Synthetic Methodologies for the Preparation of Epothilones and Analogs

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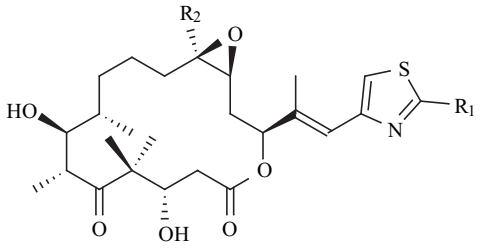
Abstract: Epothilones are natural products present in the myxobacterium *Sorangium cellulossum* strain 90. Due to their antitumoral activity, they are good candidates for the treatment of various forms of cancer, and epothilones B and D and some synthetic analogs are actually under advanced clinical trials. This review describes the synthesis of epothilones A and B and some of their analogs.

Keywords: Epothilone, antitumor compounds, total synthesis.

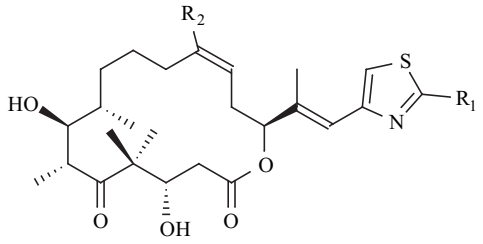
1. INTRODUCTION

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells that invade and disrupt other tissues, spreading to other areas of the body. In the middle Europe and USA, it is the second leading cause of death, after the cardiovascular diseases [1].

Antimitotic agents that target tubulin, including the taxanes and vinca alkaloids, are important compounds of current anticancer therapy. The success of these drugs is related to their mechanism of action, which leads to disruption of cell division and induction of apoptosis [2]. The clinical use of these agents is limited by the emergence of drug-resistant tumor cell and toxicity. To overcome these obstacles, several research groups have focused their efforts on developing new agents that target tubulin.



Epothilone A (**1**) R_1 = Me, R_2 = H
Epothilone B (**2**) R_1 = R_2 = Me
Epothilone E (**3**) R_1 = CH_2OH, R_2 = H



Epothilone C (**4**) R_1 = Me, R_2 = H
Epothilone D (**5**) R_1 = R_2 = Me
Epothilone F (**6**) R_1 = CH_2OH, R_2 = H

Fig. (1). Structures of natural occurring epothilones.

Epothilones (Fig. **1**) are a class of compounds isolated in 1993 from the myxobacterium *Sorangium cellulossum* strain 90 [3]. The exact structure of epothilone A was determined using X-ray crystallography in 1996 [4]. This class of compounds possesses important microtubule binding affinity and antitumor properties [5-7].

Due to the higher potency of these new compounds and their effectiveness against certain drug-resistant tumor cell lines, epothilones became a synthetic target for numerous research groups [8]. This review will focus on the different synthetic methodologies reported in the literature to prepare epothilones A and B and some of their analogs.

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2. TOTAL SYNTHESIS OF EPOTHILONES

2.1. The Danishefsky Group Strategies

The first total synthesis of both epothilones A and B, including their respective deoxy precursors C and D, were carried out in the working group of S. J. Danishefsky [8-10].

The main strategies used for the construction of the macrocycle include a macroaldolization reaction [9-11], an olefin metathesis approach [11, 12], and a macrolactonization procedure [11]. Three key step reactions were employed: Suzuki-type coupling, aldol reaction and a stereoselective Noyori reduction [12] (Fig. **2**).

2.1.1. The First Generation Ring-Closing Olefin Metathesis (Approach I, Fig. 2)

Initially, a strategy in which the C9-C10 bond would be formed during the macrocyclization reaction was chosen. Two key intermediates **11** [11, 12] and **18** [10, 11] were synthesized as shown in scheme **1**. Compound **11** was synthesized from β-benzyloxy(isobutyraldehyde) **7**: a titanium cyclocondensation, followed by a reduction with lithium aluminum hydride provided glycal **8**. Compound **9** was obtained by oxidative solvolytic fragmentation of a cycloproprane intermediate. After reductive deiodination of **9** and triphenylsilylation, cleavage of the pyran ring afforded dithioacetal **10**. Protection of alcohol, followed by olefin formation and liberation of the aldehyde function led to intermediate **11**.

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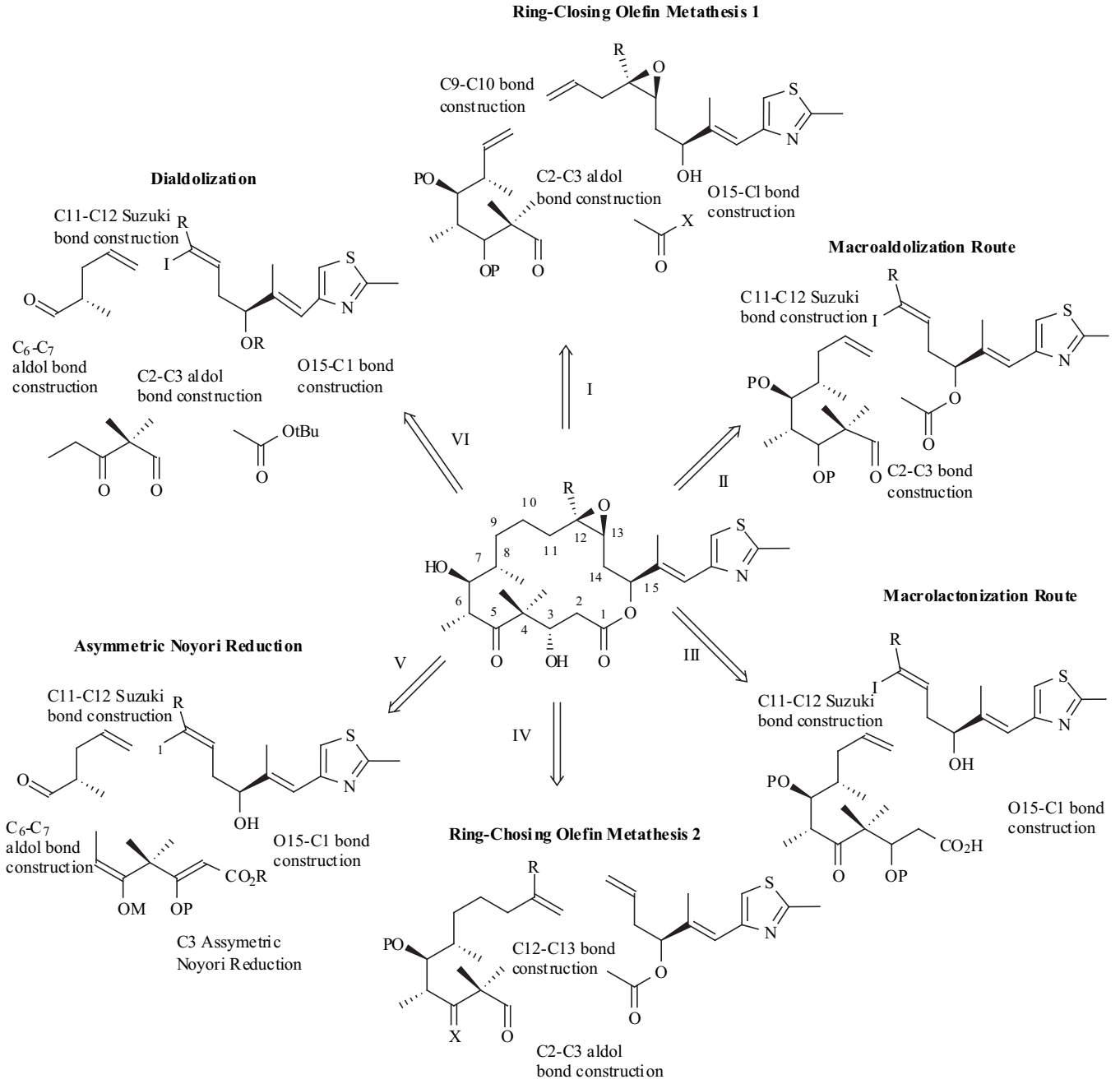


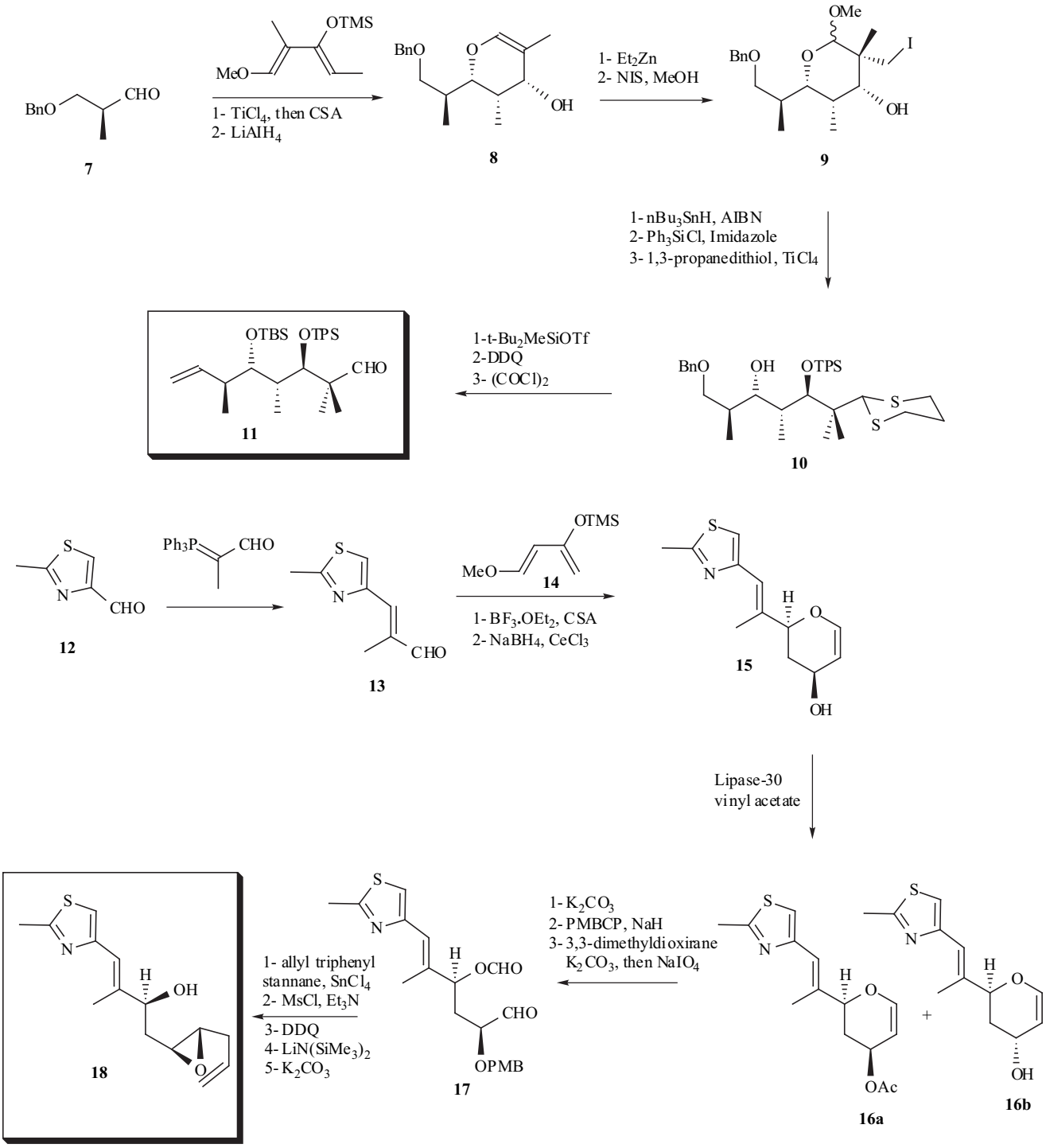
Fig. (2). Retrosynthetic disconnections for the synthesis of epothilones.

Aldehyde **12** was elongated in a Wittig-type reaction with a commercially available phosphorane, leading to aldehyde **13**. Compound **13** was then reacted with butadiene **14**, giving rise to a racemic dihydropyrone, which was reduced to racemic compound **15**. This racemic alcohol was reacted with vinyl acetate in the presence of Lipase-30 to afford alcohol **16b** and acetate **16a**. The latter was deacylated, reacted with sodium hydride and *p*-methoxybenzyl chloride, and then with 3,3-dimethyldioxirane. After reaction with sodium periodate compound **17** was obtained, further reaction of **17** with allyltriphenyl stannane, followed by mesylation, deprotection of the *p*-methoxybenzyl group and cyclization of the hydroxymesylate with lithium hexamethyldisilazide afforded the key intermediate **18**.

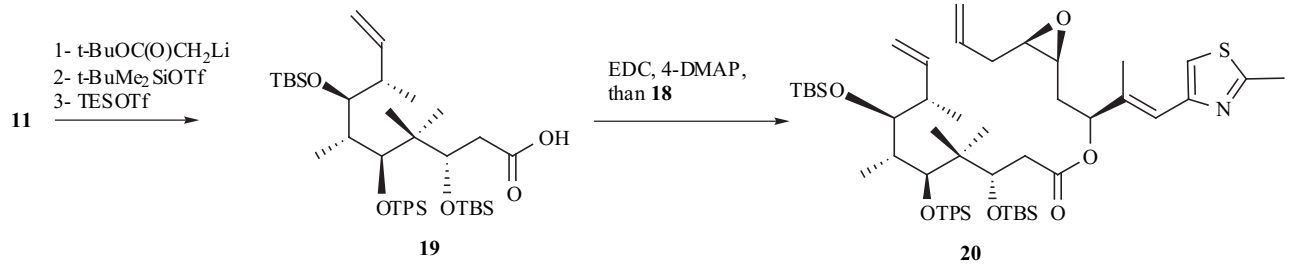
Aldehyde **11** was converted to acid **19** (scheme **2**). Coupling of the latter with alcohol **18** produced the metathesis substrate **20**. Submission of this substrate to a range of conditions and catalysts produced complicated mixtures containing only trace amounts of the desired cyclized product.

2.1.2. B-alkyl Suzuki Strategy (Approaches I and II)

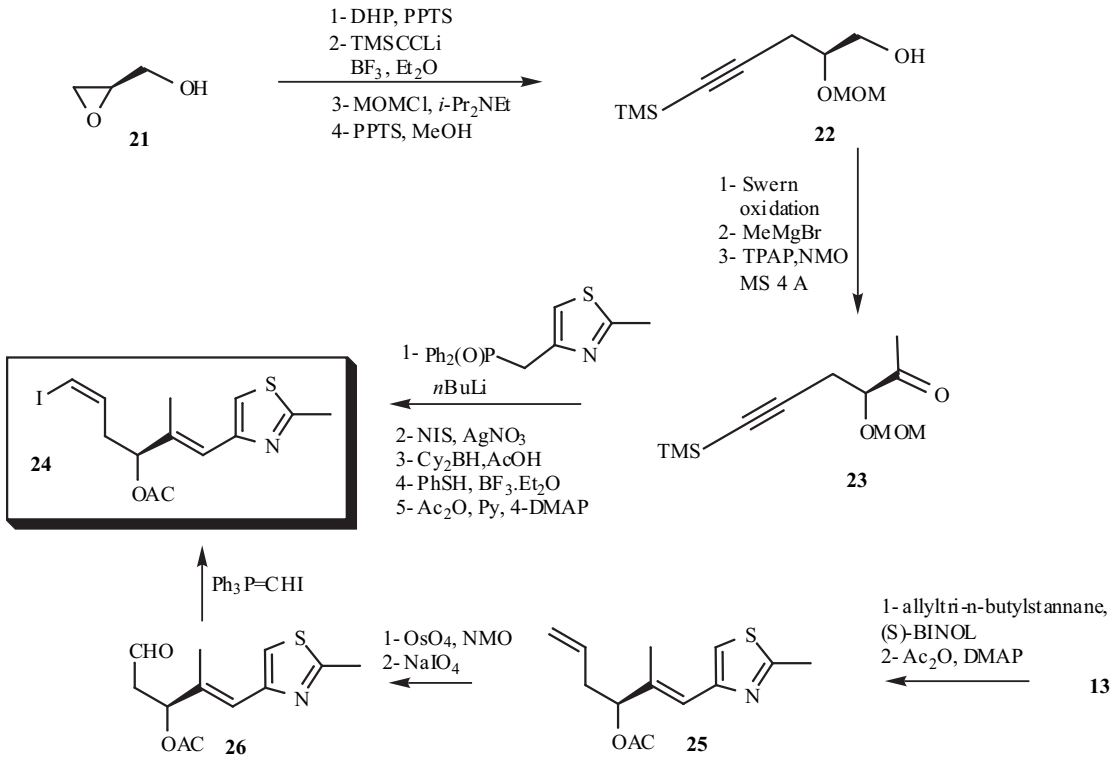
The first successful synthesis of epothilones A and B was achieved by the alkyl Suzuki method [10, 11]. Intermediates **24**, **29** and **32** (schemes **3** and **4**) were first synthesized, and the application of a stereospecific *B*-alkyl Suzuki coupling permitted the establishment of *cis* C12-C13 olefins **33** and **35** (scheme **5**).



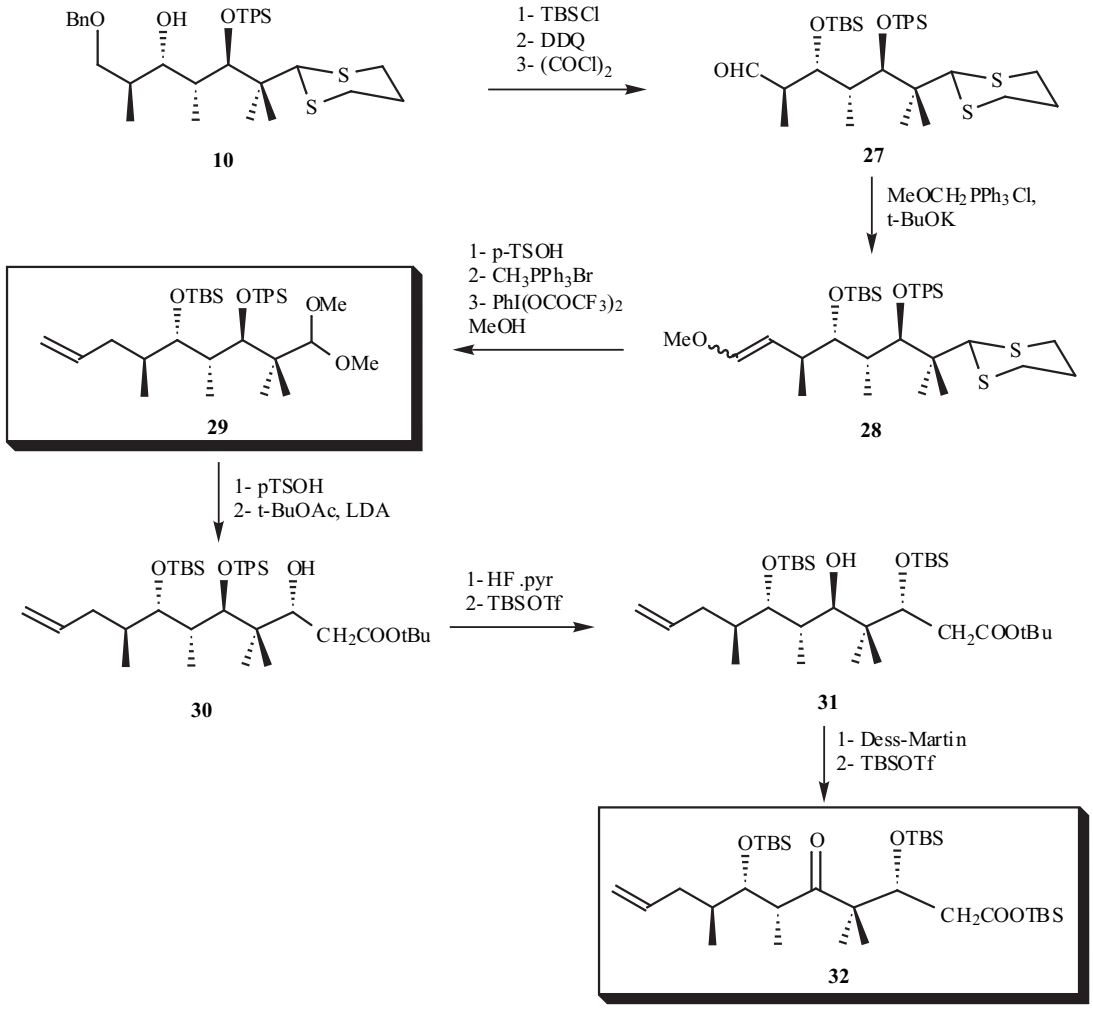
Scheme 1. Danishefsky's synthesis of key compounds **11** and **18**.



Scheme 2. Danishefsky's synthesis of metathesis substrate **20**.



Scheme 3. Danishefsky's synthesis of intermediate **24**.

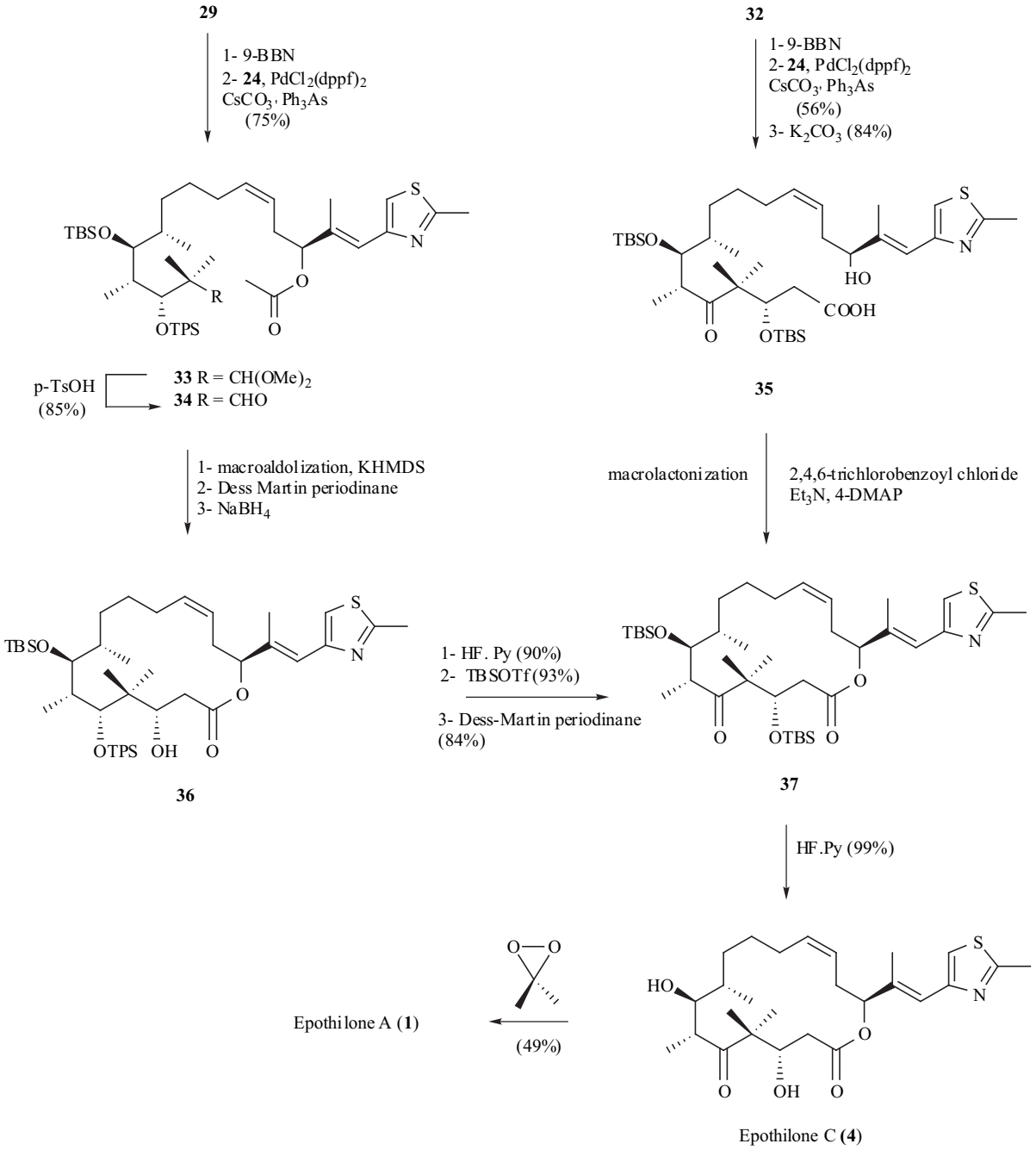


Scheme 4. Synthesis of intermediates **29** and **32**.

The synthesis of the alkyl fragment started with commercially available R-glycidol **21**, which was converted, *via* its THP derivative, into alcohol **22**. Compound **22** was converted to its methyl ketone **23**. The introduction of the thiazoyl nucleus was accomplished through an Emmons reaction. The resultant alkyne was converted into Z-iodoalkene **24**. A more concise synthesis of **24** was achieved from enal **13**, using first an allylation reaction with tri-*n*-butylstannane in the presence of (S)-BINOL. Protection of the resulting carbinol and oxidative cleavage of the acetate intermediate **25** generated β-acetoxyaldehyde **26**. Wittig reaction of the latter gave compound **24**.

Compound **10** was converted to aldehyde **27** (scheme **4**) and coupled to (methoxymethyl)triphenyl phosphorane to give **28**. The latter was subjected to sequential hydrolysis and Wittig reaction, and was then transformed in dimethyl acetal **29.** Another Suzuki coupling partner was synthesized: acetal **29** was deprotected and condensed with *tert*-butyl acetate, giving compound **30** as the major product. Compound **31** was isolated after selective cleavage of the triphenylsilyl function from the C5 oxygen and selective silylation of the C3 alcohol. C5 alcohol was then oxidized, and the *tert*-butyl ester was converted to *tert*-butyldimethylsilyl ester **32**.

The fragments of the Suzuki coupling were then assembled in two ways (scheme **5**). Hydroboration of **29**, followed by reaction with vinyl iodide **24**, in presence of palladium (II) complex gave acetate **33**, which was converted



Scheme 5. Danishefsky's macroaldolization and macrolactonization; synthesis of epothilones C and A.

to aldehyde **34**. In the same way, reaction of ketoester **32** with compound **24** gave rise to the hydroxy acid **35**.

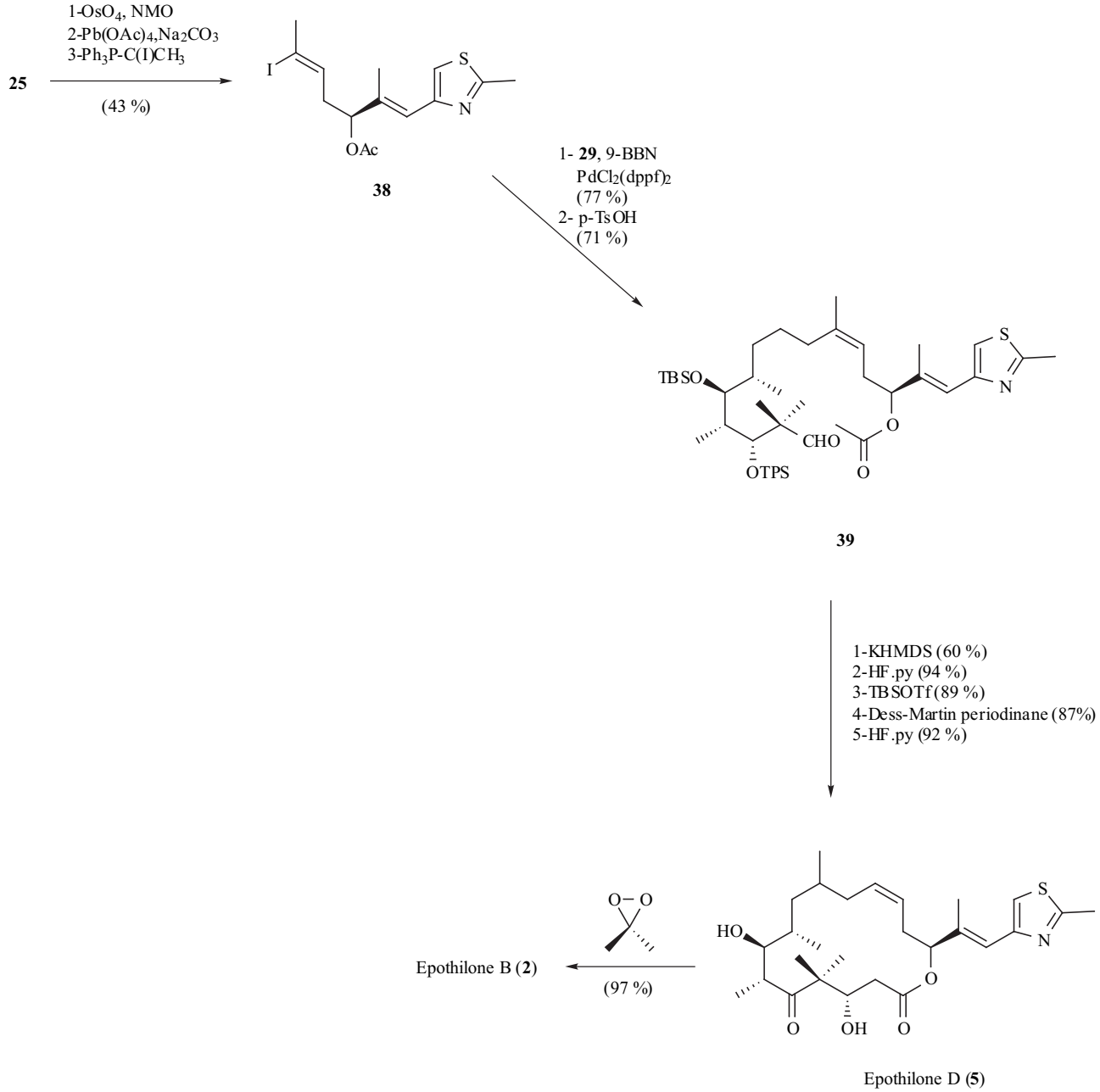
Macroaldolization of aldehyde **34** was accomplished using potassium hexamethyldisilazide, leading to the desired macrocycle **36**. Cleavage of the triphenyl silyl ether produced diol **37** which was converted to epothilone C. Epoxidation reaction of **4** with 3,3-dimethyldioxirane allowed the formation of epothilone A.

Macrolactonization of compound **35** under Yamaguchi conditions led to intermediate **37**, and then to epothilone A, accomplishing the second route.

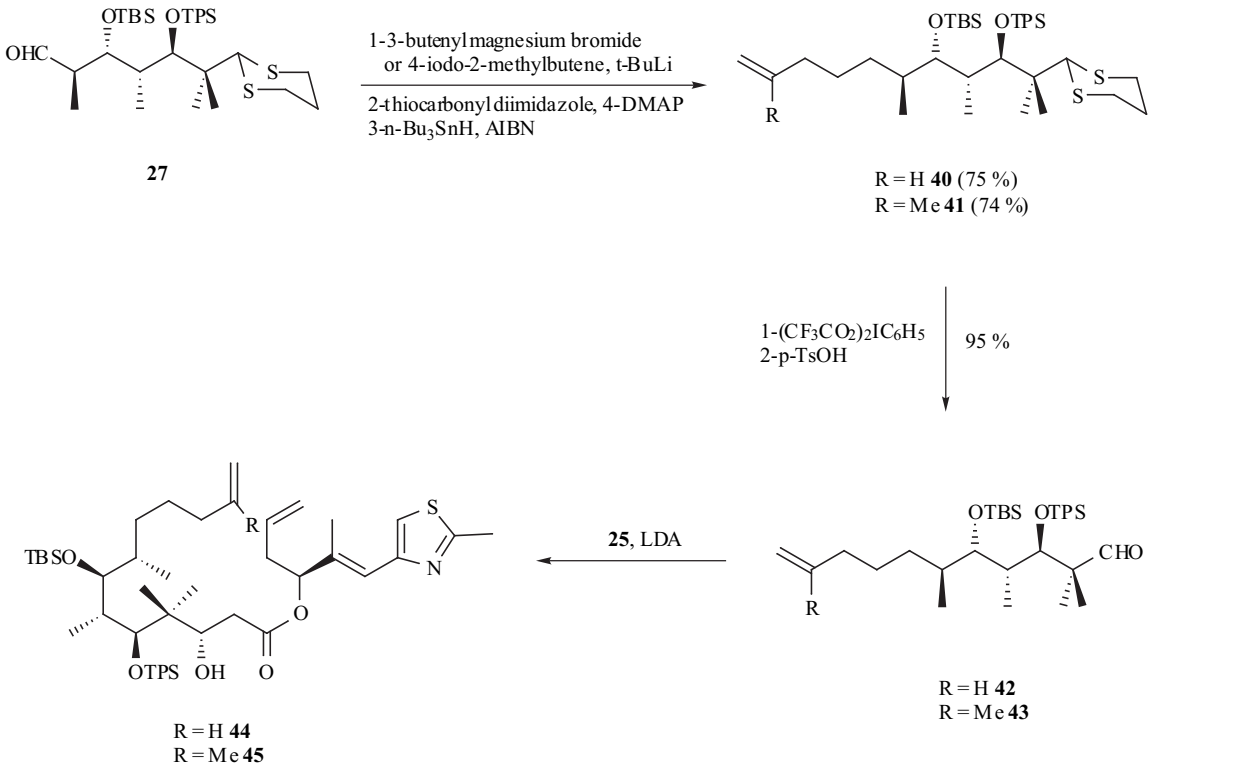
The macroaldolization reaction was also used to obtain epothilone B, starting from compound **25** (scheme **6**), which was cleaved to its correspondent aldehyde and then reacted with the appropriate Wittig reagent, leading to vinyl iodide **38**. Hydroboration of acetal olefin **29** and subsequent coupling of the resulting borane with **38** gave, after cleavage of the acetal group, aldehyde **39**. Using the same reactions as previously described for compound **34**, aldol condensation afforded epothilone D, which was epoxidized to epothilone B.

2.1.3. The Second Generation Ring-Closing Olefin Metathesis Strategy [10-13] (Approach IV)

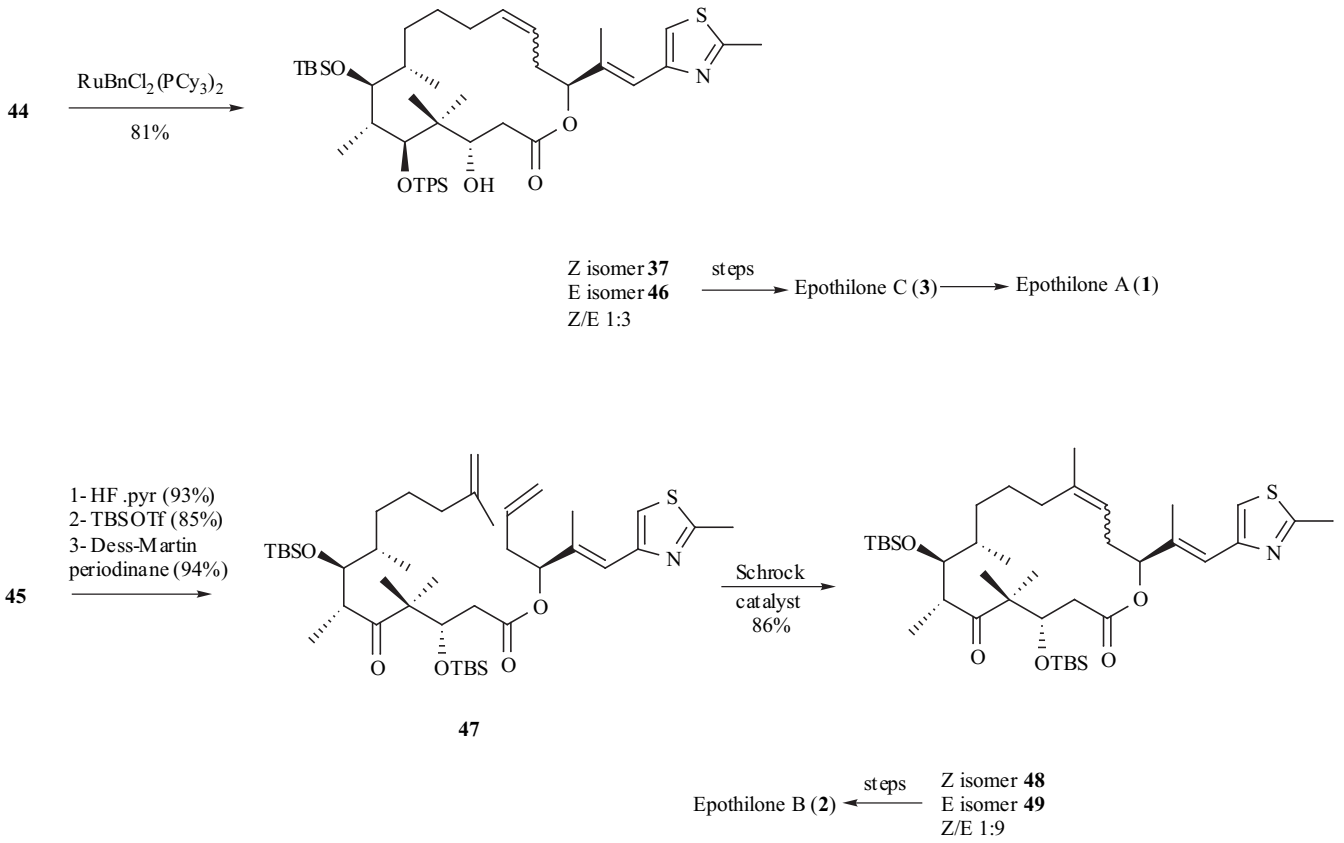
After the accomplishment of the first synthesis of epothilones A and B, the possibility of intramolecular olefin metathesis was re-investigated, focusing on the formation of C11-C12 bond during the metathesis reaction. Thus,



Scheme 6. Danishefsky's synthesis of epothilones B and D.



Scheme 7. Preparation of metathesis intermediates **44** and **45**.



Scheme 8. Danishefsky's synthesis of epothilones A and B using RCM strategy.

thioacetal aldehyde **27** was converted to compounds **40** and **41** through butenylation (or isobutenylation) and deoxygenation at C9. Cleavage of the dithiane provided aldehydes **42** and **43**.

An intermolecular condensation of the ester enolate derived from **25** with aldehydes **42** and **43** gave substrates **44** and **45** respectively.

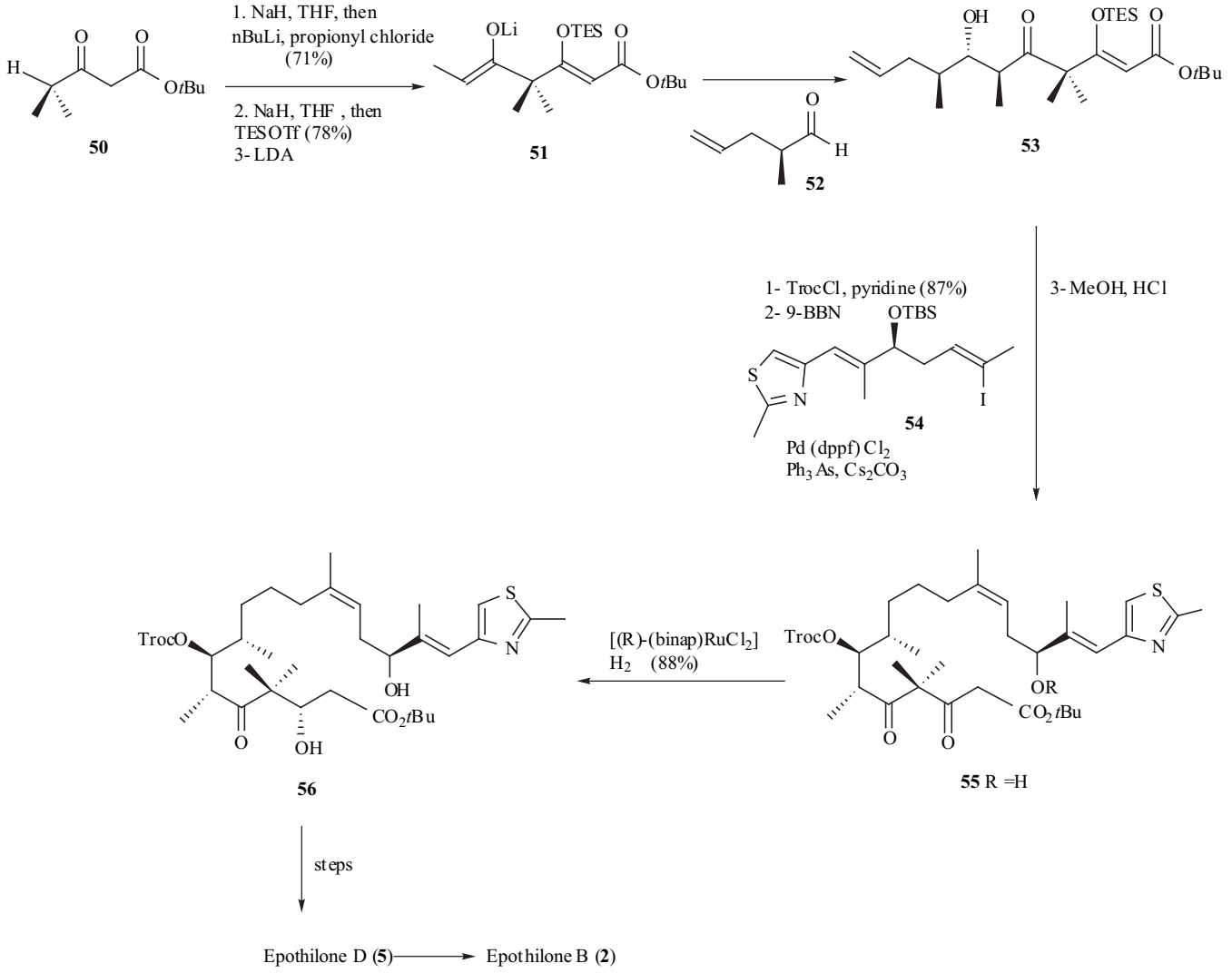
Olefin metathesis of compounds **44** and **47**, using respectively the ruthenium-based catalyst of Grubbs and the molybdenum-based catalyst of Schrock afforded the cyclized products, as mixtures of E/Z olefins. Both E- isomers **46** and **49** were deprotected and converted to the corresponding epothilones A and B.

2.1.4. Stereoselective Noyori Reduction [14, 15]

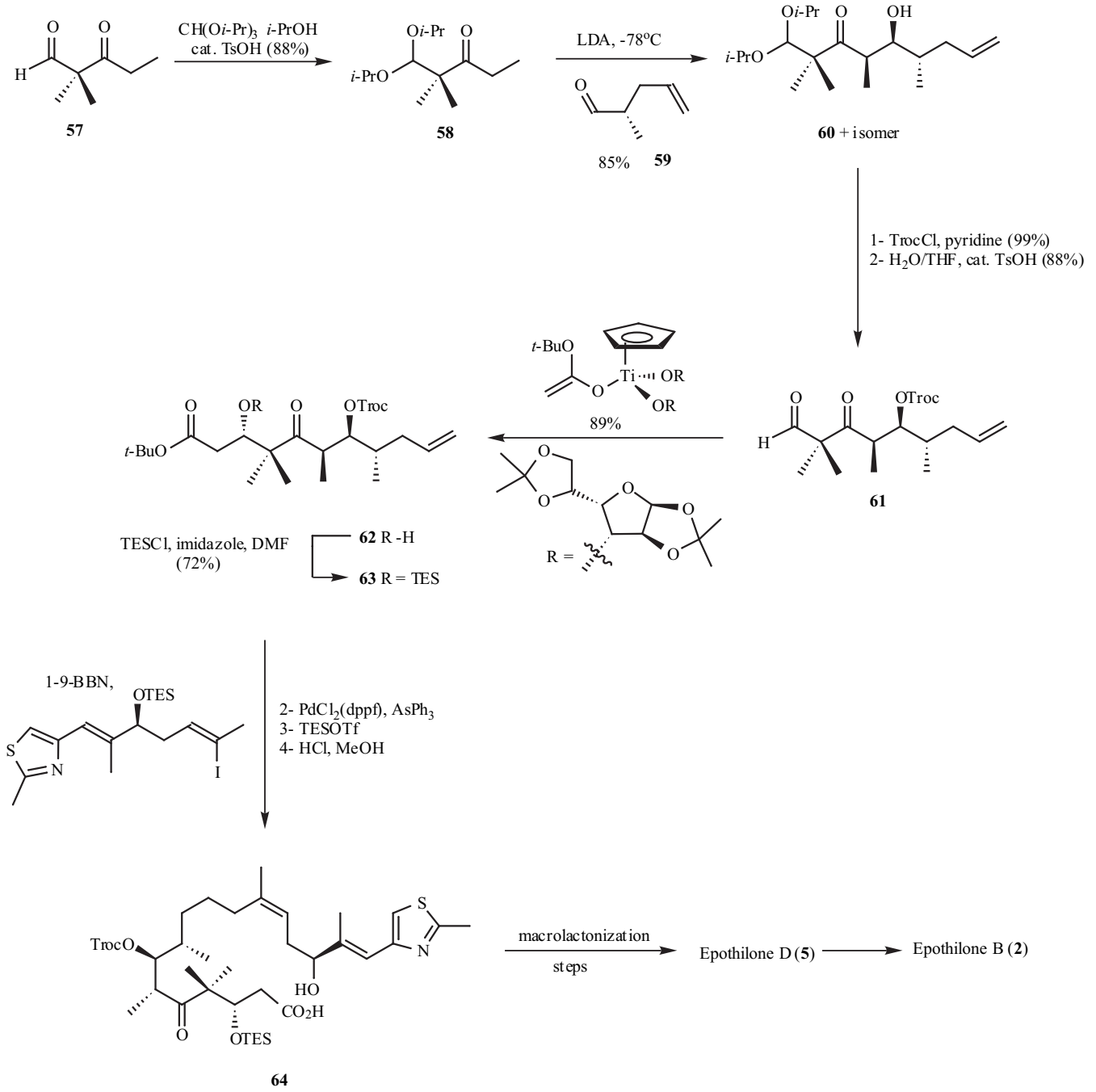
The synthesis of epothilones had to be improved, due to the need of quantities of products for assays in animals. Compound **53** was readily prepared from **50** (scheme **9**). Aldol reaction between dienolate **51** and the available (S)-aldehyde **52** provided the desired C6-C7 *syn* stereochemistry. Suzuki coupling of **53**, with the previously described vinyl iodide **54** [10] afforded, after removal of the protecting group in C-15, olefin **55**. Asymmetric catalytic reduction of **55**, under modified Noyori conditions [16], gave diol **56**. The latter was then converted to epothilones D and B, using known methodologies.

2.1.5. Dialdolization [17]

Ketoaldehyde **57** was protected as a di-isopropylacetal, and the resultant ketone was subjected to an aldol reaction with **59**, giving a mixture 4:1 of aldol adducts. The major compound **60** was protected, and further hydrolysis furnished ketoaldehyde **61**. The second asymmetric aldol reaction afforded the desired compound **62** with a high diastereoselectivity. Protection of the C-3 alcohol and functional group manipulation lead to compound **63**. The B-alkyl Suzuki coupling with the adequate vinyl iodide gave intermediate **64**, which was converted to epothilone B as previously described.



Scheme 9. Danishefsky's aldol condensation and asymmetric Noyori reduction.



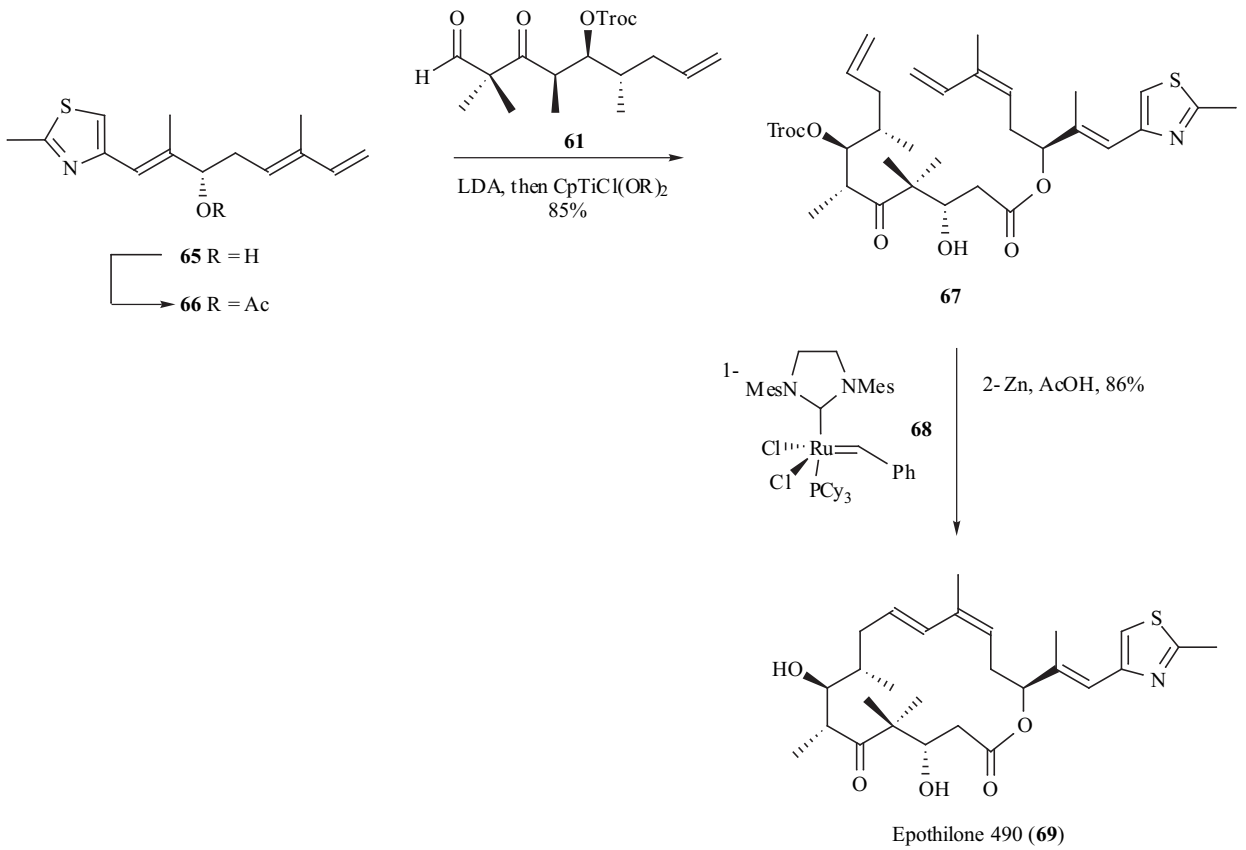
Scheme 10. Danishefsky's synthesis of epothilone B by dialdolization.

2.1.6. Analogs of Epothilones

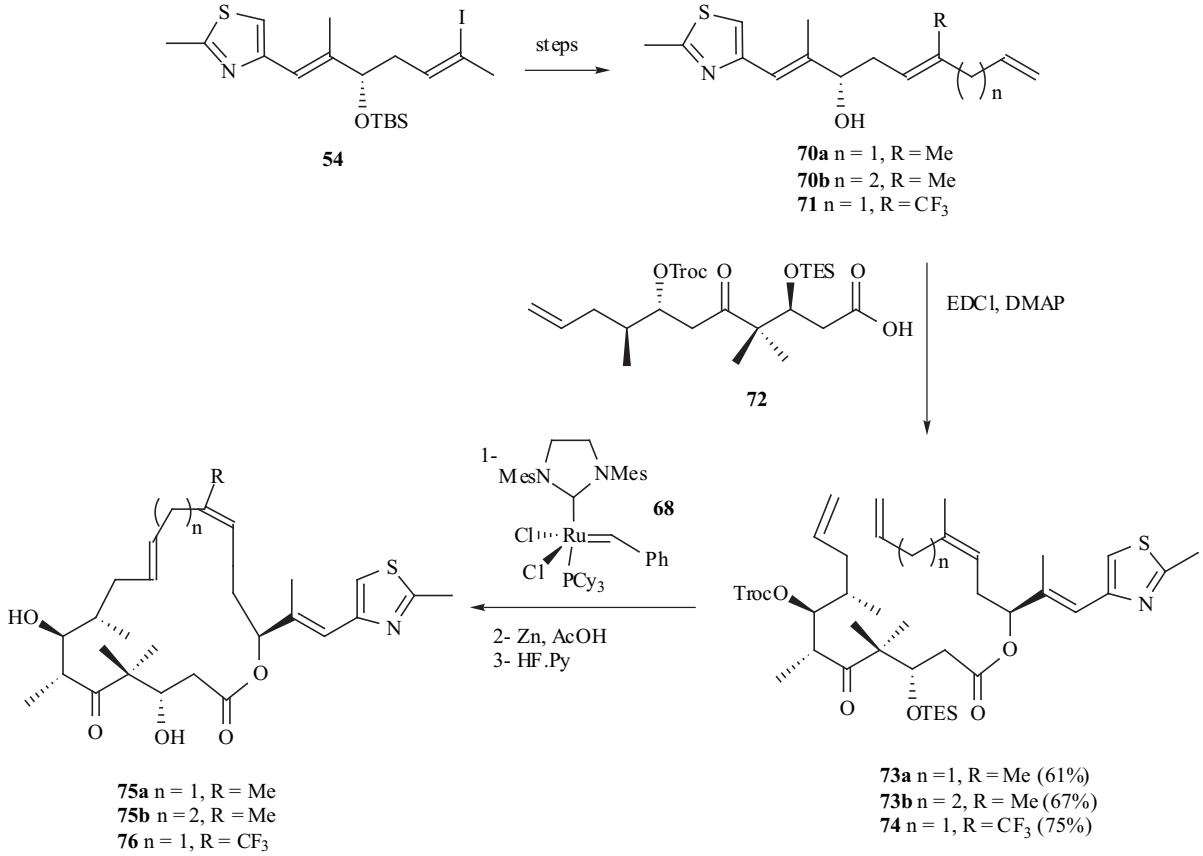
The preparation of hundreds of epothilone analogs allowed the establishment of a detailed map of structure-activity relationships, based on *in vivo* and *in vitro* studies. Among them, epothilone 490 **69**, a natural compound with high *in vitro* toxicity, and some of its analogs were synthesized by Danishefsky and its group [17-22].

Epothilone 490 contains a 10,11-E olefin, conjugated next to the usual 11,13-unsaturation. This compound was prepared using a new stereospecific ring-closing olefin metathesis [18] (scheme **11**). The lithium enolate of acetate **66** was treated with a chiral titanium reagent. Addition of aldehyde **67**, in the presence of ruthenium catalyst **68** afforded, after deprotection of the C-7 group, the desired epothilone **69**.

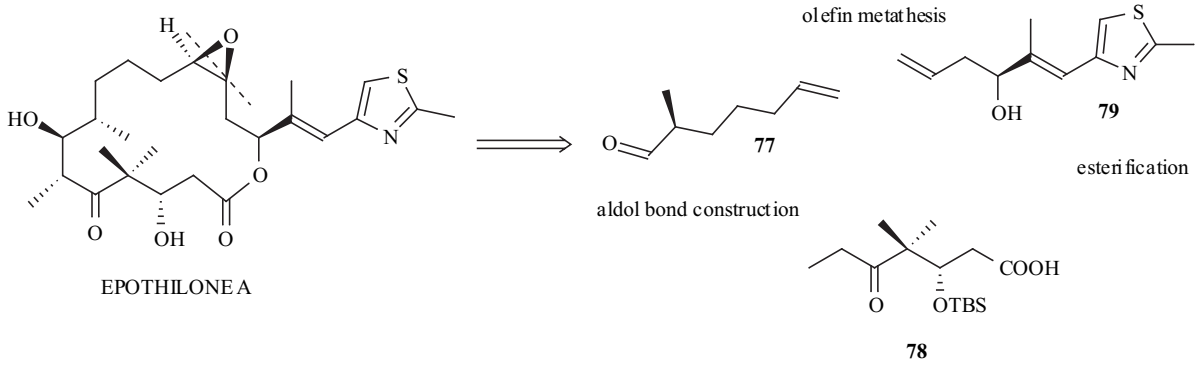
This RCM strategy was applied to the synthesis of 17- and 18- dehydrodeoxyepothilone B **73a** and 7**3b** [19] (scheme **12**). The preparation of the 17- and 18- member rings started with vinyl iodide **54**, which was converted to the corresponding 1,4 dienes **70a** and **70b**. Esterification of these allylic alcohols with acid **72** gave the corresponding RCM cyclization precursors **73a** and **73b**. Ring-closing olefin metathesis and cleavage of protecting groups gave rise to desired macrocycles **75a** and **75b**. Similar reaction conditions applied to alcohol **71** allowed the obtention of trifluorocompound **76** [20].



Scheme 11. Danishefsky´s total synthesis of epothilone 490.



Scheme 12. Synthesis of 17- and 18- dehydrodeoxyepothilone B and trifluoroanalogs.



Scheme 13. Nicolaou's retrosynthetic analysis.

2.2. The Nicolaou Group Strategies

Nicolaou and his group established different synthetic routes to epothilones and their analogs [7, 23-29], mainly based on the olefin metathesis approach and the macrolactonization strategy.

2.2.1. The Olefin Metathesis Approach

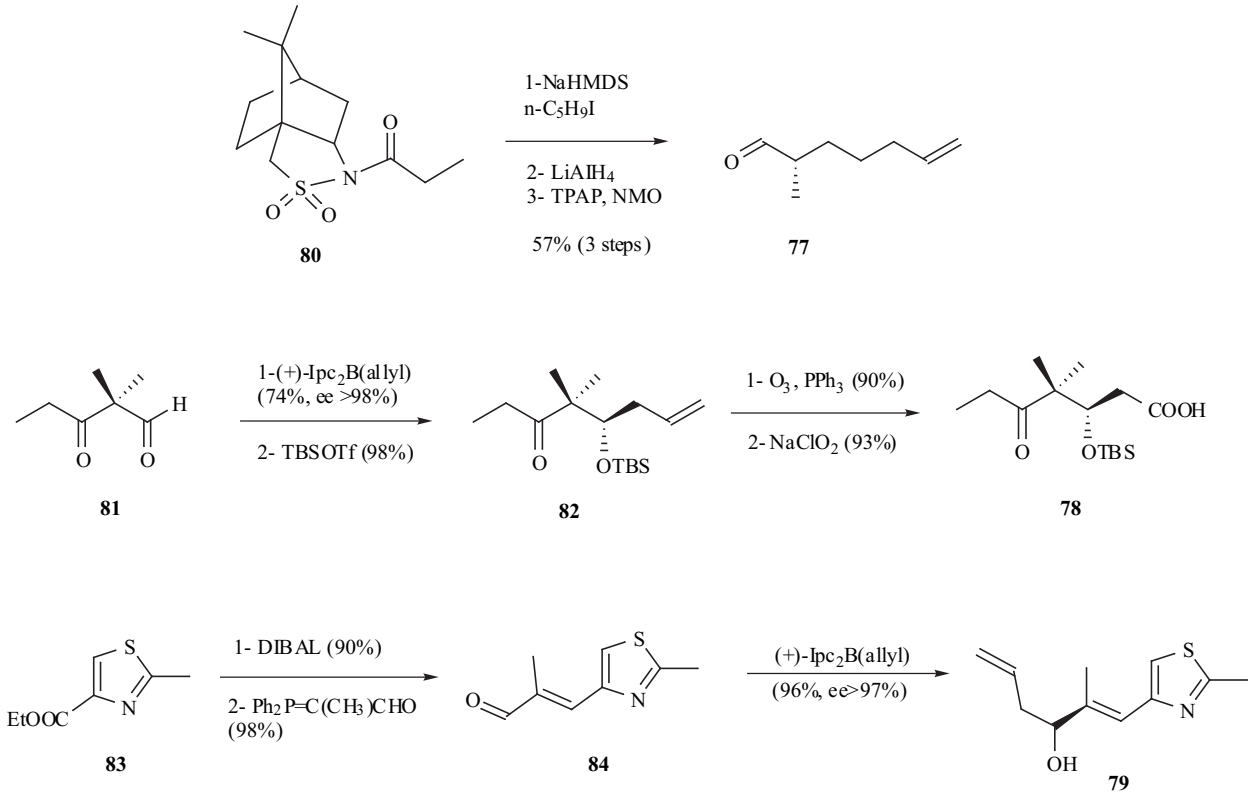
Total syntheses of epothilone A and several analogs were achieved using the olefin metathesis approach [23-24]. The retrosynthetic analysis led to three key building blocks, which were synthesized independently (scheme **13**).

Compound **77** was obtained from the acylated derivative **80**, which was alkylated with 5-iodo-1-pentene in the presence of sodium bis(trimethylsilyl)amide (NaHMDS) (scheme **14**). The resulting compound was then reduced to primary alcohol with $LiAlH_4$, which, after oxidation, furnished aldehyde **77** in 95% yield.

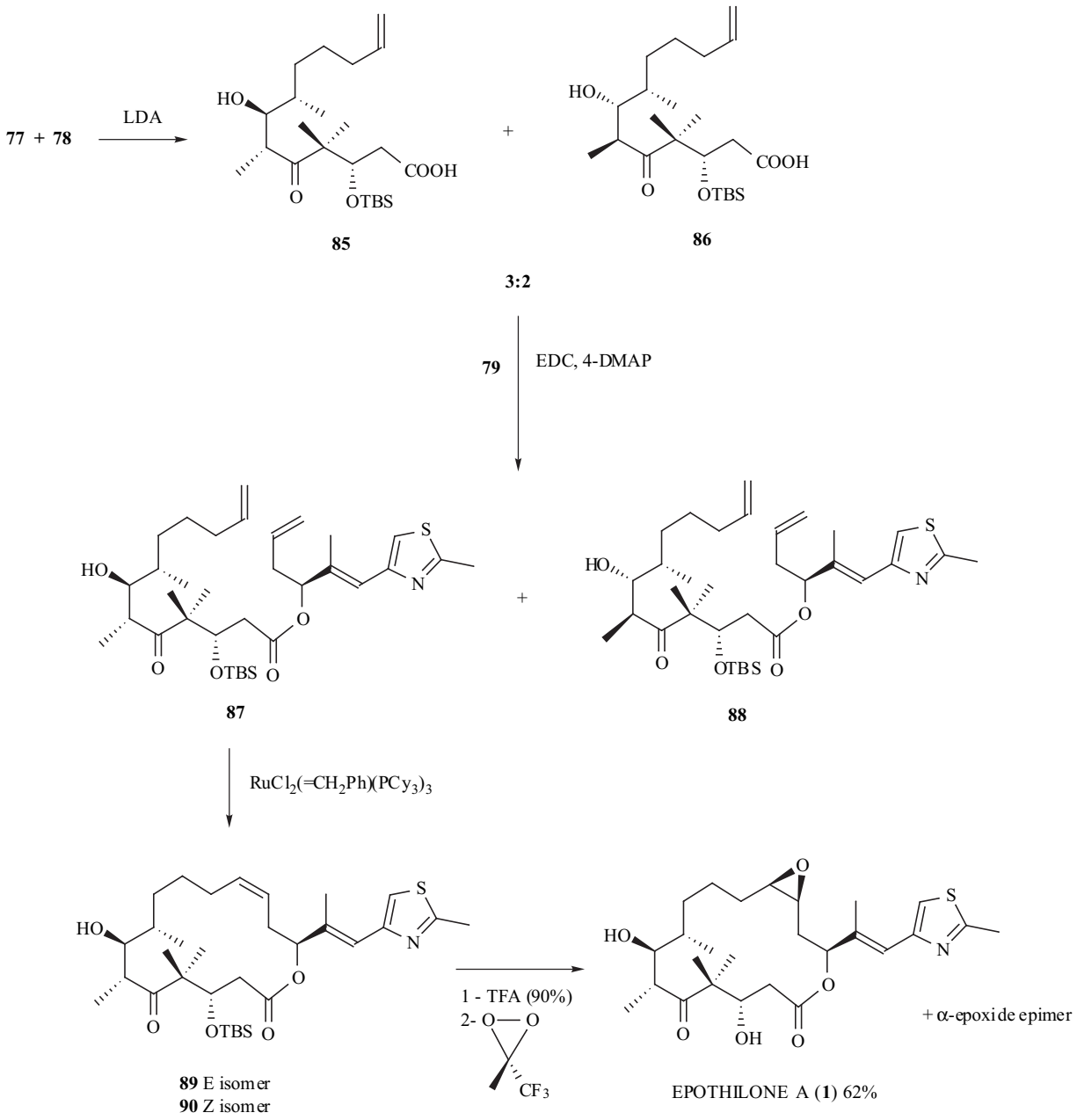
The synthesis of ketoacid **78** started with ketoaldehyde **81**. Addition of (+)-Ipc_2B(allyl), and subsequent silylation of the enantiomerically enriched alcohol (ee>98%) furnished silyl ether **82** in 98% yield. The transformation of **82** in carboxylic acid **78** was accomplished by ozonolysis followed by oxidation with $NaClO_2$.

The third building block, homoallylic alcohol **79** containing thiazole moiety, was obtained from thiazole derivative **83**. After reduction with DIBAL, the resulting aldehyde was reacted with a stabilized ylide to afford aldehyde **84**. Addition of (+)-Ipc_2 B(allyl) gave the allylic alcohol **79** in 90% yield.

Aldol condensation of **78** with aldehyde **77** afforded diastereomeric products **85** and **86** (3:2 ratio). The mixture was reacted with alcohol **79**, yielding esters **87** and its isomer **88** (scheme **15**).



Scheme 14. Synthesis of building blocks **77**, **78** and **79**.



Scheme 15. Nicolaou´s synthesis of epothilone A using the metathesis strategy.

The olefin metathesis reaction of **87** proceeded in the presence of a ruthenium catalyst, to afford cyclic compounds **89** and its isomer **90**. After cleavage of the silyl ethers, *cis* olefin **89** was converted to epothilone A, together with its α-epoxide epimer.

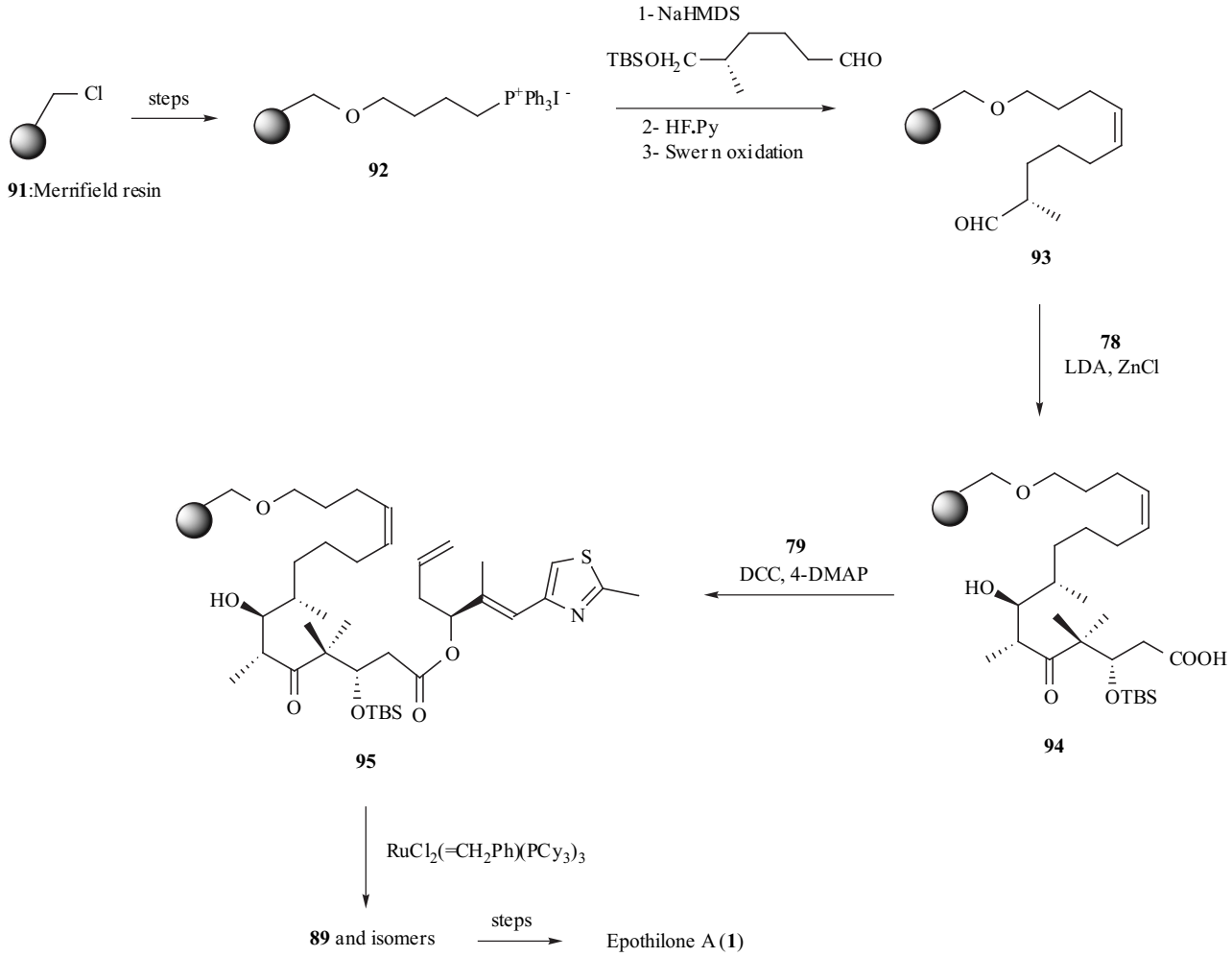
Based on the olefin metathesis strategy, a solid phase synthesis of epothilone A was reported [25]. One of the key compounds, fragment C7-C12 **93**, is a polymer-bounded aldehyde. After aldol condensation and introduction of the heterocyclic part, exposure to the ruthenium catalyst released epothilone C precursor from the resin (scheme **16**).

2.2.2. The Macrolactonization-Based Strategy

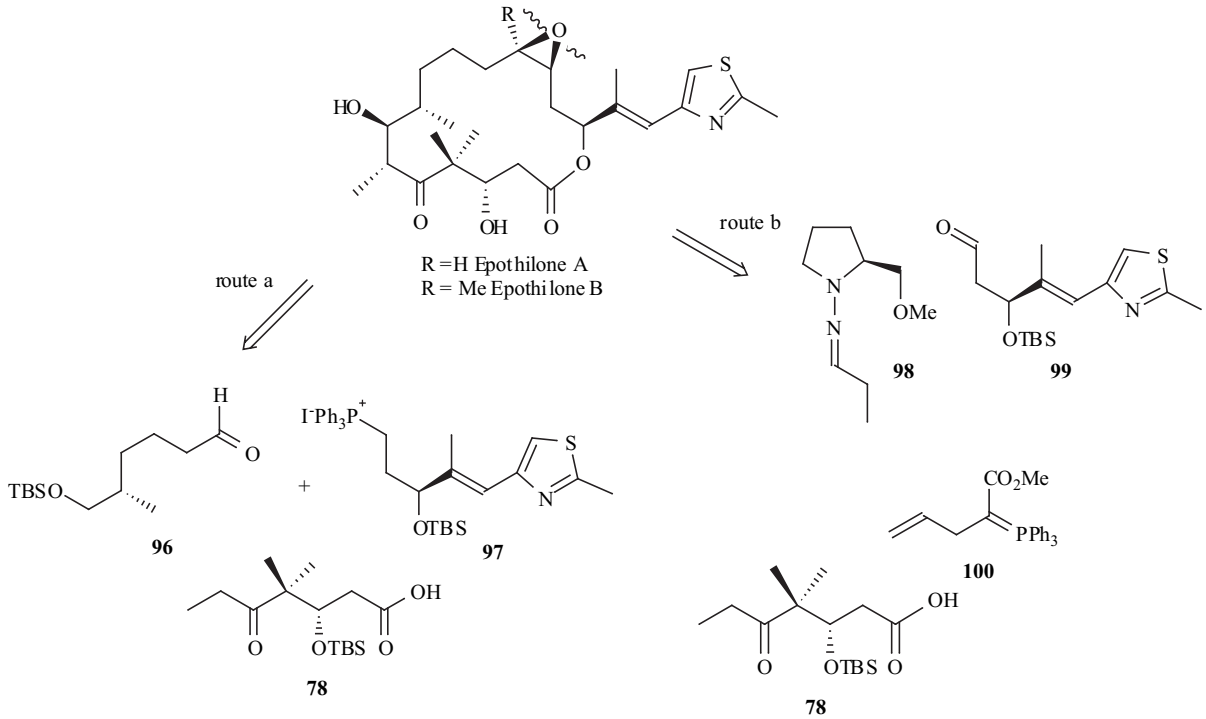
Another strategy used by Nicolaou and co-workers for the synthesis of both epothilones A and B, is based on a macrolactonization reaction [26]. The retrosynthetic analysis (scheme **17**) shows that three or four building blocks are necessary for the synthesis (respectively route a and route b).

Compound **97** was synthesized from allylic alcohol **79** (scheme **18**). Protection of the hydroxyl group with TBSCl, followed by chemoselective hydroxylation of the terminal olefin and cleavage of the resulting diol with $Pb(OAc)_4$ furnished aldehyde **99**. $NaBH_4$ reduction of the latter, followed by iodination and phosphonium salt formation gave the heterocycle fragment **97**.

Aldehyde **96** was obtained from SAMP hydrazone **98** (scheme **19**). Treatment of the latter with LDA and 4-iodo-1-(benzyloxy)butane led to **100** (yield 92%). Cleavage of the hydrazone moiety and subsequent reduction of the resulting aldehyde with $NaBH_4$ furnished alcohol **101**. Compound **101** was then silylated, and the benzyl ether was cleaved by



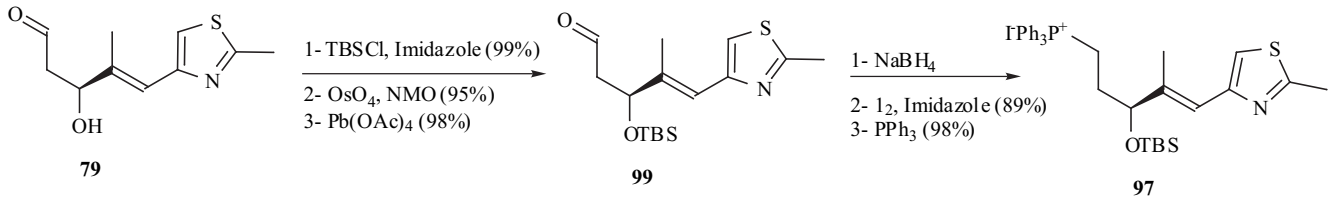
Scheme 16. Solid phase olefin metathesis synthesis of epothilone A.



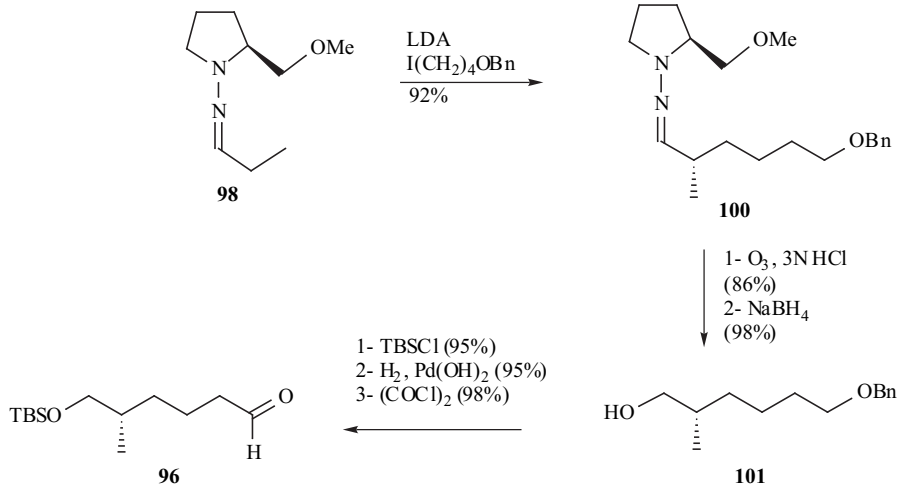
Scheme 17. Nicolaou´s retrosynthetic analysis for epothilones A and B, using the macrolactonization strategy.

hydrogenolysis to give a primary alcohol, which was oxidized to aldehyde **96** (Swern oxidation). The total synthesis of epothilone A from building blocks **78**, **96** and **97** is shown in scheme **20**. Treatment of **97** with NaHMDS, followed by reaction with aldehyde **96** led to compound **102**: olefin Z, as the predominant product, was isolated by chromatography. Selective desilylation of primary alcohol and its subsequent oxidation furnished aldehyde **103**. Reaction of the dilithium derivative of **78** with aldehyde **103** resulted in a mixture of **104** and its 6S, 7R diastereoisomer. The mixture was first silylated and then treated with K_2CO_3 in methanol to afford the correspondent carboxylic acids, which were separated by chromatography. Treatment of the isolated compound with TBAF was followed by the key macrolactonization step using the Yamaguchi method. Removal of TBS group and treatment with methyl (trifluoromethyl)dioxirane led to epothilone A.

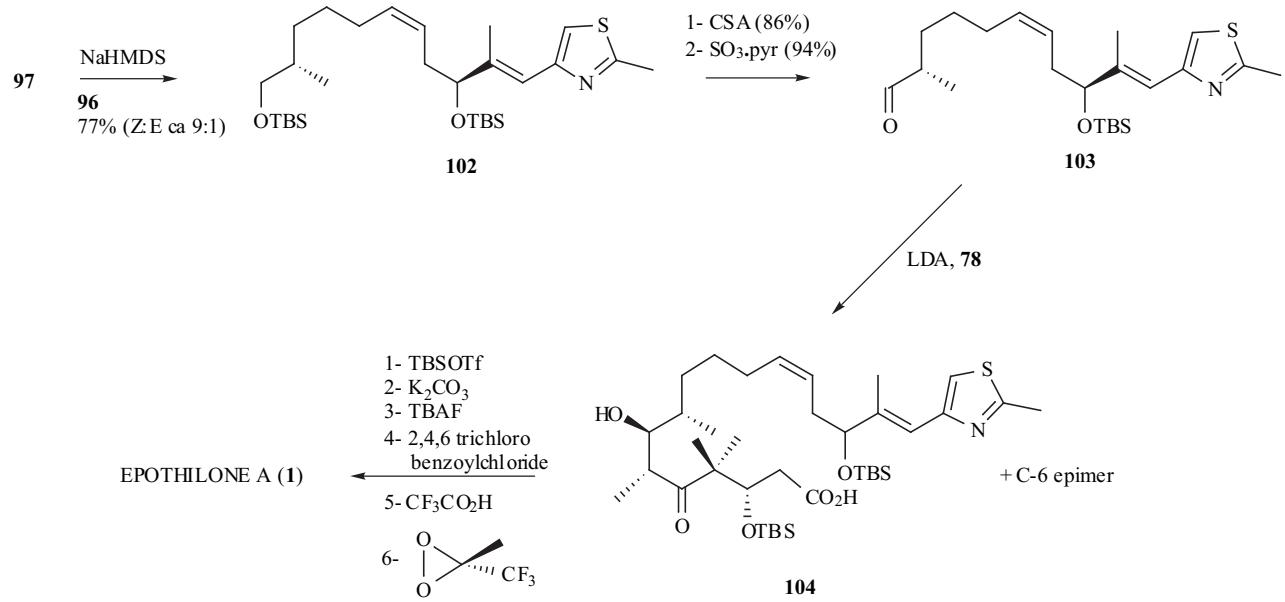
Epothilone B was synthesized from aldehyde **99** (scheme **21**). Condensation of the latter with the stabilized ylide **105**, followed by a DIBAL reduction of the ester group led to allylic alcohol **106**. After deoxygenation and hydroboration of the intermediate olefin, the primary alcohol **107** was obtained, which was treated with iodide, imidazole and triphenylphosphine and then used in an Enders alkylation



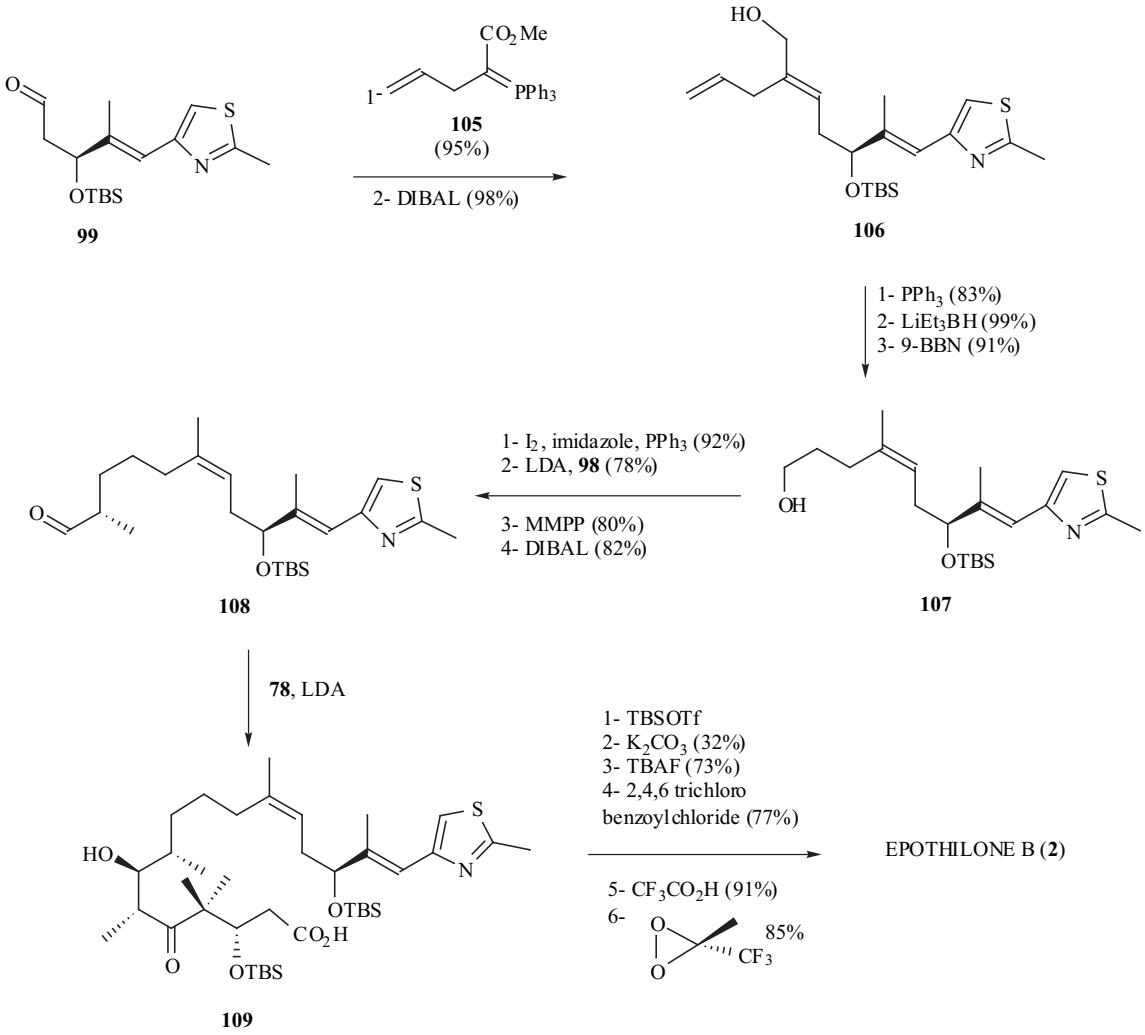
Scheme 18. Preparation of building blocks **97** and **99**.



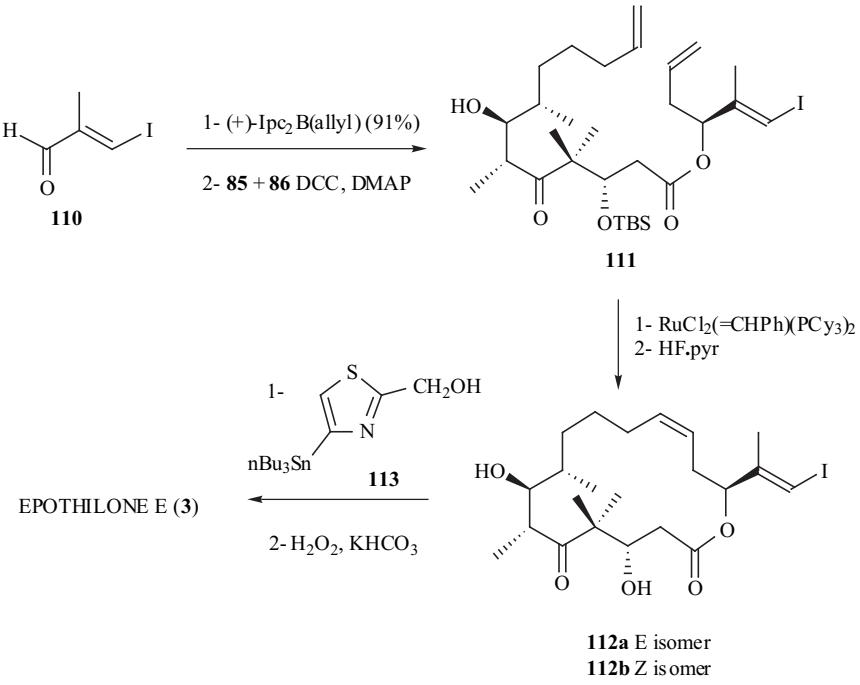
Scheme 19. Preparation of aldehyde **96**.



Scheme 20. Synthesis of epothilone A *via* macrolactonization.



Scheme 21. Nicolaou's synthesis of epothilone B *via* macrolactonization.



Scheme 22. Nicolaou's synthesis of epothilone E.

reaction with SAMP hydrazone **98**. Treatment of the resulting hydrazone with monoperoxyphthalic acid magnesium salt (MMPP) and subsequent exposure to DIBAL offered aldehyde **108**. Condensation of the dianion **78** with **108** produced the macrolactonization intermediate **109** and its C-6 isomer. The same procedure used for the synthesis of epothilone A was then applied to **109** to prepare epothilone B.

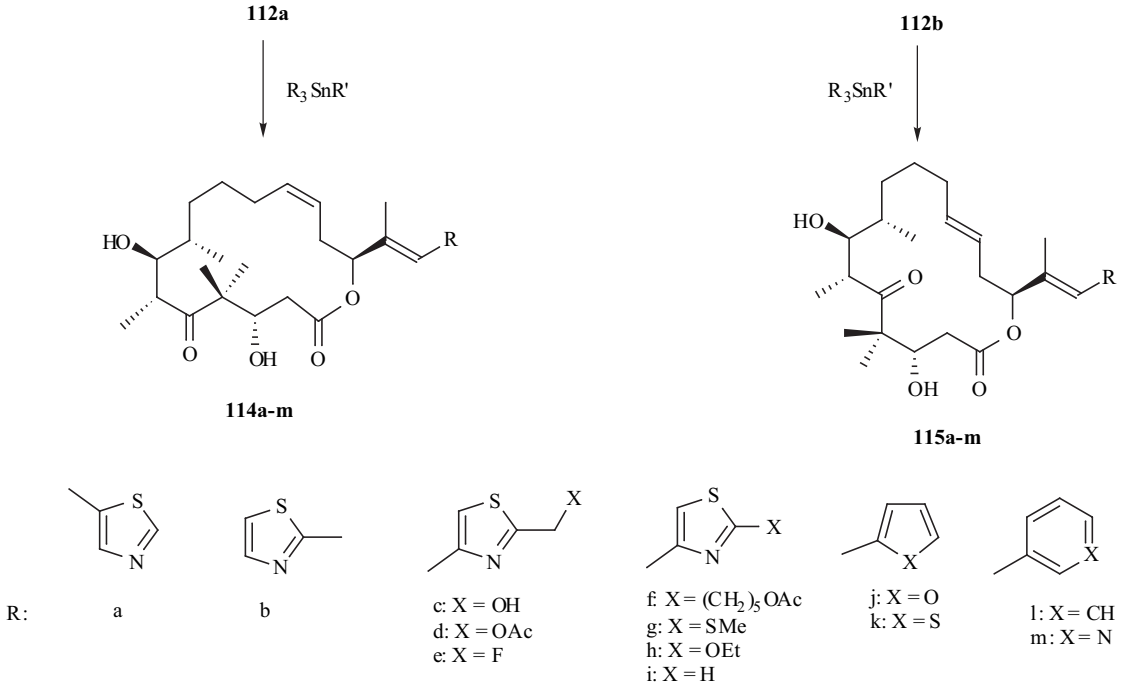
2.2.3. Stille Coupling Based Strategy

The first total synthesis of epothilone E, using a Stille coupling reaction as a key step was reported [27]. The macrolactone fragment was prepared *via* a ring-closing olefin metathesis, from aldehyde **110** (scheme **22**). Asymmetric allylboration of compound **110** using Brown´s methodology, and subsequent coupling with a mixture of alcohols **85** and **86** afforded metathesis precursor **111**, along with its C-6 diastereoisomer (which were separated from the mixture). Treatment of **111** with a ruthenium complex, and subsequent cleavage of the silyl group provided the desired macrocyclic compound **112a** and its Z isomer. Coupling of vinyl iodide **112** with stannane **113** furnished, after epoxidation with methylperoxycarboximidic acid, epothilone E.

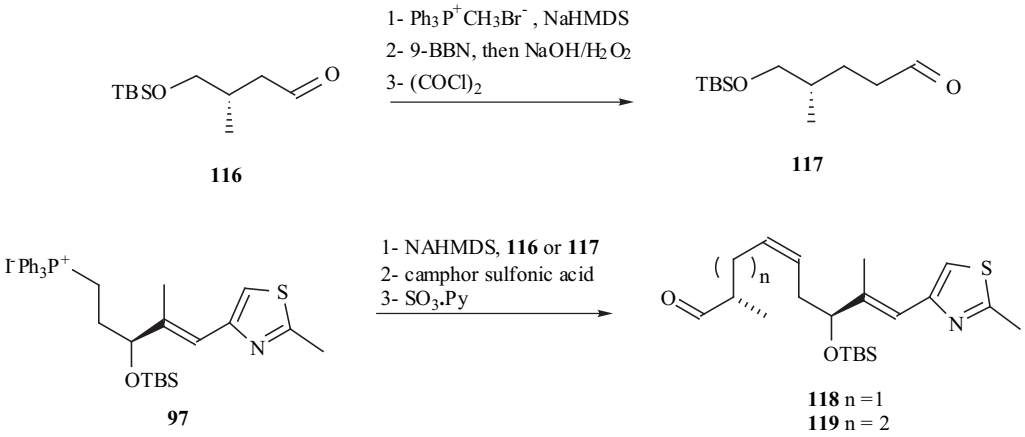
2.2.4. Synthesis of Epothilone Analogs

Using a variety of thiazole stannanes, various analogs **114a-m** and **115a-m** could be synthesized from macrolactone precursors **112a** and **112b** (scheme **23**).

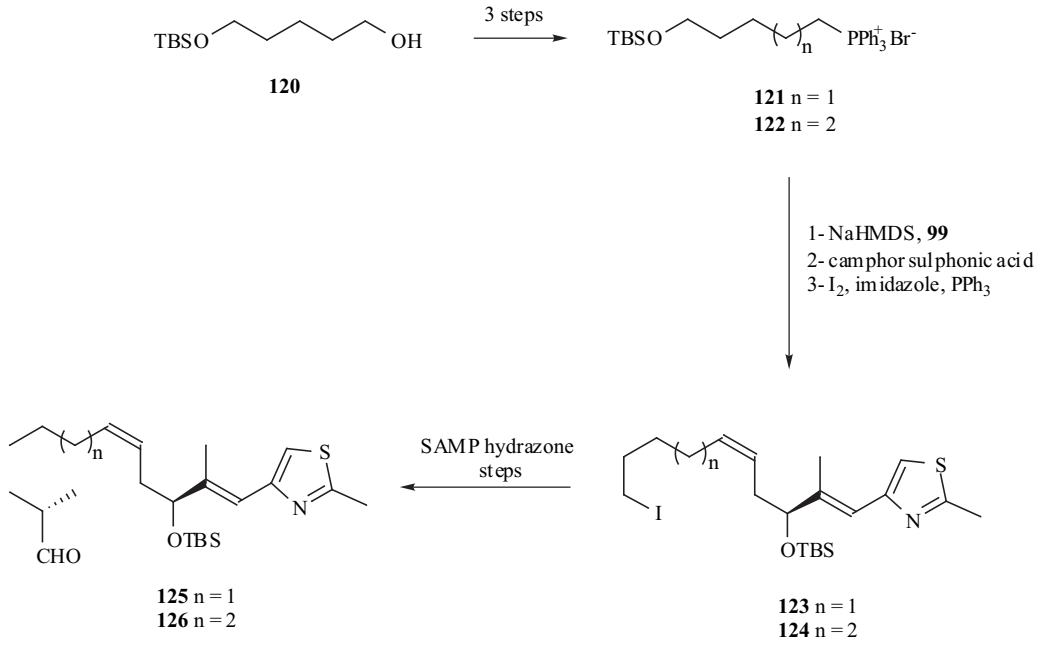
To probe the effect of the size of the macrocycle on its biological activity, 14-, 15-, 17- and 18- epothilones **132-135** were synthesized [27]. Fragments **116**, **117** and **97** were necessary for the synthesis of key building blocks **118** and **119** (scheme **24**). The synthesis of building blocks **125** and **126** required the preparation of intermediates **99**, **121** and **122** (scheme **25**). Coupling of fragments **118**, **119**, **125** or **126** with compound **127** and further macrolactonization gave analogs **132-135** (scheme **26**).



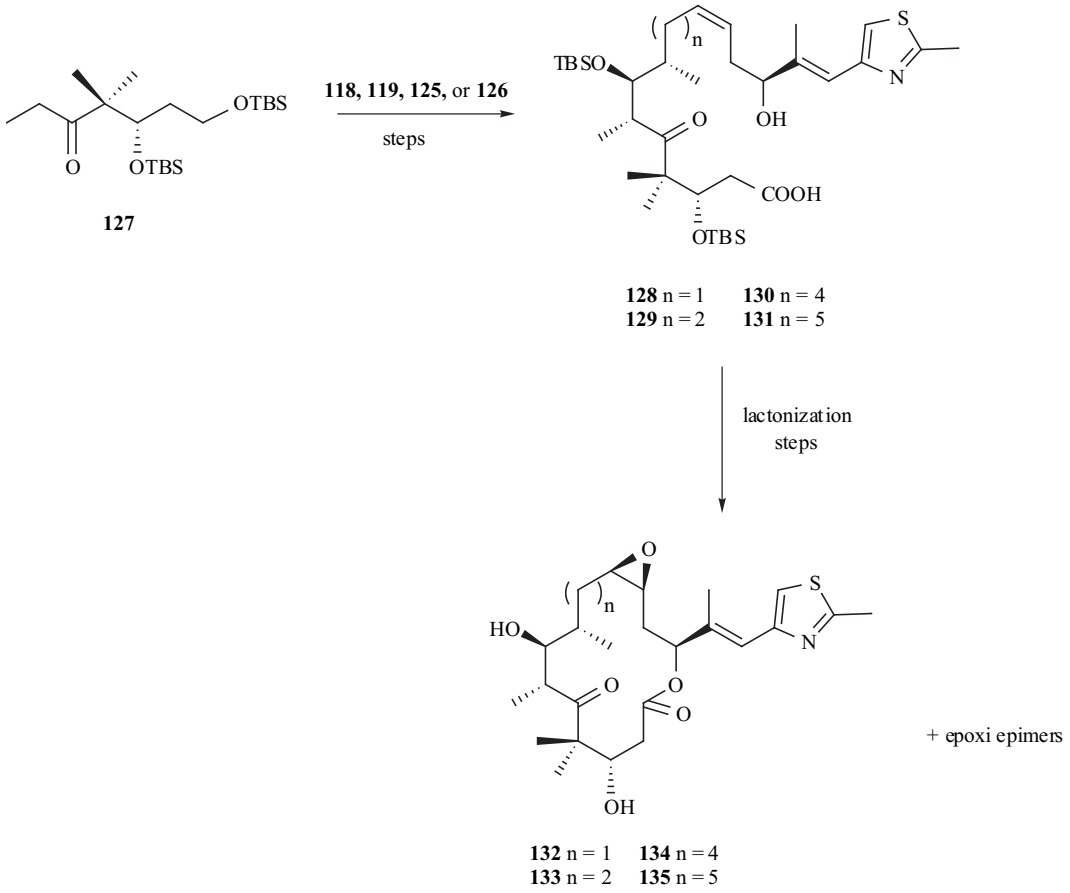
Scheme 23. Synthesis of deoxyepothilones **114a-m** and **115a-m**.



Scheme 24. Synthesis of intermediates **118** and **119**.



Scheme 25. Synthesis of intermediates **125** and **126**.

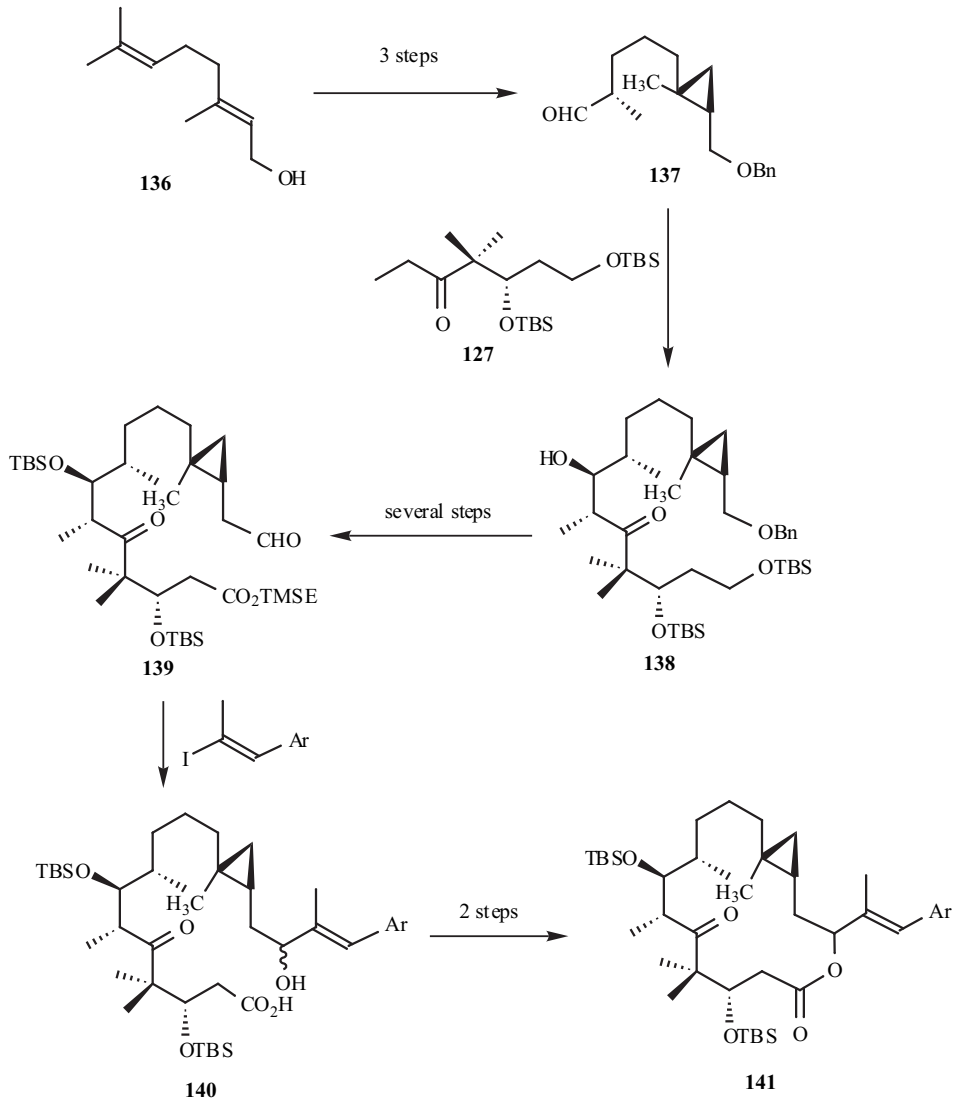


Scheme 26. Synthesis of analogs **132-135**.

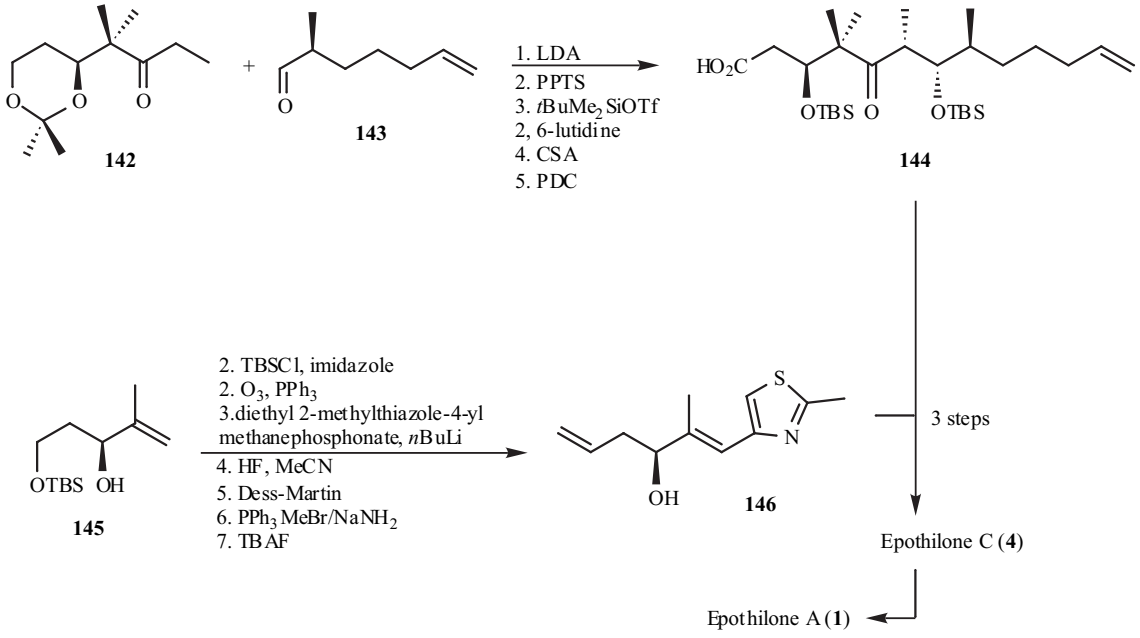
In another work [29], Nicolaou's group prepared the analog **141** using a Nozaki-Hiyama-Kishi coupling to introduce the side chain prior to Yamagushi lactonization (scheme **27**).

2.3. Other Works

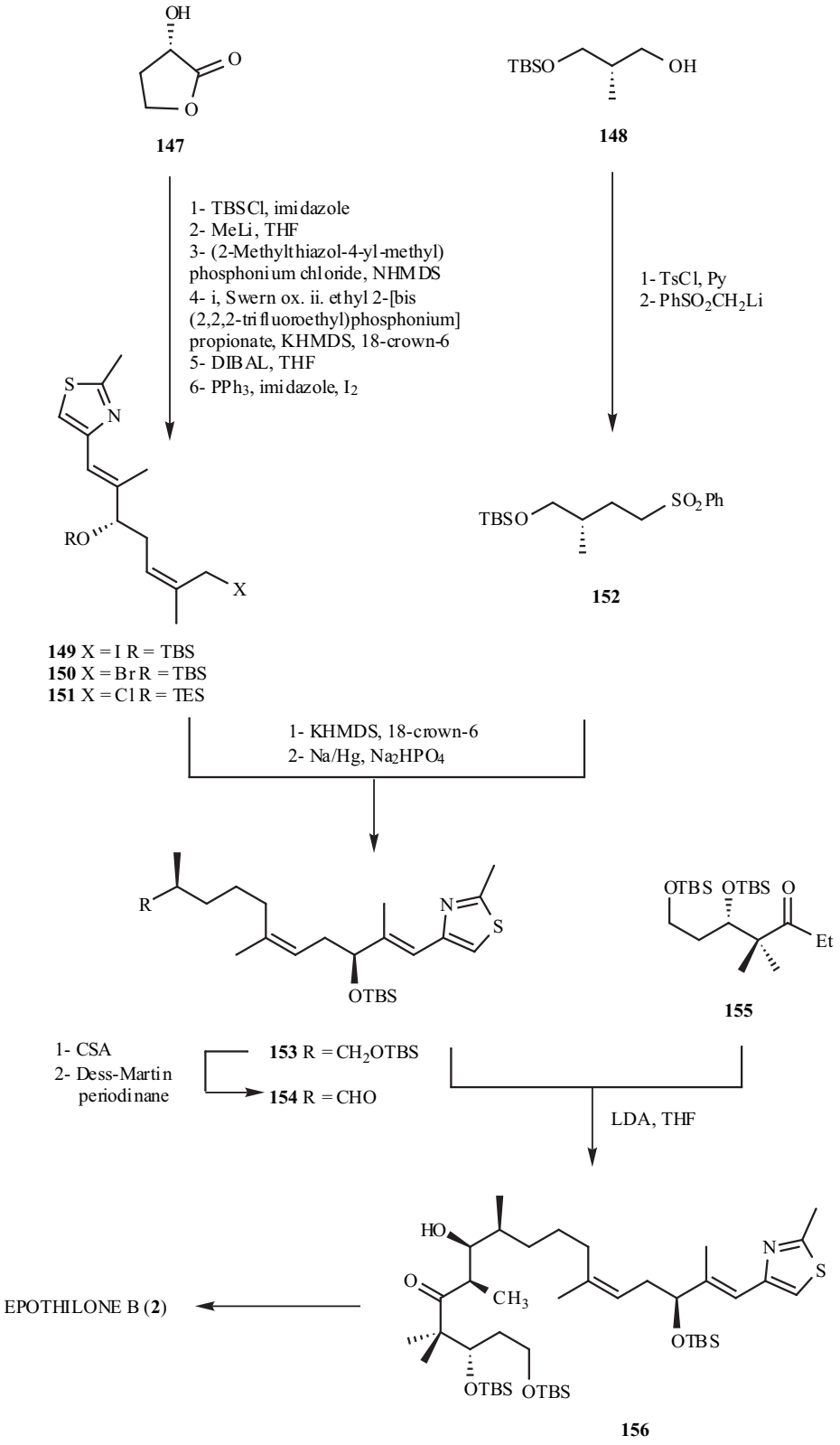
Many approaches to the synthesis of epothilones have been documented in the last years [30-56].



Scheme 27. Synthesis of analog **141**.



Scheme 28. Schinzer's synthesis of epothilone A.



Scheme 29. Mulzer's synthesis of epothilone B.

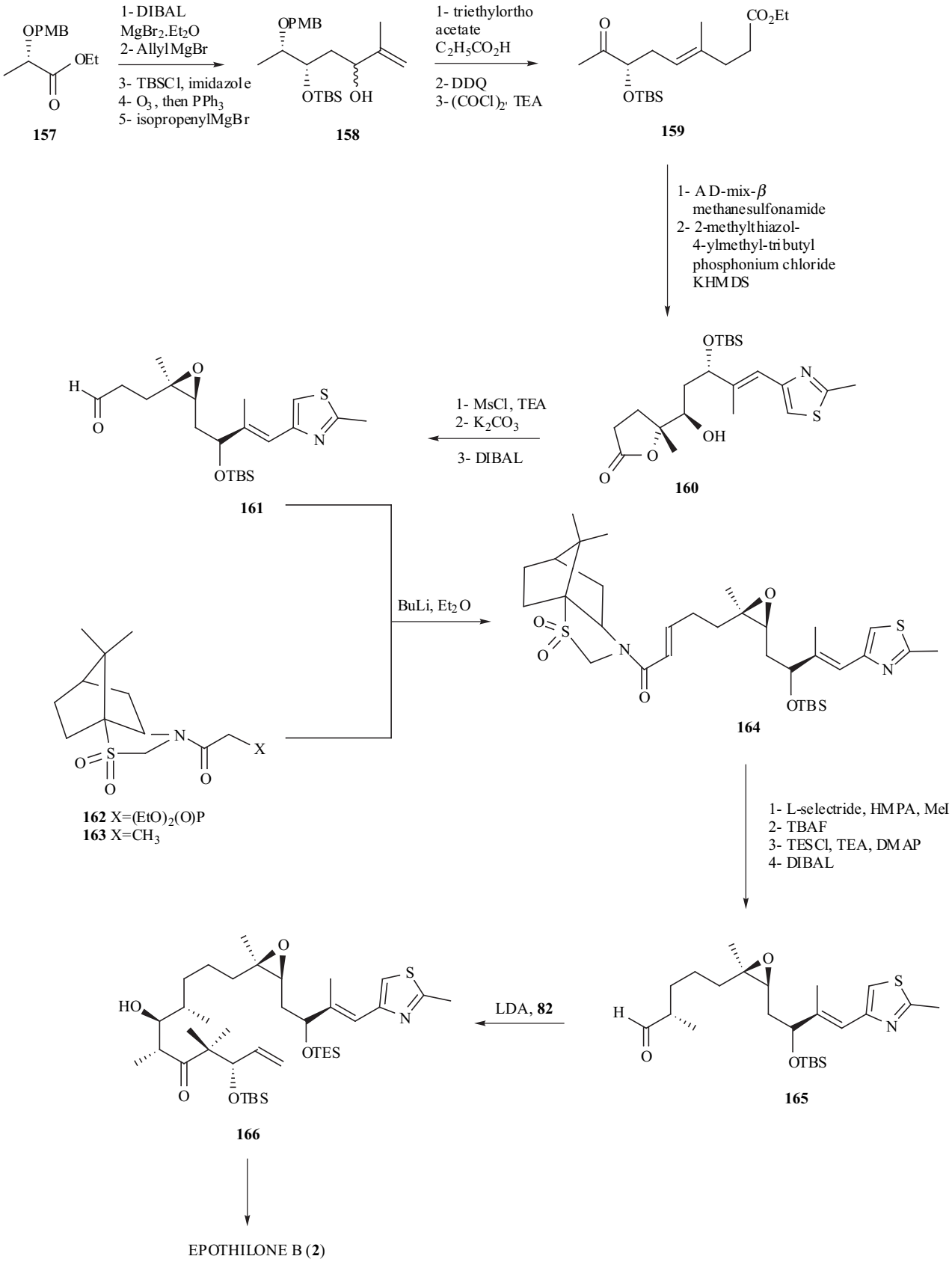
The Schinzer group reported the synthesis of epothilones A and C using the olefin metathesis approach (scheme **28**) [30].

Mulzer and his group reported an easy access to epothilones B and D [31, 32] in which four fragments are connected successively *via* a sulfone alkylation between **149** and **152** and an aldol addition between aldehyde **154** and ketone **155** (scheme **29**).

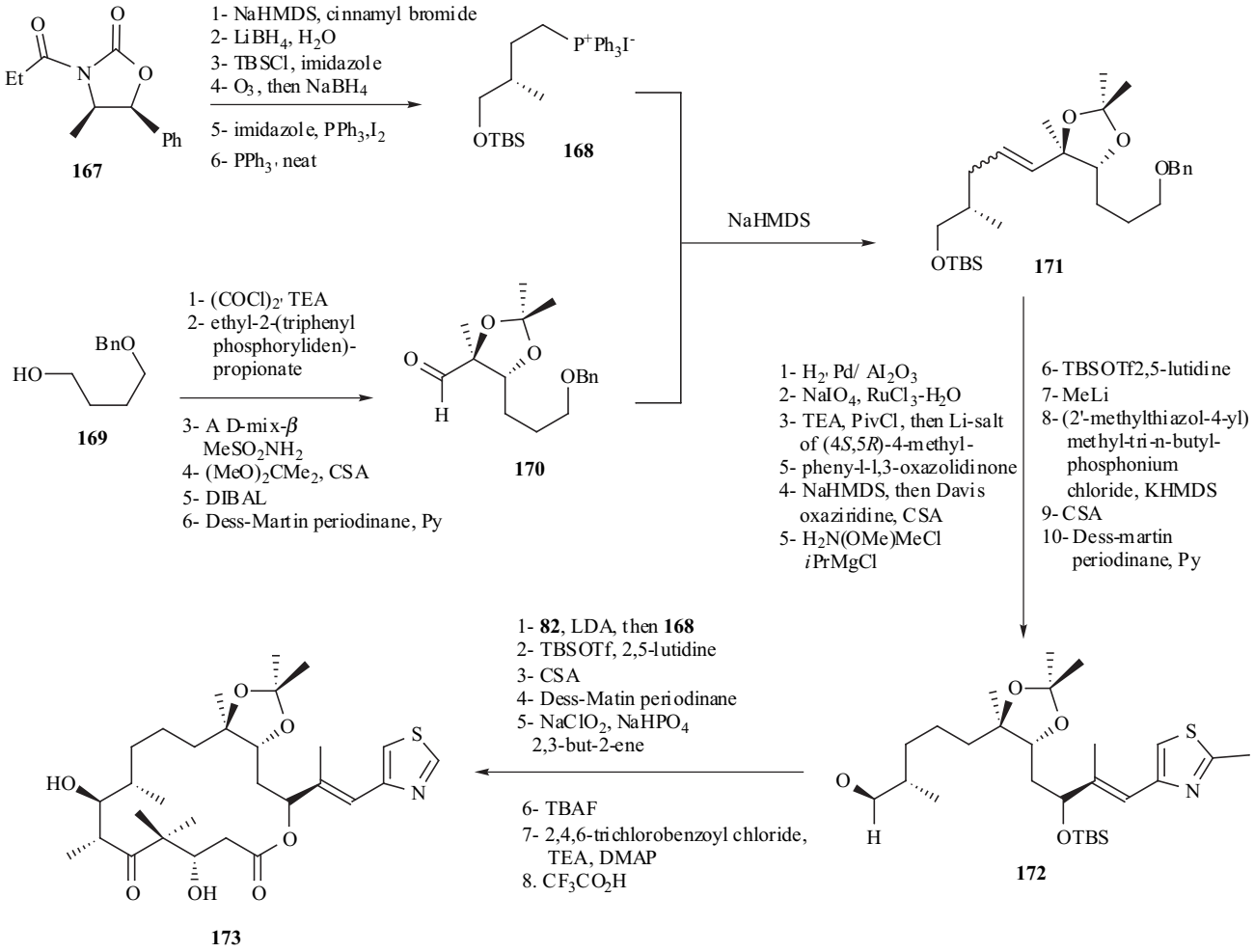
A novel synthesis of epothilone B was described by the same research group, *via* a highly stereoselective aldol

addition involving the C7-C5 epoxyaldehyde fragment **165** (scheme **30**) [33].

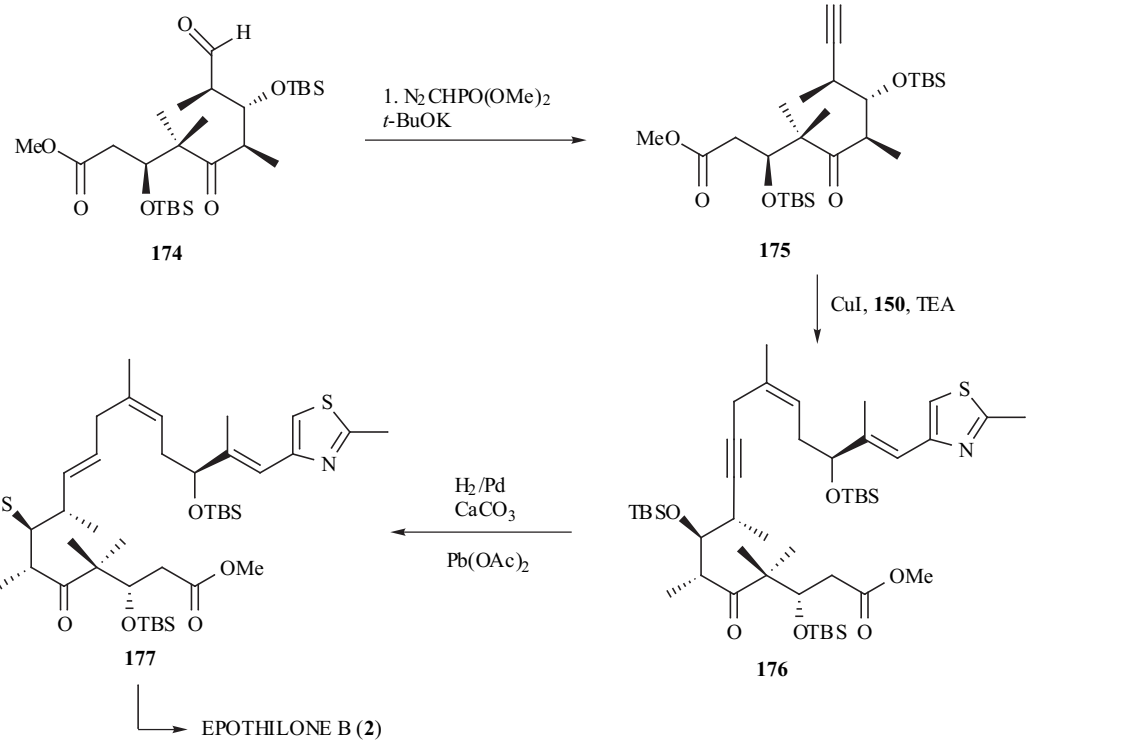
Another important advance was the stereoselective synthesis of the intermediate **171** *via* Sharpless AD-reaction



Scheme 30. Mulzer's synthesis of intermediate **166**.



Scheme 31. Mulzer´s synthesis of novel derivative **173**.



Scheme 32. White's synthesis of epothilone B.

and Davis–Evans-Hydroxylation in the synthesis of epothilone B and its novel derivative **173** (scheme **31**) [34].

The work of White's group [35-37] involved the assembly of two key fragments of epothilone B: an allylic bromide **150** and a terminal acetylene **175**, to form the C10-C11 bond of the macrocycle (scheme **32**).

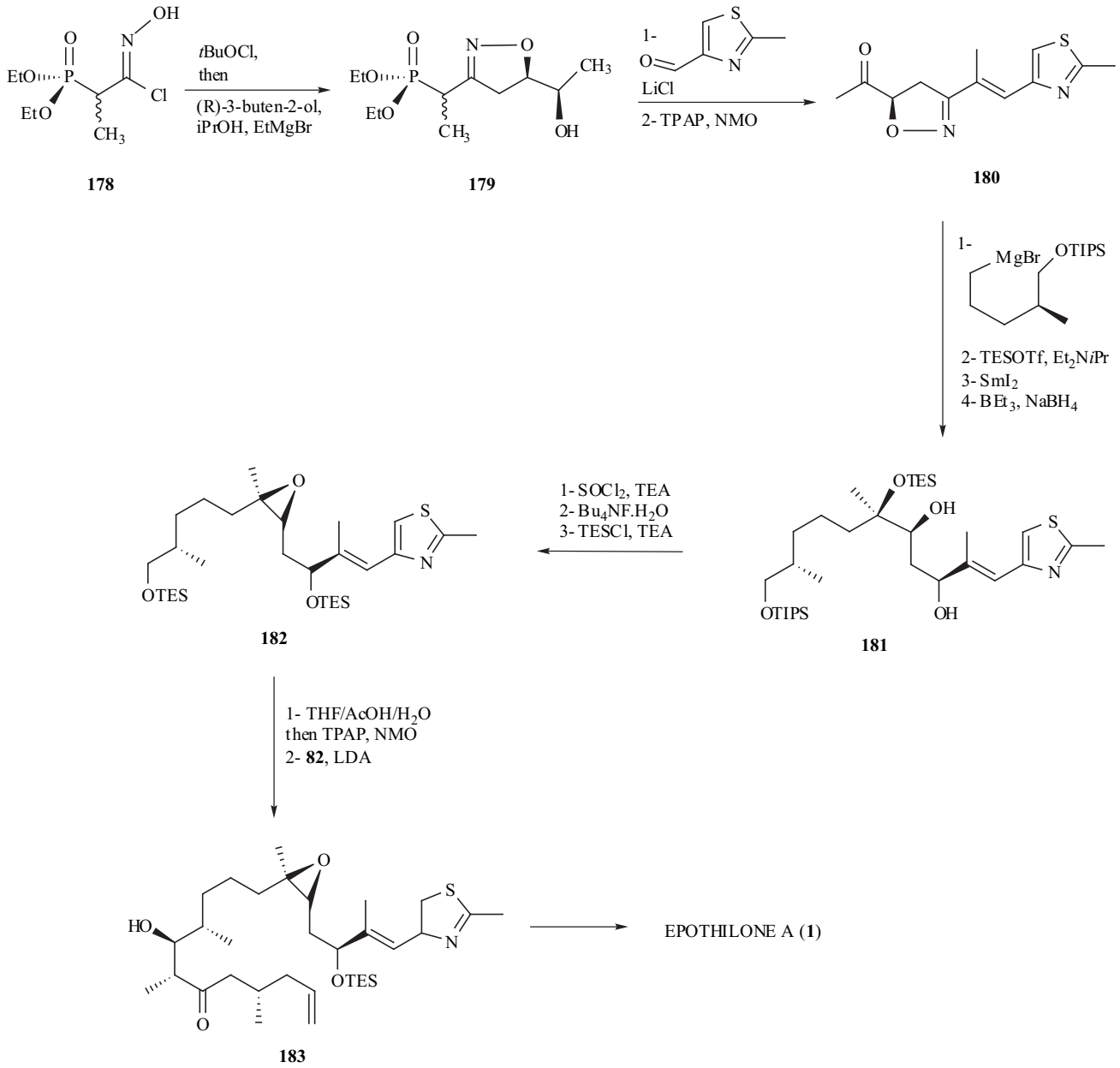
In the Carreira's synthesis [38, 39], the key step is a cycloaddition of nitrile oxide **178** with a chiral allylic alcohol, furnishing compound **179** as a single *syn* diastereoisomer at the isoxazoline oxygen (scheme **33**). Combined with Mulzer's diastereoselective aldol coupling, this approach provides concise synthesis of the epothilones.

An enantioselective total synthesis of epothilones A and B was achieved by Sawada and his group [40, 41], from three key intermediates. Compounds **187** and **188** were obtained using a catalytic asymmetric cyanosilylation as a key step (scheme **34**).

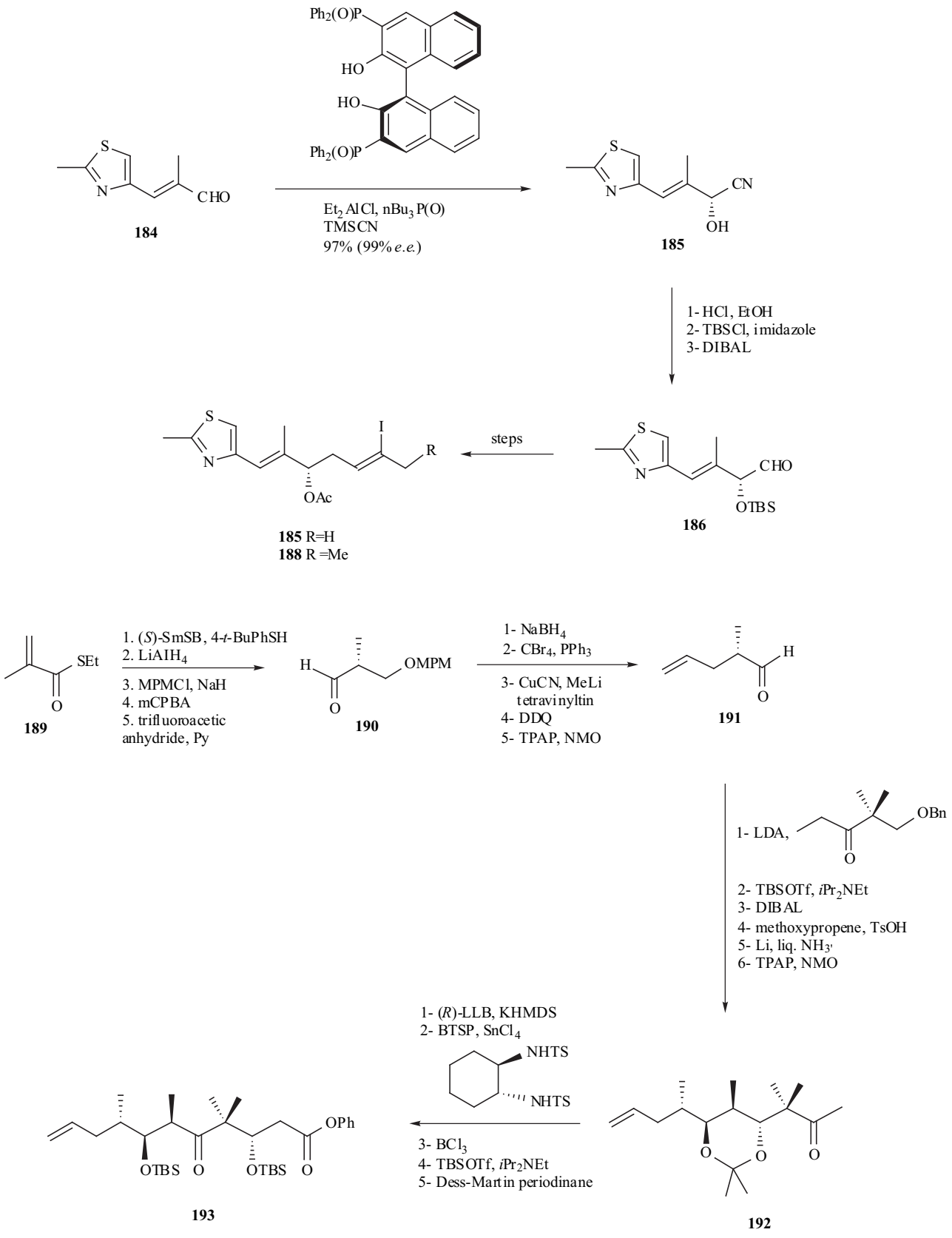
Intermediate **193** was obtained using a catalytic asymmetric protonation in the conjugate addition of a thiol to a conjugated ester (scheme **34**).

Suzuki cross-coupling of fragments **187** and **188** with **193**, followed by Yamaguchi lactonization led respectively to epothilones A and B.

Avery´s group developed a convergent total synthesis of epothilone A in which the key steps are a diastereoselective aldol condensation of aldehyde **197** with **78**, a macrolactonization and a Wadsworth-Emmons reaction of a methyl ketone with a phosphonate reagent (scheme **35**) [42]. Epothilone B was prepared using a Normant reaction, Wadsworth - Emmons reaction and a diastereoselective aldol



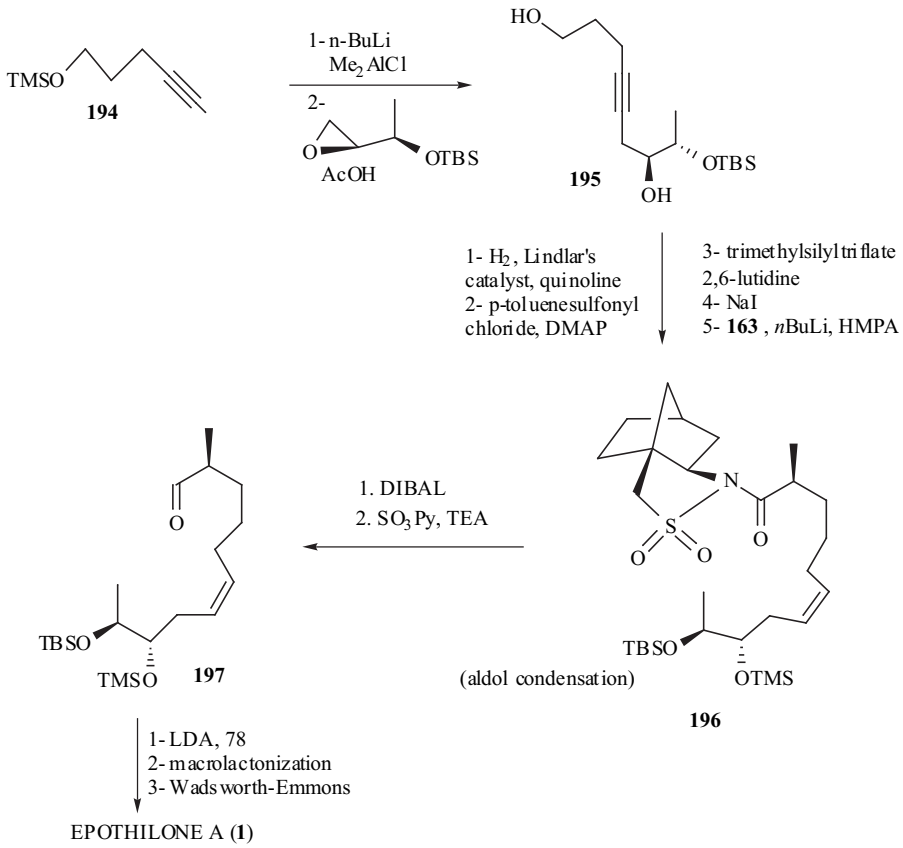
Scheme 33. Carreira's stereoselective synthesis of epothilone A *via* nitrile oxide cycloaddition.



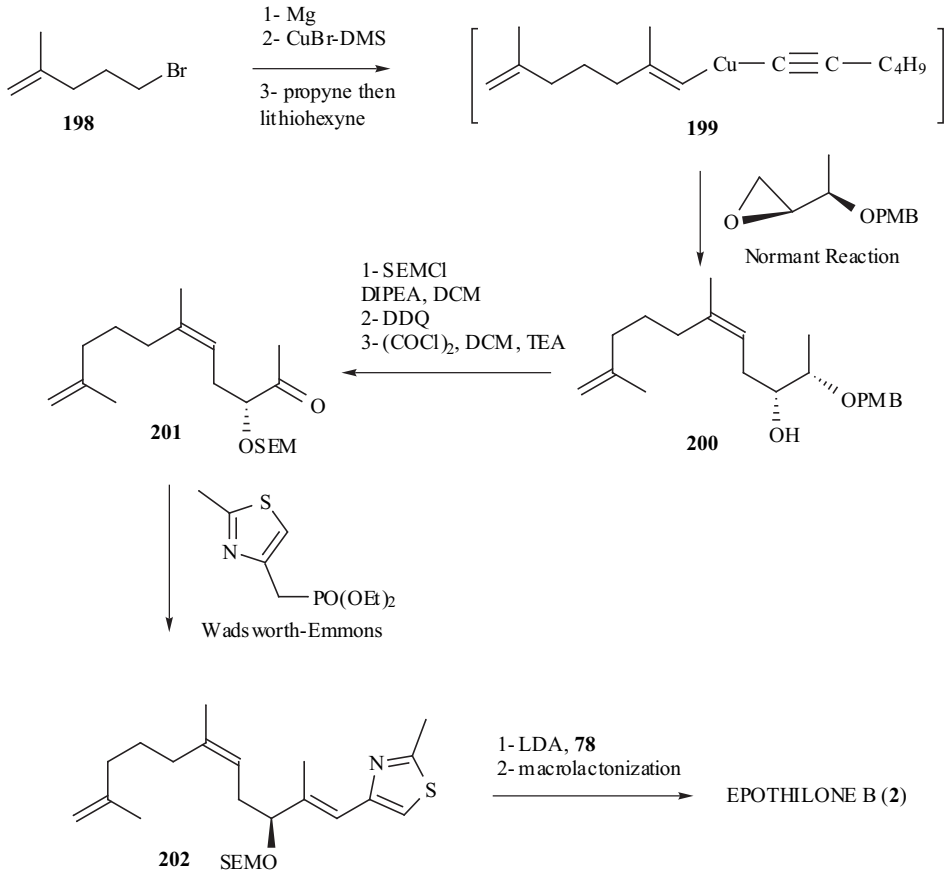
Scheme 34. Sawada's synthesis of key fragments **187**, **188** and **193**.

condensation followed by a macrolactonization step (scheme **36**) [43].

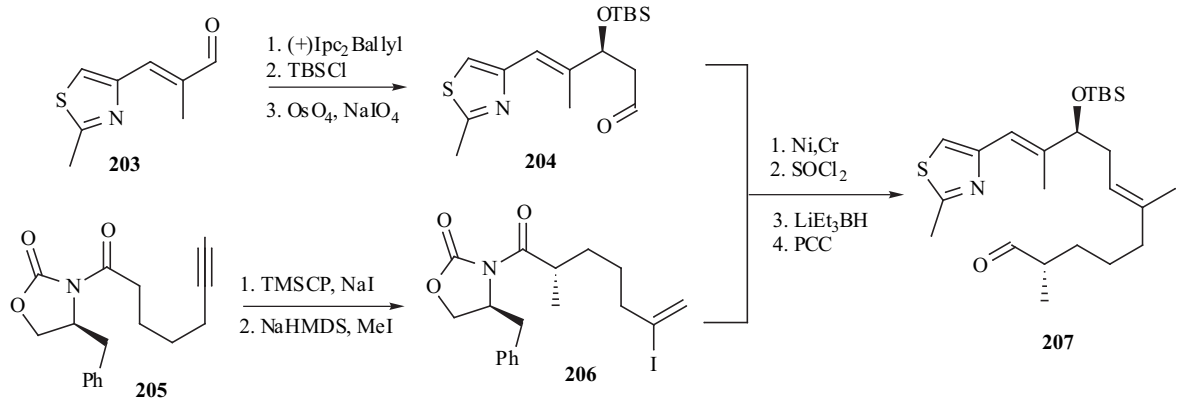
Taylor's synthesis used a sequential Nozaki-Hiyama-Kishi coupling to generate the C12-C13 fragment (scheme **37**) [44].



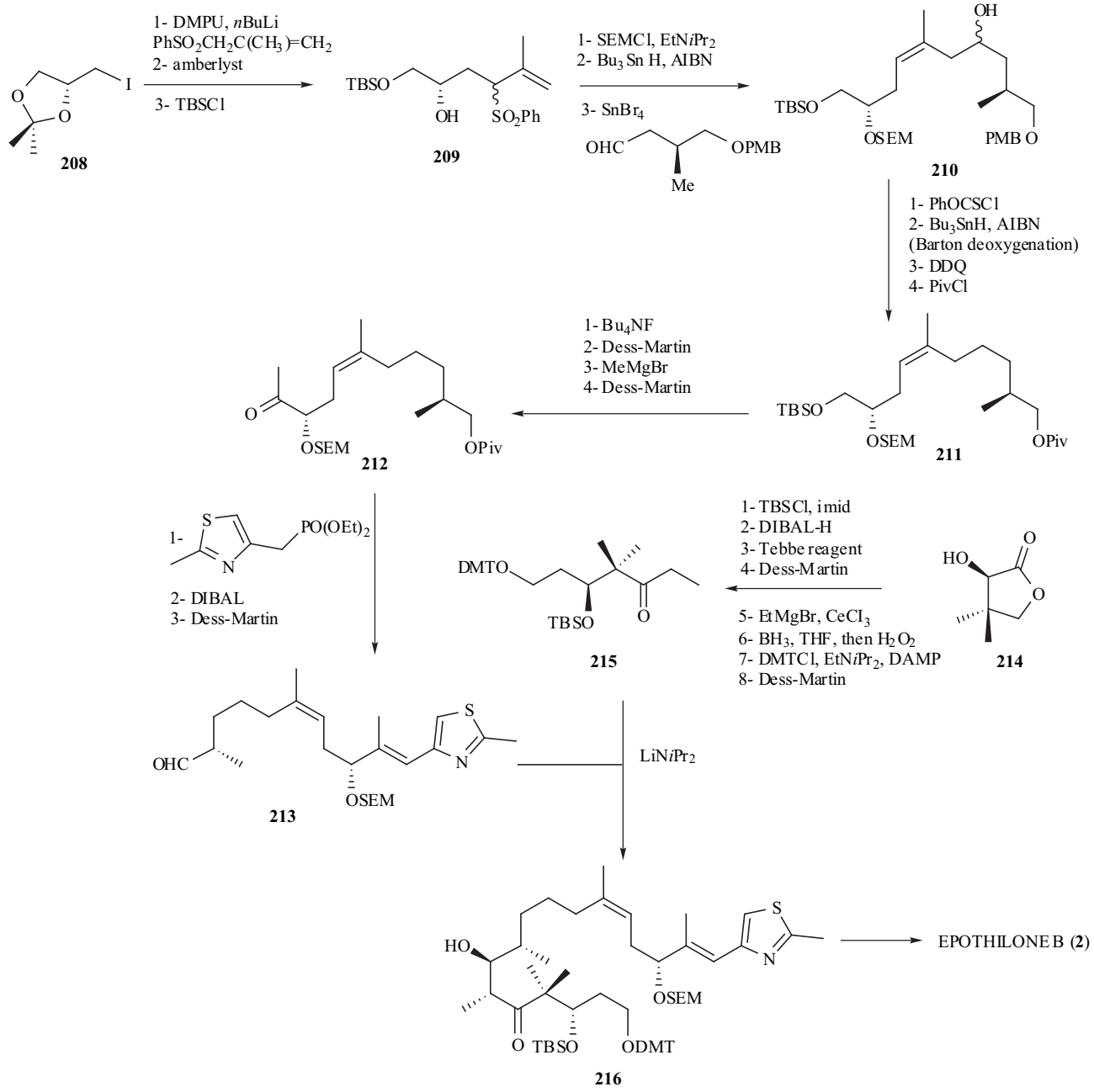
Scheme 35. Avery's synthesis of epothilone A.



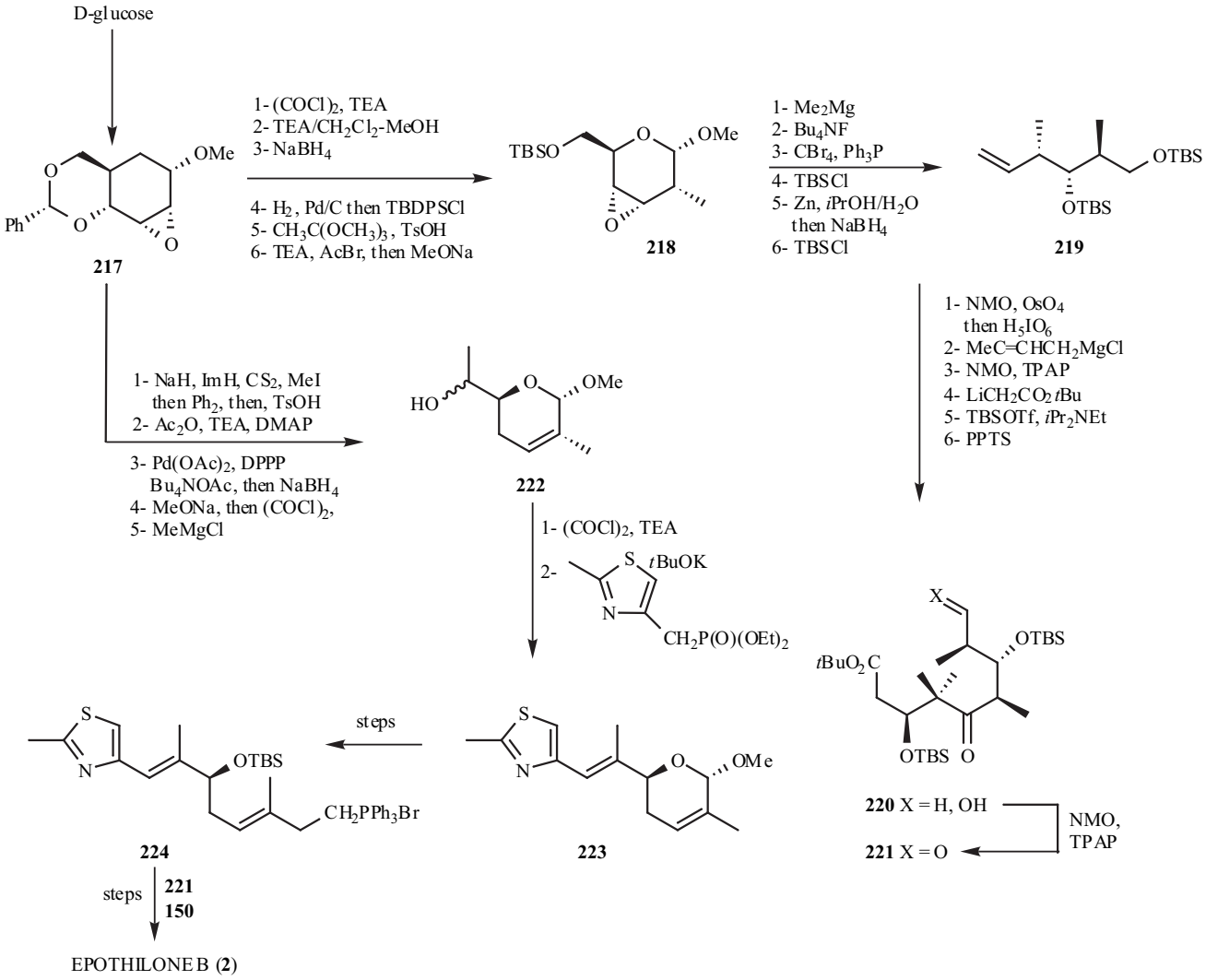
Scheme 36. Avery's synthesis of epothilone B.



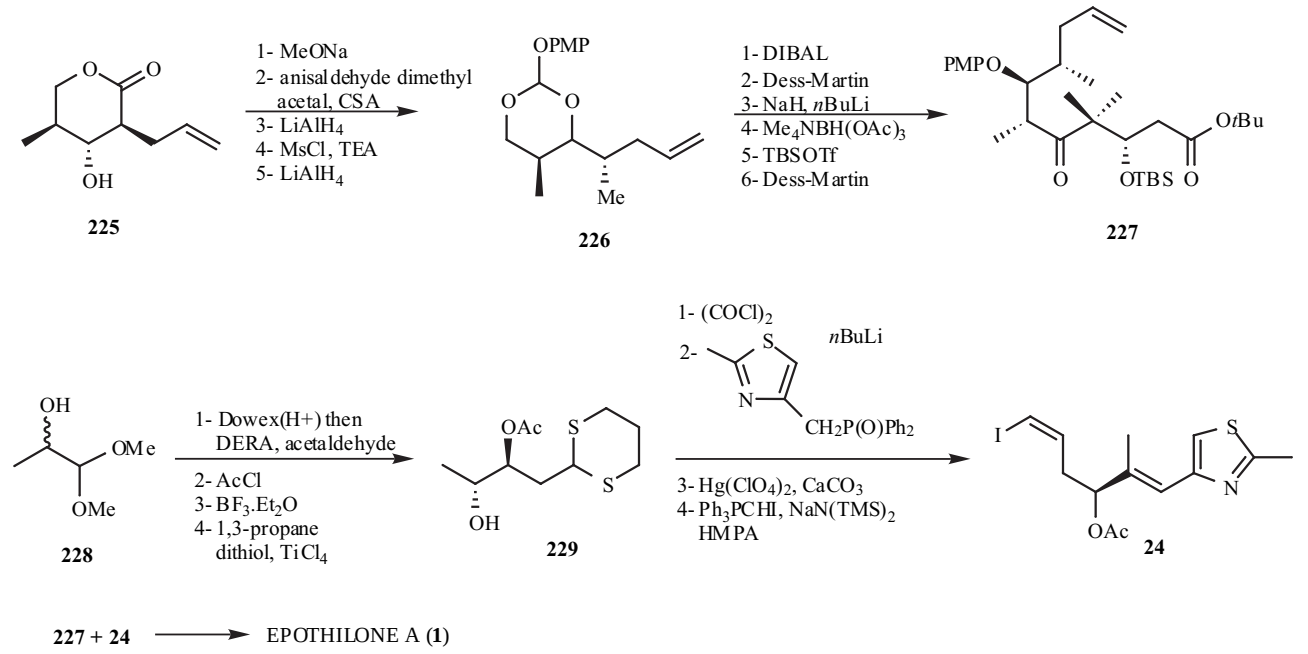
Scheme 37. Taylor's synthesis of C12-C13 fragment.



Scheme 38. Martin and Thomas's synthesis of epothilones D and B.



Scheme 39. Ermolenko's synthesis of epothilone B from D-glucose.



Scheme 40. Wong's enzyme catalyzed synthesis of epothilone A.

In the work of Martin and Thomas [45], a Barton deoxygenation of compound **210** and subsequent reactions gave the C7-C15 fragment **213**. An aldol condensation with the ethyl ketone **215** gave the adduct **216**, which was taken through to epothilone D and then to epothilone B (scheme **38**).

Ermolenko and Potier [46] reported a convergent enantiospecific total synthesis of epothilones B and D from D-glucose (scheme **39**).

Liu and Wong [47] used the enzyme 2-deoxyribose-5-phosphatate aldolase (DERA) to form epothilones A and C (scheme **40**).

Many others groups [48-55] are still working to improve the synthesis of epothilones and to find new efficient analogs against cancer.

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