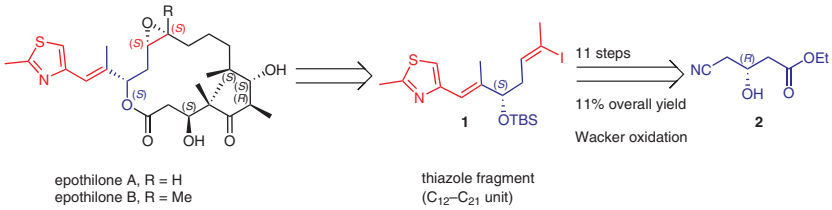
Synlett R. Kommera et al. Letter

A Scalable Approach for the Synthesis of Epothilone Thiazole Fragment (C_{12}–C_{21} unit) Via Wacker Oxidation

Rajashekar Kommera[a,b]
Venkateshwer Reddy Kasireddy[c]
Venkat Reddy Ghojala[b]
Markandeya Bekkam[b]
Pradeep Rebelli[b]
Jayaprakash Rao Yerrabelly*[d,e]

[a] Department of Chemistry, Jawaharlal Nehru Technological University College of Engineering, Hyderabad 500085, India
[b] Department of Research and Development, MSN R&D Center, Pashamylaram, Medak, Telangana 502307, India
[c] Department of Chemistry, CMR Engineering College, Jawaharlal Nehru Technological University, Hyderabad 501401, India
[d] Department of Chemistry, University College of Science, Saifabad, Osmania University, Hyderabad 500004, India
[e] Department of Organic Chemistry, Telangana University, Nizamabad, Telangana 503322, India
yjpr_19@yahoo.com



Received: 17.12.2017
Accepted after revision: 29.01.2018
Published online:
DOI: 10.1055/s-0036-1591942; Art ID: st-2017-b0907-l

Abstract A new scalable synthesis of the common thiazole fragment (C_{12}–C_{21} unit) of epothilone family of molecules (epothilone A–D) has been developed via palladium-catalyzed Wacker oxidation as a key step using (*S*)-2,2,3,3,9,9,10,10-octamethyl-5-vinyl-4,8-dioxa-3,9-disilaundecane, which has been prepared from commercially available chiral synthon (*R*)-ethyl-4-cyano-3-hydroxybutanoate. Then further chemical modifications using Horner–Wadsworth–Emmons reaction and Wittig reaction result in the common thiazole fragment (C_{12}–C_{21} unit) in good yields.

Key words thiazole fragment, epothilone, Wacker oxidation, ixabepilone, C_{12}–C_{21} unit of epothilone

Natural products play an important role in the drug discovery, especially, in the treatment of an incurable disease like cancer, which affects one in every three persons in the developed countries. Around 47% of the anticancer drugs in the market are from natural products or natural product derived compounds.[1] The epothilones, discovered by Höfle et al.[2,3] from the fermentation of myxobacterium, *Sorangium cellulosum*, have potential anticancer properties. These epothilones (Figure 1) have high in vivo activity but show moderate in vitro cytotoxicity.[4] However, the epothilones are being paid much more attention towards the development of new chemical entities due to their easy synthesis and are more amenable to modification. Ixabepilone is one of the semi-synthetic analogues[5] of epothilone B, has been developed by Bristol–Mayers Squibb and got approval in 2007 by FDA for the treatment of breast cancer under the trade name of Ixempra.

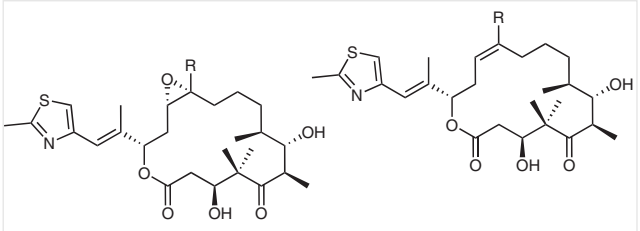
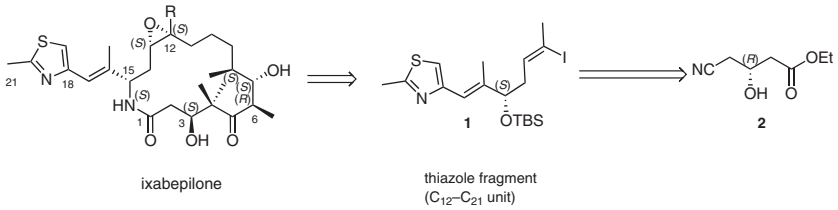


Figure 1 Structures of the epothilones A, B, C and D

In the present study, as a part of research on ixabepilone synthesis, we report a new scalable synthetic approach for the preparation of common thiazole fragment **1** (C_{12}–C_{21} unit) in epothilone family by involving Wacker oxidation as a key step. This thiazole building block **1** was reported in preceding synthesis[6,7] which includes the establishment of a chiral center at C15 carbon by Sharpless resolution. The preparation of thiazole fragment precursor **9** was also reported in literature,[8–10] based on the Brown enantioselective allyl boration reaction to introduce a stereocenter at C15 carbon or asymmetric biochemical synthesis. It is well known to the person skilled in the art, that using a chiral synthon will give more advantages than the resolution of chiral center in later stages. Hence, we opted for an alternate technique for the preparation of this thiazole fragment **1** by employing a chiral synthon **2** (Scheme 1).

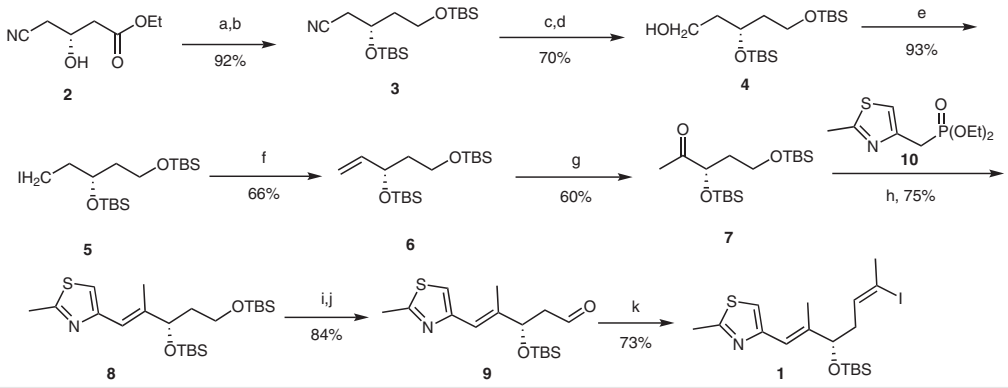


Scheme 1 Retrosynthesis of ixabepilone from chiral synthon **2**

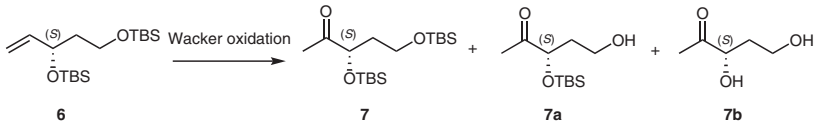
The current study (Scheme 2) was started by selecting the (*R*)-ethyl-4-cyano-3-hydroxybutanoate (**2**) as the starting material, since it is commercially available[11] in the required enantiomerically pure form. This chiral synthon **2**, was reduced under the prominent reducing conditions,[12] using sodium borohydride in methanol to yield the corresponding diol in good yield. With the diol compound in hand, the efforts were continued to protect the alcohol function groups, using various protecting reagents such as acetyl chloride, *p*-methoxybenzyl ether, *tert*-butyldimethylsilyl chloride, trimethylsilyl chloride and *tert*-butyldimethylsilyl chloride (TBDMS-Cl). Among all reagents TBDMS-Cl protection yielded the new diprotected cyano compound **3** in quantitative overall yield from **2** (92%). This diprotected cyano compound **3** on further reduction with DIBAL-H at lower temperature yielded the corresponding aldehyde in good yield. But thus obtained aldehyde was found to be unstable for longer periods of time; hence we went ahead to the next stage without storing the aldehyde. This aldehyde on reduction with sodium borohydride gave the alcohol **4** in 70% overall yield from compound **3**.

Alcohol **4** was converted to the corresponding iodide **5** by treating with iodine, triphenylphosphine and imidazole[13] with 93% yield. The crude iodo compound **5** obtained by this process was pure enough to proceed further without purification. This iodo compound **5** on treatment with potassium *tert*-butoxide in THF at 0 °C underwent elimination reaction to yield the alkene product **6**. This alkene **6** was further converted into the desired methyl ketone compound via Wacker oxidation, which has prominent position in conversion of terminal alkenes to methyl ketones (Scheme 3).

For the first attempt the reported Wacker oxidation conditions[14] were employed by using palladium(II) chloride and copper(I) chloride at 25 °C under balloon pressure of oxygen (Table 1, entry 1). Under these conditions reaction was sluggish. To enhance the rate of reaction, the tempera-



Scheme 2 Synthesis of thiazole fragment (C_{12}–C_{21} unit). *Reagents and conditions*: (a) $NaBH_4$, MeOH, 0 °C to r.t., 8 h; (b) TBDMS-Cl, imidazole, DMAP, DMF, 75 °C, 7 h; (c) DIBAL-H, CH_2Cl_2, –78 °C, 2h; (d) $NaBH_4$, MeOH, 0 °C to r.t., 2 h; (e) imidazole, TPP, I_2, CH_2Cl_2, 0 °C to r.t., 1 h; (f) *t*-BuOK, THF, 0 °C, 2 h; (g) O_2, $PdCl_2$, $Cu(OAc)_2·H_2O$, DMA, H_2O, 40 °C, 30 h, TBS-Cl, imidazole, DMAP, DMF, 75 °C, 2 h; (h) NaHMDS, THF, –78 °C to r.t., 12 h; (i) (*D*)-camphor sulphonic acid, MeOH, 0°C, 4 h; (j) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t., 2 h; (k) ethyl triphenyl phosphonium iodide, THF, *n*-BuLi, –10 °C, 30 min then I_2, –78 °C to –30°C then NaHMDS, 1 h.



Scheme 3 Wacker oxidation and possible impurities

ture was raised to 30 °C and 40 °C (Table 1, entries 2 and 3, respectively). At 40 °C, not surprisingly, monodeprotected **7a** and dideprotected **7b** products were formed in major concentration. The basic assumption of this result was the by-product, HCl, releasing in Wacker oxidation handled the deprotection of **7**. To conclude the assumption we tried an experiment at 40 °C by replacing copper(I) chloride with copper(II) chloride (Table 1, entry 4). This condition caused the sharp increase (90%) in the concentration of dideprotected intermediate **7b**. Based on this conclusion, we switched over to modified Wacker oxidation condition[15] reported by Smith et al. in 1998, by replacing the oxidizing reagent, copper(I) chloride with copper(II) acetate (Table 1, entry 5). This condition yielded the required intermediate **7** in major concentration, along with **7a** and **7b** in minor concentration. This reaction was also tried by changing the catalyst, palladium(II) acetate (Table 1, entries 6 and 7), but it did not succeed. Finally, we continued our work by doing silylation of the crude reaction mass under standard TBS protection conditions to afford the compound **7** in 60% yield.

Table 1 Reaction Conditions and Reagents used for Wacker Oxidation Reaction[a]

Entry	Catalyst (0.08 equiv)	Oxidizing reagent (1 equiv)	Temp (°C)	7 (%)	7a (%)	7b (%)
1	$PdCl_2$	CuCl	25 °C	No reaction		
2	$PdCl_2$	CuCl	30 °C	No reaction		
3	$PdCl_2$	CuCl	40 °C	ND[b]	30	70
4	$PdCl_2$	$CuCl_2$	40 °C	ND[b]	10	90
5	$PdCl_2$	$Cu(OAc)_2$	40 °C	80	15	5
6	$Pd(OAc)_2$	$CuCl_2$	40 °C	No reaction		
7	$Pd(OAc)_2$	$Cu(OAc)_2$	40 °C	No reaction		

[a] All reactions were monitored by TLC and described results are isolated yields after 24 h maintenance.
[b] ND: Not detected.

Compound **7** was treated with phosphonate **10**[6] in the presence of sodium hexamethyldisilazane (NaHMDS) under Horner–Emmons condition giving compound **8** with 75% yield. The intermediate **8** was then subjected to selective deprotection by using *D*-camphor sulphonic acid in methanol followed by oxidation with Dess–Martine periodinane giving **9** with a good average yield (84%). Compound **9** underwent *Z*-selective Witting reaction with 1-iodoethyl triphenylphosphorane[16] leading to the desired thiazole fragment **1** in 60% yield as the chirally pure stereoisomer.

In conclusion, an alternate synthetic approach to thiazole fragment (C_{12}–C_{21} unit) has been achieved in 11 steps and 11% overall yield, by using commercially available chiral synthon, (*R*)-ethyl-4-cyano-3-hydroxybutanoate (**2**). In this report, we have presented an alternative route to the synthesis of thiazole fragment (C_{12}–C_{21} unit) via Wacker oxidation. Moreover, the whole process for the preparation of intermediates and final product do not require chromatographic separation, allowing it to be performed on a large scale (greater than 100-g scale in our hands) and facilely transferable to an industrial scale.

Acknowledgment

One of the authors (Rajashekar Kommera) thanks the HOD's Osmania University and JNTU Hyderabad for giving opportunity to pursue Ph.D. We express our sincere thanks to Dr. M.S.N. Reddy, S. Eswaraiah, S.T. Rajan (MSN Laboratories pvt. Ltd.) for providing facilities to do this research work.
This is MSNRD communication number 22.s

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591942.

References and Notes

(1) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461.
(2) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem.* **1996**, *35*, 1567.
(3) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 560.
(4) Cortes, J.; Baselga, J. *Oncologist* **2007**, *12*, 271.
(5) Goodin, S. *Am. J. Health Syst. Pharm.* **2008**, *65*, S10(10 Supplement 3).
(6) Schinzer, D.; Limberg, A.; Böhm, O. M. *Chem. Eur. J.* **1996**, *2*, 1477.
(7) Schinzer, D.; Limberg, A.; Böhm, O. M.; Bauer, A. *Chem. Eur. J.* **1999**, *5*, 2483.
(8) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R.V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974.
(9) Taylor, R. E.; Chen, Y. *Org. Lett.* **2001**, *3*, 2221.
(10) Reiff, E. A.; Nair, S. K.; Narayan Reddy, B. S.; Inagaki, J.; Henri, J. T.; Greiner, J. F.; Georg, G. I. *Tetrahedron Lett.* **2004**, *45*, 5845.
(11) For the import data and price of ethyl 4-cyano-3-hydroxybutanoate in India (Zauba), see: https://www.zauba.com/import-ethyl-4-cyano-3-hydroxy-butanoate-hs-code.html.
(12) Soai, K.; Oyamada, H.; Ookawa, A. *Synth. Commun.* **1982**, *12*, 463.
(13) Crimmins, M. T.; Slade, D. J. *Org. Lett.* **2006**, *8*, 2191.
(14) Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth., Coll. Vol. 7*; Wiley: New York, **1990**.
(15) Smith, A. B. III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765.
(16) Schinzer, D.; Bauer, A.; Schieber, J. *Chem. Eur. J.* **1999**, *5*, 2492.