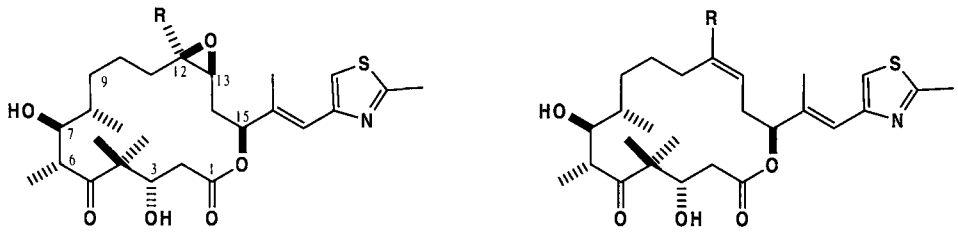
Total Syntheses of Epothilones B and D

Jae-Chul Jung, Rajashaker Kache, Kimberly K. Vines,

Yan-Song Zheng, and Mitchell A. Avery [1,2,3]

1Department of Medicinal Chemistry, School of Pharmacy, 2Department of Chemistry, and National Center for Natural Products Research, University of Mississippi, *P.O. Box 1848, University, Mississippi 38677–1848*

The naturally occurring macrolactones, epothilones A (**1**) and B (**2**) (Figure 1), first isolated and characterized by Höfle *et al.*, from the myxobacterium *Sorangium cellulosum*, have evoked a great deal of interest in recent years due to their novel molecular architecture and taxol–like, antitumor mechanism of action. Both the taxanes and the epothilones exert their therapeutic effects by promoting tubulin polymerization and the formation of stable microtubules, thereby causing cell death through disruption of the normal microtubule dynamics. Since the discovery of the epothilones in 1993, more than 500 reports have been published, further indicating the interest in this class of compounds. Taxol® (paclitaxel) is currently used in the chemotherapy of a broad range of tumor types including breast, ovarian, lung, head, neck, and AIDS–related cancers (Karposi's sarcoma). Taxol® also has activity in malignancies that are refractory to conventional chemotherapy, including previously–treated lymphoma and small–cell lung cancers. Unfortunately, the effectiveness of taxol® has been hampered by the emergence of multi–drug resistance and by side–effects (hypersensitivity, neurotoxicity, and hematological toxicity). Furthermore, the development of multi–drug resistance in patients treated with Taxol® fuels the need for the development of additional chemotherapeutics which possess potency equal to or greater than Taxol® without the associated undesirable characteristics. Most significantly, epothilones, unlike paclitaxel (Taxol®), are equally active against drug–sensitive and multidrug–resistant cancer cell lines *in vitro* and epothilone B has shown potent *in vivo* antitumor activity in Taxol®–resistant human tumor models. Epothilone B is currently undergoing phase II clinical trials.

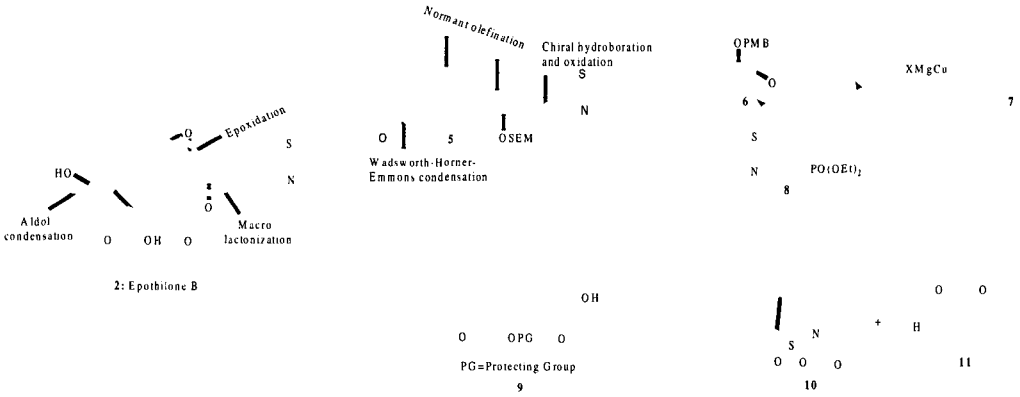


1: R = H, Epothilone A
2: R = Me, Epothilone B

3: R = H, Epothilone C
4: R = Me, Epothilone D

Figure 1. Structures of epothilones A–D (**1**–**4**)

A convergent, total synthesis of epothilones B (**2**) and D (**4**) will be discussed. The key steps are Normant coupling to establish the desired (*Z*)–stereochemistry at C12–C13, Wadsworth-Emmons olefination, diastereoselective aldol condensation of aldehyde **5** with the enolate of keto acid derivatives to form the C6–C7 bond, selective deprotection, and macrolactonization. Retrosynthetic analysis of epothilones B (**2**) and D (**4**) reveals a convergent, two-step sequence involving a double–diastereoselective aldol condensation of aldehyde **5** and keto acid **9** (derived from acetyl sultam **10** and keto aldehyde **11**), followed by Yamaguchi macrolactonization to give the target framework (Scheme 1). The (*Z*)–olefin, an essential feature of the epothilones, has traditionally been prepared by Wittig olefination methods or ring–closing metathesis approaches. We envisioned utilizing the classic Normant alkyne cupration reaction and electrophile trapping to establish not only the necessary (*Z*)–stereochemistry of olefin **5**, but also to fix the stereochemistry at C9 (**5**) in a single step. Organocuprate **7**, propyne and PMB–protected epoxy alcohol **6** could be coupled to accomplish this goal. Furthermore, the resulting Normant alkyne cupration product would provide easy access to fragment **5** through a reaction sequence involving deprotection, oxidation and Wadsworth–Horner–Emmons condensation.



Scheme 1. Retrosynthetic analysis of epothilone B (**2**)