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Studies of the Total Synthesis of Epothilone B and D: A Facile Synthesis of C7-C14 and C15-C21 Fragments

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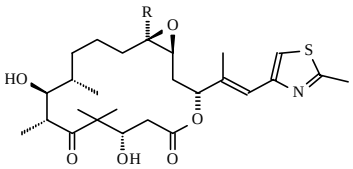
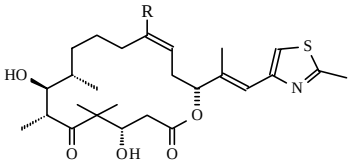
Abstract: A mild and highly efficient synthesis of C7-C14 and C15-C21 fragments of epothilone B and D is described in which racemic C7-C14 fragment is prepared from nerol through four steps, and C15-C21 fragment is obtained from 1, 3-dichloroacetone, thioacetamide and propionaldehyde.

Keywords: Epothilone B and D, anticancer drugs, nerol, synthesis.

Epothilones **1-4** represent a new class of natural products with taxol-like effects. They have a greater advantage over taxol for effects on taxol-resistant tumors and possess more water solubility. Due to their interesting molecular architecture and considerable potential in medicine, total syntheses of these macrolides and analogues have been reported[1].



1 R=H,epothilone A
2 R=Me,epothilone B



3 R=H, epohtione C
4 R=Me,epothilone D

In vitro and *in vivo* evaluation showed that epothilone B **2** and epothilone D **4** are potential taxol successors[2]. In this paper we would like to report our preliminary results towards the synthesis of epothilone B and D.

Retrosynthetic analysis of our approach to epothilones indicated that the three fragments C1-C6, C7-C14 and C15-C21 are the key intermediates (**Scheme 1**). With these structures in hand, our strategy is to coustruct the C14-C15 bond from sulfone coupling and to form C6-C7 bond through aldol condensation and finally to conclude the total synthesis with Yamaguchi macrolactonization

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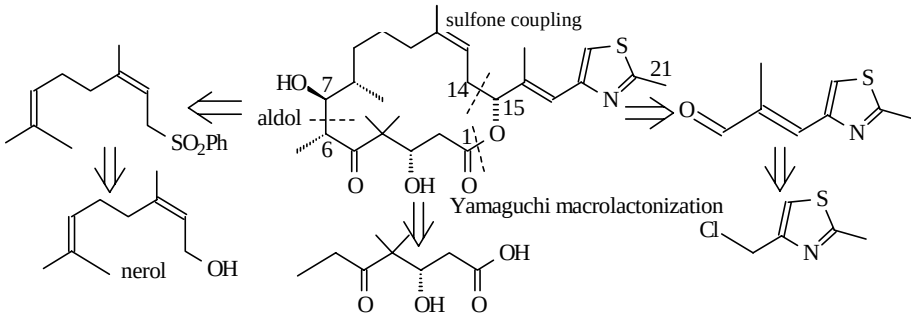
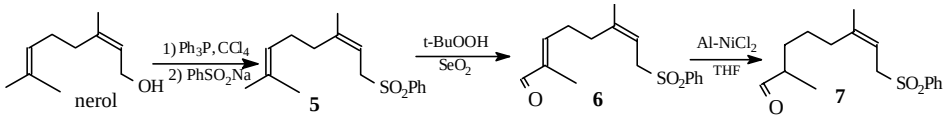
Scheme 1 Retrosynthetic analysis of epothilone B and D

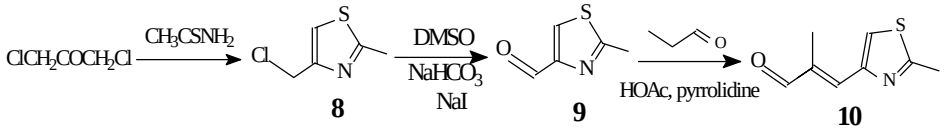


Scheme 2 Synthesis of C7-C14 fragment



Commercially available nerol has the carbon skeleton with trisubstituted Z-double bond,was used as starting material, which was converted into sulfone **5**[3] according to reference[3], **5** was oxidized to α, β-unsaturated aldehyde **6** by use of t-BuOOH with catalytic SeO_2. Reduction of **6** with Al-$NiCl_2$[4] furnished the saturated aldehyde **7** as C7-C14 fragment[5](**Scheme 2**).

Scheme 3 Synthesis of C15-C21 fragment



For the synthesis of the C15-C21 fragment, reaction of 1, 3-dichloroacetone and thioacetamide provided 4-(chloromethyl)-2-methyl-1, 3-thiazole **8**[6] in 78% yield[7]. Oxidation of **8** using DMSO together with $NaHCO_3$ and NaI afforded aldehyde **9** in 50% yield,which was reacted with propionaldehyde in the presence of pyrrolidine and acetic acid to provide the desired C15-C21fragment, a known α, β-unsaturated aldehyde **10** in 60% yield which is a key constituent of epothilones (**Scheme 3**). The spectra data of aldehyde **10** were in satisfactory agreement with the reported data[6]. It should be mentioned that the present methold for the preparation of aldehyde **10** has the follow advantages over the reported:(a) mild reaction conditions and simple experimental procedure (b) the yields are good and reproducible (c) all the reagents are not expensive and all the reactions show actom economy (d) applicable to a large scale synthesis.

Connection of C7-C14 and C15-C21 fragments, synthesis of C1-C6 fragment and

total synthesis of epothilone B and D will be reported in due course.

In conclusion, we have developed an efficient synthetic approach to C7-C14 and C15-C21 fragments of epothilone B and D from commercially available nerol, 1, 3-dichloroacetone, thioacetamide and propionaldehyde.

Acknowledgment

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References and Notes

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5. **7:** ^{1}HNMR(90MHz,$CDCl_3$) δ :1.08(s,3H,-CH_3),1.34(s,3H,CH_3C=C), 2.17(s,1H), 2.3 (m,6H, 3×CH_2),3.85(d,2H,-CH_2SO_2Ph),5.20(br,1H,=CH-),7.5-7.9(m,5H,C_6H_5-), 9.60 (s,-CHO). IR: 2930,2715,1720,1585,1305,1085cm^{-1}
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7. All the yields in this paper are not optimum.

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