Research Proposal

Formal Synthesis of Theopederin E and It's Analogues

Dr. Jadhav Vivekanand Baliram

Introduction

Marine natural products have attracted the attention of biologists and chemists the world over for the past five decades. As a result of the potential for new drug discovery, marine natural products have attracted scientists from different disciplines, such as organic chemistry, bioorganic chemistry, pharmacology, biology and ecology. This interest has led to the discovery of thousands of marine natural products to date and many of the compounds have shown very promising biological activity. The ocean is now considered to be a great source of potential drugs.

Mycalamides[1], Onnamides[2], and Theopederins[3] (fig-02) belong to a class of structurally related marine natural products. These compounds possess strong antitumor and antiviral activities, and some members showed potential at subnanomolar concentrations in cells as a consequence of protein synthesis inhibition[4]. Theopederin E **(1)**, isolated from marine sponge belonging to the *Theonella* genus found in the coast of Japan, has unusual amidotrioxadecalin unit, nine stereocentres, and has an IC_{50} value of 9.0 ng/mL against murine P388 leukemia cells.[3a]

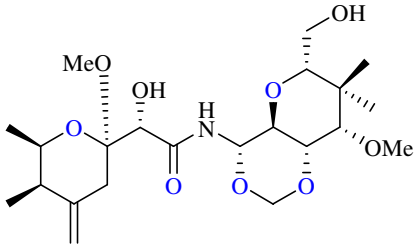


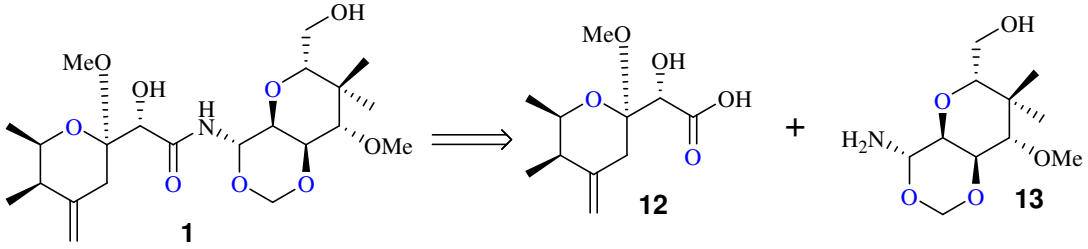
Fig-01: Theopederin E **(1)**

Some researchers completed the synthesis of Theopederin B[5], Theopederin D [6]. So far no synthesis was reported for Theopederin E **(1)**. Because of interesting structural pattern and promising activity, my aim was to synthesize Theopederin E and its analogues with derivatizations and then we can test the activities of all compounds in different cell lines. Again from fig-02 it is observed that once synthesis of Theopederin E was achieved, we can generate other analogues easily, so one need a highly flexible synthesis from easily available starting material to generate functionality easily and complete the total synthesis in quantitative yield.

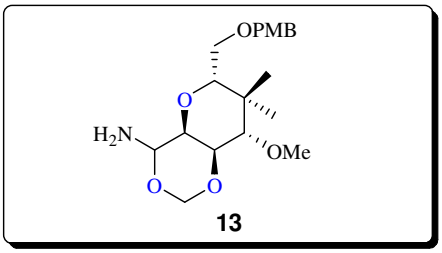
Results and Discussion

Our reterosynthetic analysis of **1** depicted in **Scheme 1**. The disconnection of molecule to the two fragments 1**2**, **13**.

Scheme 1

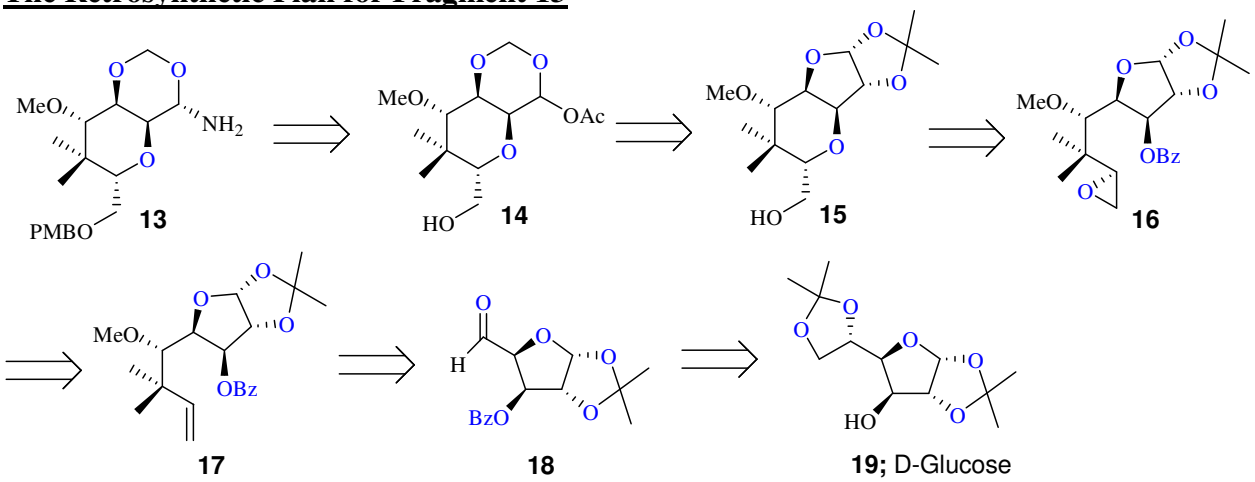


As the left part **12** can be synthesized from any known method available, while the right half of Theeopederin E i.e. **13** can be visualized from D-Glucose as a good starting material to access the fragment easily in a quantative yield. The retrosynthetic plan is given as follows.



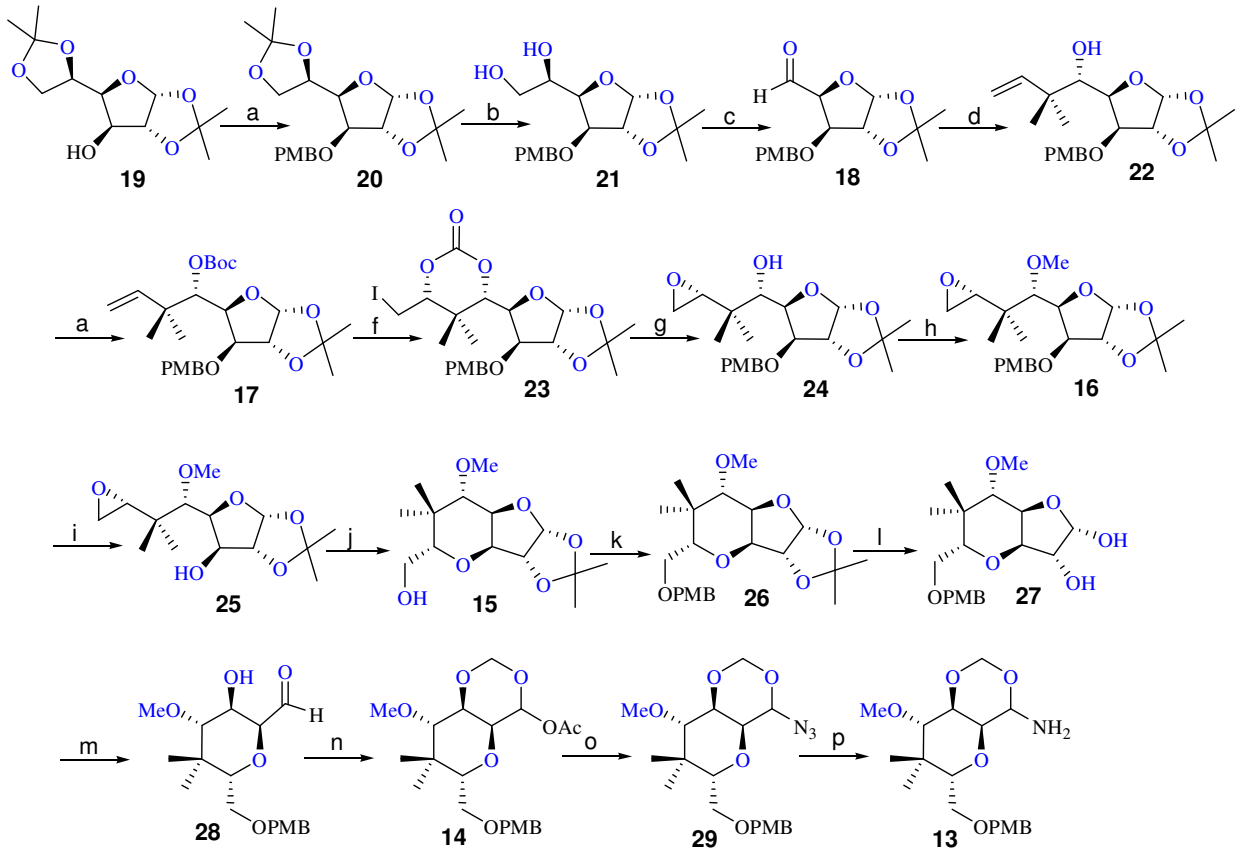
13

The Retrosynthetic Plan for Fragment 13



The synthesis of fragment **13** is outlined in Scheme **03** as follows. The synthesis started from commercially available cheap D-Glucose which was protected as PMB ether which on acidic hydrolysis subjected o oxidative cleavage to give the sugar aldehyde **18**. This aldehyde on prenyllation reaction gives the allylic alcohol **22**. The alcohol was treated with di(tert-butyl) dicarbonate in the presence of DIPEA in MeCN forming the homoallylic *tert*-butyl carbonate **17** in quantative yield, which was prepared for the diastereoselective I_2-induced electrophilic cyclization[7] to introduce the required 1,3 syn diol stereogenic centre. The treatment of **17** with I_2 in MeCN at -20^{o}C formed the iodocarbonate **23**, which was subsequently treated with K_2CO_3 in MeOH to give the desired syn-epoxy alcohol **24**. Further this epoxy alcohol **24** was protected as methyl ether and subsequently deprotected the PMB ether group in DDQ conditions to form the alcohol **25**. Further this alcohol was treated with K_2CO_3 in MeOH to give the pyranose alcohol **15** effectively which was again protected as PMB ether and this pyranose PMB ether alcohol was subjected to reflux conditions to carry the cleavage of 3,4 diol **27**. Again this diol **27**, was subjected to oxidative cleavage to form the aldehyde **28,** which was treated with paraformaldehyde with conc. HCl in THF, which upon simultaneous acetylation afforded the acetate **14**. This acetate **14** was treated with $TMSN_3$ and TMSOTf to transform the anomeric acetate to an azide which on hydrogenation gives the desired amine unit **13** effectively.

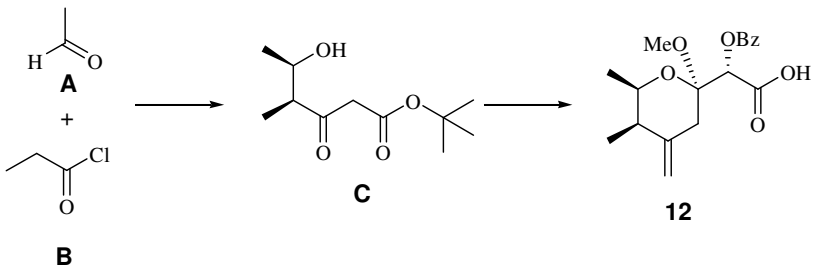
Scheme 03



Reagents & Conditions: a) PMB-Cl, NaH, THF, 0°C-RT; b) 60 % AcOH: H_2O; c) $NaIO_4$, MeOH, sat. $NaHCO_3$; d) Zn, aq. NH_4Cl/THF (2:3), Prenyl Bromide, 0°C; e) $(BoC)_2O$, DIPEA, 0°C-RT; f) ICl, TEA,CH_3CN, -20°C; g) K_2CO_3, MeOH, 0°C-RT; h) MeI, NaH, 0°C-RT; i) DDQ, DCM, 0°C-RT; j) K_2CO_3, MeOH, 0°C-RT; k) PMB-Cl, NaH, THF; 0°C-RT; l) Amberlyst, MeOH, reflux; m) $NaIO_4$, MeOH, sat. $NaHCO_3$; n) i) $(CHO)_n$, Conc. HCl, THF; ii) Ac_2O, DMAP, Pyridine; o) $TMSSN_3$, TMSOTf, CH_3CN, -78 - 0°C ; p) H_2, Pd/C, EtOAc.

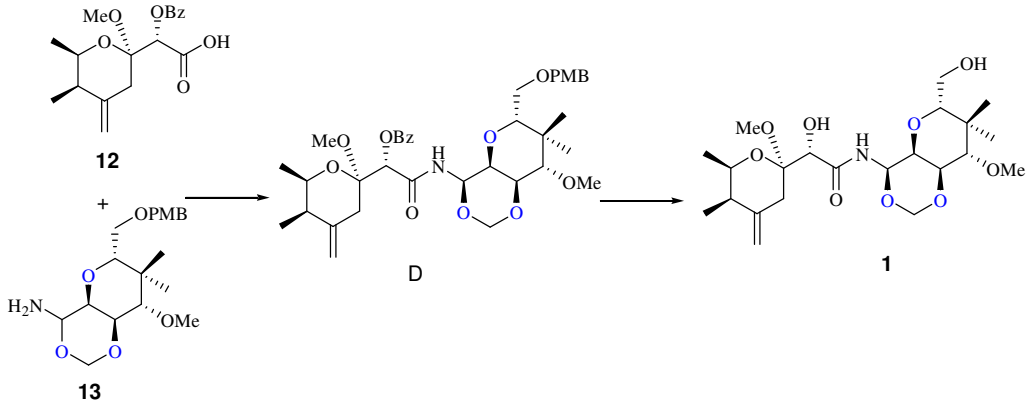
The left side fragment **12**, can be synthesized efficiently using Paul E. Floreancig[6b] approach as follows for in Scheme 04

Scheme 04



Finally coupling of the two partners **12** and **13** was carried out using DCC and DMAP in dichloromethane to get the desired product D, in good amount of yield which on deprotection of PMB ether and hydrolysis gives the Theopederin E **(1)** as follows in Scheme **05.**

Scheme 05



By using the same analogy by changing and making modifications of Scheme 03, we can able to synthesize a diverse variety of Theopedrin and it's different analogues successfully to test these species for more potent activity through a highly feasible high yielding synthesis from a cheap starting material successfully. The different analogues of Theopedrin isolated are summarized below in fig-02 which can be easily synthesized by following the scheme as described as above .

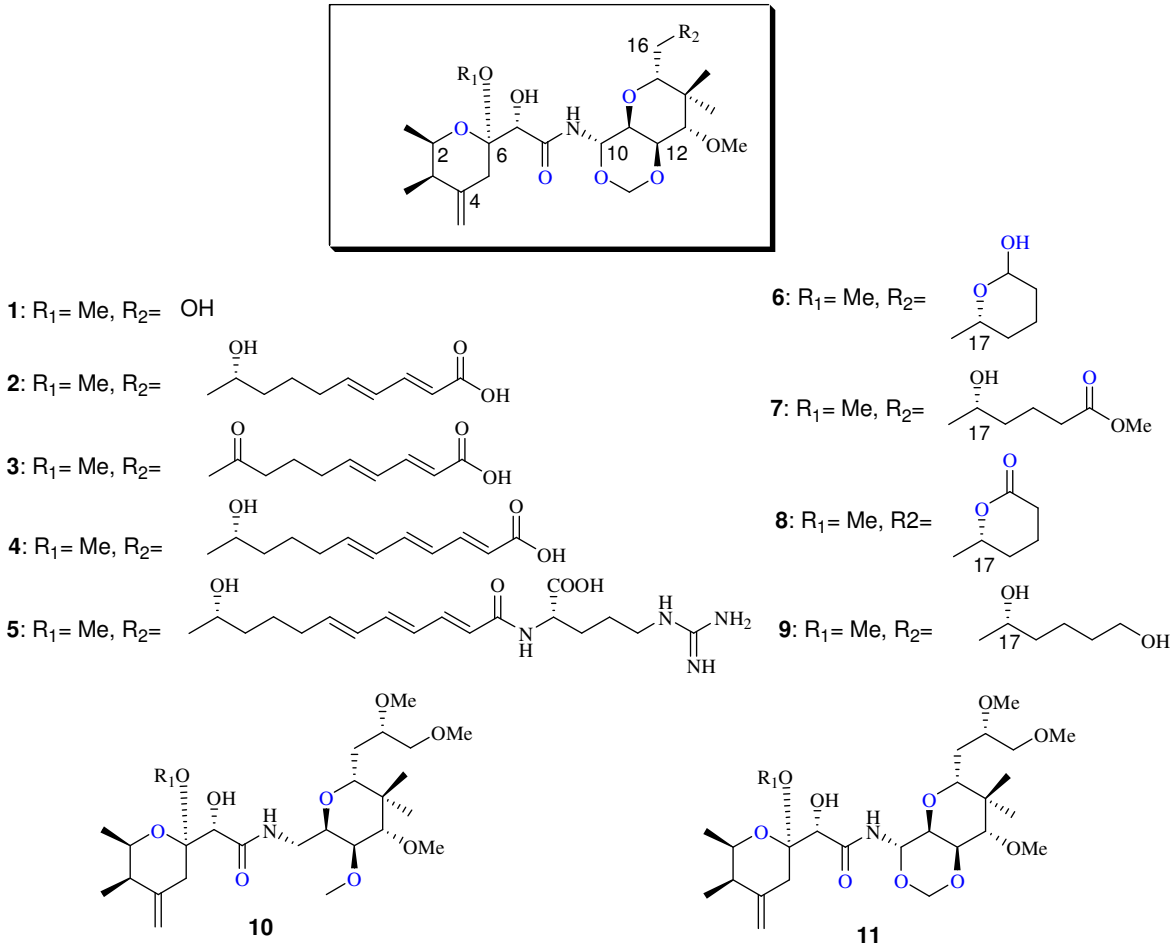
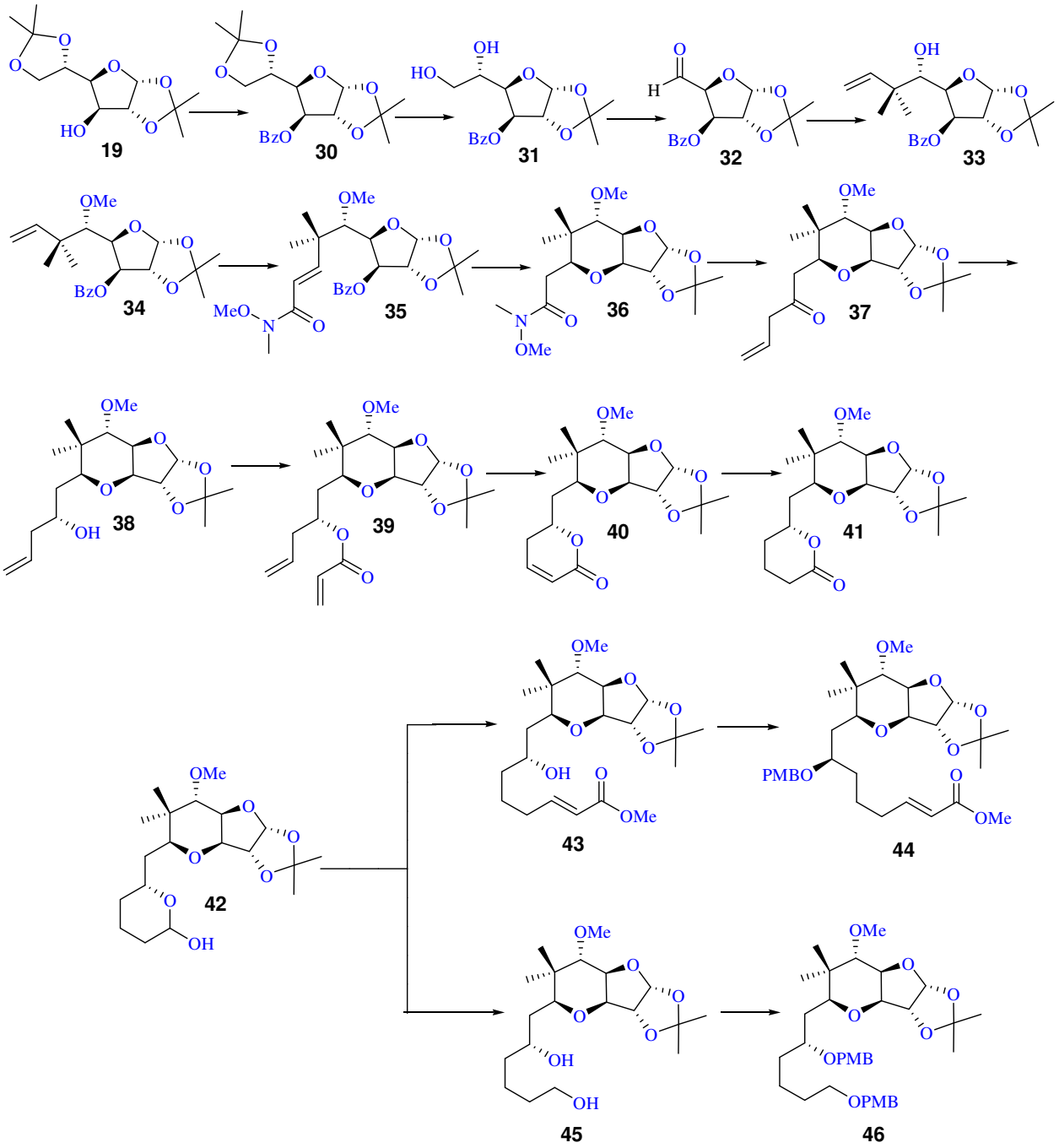


Fig-02

For synthesis of diverse variety of different analogues of Theopederin the following scheme is modified as per functional group group installment and the more potent analogues are synthesized easily as follows.

Scheme-06



Thus following the same procedure described for the synthesis of Theopederin E the right half fragment can be synthesized and coupling with left fragment will give us more potent Theopederin analogues easily in high yield.

In conclusion, we can complete concise and efficient formal synthesis of Theopedrin E and it's analogues successfully. The salient features of this scheme is that

1. Flexible Chiron approach from commercially available cheap starting material i.e D-Glucose
2. Without using any toxic metal catalyst or reagent.
3. With single protecting group synthesis.
4. Little modifications leads to different analogues of Theopedrin.

References

(1) (a) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Am.Chem. Soc.* **1988**, *110*, 4850. (b) Perry, N. B.; Blunt, J. W.; Munro, M.H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223. (c) Simpson, J. S.; Garson, M. J.; Blunt, J. W.; Munro, M. H. G.; Hooper, J. N. A. *J. Nat Prod*. **2000**, *63*, 704. (d) West, L. M.; Northcote, P. T.; Hood, K. A.; Miller, J. H.; Page, M. J. *J. Nat. Prod*. **2000**, *63*, 707.

(2) (a) Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy, G.; Higa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4851. (b) Matsunaga, S.; Fusetani, N.; Nakao, Y. *Tetrahedron* **1992**, *48*, 8369. (c) Kobayashi, J.; Itagaki, F.; Shigemori, H.; Sasaki, T. *J. Nat. Prod*. **1993**, *56*, 976. (d) Vuong, D.; Capon, R. J.; Lacey, E.; Gill, J. H.; Heiland, K.; Friedel, T. *J. Nat. Prod*. **2001**, *64*, 640.

(3) (a) Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem*. **1992**, *57*, 3828. (b) Tsukamoto, S.; Matsunaga, S.; Fusetani, N.; Toh-e, A. *Tetrahedron* **1999**, *55*, 13697. (c) Paul, G. K.; Gunasekera, S. P.; Longley, R. E.; Pomponi, S. A. *J. Nat. Prod*. **2002**, *65*, 59.

(4) (a) Burres, N. S.; Clement, J. J. *Cancer Res*. **1989**, *49*, 2935. (b) Ogawara, H.; Higashi, K.; Uchino, K.; Perry, N. B. *Chem. Pharm. Bull*. **1991**, *39*, 2152. (c) Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Clark, B. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1025. (d) Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Perry, N. B. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1233.

(5) Nishii, Y.; Higa, T., Takahashi, S., Nakata, T. *Tetrahedron Lett.,* **2009**, *50*, 3537.

(6) (a) Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrujia, L.J.; Muir, K.; Boyle, F.T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357. (b) Green, M. E.; Rech, J. C.; Floreancig, P. E. *Angew.chem.Int.Ed.* **2008**, *47*, 7317.

(7) (a) P. A. Bartlett, J. D.Meadows, E. G. Brown,A.Morimoto, K. K. Jernstedt, J. Org. Chem. 1982, 47, 4013; (b) A. Bongini, G. Cardillo, M. Orena, G. Porzi, S. Sandri, J. Org. Chem. 1982, 47, 4626