T. Deligeorgiev, D. Zaneva, I. Ivanov. *J. Photochem. And Photobiol. A: Chem.*, **130**, 7 (2000).
[7] V.C. Rucker, S. Foister, C. Melander, P.B. Dervan. *J. Am. Chem. Soc.*, **125**, 1195 (2003).
[8] Q. Wang, H. Li, Y. Li, R. Huang. *J. Agric. Food Chem.*, **52**, 1918 (2004).
[9] K. Yanagimoto, K.G. Lee, H. Ochi, T. Shibamoto. *J. Agric. Food Chem.*, **50**, 5480 (2002).
[10] B. Henkel, B. Beck, B. Westner, B. Mejat, A. Domling. *Tetrahedron Lett.*, **44**, 8947 (2003).
[11] M. Ojika, Y. Suzuki, A. Tsukamoto, Y. Sakagami, R. Fudou, T. Yoshimura, S. Yamanaka. *J. Antibiot.*, **51**, 275 (1998).
[12] Y. Suzuki, M. Ojika, Y. Sakagami, R. Fudou, S. Yamanaka. *Tetrahedron*, **54**, 11399 (1998).
[13] K. Gerth, H. Irschik, H. Reichenbach, W. Trowitzsch. *J. Antibiot.*, **33**, 1474 (1980).
[14] W. Trowitzch, G. Reifenstahl, V. Wray, K. Gerth. *J. Antibiot.*, **33**, 1480 (1980).
[15] B. Bohlendorf, M. Herrmann, H.J. Hecht, F. Sasse, E. Forche, B. Kunze, H. Reinchenbach, G. Hofle. *Eur. J. Org. Chem.*, 2601 (1999).
[16] D.R. Williams, S. Patnaik, M.P. Clark. *J. Org. Chem.*, **66**, 8463 (2001).
[17] H. Akita, K. Kato, A. Nishimura, Y. Yamamoto. *Tetrahedron Lett.*, **43**, 643 (2002).
[18] P.L. DeRoy, A.B. Charette. *Org. Lett.*, **5**, 4163 (2003).
[19] P. Crew, Y. Kakou, E. Quinoa. *J. Am. Chem. Soc.*, **110**, 4365 (1988).
[20] A. Cutignano, I. Bruno, G. Bifulco, A. Casapullo, C. Debitus, L. Gomez-Paloma, R. Riccio. *Eur. J. Org. Chem.*, **66**, 775 (2001).
[21] H. Sugiyama, F. Yokokawa, T. Shiori. *Tetrahedron*, **59**, 6579 (2003).
[22] S. Yoshimura, T. Tsuruni, S. Takase, M. Okuhara. *J. Antibiotics*, **48**, 1073 (1995).
[23] Y. Tsuruni, H. Ueda, K. Hayashi, S. Takase, M. Nishikawa, S. Kiyoto, M. Okuhara. *J. Antibiotics*, **48**, 1073 (1995).
[24] W.C. Patt, M.A. Massa. *Tetrahedron Lett.*, **38**, 1297 (1997).
[25] M.A. Massa, W.C. Patt, K. Ahn, A.M. Sisneros, S.B. Herman, A. Doherty. *Bioorg. Med. Chem. Lett.*, **8**, 2117 (1998).
[26] S.T. Huang, D.M. Gordon. *Tetrahedron Lett.*, **39**, 9335 (1998).
[27] E.L. Stangeland, T. Sammakia. *J. Org. Chem.*, **69**, 2381 (2004).
[28] J.F. Bunnett. *Acc. Chem. Res.*, **5**, 139 (1972).
[29] B.S. Davidson. *Chem. Rev.*, **93**, 1771 (1993).
[30] P. Wipf. *Chem. Rev.*, **95**, 2115 (1995).

[31] B.M. Degnan, C.J. Hawkins, M.F. Lavin, E.J. McCaffrey, D.L. Parry, D.J. Watters. *J. Med. Chem.*, **32**, 1354 (1989).
[32] M.P. Foster, G.P. Concepcion, G.B. Caraan, C.M. Ireland. *J. Org. Chem.*, **57**, 6671 (1992).
[33] L.J. Perez, D.J. Faulkner. *J. Nat. Prod.*, **66**, 247 (2003).
[34] S.L. You, J.W. Kelly. *Tetrahedron*, **61**, 241 (2005).
[35] S.L. You, S. Deechongkit, J.W. Kelly. *Org. Lett.*, **6**, 2627 (2004).
[36] J.R.P. Cetusic, F.R. Green, P.R. Graupner, M.P. Olivier. *Org. Lett.*, **4**, 1307 (2002).
[37] H. Sone, T. Kondo, M. Kiryu, H. Ishiwata, M. Ojika, K. Yamada. *J. Org. Chem.*, **60**, 4774 (1995).
[38] M. Hara, K. Asano, I. Kawamoto, T. Takiguchi, S. Katsumata, K.I. Takahashi, H. Nakano. *J. Antibiot.*, **42**, 333 (1989).
[39] M. Hara, K. Asano, I. Kawamoto, T. Takiguchi, S. Katsumata, K.I. Takahashi, H. Nakano. *J. Antibiot.*, **42**, 1768 (1989).
[40] N. Hirayawa, E.S. Natsuzawa. *Chem. Lett.*, **11**, 1957 (1993).
[41] Y. Kanda, T. Fukuyama. *J. Am. Chem. Soc.*, **115**, 8451 (1993).
[42] M. Hara, Y. Saitoh, H. Nakano. *Biochemistry*, **29**, 5676 (1990).
[43] A. Asai, M. Hara, S. Kakita, Y. Kanda, M. Yoshida, H. Saito, Y. Saitoh. *J. Am. Chem. Soc.*, **118**, 6802 (1996).
[44] Br. Leonid, H. Zang, K. Mitra, K.S. Gates. *J. Am. Chem. Soc.*, **123**, 2060 (2003).
[45] K.S. Gates. In *Comprehensive Nat. Products Chemistry*, E.T. Kool (Ed.), p. 491, Pergamon, Oxford (1999).
[46] K.S. Gates. *Chem. Res. Toxicol.*, **13**, 953 (2000).
[47] T. Chattergi, M. Kizil, K. Keerthi, G. Chowdhury, T. Pospisil, S.K. Gates. *J. Am. Chem. Soc.*, **125**, 4996 (2003).
[48] H. Zang, K.S. Gates. *Chem. Res. Toxicol.*, **16**, 1539 (2003).
[49] T. Nooner, S. Dutta, S.K. Gates. *Chem. Res. Toxicol.*, **17**, 942 (2004).
[50] P.T. Northcote, J.W. Blunt, M.H.G. Munro. *Tetrahedron Lett.*, **32**, 6411 (1991).
[51] R.M. Rzasa, J.W. Blunt, M.H.G. Munro. *Tetrahedron, Lett.*, **36**, 5307 (1995).
[52] Immunosuppressive activity was first discovered by Dr. Glynn Faircloth, PharmaMar Inc. Cambridge, MA (private communication).
[53] D. Romo, R. Rzasa, H.A. Shea, K. Park, J.M. Langenhan, L. Sun, A. Akhiezer, J.O. Liu. *J. Am. Chem. Soc.*, **120**, 12237 (1998).
[54] M.J. Remuinan, G. Pattenden. *Tetrahedron Lett.*, **41**, 7367 (2000).
[55] D. Romo, N.S. Choi, S. Li, I. Buchler, Z. Shi, J.O. Liu. *J. Am. Chem. Soc.*, **126**, 10582 (2004).