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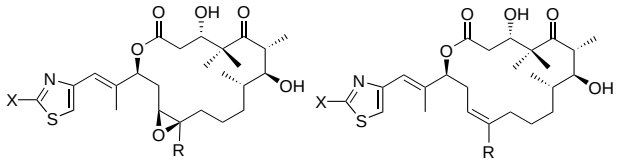
Stereoselective Total Synthesis of Epothilones by the Metathesis Approach Involving C9–C10 Bond Formation**

Jian Sun and Subhash C. Sinha*

Epothilones A – F (**1** – **6**, Scheme 1), a new family of natural products initially isolated by Höfle et al. from myxobacteria,[1] exhibited remarkably high anticancer activity,[2] especially to taxol-resistant cell lines. These compounds possess a taxol-like mode of action and function through the stabilization of



1: Epothilone A; R = H, X = Me
2: Epothilone B; R = X = Me
3: Epothilone C; R = H, X = Me
4: Epothilone D; R = X = Me
5: Epothilone E; R = H, X = CH_2OH
6: Epothilone F; R = Me, X = CH_2OH

Scheme 1. Structures of naturally occurring epothilones, **1** – **6**.

cellular microtubules.[3] The structural novelty of these compounds and the growing awareness of potential advantages shown by them over taxol, including a higher level of cytotoxicity against multidrug-resistant (MDR) cell lines and better water solubility, spurred interest in their total synthesis.[4] In the past six years, a large number of publications have emerged on the partial and total synthesis of epothilones.[5]

Ring-closing metathesis (RCM) is undoubtedly one of the three most successful and efficient methods used to construct the 16-membered macrolide ring of epothilones.[6] Compound **I** and its analogues are metathesized to establish the C12–C13 bond of the corresponding macrolide. The metathesis, however, always yields a $\approx$1:1 mixture of the *E* and *Z* isomers (**II** and **III**, Scheme 2).[7, 8] Furthermore, the subsequent epoxidation of the C12–C13 double bond in **II** and **III** gives a mixture of α and β-diastereoisomers of **IV** – **VII**, in an approximate ratio ranging from 1:1:1:1 to 3:3:5:1, depending upon the substitution pattern at C12 and C13. Thus, a substantial portion (55 – 75%) of the precursor is transformed to the undesired products (**V** – **VII**), which limits the usefulness of this approach to the stereospecific synthesis of epothilones.

To circumvent these problems, we decided to explore RCM of dienes such as **7**, to form the C9–C10 bond after all the

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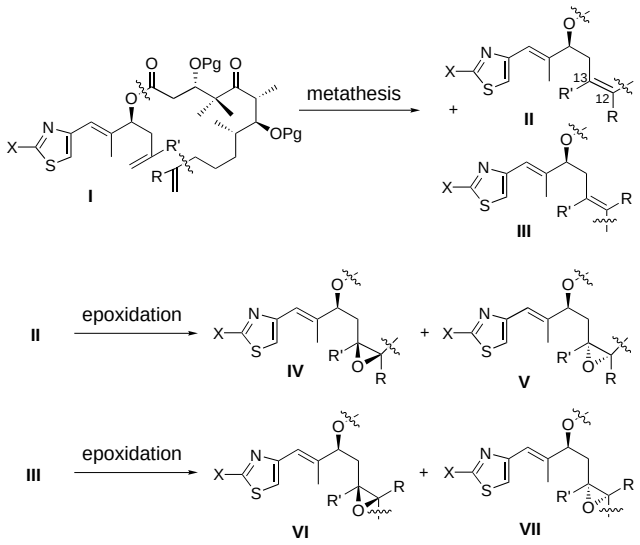
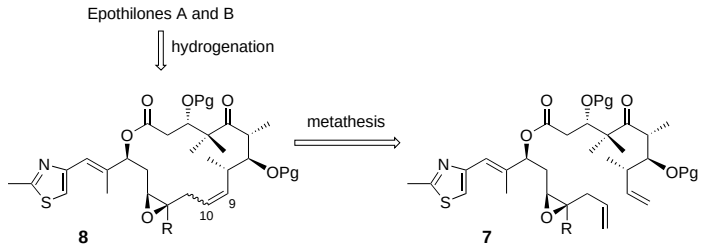
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.



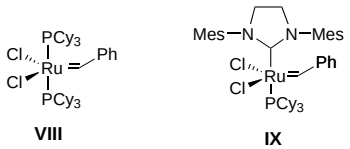
Scheme 2. RCM route to the synthesis of epothilones and their analogues by the formation the of C12–C13 double bond (Pg = H, TBS; X = Me, CH_2OH, SMe; R = H, Me; R′ = H, Me, Et; etc).

chiral centers were stereoselectively installed (Scheme 3). A selective hydrogenation of the C9–C10 bond in the expected product **8**, followed by deprotection, should afford epothilones without the formation of undesired isomers.



Scheme 3. Proposed RCM route to the stereoselective synthesis of epothilones A and B by the formation of the C9–C10 bond (epothilone A, Pg = TBS, R = H; and epothilone B, Pg = TBS, R = Me).

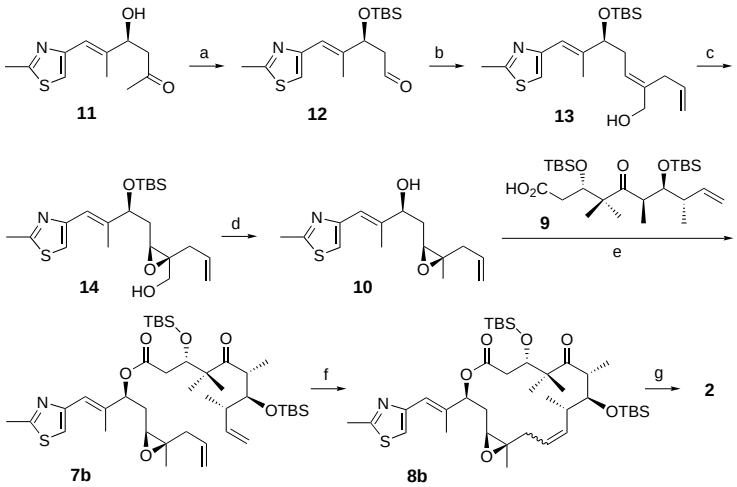
The proposed metathesis approach to form the C9–C10 bond in the total syntheses of epothilones was investigated by Danishefsky and co-workers.[9] In a model system with less functionality around the olefins, the metathesis took place in the presence of various metathesis catalysts, including the Grubbs catalyst **VIII**.[10] Unfortunately, the metathesis of the fully functionalized



dienes (**7** and analogues) did not take place using **VIII** and other metathesis catalysts known at that time.[9] Failure of the RCM of compounds **7** and their derivatives was attributed to the highly functionalized C3–C8 region of the molecule, which renders the macrocyclization energetically unfavorable.

Recently, Grubbs and co-workers reported a very efficient catalyst **IX** that possesses significantly improved activity over **VIII**.[11] The improved activity of **IX** stems from the greater electron-donating property of the dihydroimidazolylidene ligand than the tricyclohexyl phosphane. We noticed that, unlike with **VIII**, the metathesis of diene **I** (R′ = H, R = Me; R′ = Me or Et, R = H) could be achieved very simply with **IX** to form a tri-substituted C12–C13 double bond in epothilones D, F[12], and 13-alkylepothilones.[13] Hence, a remarkable capability of the catalyst **IX** to establish multisubstituted C=C bonds by RCM in the epothilone system led us to assume that the RCM at the C9–C10 site could be achieved by this new catalyst. We confirmed this speculation in the synthesis of epothilone B (**2**).

Compound **7b** was synthesized from two immediate precursors, acid **9** and thiazole alcohol **10** (Scheme 4). Compound **9** was synthesized from a known aldol compound in six steps.[14] The thiazole alcohol **10** was prepared from the aldol compound **11** via the aldehyde **12**[12] and allylic alcohol **13**.[15] Sharpless asymmetric epoxidation of **13** afforded the epoxide **14** in more than 95% *ee*. Deoxygenation of the primary alcohol in **14** was achieved as described by Nicolaou et al. in a related system[15] and then the secondary alcohol was deprotected to afford the alcohol **10**. Esterification of **9** and **10** afforded the key intermediate **7b**. Metathesis of **7b** (3 mM solution in CH_2Cl_2) with 30% of catalyst **IX** in CH_2Cl_2 at reflux temperature took place smoothly. All of the starting compound disappeared completely after 48 h to afford new products, which were characterized as **8b** (*E*:*Z* = 1:1) from an ^{1}H NMR spectrum and mass spectrometry analyses. Hydrogenation of the newly formed C9–C10 double bond in **8b**,[16, 17] followed by deprotection of the *tert*-butylsilyl (TBS)



Scheme 4. Stereoselective synthesis of epothilone B (**2**), by the formation of the C9–C10 bond. Key: a) reference [12]; b) reference [15]; c) Ti-(*i*OPr)$_4$, (+)-DET, TBHP, CH_2Cl_2, (85%, >95% *ee*); d) 1. TsCl, Et_3N, CH_2Cl_2, (90%), 2. NaI, acetone, (95%), 3. $NaBH_3CN$, HMPA, 4. TBAF, THF, (65%); e) EDC, DMAP, CH_2Cl_2, 0 °C, 2–8 h, (82%); f) **IX**, CH_2Cl_2, 45 °C, 8–48 h, (89%); g) see references [16] and [17]. DET = diethyl tartrate, TBHP = *tert*-butyl hydroperoxide, TsCl = Tosyl chloride, HMPA = hexamethyl phosphoramide, TBAF = tetrabutylammonium fluoride, EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, DMAP = 4-dimethylaminopyridine.

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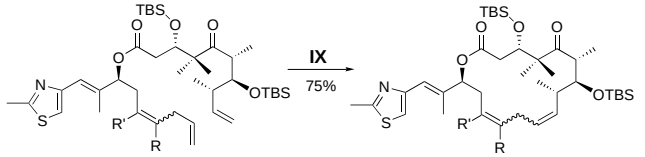
protected hydroxyl groups, resulted in **2** as a single enantiomer.

This metathesis approach could also be utilized for a stereoselective synthesis of other natural and non-natural epothilones. For example, the metathesis of compound **7a** (diastereomeric mixture at epoxide carbons) with 30% of catalyst **IX** in CH_2Cl_2 also took place satisfactorily at reflux temperature, as was the case with **7b**. Consistent with the report by Danishefsky et al., reaction of **7a** with catalyst **VIII** did not afford any desired product.[9] Compounds **15a** and **15b**, which contained a double bond between C12–C13, were also effectively metathesized by the catalyst **IX** to give the corresponding products (**16a** and **16b**), respectively.[18] Removal of all of the protecting groups in **16b** with HF.py (py = pyridine), followed by hydrogenation, Sharpless asymmetric epoxidation (SAE), and deoxygenation of the primary hydroxyl group, furnished epothilone B; this is the second successful stereoselective synthesis of epothilone B by metathesis at the C9–C10 bond (Scheme 5).[19]



15a: R = H, R' = Me (mixture of *EZ* dienes)
15b: R = CH_2OMOM, R' = H (only *Z* isomer)
16a: R = H, R' = Me (mixture of *EZ-EZ* dienes)
16b: R = CH_2OMOM, R' = H (mixture of *Z-EZ* dienes)

Scheme 5. Metathesis of dienes **15a** and **15b**, which results in the formation of the C9–C10 bond; MOM = methoxymethyl.

In summary, we have shown that ring-closing metathesis at the C9–C10 site for the total synthesis of epothilones can be achieved with the Grubbs second-generation catalyst **IX**. In contrast to the Grubbs first-generation catalyst **VIII**, this new catalyst **IX** was found to be highly active, and overcame the high-energy barrier of the intramolecular, macrocyclic ring-closing metathesis of a highly functionalized system such as **7** and **15**. This approach, originally conceived by Danishefsky and co-workers,[9] now leads to a highly stereoselective synthesis of epothilones by the RCM route as shown by the total synthesis of epothilone B.

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