DOI: 10.1002/ejoc.200600149

Recent Developments in the Syntheses of the Epothilones and Related Analogues

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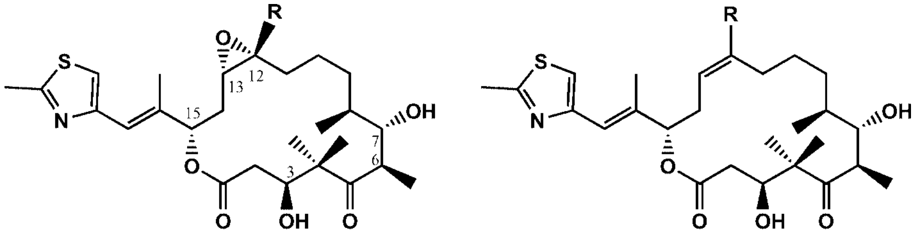
Keywords: Epothilones / Macrocycles / Anti-cancer agents / Total synthesis / Microtubule stabilization

The macrocyclic class of antitumor compounds known as the epothilones has generated considerable interest since its discovery in 1993. Numerous total syntheses of this class of molecules have been published and countless structural analogues have been developed and tested for their abilities to promote tubulin polymerization. Several of these compounds are presently in clinical trials.

I. Introduction

Abbreviations: CBS = Corey–Bakshi–Shibata reagent, CSA = 10-camphorsulfonic acid, DAST = diethylaminosulfur trifluoride, DCM = dichloromethane, DIPEA = diisopropylethylamine, DMDO = 3,3-dimethyldioxirane, DMS = dimethyl sulfide, dppf = bis(diphenylphosphanyl)ferrocene, Ipc_2B = diisopinocampheylborane, NMO = *N*-methylmorpholine *N*-oxide, PMB = 4-methoxybenzyl, PPTS = pyridinium *para*-toluenesulfonate, SEM-Cl = [2-(trimethylsilyl)ethoxy]methyl chloride, TBODPSCl = *tert*-butoxydiphenylsilyl chloride, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, TES = triethylsilyl, TFA = trifluoroacetic acid, TPAP = tetrapropylammonium perruthenate, TrocCl = (trichloroethoxy)carbonyl chloride.

The 16-member macrolides, epothilones A (**1**) and B (**2**) (Figure 1), were first isolated by Höfle and co-workers in 1993 from the myxobacterium *Sorangium cellulosum*.[1–3] The confirmation by Bollag et al., from the research laboratories at Merck, that this new class of compounds operated through a paclitaxel-type mechanism of action, arresting mitosis at the G_2-M phase transition, resulting in apoptotic cell death,[4] stimulated a vast interest in this class of molecules, culminating in the publication of numerous total and partial syntheses and the development of an immense number of structural analogues (vide infra).[5–14] Several of these potent analogues are now in phase I and phase II clinical trials.[15–17]



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

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

Figure 1. The epothilones A–D (**1**–**4**).

Scientific interest in the epothilones resulted from the clinical success of the tubulin-binding, anticancer agents[18–24] known as the taxanes. Taxol® (paclitaxel) was first isolated from the Pacific yew tree, *Taxus brevifolia*, in

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

1971 by Wall and co-workers.[25] Taxol® and a semi-synthetic derivative, Taxotere®, have since emerged as leading chemotherapeutic agents and have found extensive use on the pharmaceutical market for the treatment of breast and non-small-cell lung carcinomas. Taxol® has also been approved for the treatment of ovarian cancer as well.[26]

Unfortunately, the clinical success of the taxanes has been hindered by a variety of problems. Many of these problems have been remedied by the discovery of the epothilones. In contrast to the structurally complex taxanes, the epothilones possess a simpler overall architecture. This feature makes access to this new class far easier than current access to the taxanes. Additionally, the epothilones have been shown to be more water soluble than Taxol®,[3] thus eliminating the need for formulation with problematic agents such as Cremophor EL®.[27–29] Furthermore, unlike Taxol® and its derivatives, the epothilones are not substrates for the P-glycoprotein efflux pump and are thus capable of inhibiting the growth of multi-drug-resistant (MDR) cancer cell lines, including those with mutations in β-tubulin, which are Taxol®-resistant.[30, 31]

Multiple reviews have appeared in the literature detailing the various total syntheses of epothilones A (**1**) and B (**2**), as well as other related compounds and their structure activity relationships.[5–14] The goal of this review is to summarize the recent literature surrounding the epothilones (primarily 2003–2005) including new total and partial syntheses along with new epothilone analogues and their corresponding syntheses.

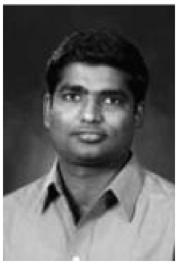
II. Recent Total Syntheses of the Epothilones

Multiple total syntheses of members of the epothilone family of compounds (Figure 1) have appeared in the literature. Several new or improved total syntheses of the epothilones have appeared in the recent literature. We will highlight these new approaches and the improvements associated with each.

Previous work from our laboratory has resulted in the total syntheses of epothilones A–D (**1**–**4**).[32–35] Our overall retrosynthetic approach to this class of molecules is shown in Scheme 1.[33] We envisioned using a convergent, two-step sequence involving a double-diastereoselective aldol condensation between the aldehyde **5** and the keto acid **6**, followed by Yamaguchi macrolactonization to form the target epothilone framework.

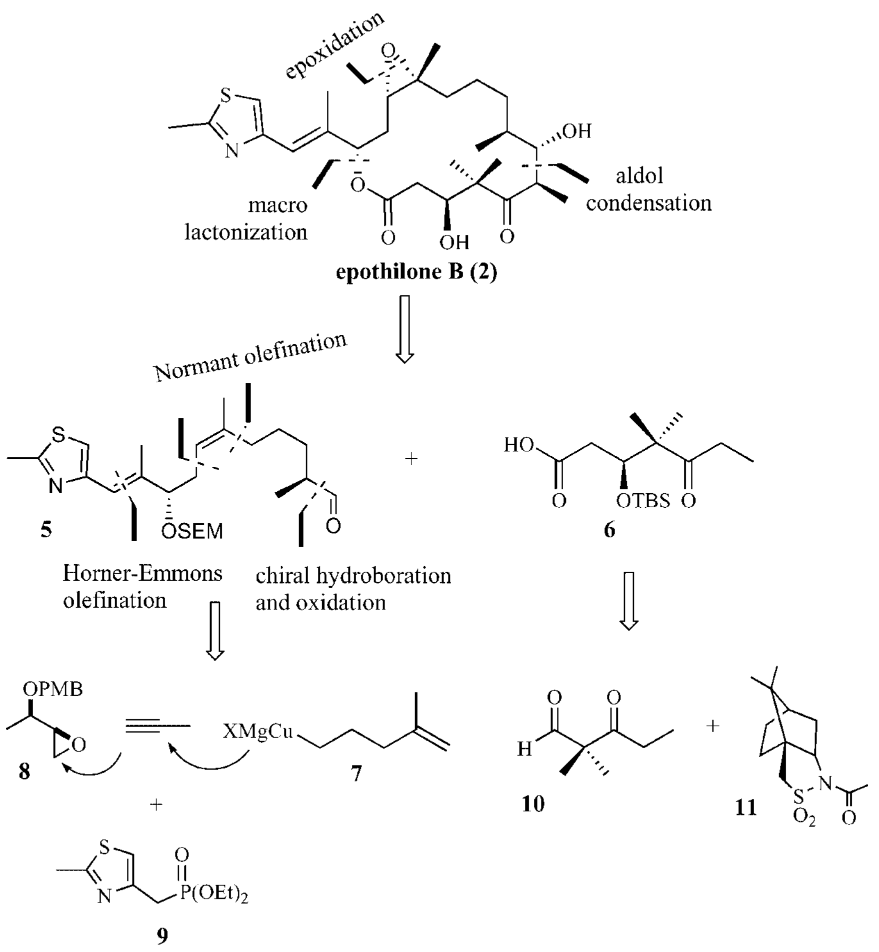
The (*Z*)-olefin, an essential feature of the epothilones, has traditionally been prepared by classical Wittig olefination methods or through ring-closing metathesis approaches. We envisioned formation of the desired trisubstituted olefin **5**, with the required (*Z*)-stereochemistry, making use of a modification of the classic Normant alkyne cupration reaction and subsequent electrophile trapping.

Blake Watkins was born in Memphis, Tennessee, and received his undergraduate degree in chemistry and mathematics from Union University in Jackson, Tennessee, in 1994. He received his Ph.D. degree in 2000 under the direction of Professor Robert S. Phillips in the Department of Chemistry at the University of Georgia working on the synthesis and kinetics of small molecule inhibitors of tyrosine phenol lyase. His postdoctoral research, under the direction of Professor Mitchell A. Avery in the Department of Medicinal Chemistry at the University of Mississippi focused on ultra high pressure cyclization reactions and the synthesis of chiral vinyl boronates for use in asymmetric ultra high pressure Diels–Alder reactions. Currently he is a Research Assistant Professor of Medicinal Chemistry at the University of Mississippi and is working on the total synthesis of naturally occurring antifungal agents.



Amar G. Chittiboyina was born in 1973 and raised in Machilipatnam, India. He earned his M.Sc. degree in chemistry with highest distinction from the National Institute of Technology, Warangal, India, in 1995. He then joined the group of Subhash P. Chavan at the National Chemical Laboratory, Pune, India, where he developed a short and efficient synthesis of (+)-biotin. Upon completing his Ph.D. in 2002, he moved to the Department of Medicinal Chemistry at the University of Mississippi to work with Professor Mitchell A. Avery on the design and synthesis of novel chemical entities for the treatment of diabetes, hypertension and malaria. Currently he is working as a research scientist. His research interests have focused on the asymmetric synthesis of biologically active natural products, structure-based drug design, and the development of new synthetic methodologies.

Professor Mitchell A. Avery received his B.S. in Chemistry in 1975 from Oregon State University and his Ph.D. in Organic Chemistry in 1979 from the University of California, Santa Cruz. After working as a postdoctoral researcher from 1979–1981 at the University of California, San Diego and Oregon State University, he became a research associate in the Life Sciences Division of SRI International, Menlo Park, CA, USA, eventually becoming Director of the Steroids and Natural Products Program. Rejoining academia in 1990, Professor Avery was an Associate Professor in the Department of Chemistry at the University of North Dakota in Grand Forks until he joined the Department of Medicinal Chemistry at University of Mississippi in 1994. He is currently the Interim Chair of the Department of Medicinal Chemistry, a professor of Medicinal Chemistry, Chemistry, and Biochemistry, and Research Professor through the Research Institute of Pharmaceutical Sciences and National Center for Natural Products Research at the University of Mississippi. He is also the director of the "Laboratory of Applied Drug Design and Synthesis" at the University of Mississippi, which is funded through the Centers for Disease Control and Prevention to further his work in developing new drugs for combating malaria and other infectious diseases worldwide. During his research career, Dr. Avery's work has focused on a number of rational methods for discovery and/or development of new bioactive substances for human or veterinary use.



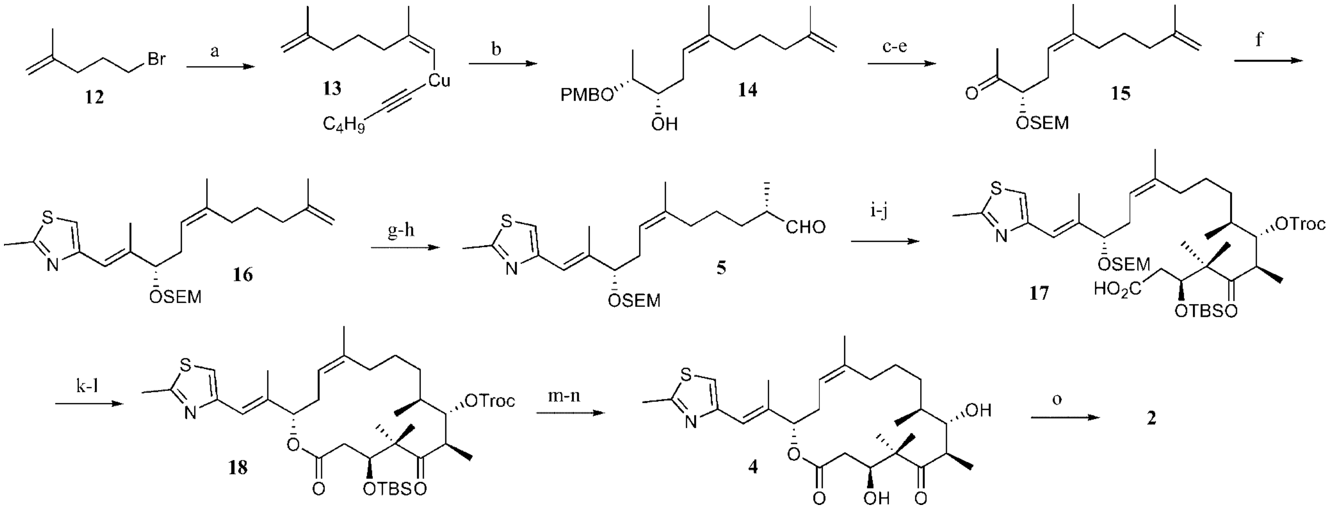
Scheme 1. Avery's retrosynthetic approach to epothilones B (**2**) and D (**4**).

Not only would this establish the required regiochemistry but it would also establish the stereochemistry at C15, arguably one of the more difficult centers to set in this class of compounds. Analysis of **5** revealed that the cuprate **7** could be coupled with propyne and the PMB-protected epoxy alcohol **8** in a one-pot reaction to accomplish this goal.

Our synthesis of epothilones B (**2**) and D (**4**) is summarized in Scheme 2. Our overall approach to these molecules involved the assembling of the two "hemispheres" and coupling these through a stereoselective aldol condensation to establish the C6–C7 stereochemistry. Construction of the "northern hemisphere" was accomplished using a modification of the classic Normant reaction. Treatment of bromo-4-methylpent-4-ene (**12**) with magnesium and transmetalation of the resulting Grignard reagent with copper(I) bromide–dimethyl sulfide complex (CuBr–DMS) at –23 °C afforded **7**. Stepwise addition of propyne and freshly prepared lithiohexyne at –78 °C gave the desired cuprate **13**. Addition of the vinyl cuprate **13** to the epoxy PMB ether **8** gave **14** with the required regiochemistry at C12–C13, along with the proper stereochemistry at C15. Protecting group manipulation and Swern oxidation of the resulting secondary alcohol gave **15**. The thiazole side chain was incorporated using standard Horner–Wadsworth–Emmons conditions, which gave the (*E*)-olefin in 86% yield. Asymmetric hydroboration of the terminal olefin **16** followed by oxidative workup and Swern oxidation gave **5**, thus completing the synthesis of the "northern hemisphere" of the epothilones.

The completed epothilone framework was assembled through an intermolecular aldol reaction between the aldehyde **5** and the keto acid **6**.[36] The reaction proceeded to give the desired diastereomer **17** in a ratio of 2.3:1.0 with a total yield of 85%. We have examined other aldol substrates and various reaction conditions to optimize both stereoselectivity and product yield. Using Oppolzer's sultam of **6** under $TiCl_4$ conditions, we were able to achieve 10:1 stereoselectivity. Unfortunately, the product yield was only 60%, and we encountered great difficulty in the hydrolysis of the chiral auxiliary. Therefore, we chose to keep with our original keto acid for the aldol condensation. Selective deprotection and Yamaguchi macrolactonization gave **18**, which was easily converted into epothilone D (**4**) following global deprotection. Diastereoselective epoxidation (9.5:1.0) of **4** with dimethyldioxirane (DMDO) at –78 °C completed our synthesis of epothilone B (**2**).

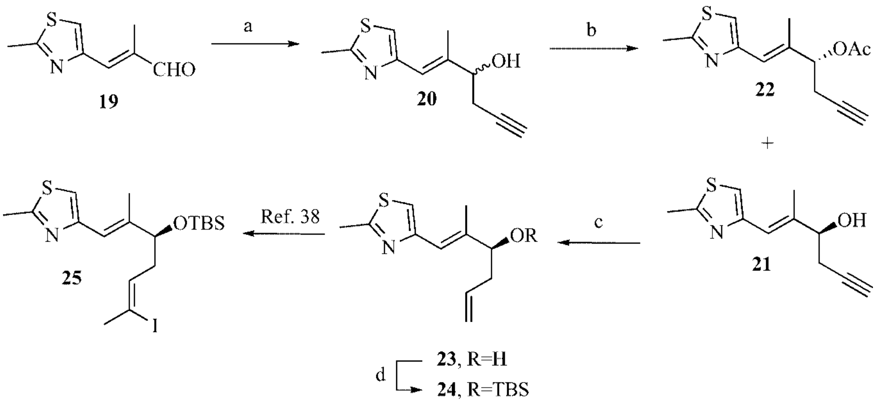
Other groups have recently reported new syntheses or improvements of their prior syntheses. Broadrup's approach to epothilone D (**4**)[37] involved a convergent scheme utilizing a palladium-catalyzed Suzuki coupling between the vinyliodide **25** and the olefin **36** (Scheme 3 and Scheme 4). The



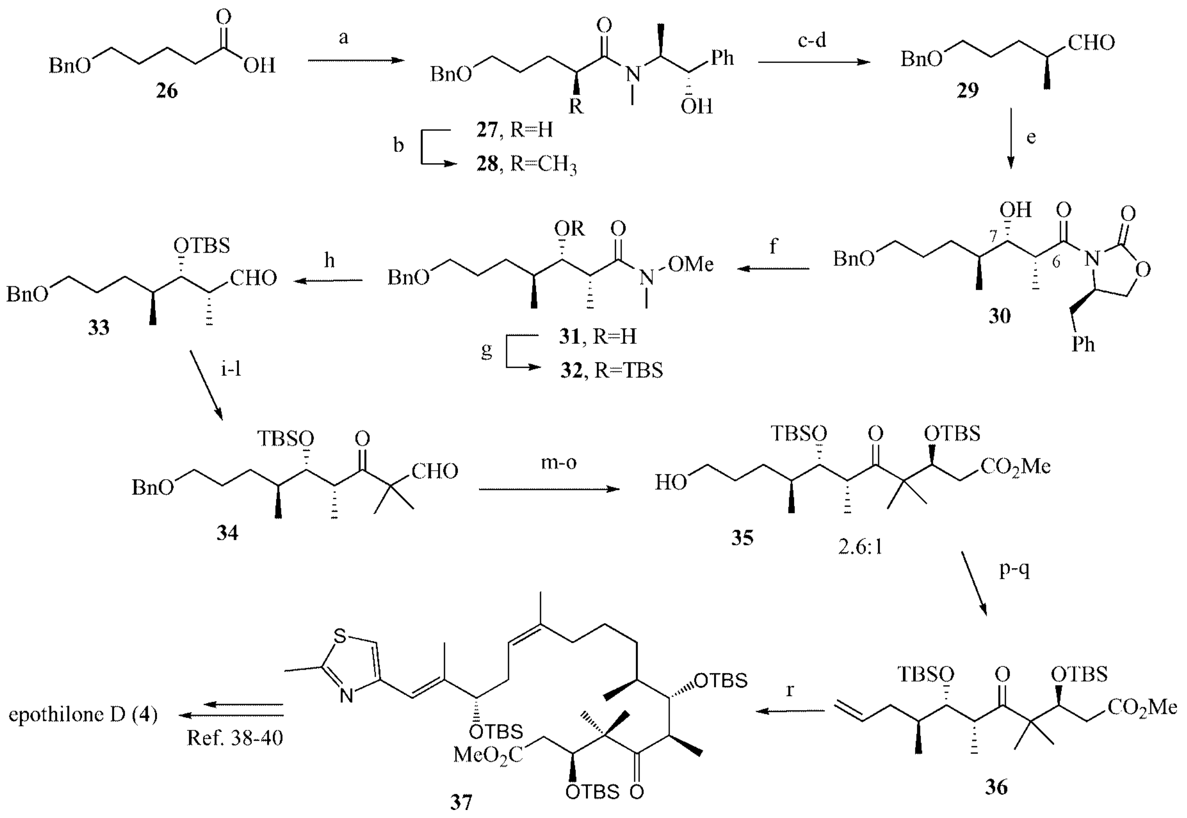
Scheme 2. Avery's synthesis of epothilones B (**2**) and D (**4**). Reagents and conditions: a) i. Mg, diethyl ether, room temp. to reflux, 1 h; ii. CuBr–DMS, diethyl ether, DMS, –45 °C, 2 h; iii. propyne, –23 °C, 4 h, then lithiohexyne, –78 °C, 1 h; b) **8**, –78 °C, 3 h; –25 °C, 14 h, 75% from **12**; c) SEM-Cl, DIPEA, DCM, 0 °C; then room temp., 6 h, 92%; d) DDQ, DCM/H_2O (8:2), room temp., 3 h, 91%; e) DMSO, $(COCl)_2$, TEA, DCM, –78 °C, 2 h, 85%; f) **9**, *n*BuLi, THF, –78 °C, 1 h; then room temp., 12 h, 86%; g) Ipc_2BH, THF, room temp., 30 min; then LiOH (aq), $NaBO_3$ (aq), room temp., 2 h, 78%; h) DMSO, $(COCl)_2$, TEA, DCM, –78 °C, 1 h, 94%; i) LDA,–5 °C, 20 min; then **6**, THF, –78 °C, 15 min; then –40 °C, 1 h; $ZnCl_2$ (2.5 equiv.), –78 °C, 30 min; then **5** (1.0 equiv.), THF,–78 °C, 15 min, 85% combined yield, *dr* 2.3:1.0; j) i. TBSCl (1.2 equiv.), pyridine (10 equiv.), DCM, 0 °C, 1 h; then TrocCl, DCM, room temp., 5 h; ii. AcOH, THF/H_2O (8:2), 0 °C, 3 h, 36%; k) $MgBr_2$ (6.0 equiv.), $MeNO_2$ (6.0 equiv.), *n*BuSH (3.0 equiv.), diethyl ether, room temp., 1 h; l) 2,4,6-trichlorobenzoyl chloride (3.0 equiv.), TEA (3.6 equiv.), THF, 0 °C, 1 h; then toluene, added to DMAP (6.0 equiv.) in toluene, room temp., 4 h, 38% for three steps; m) Zn, NH_4Cl, MeOH, reflux, 20 min, 92%; n) HF–pyridine, THF, room temp., 16 h, 95%; o) 3,3-dimethyldioxirane, DCM, –78 °C; then –50 °C, 2 h, 53%, *dr*, 9.5:1.0.

vinyl iodide **25** was synthesized in several steps from the known thiazole aldehyde **19**. Treatment of the aldehyde **19** with propargyl bromide and activated zinc gave **20** as a racemic mixture. Enzymatic resolution with *Pseudomonas* AK lipase in the presence of vinyl acetate and molecular sieves at 40 °C for 18 hours afforded (*S*)-**21** and its epimeric acetate **22**. Lindlar reduction and protection afforded **24** which was converted into the vinyl iodide **25** according to literature procedures.[38]

The second fragment necessary for the Suzuki coupling, the olefin **36**, was assembled from the known 5-benzyloxypentanoic acid (**26**) (Scheme 4). Utilizing Myer's chiral auxiliary, the C8 methyl group was introduced in 94% yield onto **27** with a diastereoselectivity of >99%. Following reductive removal of the chiral auxiliary with borane–ammonia complex and LDA, the resulting alcohol was oxidized by Swern conditions to the aldehyde **29**. To establish the desired stereochemistry at C6–C7, Broadrup made use of



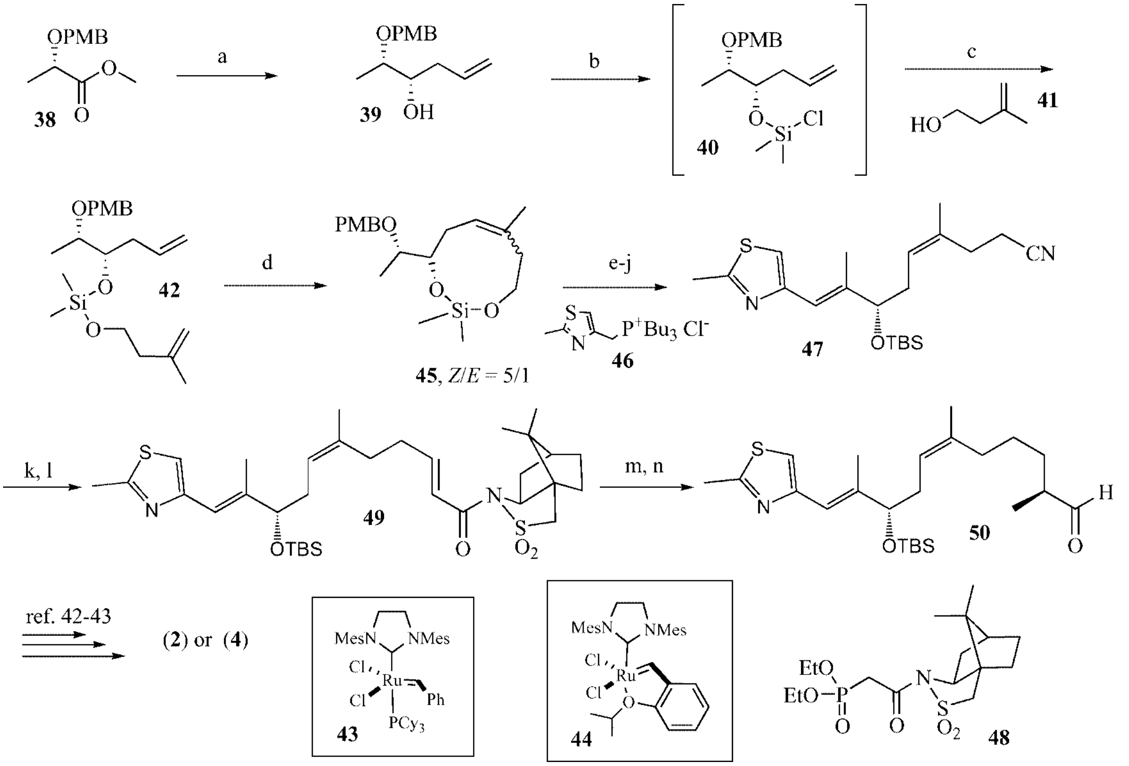
Scheme 3. Broadrup's synthesis of the vinyl iodide **25**. Reagents and conditions. a) propargyl bromide, activated Zn dust, THF, room temp., 18 h, 80%; b) *Pseudomonas* AK lipase, vinyl acetate, 3-Å molecular sieves, 40 °C, 18 h, 80%, >99% *ee*; c) H_2/Lindlar catalyst, THF, room temp., 1 h, 94%; d) TBDMS–OTf, 2,6-lutidine, CH_2Cl_2, 0 °C.



Scheme 4. Broadrup's synthesis of epothilone D (**4**). Reagents and conditions: a) (1*S*,2*S*)-pseudoephedrine, pivaloyl chloride, Et_3N, THF/CH_3CN, 0 °C to room temp., 87%; b) LDA, LiCl, MeI, THF, –78 °C to 0 °C, 94%, >99% *de*; c) $BH_3 \cdot NH_3$ complex, LDA, THF, 0 °C to room temp., 75%; d) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, –78 °C to –30 °C, 84%; e) Bu_2B–OTf, Et_3N, CH_2Cl_2, (*S*)-4-benzyl-3-propionyloxazolidinone, –78 °C to 0 °C, 95%, 96:4; f) $CH_3ONHCH_3 \cdot HCl$, Me_3Al, THF, –5 °C to room temp., 80%; g) TBDMS–OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 96%; h) DIBAL-H, THF, –78 °C to –50 °C, 91%; i) prenylmagnesium chloride, THF, room temp., 1 h, 94%; j) TPAP, NMO, CH_3CN/CH_2Cl_2 (4:1), room temp., 2 h, 76%; k) OsO_4, NMO, THF/*tert*-butyl alcohol/H_2O (4:2:1), room temp., 16 h; l) $NaIO_4$, THF/H_2O (1:1), room temp., 6 h, 92% (2 steps); m) 1-*tert*-butyldimethylsilyloxy-1-methoxyethene, $BF_3 \cdot Et_2O$, CH_2Cl_2, –78 °C, 5 h, 97%; n) TBDMS–OTf, 2,6-lutidine,CH_2Cl_2, 0 °C, 30 min, 97%; o) H_2, $Pd(OH)_2/C$, room temp., 1 atm., MeOH, 7 h, 68%; p) 2-NO_2-PhSeCN, Bu_3P, pyridine, THF, room temp., 16 h, 96%; q) *m*CPBA, CH_2Cl_2, –15 °C (30 min); (*i*Pr)$_2$NH, room temp., 30 min, 67%; r) 9-BBN, THF, room temp., 6 h, then **25**, $PdCl_2(dppf)$, Cs_2CO_3, Ph_3As, DMF, H_2O, room temp., 15 h, 84%.

(*S*)-4-benzyl-3-propionyloxazolidinone and Evans' aldol reaction with the aldehyde **29**. The reaction proceeded to give **30** as a 96:4 mixture of inseparable isomers. Conversion of **30** to the Weinreb amide **31** through transamidation with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum permitted separation of the two isomers with the required diastereomer being isolated in 80% yield. Silylation of **31** and reduction of the Weinreb amide with DIBAL-H afforded the aldehyde **33**. Grignard addition of prenylmagnesium chloride to **33** followed by TPAP/NMO oxidation of the resulting alcohol and oxidative olefin cleavage with $OsO_4/NaIO_4$ gave the aldehyde **34** in excellent yield. Mukaiyama aldol condensation of **34** with 1-*tert*-butyldimethylsilyloxy-1-methoxyethene in the presence of boron trifluoride–diethyl ether resulted in an inseparable mixture of diastereomers (2.6:1). Silyl protection and debenzylation permitted easy separation of the two isomers and gave **35** in 68% yield. The olefin **36** was obtained from **35** by treatment with 2-nitrophenylselenenyl cyanide and tributylphosphane and oxidative elimination. Conversion of **36** to the alkyl borane by treatment with 9-BBN allowed Suzuki coupling to occur with the vinyl iodide **25** in the presence of $PdCl_2(dppf)$, Cs_2CO_3, and Ph_3As. Completion of the synthesis of **4** from **37** was achieved according to the literature.[38–40]

Mulzer's approach to epothilones B (**2**) and D (**4**)[41] centered on a silicon-tethered ring-closing metathesis (RCM) reaction to assemble the northern hemisphere of the molecule and to establish the required (*Z*)-stereochemistry at C12–C13 (Scheme 5). DIBAL-H reduction of the ester **38** and subsequent Grignard addition of allylmagnesium bromide in the presence of magnesium(II) bromide resulted in the formation of **39**. Preparation of the RCM precursor proceeded in one pot by treatment of **39** with *n*BuLi and $Si(Me)_2Cl_2$ followed by addition of **41** and DMAP. Exposure of **42** to Grubbs catalyst **43** or **44** at 40 °C for 16 h led to clean conversion to the nine-membered ring olefin **45** in a regioisomeric mixture of 5:1 (*Z*/*E*). The mixture of regioisomers was desilylated and separated by column chromatography. Protection of the resulting diol as the bis-TBS ether followed by mono-deprotection set the stage for a one-carbon homologation using Mitsunobu conditions

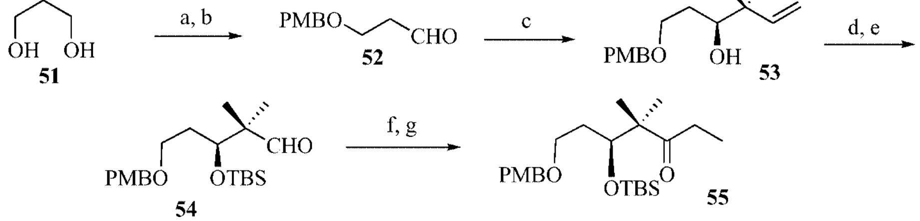


Scheme 5. Mulzer's synthesis of epothilones B (**2**) and D (**4**). Reagents and conditions: a) DIBAL-H, DCM, –78 °C, 2 h; MgBr$_2$; allylmagnesium bromide, 73%; b) THF, –78 °C, *n*BuLi; Si(Me)$_2$Cl$_2$, room temp.; c) DMAP, DMF, **41**, room temp. 24 h, 84%; d) **43** or **44** (15 mol-%), DCM, 40 °C, 16 h, 98%; e) TBAF, THF, 12 h, 84%; f) TBSOTf, DCM, 2,6-lutidine, HF, 88%; g) PPh$_3$, DEAD, acetone cyanohydrin, diethyl ether, 0 °C to room temp., 22 h, 89%; h) DDQ, DCM/H$_2$O (20:1), 0.5 h, 91%; i) oxalyl chloride, DCM, DMSO, –78 °C, 1 h, 95%; j) *n*BuLi, THF, 0 °C, 1 h; **46**, 1 h, 94%; k) DIBAL-H, toluene, –78 °C, 2 h, 84%; l) **48**, LiOH, THF, 0 °C, 0.5 h, 83%; m) L-selectride, THF, –78 °C, LDA, MeI, HMPA, 16 h, room temp., 90%; n) DIBAL-H, –90 °C, DCM, 0.5 h, 90%.

and acetone cyanohydrin. PMB removal, Swern oxidation and subsequent Wittig olefination with **46** afforded the thiazole **47**. Introduction of the C8 methyl group in an asymmetric fashion was accomplished in a series of steps beginning with DIBAL-H reduction of the nitrile **47** to the aldehyde and treatment with Oppolzer's chiral phosphonate **48** under Horner–Wadsworth–Emmons conditions to give the thiazole **49**. Reductive methylation of **49** and reductive cleavage of the chiral auxiliary led to the aldehyde **50** in 81% yield with a *de* >95%. Aldehyde **50** was converted into epothilones B (**2**) and D (**4**) according to Mulzer's earlier scheme.[42,43]

III. Recent Partial Syntheses of the Epothilones

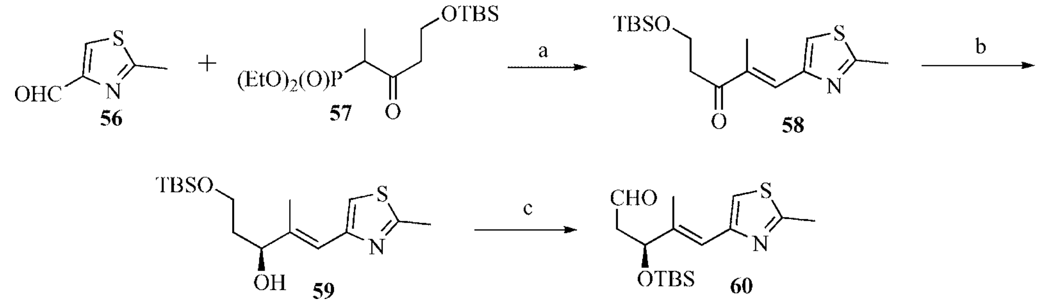
Numerous syntheses of epothilone fragments have appeared in the recent literature. Ramachandran has demonstrated[44,45] the synthetic usefulness of *B*-γ,γ-dimethylallyldiisopinocampheylborane in natural product synthesis by applying it to the enantioselective formation of the C3–C4 bond of his C1–C6 epothilone fragment as shown in Scheme 6. Monoprotection of the 1,3-propanediol **51** as the PMB ether and oxidation to the corresponding aldehyde using Swern conditions gave **52**, which was subjected to dimethylallylboration conditions using *B*-γ,γ-dimethylallyldi-



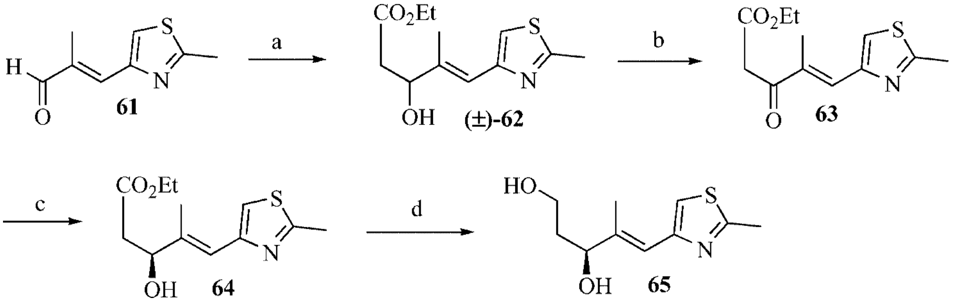
Scheme 6. Ramachandran's synthesis of the epothilone C1–C6 fragment (**55**). Reagents and conditions: a) NaH, *p*-CH$_3$OC$_6$H$_4$CH$_2$Cl, $N^+Bu_4I^-$, 80%; b) oxalyl chloride, DMSO, Et$_3$N, 85%; c) *B*-γ,γ-dimethylallyldiisopinocampheylborane, 82%; d) TBSOTf, 2,6-lutidine, 90%; e) O$_3$, 78%; f) EtMgBr; g) DMP, 88% (2 steps).

isopinocampheylborane to afford the alcohol **53** in 95% *ee*. Silyl protection and ozonolysis followed by Grignard addition to the resulting aldehyde **54** and Dess–Martin oxidation gave the desired C1–C6 fragment **55** in 88% yield (2 steps).

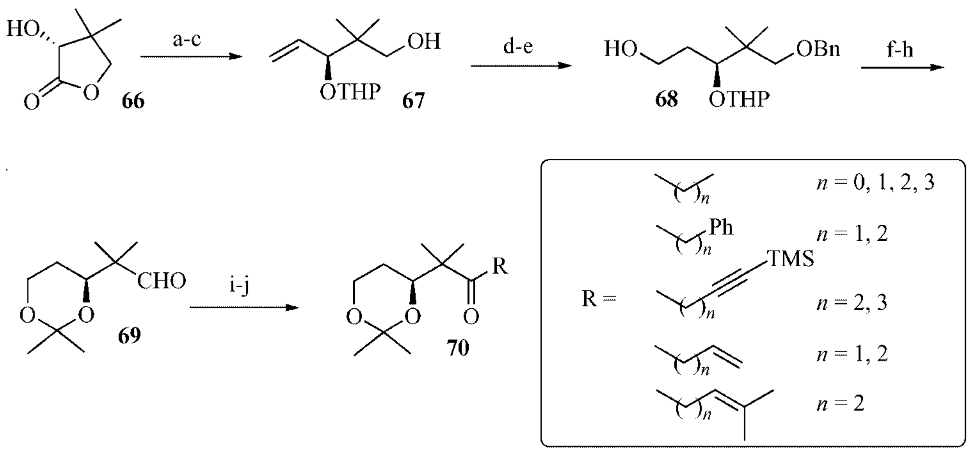
With the goal of developing a synthetic route to the epothilones that would grant easy access to analogues with variously substituted aryl side chains, Georg and coworkers[46] demonstrated the utility of two chiral asymmetric reduction methods, Itsuno–Corey reduction and Noyori reduction as described in Scheme 7 and Scheme 8, respectively. In their syntheses of two similar C12–C21 fragments (**60** and **65**), asymmetric reduction was utilized to establish the stereochemistry of the C15 hydroxy group. In their first approach (Scheme 7), the commercially available aldehyde **56** was coupled with the phosphonate **57** under modified



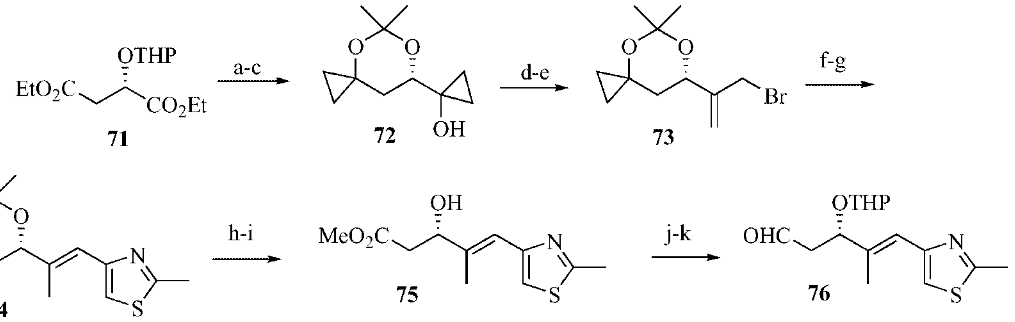
Scheme 7. Georg's synthesis of C12–C21 (**60**) using Itsuno–Corey reduction. Reagents and conditions. a) $Ba(OH)_2{\cdot}8H_2O$, THF, 45 min, room temp., then **56** in THF/H_2O (40:1), 0 °C, 1 h, then room temp., 45 min, 75%; b) (*R*)-2-Me-CBS-oxazaborolidine (0.5 equiv.), $BH_3{\cdot}Me_2S$ (1.5 equiv.), DCM, 0 °C, then **58**, 0 °C, 2 h, then ethanolamine, room temp., 16 h, 98%; c) i. TBSOTf, 2,6-lutidine, DCM, –78 °C, 15 min, 94%, ii. HF (48% aq.), glass splinters, MeCN/diethyl ether (1:1), 0 °C, 2 h, 82%, iii. DMP, DCM, room temp., 1 h, 98%.



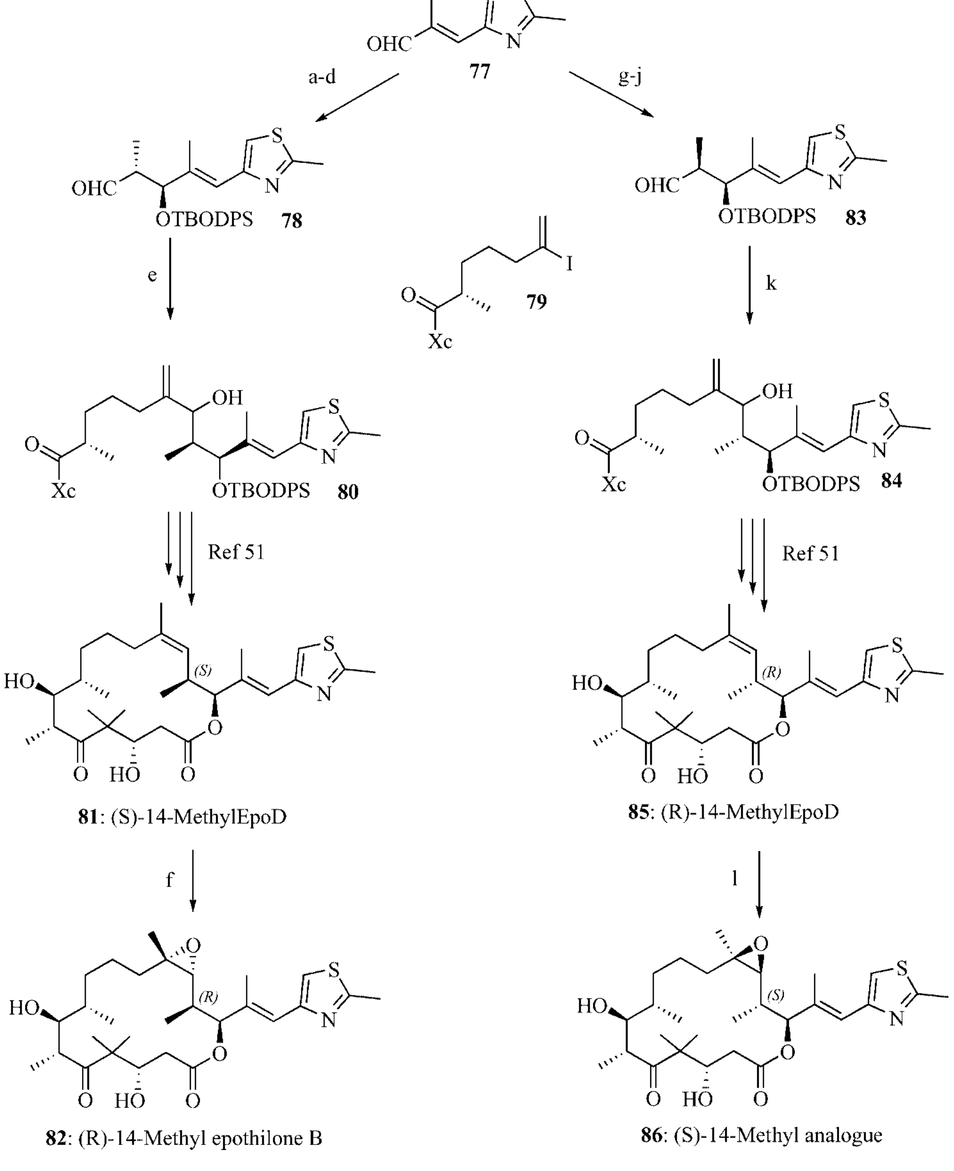
Scheme 8. Georg's synthesis of the C12–C21 fragment **65** using Noyori reduction. Reagents and conditions: a) LDA, THF, –78 °C, EtOAc, 10 min, 76%; b) MnO_2, $CHCl_3$, 0 °C, 2 h, 91%; c) $RuBr_2$-(*S*)-BINAP, H_2, MeOH, 50 psi, room temp., 2 h, 50%, 83% *ee*; d) DIBAL-H, DCM, –78 °C, 1 h, then room temp., 2 h, 70%.



Scheme 9. Klar's synthesis of a C1–C6 fragment **70**. Reagents and conditions: a) DHP, PPTS, DCM, room temp.; b) DIBAL-H, toluene, –70 °C; c) $MeP^+Ph_3Br^-$, BuLi, THF, 0 °C to room temp., 77%; d) BnBr, KO*t*Bu, dioxane, 50 °C, 99%; e) i. $BH_3{\cdot}THF$, THF, room temp.; ii. H_2O_2, NaOH, 59%; f) $Me_2C(OMe)_2$, *p*TsOH, acetone, room temp., 88%; g) Pd/C (10%), H_2, EtOH, room temp., 96%; h) Swern oxidation; i) R-MgBr or R-Li, diethyl ether or THF, 0 °C to room temp., 44–88%; j) TPAP, NMO, 4 Å MS, DCM, room temp., 62–96%.



Scheme 10. Kulinkovich's synthesis of a C13–C21 fragment **76**. Reagents and conditions: a) EtMgBr (6 equiv.), Ti(O*i*Pr)$_4$ (50 mol%), room temp.; b) MeOH, PPTS (5 mol%), reflux, 15 min; c) acetone, CuSO$_4$ (2 equiv.) PPTS (5 mol%); d) MsCl (1.5 equiv.), Et$_3$N (3 equiv.), diethyl ether; e) MgBr$_2$ (3 equiv.) diethyl ether–chloroform, reflux, 5 h; f) (2-methylthiazol-4-yl)magnesium bromide (1.5 equiv.), CuI (10 mol-%), 0 °C to room temp.; g) 0.25 M *t*BuOK in *t*BuOH, reflux, 1.5 h; h) MeOH, PPTS (5 mol%), reflux; i) PhI(OAc)$_2$ (1 equiv.), MeOH, room temp., 2 h; j) DHP (3 equiv.), PPTS (5 mol-%), CHCl$_3$, reflux; k) DIBAL-H (1.3 equiv.), toluene, –78 °C, 1 h.

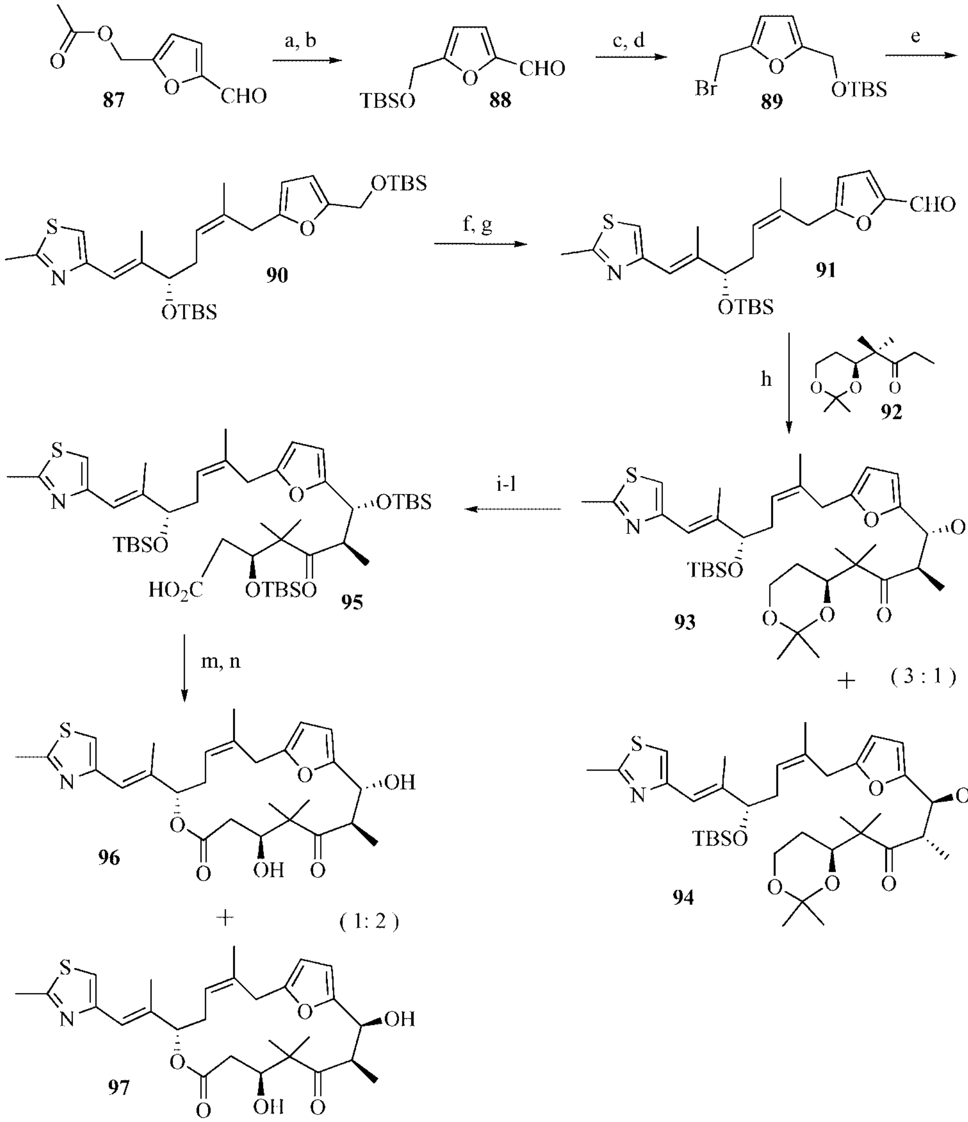


Scheme 11. Taylor's synthesis of C14-methyl analogues. Reagents and conditions: a) (*E*)-crotyl-(+)-Ipc$_2$B, 70%, 99% *ee*; b) TBODPSCl, 93%; c) OsO$_4$, NMO; d) NaIO$_4$, 65%; e) **79**, NiCl$_2$, CrCl$_2$, 75%; f) *m*CPBA, 57%; >20:1; g) (*Z*)-crotyl-(+)-Ipc$_2$B, 66%, 94% *ee*; h) TBODPSCl, 92%; i) OsO$_4$, NMO; j) NaIO$_4$, 82%; k) NiCl$_2$, CrCl$_2$, 88%, 1:1 *dr*; l) *m*CPBA, 55%, >20:1.

Horner–Wadsworth–Emmons conditions to give the enone **58** in 75% yield. Exposure of **58** to (*R*)-2-Me-CBS-oxazaborolidine (Itsuno–Corey conditions) afforded the chiral allylic alcohol **59** in 98% yield and with a 95% *ee*. Silyl protection of the resulting alcohol **59**, selective desilylation and Dess–Martin periodinane oxidation furnished the required aldehyde fragment **60**.

In their second approach to the C12–C21 fragment, Georg et al. used Noyori reduction to establish the C15 stereochemistry (Scheme 8).[46] Condensation of the aldehyde **61** with the lithium enolate of ethyl acetate gave the hydroxy ester **62** as a racemic mixture. Allylic oxidation of **62** with MnO_2 and Noyori reduction of **63** afforded **64** with the required stereochemistry in 50% yield and in 83% *ee*. DIBAL-H reduction of the ester **64** furnished the required C12–C21 fragment **65**. The authors contribute the lower reduction yield and lower enantiomeric excess to the coordination of the thiazole moiety with the catalyst thus promoting various side reactions. Reductions of enones with the thiazole ring replaced by phenyl rings gave much higher yields and higher *ee* values.

Klar and co-workers at the Research Laboratories of Schering AG have developed an efficient chiral pool synthesis of the C1–C6 fragment leading to the production of numerous segments and ultimately to the production of various C-6 epothilone analogues (Scheme 9).[47] Their synthesis begins with the chiral lactone, (–)-pantolactone **66**, which contains the requisite C2–C5 atoms and a geminal



Scheme 12. Schinzer's synthesis of furano-epothilone D (**96**). Reagents and conditions: a) K_2CO_3, MeOH, room temp., 18 h, 98%; b) TBSCl, imidazole, DMF, room temp., 18 h, 89%; c) $NaBH(OAc)_3$, benzene, reflux, 3 h, 93%; d) PPh_3, imidazole, Br_2, DCM, 0 °C, 10 min; e) Rieke Zn in THF, –30 °C, then **89** in THF, $[Pd(PPh_3)_4]$, then **25** in THF, 60 °C, 1 h, 85%; f) NH_4F, MeOH, reflux, 1 h, 93%; g) NMO, 4-Å molecular sieves, DCM, 0 °C, 15 min, TPAP, room temp., 15 min, 87%; h) **92**, LDA, THF, –78 °C, 1 h, then **91**, –78 °C, 15 min, 91%; i) PPTS, MeOH, room temp., 48 h, 84%; j) TBSOTf, 2,6-lutidine, DCM, –50 °C, 1 h, 71%; k) NH_4F, MeOH, reflux, 2.5 h, 73%; l) PDC, DMF, room temp., 19 h, 80%; m) aq. HF (40%), CH_3CN/diethyl ether, glass splinters, 2d, 1:2, 25:47%; n) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C, 15 min, then DMAP in toluene, room temp., 1 h, 51%.

dimethyl group at C4. THP protection, reduction to the lactol, and Wittig reaction led to olefin **67** and introduction of the C1 carbon. Protection of the primary alcohol as its benzyl ether and subsequent hydroboration gave alcohol **68**. After formation of the acetonide, the benzyl protecting group was removed, and the resulting alcohol was oxidized to the aldehyde **69** under Swern conditions. Treatment of **69** with various Grignard reagents or alkyllithium reagents followed by TPAP/NMO oxidation afforded an array of C1–C6 analogues **70** for epothilone synthesis.

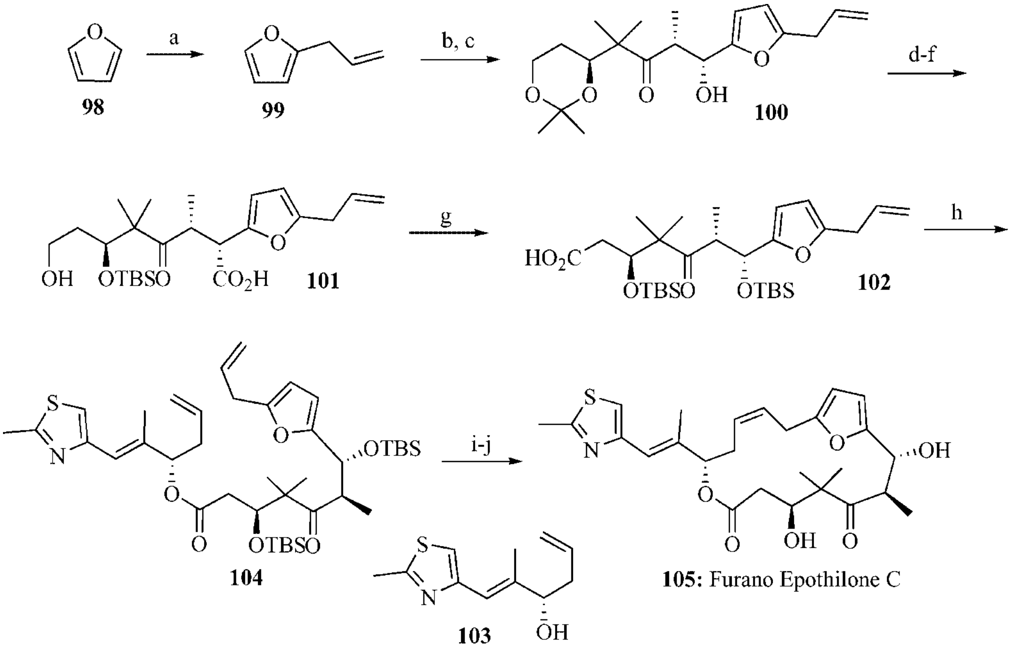
The Kulinkovich research group has developed an unique titanium-catalyzed cyclopropanation approach to the C13–C21 fragment of the epothilones (Scheme 10).[48] Bis-cyclopropanation of the diester **71** by treatment with ethylmagnesium bromide in the presence of titanium tetraisopropoxide resulted in the bis-cyclopropanol, which was deprotected and selectively re-protected as the acetonide **72**. Conversion of **72** to the mesylate followed by $MgBr_2$-promoted cyclopropyl–allyl rearrangement afforded allylic bromide **73** in 76% yield over two steps. Copper-catalyzed addition of (2-methylthiazol-4-yl)magnesium bromide and base-catalyzed isomerization of the resulting olefin gave **74** in excellent yield. Methanolysis of the acetonide **74** and oxidation of the resulting cyclopropanol afforded **75** in 70% yield over two steps. Hydroxy protection and reduction of the ester to the aldehyde gave the target molecule **76** in 80% yield.

IV. Recent Syntheses of New Epothilone Analogues

To further explore the biologically active conformation of the epothilones bound to tubulin, the Taylor group has been actively involved in analog synthesis and conformational studies, using both high field NMR techniques and computer-based molecular modeling.[49, 50] To this end, they have synthesized 14-methyl-epothilone derivatives (**82** and **86**, Scheme 11) utilizing their previous synthetic route[51] to epothilones B (**2**) and D (**4**). The syntheses of both derivatives began with Brown's asymmetric crotylboration of aldehyde **77**. Hence, treatment of aldehyde **77** with (*E*)-crotyl-(+)-Ipc_2B gave the desired product in 70% yield with an enantiomeric excess of 99% and both the C14 and C15 stereocenters set. Protection of the resulting secondary alcohol as the *tert*-butoxydiphenylsilyl ether followed by oxidative cleavage of the olefin afforded the aldehyde **78** which was coupled to the vinyl iodide **79** using Ni/Cr coupling conditions to give the allylic alcohol **80** as a single diastereomer in 75% yield. Using conditions from their previous synthesis of epothilone B[51] the synthesis of (*S*)-14-methyl-epothilone D (**81**) and (*R*)-14-methyl-epothilone B (**82**) was completed.

Likewise, treatment of the aldehyde **77** with (*Z*)-crotyl-(+)-Ipc_2B under Brown's asymmetric crotylboration conditions afforded the desired alcohol in 66% yield and 94% *ee* with both the C14 and C15 stereocenters established. Silyl protection of the resulting alcohol and oxidative cleavage of the terminal olefin gave **83**, which was coupled with **79** in a similar fashion as above to give **84** as a 1:1 mixture of diastereomers. The allylic alcohol **84** was converted into (*R*)-14-methyl-epothilone D (**85**) and its (*S*)-14-methyl analogue **86** using previous conditions.[51]

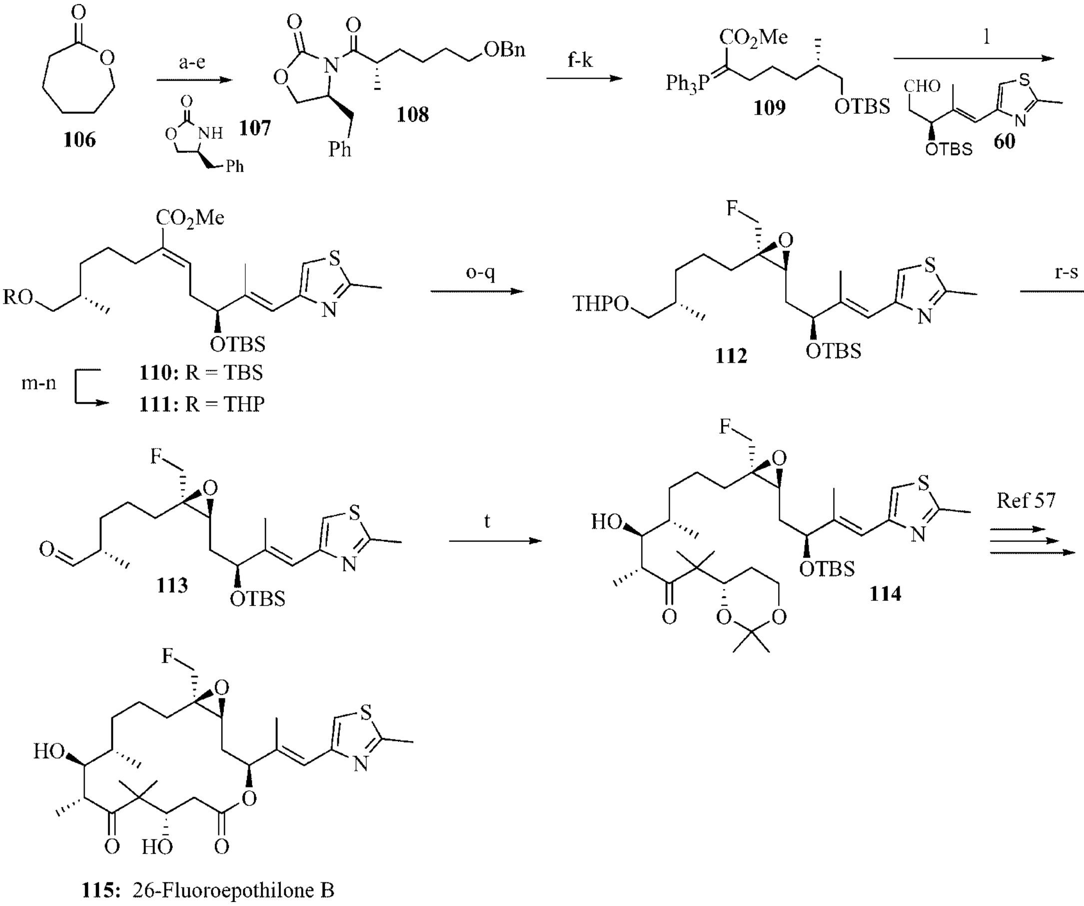
The Schinzer group has devised a furano derivative of epothilone D after careful analysis of the X-ray crystal structure of epothilone B.[52] The synthesis of this furano epothilone D is outlined in Scheme 12. Saponification of



Scheme 13. Schinzer's synthesis of furano epothilone C (**105**). Reagents and conditions: a) *n*BuLi, allyl bromide, THF, –78 °C, 52%; b) DMF, $POCl_3$, 0 °C, 56%; c) LDA, **92**, THF, –78 °C, 50 min, 5 min (3.2:1); d) PPTS, MeOH, reflux, 82%; e) TBSOTf, lutidine, DCM, –30 °C, 71%; f) NH_4F, MeOH, reflux, 80%; g) PDC, DMF, 46%; h) **103**, DCC, DMAP, toluene, 64%; i) **43**, DCM, 55% *Z*, 22% *E*; j) CsF, DMF, separate, repeat, 35%.

the ester **87** with potassium carbonate followed by silyl protection afforded the silyl ether **88**. Reduction of the aldehyde **88** with sodium triacetoxyborohydride gave the alcohol, which was converted into **89** by treatment with bromine in the presence of imidazole and triphenylphosphane. Palladium-catalyzed coupling of the bromide **89** with the vinyl iodide **25** in the presence of Rieke zinc provided the bis-silyl ether **90** in 85% yield. Selective deprotection was accomplished with ammonium fluoride in methanol. TPAP/NMO oxidation of the resulting primary alcohol gave **91**. Aldol condensation of **91** with the ketone **92** afforded a 3:1 mixture of products (**93** and **94**). The two isomers were separated by chromatography, and the ketal protecting group of **93** was removed by treatment with PPTS. Exhaustive protection with TBSOTf afforded the tetrakis(silyl) ether in 71% yield. Selective removal of the TBS group from the primary alcohol and subsequent oxidation with PDC in DMF gave the requisite acid **95** in 80% yield. Selective deprotection of **95** proved to be impossible. Complete deprotection of **95** with aqueous HF (40%) in acetonitrile/diethyl ether gave a mixture of two diastereomers (1:2, 25:47%) due to epimerization of the C7 carbon. Separation of the diastereomers and subjection to Yamaguchi macrolactionization conditions gave the epimeric furano-epothilone derivatives (**96** and **97**). Compound **96** showed weak activity in a microtubule assembly assay, indicating that the chirality at C8 may not be important for biological activity.

Schinzer's approach[53] to furano epothilone C **105** involves allylation of furan **98** to **99** followed by a Vilsmeier–Haack reaction and aldol condensation with the ethyl ketone **92** to give **100** as a 3.2:1 mixture of diastereomers (*de* = 52%) in favor of the required *anti*-Cram/Felkin product (Scheme 13). Removal of the acetonide protecting group with PPTS and global silylation with TBSOTf gave the trisilyloxy derivative which was selectively deprotected to release the primary alcohol **101**. PDC oxidation in DMF afforded acid **102** which was esterified with **103** to give the ring-closing metathesis precursor **104**. RCM with Grubbs catalyst **43** gave a 2.5:1 mixture of regioisomers in favor of the required *Z*-isomer. Global deprotection proved to be quite difficult but was accomplished in 35% yield after three iterations of cesium fluoride treatment. Furano deriv-



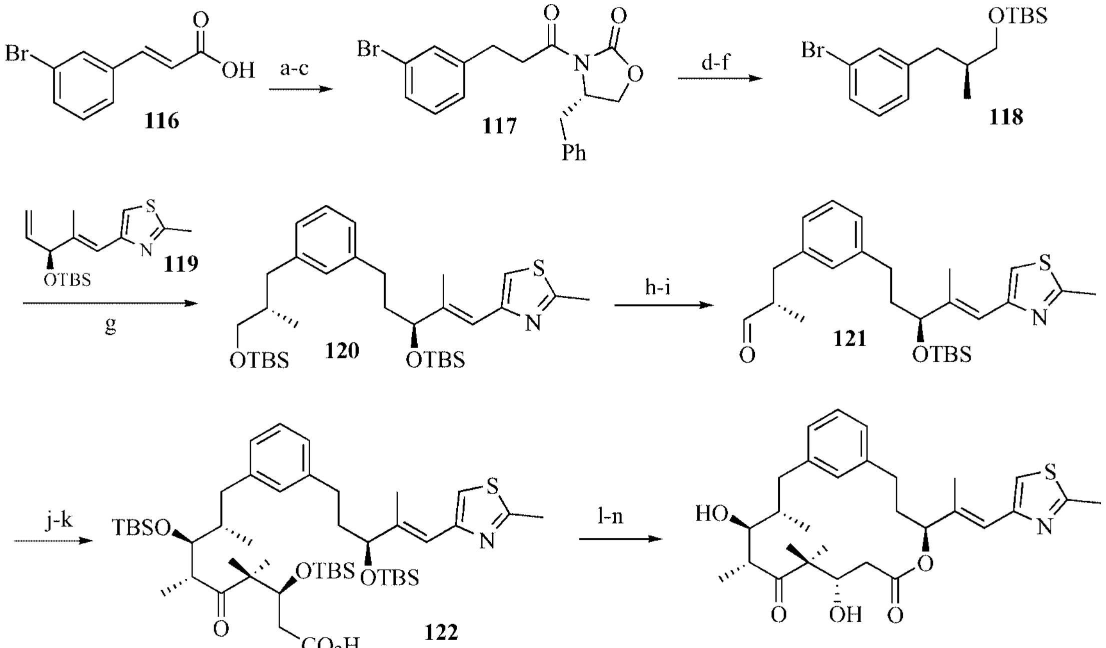
Scheme 14. Novartis synthesis of 26-fluoroepothilone B (**115**). Reagents and conditions: a) KOH/BnCl, toluene, reflux, 76%; b) oxalyl chloride, toluene, room temp.; c) **107**, hexyl-Li; d) NaHDMS, THF, –78 °C; e) MeI, –78 °C, 81%; f) $LiAlH_4$, THF, 0 °C, 79%, 87% *ee*; g) TBDMSCl, imidazole, DMF, room temp., 79%; h) H_2, $Pd(OH)_2/C$, THF, room temp., 100%; i) PPh_3, imidazole, I_2, CH_3CN, toluene, 0 °C, 97%; j) PPh_3, 100 °C; k) KHMDS, $ClCO_2CH_3$, THF, 0 °C, –78 °C; l) **60**, toluene, 40 °C; m) TFA, H_2O, THF, room temp.; n) DHP, PPTS, DCM, room temp., 65%; o) DIBAL-H, THF, –78–0 °C, quant.; p) (+)-diethyl-L-tartrate, $Ti(OiPr)_4$, *t*BuOOH, DCM, 4-Å mol. sieves, –30 °C, 2 h, 70%; q) DAST, DCM, room temp., 70%); r) PPTS, EtOH, 65 °C; s) oxalyl chloride, DMSO, Et_3N, DCM, –78 °C; t) **92**, LDA, –78 °C, 77%.

ative **105** displayed weak inhibition compared to epothilone B in a cell growth inhibition assay using human epidermoid carcinoma cell lines DB-31 and KB-8511.

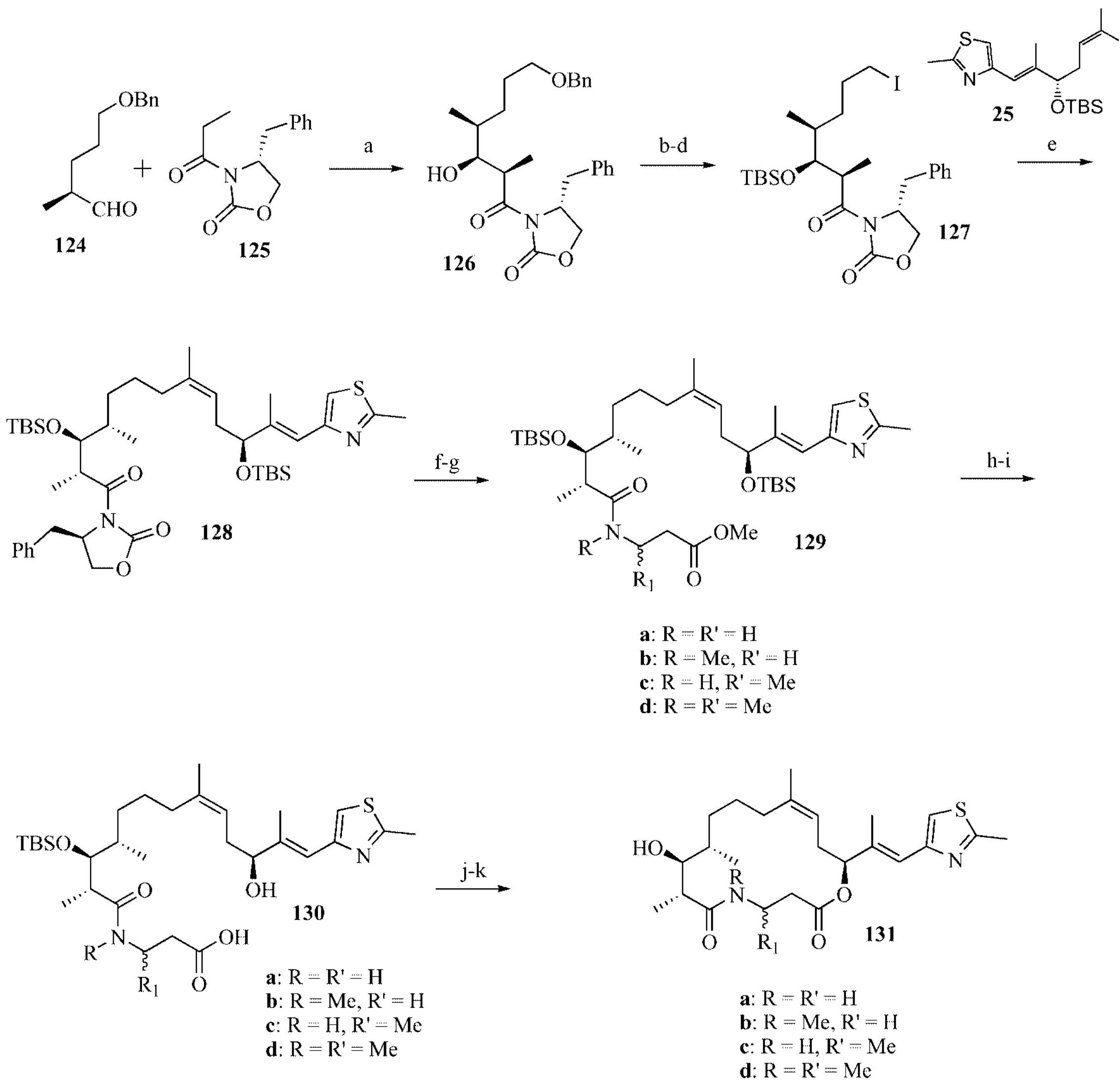
A series of epothilone related compounds have been developed and synthesized by research groups from Novartis.[54–56] Some of the more recent contributions include an improved synthesis of 26-fluoroepothilone B (**115**)[56] (Scheme 14). Hydrolysis of caprolactone **106** and in situ benzylation followed by conversion of the resulting acid to the acid chloride and coupling with the Evans chiral auxiliary derived from L-phenylalanine (**107**) set the stage for diastereoselective methylation to give **108** in 81% yield with a *de* of 87%. A series of protection and deprotection steps, conversion of the primary hydroxy group to the iodide and treatment with triphenyl phosphane gave the Wittig salt. Treatment with KHMDS and in situ acylation with methyl chloroformate provided ylide **109**. The ylide **109** was then coupled with aldehyde **60** to provide **110**. Due to difficulties later in the synthesis with fluorination in the presence of a TBS-protected primary alcohol, the TBS group was exchanged for a THP protecting group **111**. Reduction of **111** with DIBAL-H, Katsuki–Sharpless epoxidation of the resulting allylic alcohol and fluorination with DAST gave **112** as a single diastereomer. Removal of the THP protecting group and subsequent Swern oxidation afforded **113** which was coupled with the lithium enolate of **92** to give **114** as a single diastereomer in 77% yield. Completion of the synthesis followed the Schinzer synthesis of epothilone B.[57]

An additional structural epothilone analog has been developed by the Altmann group at Novartis (Scheme 15).[55] The C10/C12 phenylene-bridged analogue of epothilone D (**4**) was synthesized from 3′-bromocinnamic acid (**116**). Using standard conditions, the cinnamic acid **116** was converted into the acid chloride and coupled with Evans' chiral auxiliary to give **117**. Diastereoselective methylation (13:1), reductive removal of the chiral auxiliary and silylation of the resulting primary hydroxy group furnished **118** in good yield. Hydroboration of **119** with 9-BBN provided the necessary components for the Suzuki coupling with the bromide **118**. Selective desilylation and TPAP/NMO oxidation of **120** afforded **121**, which was coupled with the lithium dienolate of **6** to provide **122** as a 5:1 mixture of diastereomers after TBS protection. Selective desilylation, Yamaguchi macrolactionization, and global deprotection gave the desired analogue **123**. Phenylene derivative **123** failed to show any biological activity in a tubulin polymerization assay and in a cell growth inhibition assay.

The Altmann group of Novartis has also developed a series of 4-aza epothilone D analogues **131** to mimic proposed structural conformations during tubulin binding.[54] The synthesis of these derivatives is shown in Scheme 16. Diastereoselective aldol condensation between the aldehyde **124** and the oxazolidinone **125** afforded **126** as a single diastereomer. Protection of the resulting secondary alcohol, debenzylation and functional group manipulations gave the iodide **127**. Palladium-catalyzed coupling of the zincate of **127** and the vinyl iodide **25** provided **128** as a single regioisomer in good yield. Oxidative hydrolysis of the chiral auxiliary and coupling with a series of four amino esters furnished **129**. Selective removal of the C15



Scheme 15. Novartis synthesis of a phenylene-bridged epothilone D **123**. Reagents and conditions: a) Pt/C, H_2, 65%; b) oxalyl chloride, DMF, benzene, 77%; c) Evans' auxiliary, BuLi, THF, 100%; d) NaHMDS, MeI, THF, 72%; e) $LiBH_4$, THF, 94%; f) TBSCl, 1*H*-imidazole, DMF, 100%; g) **119**, 9-BBN, THF; then **118**, [$PdCl_2$(dppf)], NaOH, THF, 83%; h) CSA, DCM, MeOH, 96%; i) TPAP, NMO, DCM, CH_3CN, 60%; j) LDA, **6**, THF; k) TBSOTf, 2,6-lutidine, DCM; l) TBAF, THF, 44%; m) $Cl_3C_6H_2COCl$, DMAP, 39%; n) TFA/DCM, 72%.



Scheme 16. Novartis synthesis of 4-aza analogues of epothilone D (**131**). Reagents and conditions: a) Bu_2BOTf, Et_3N, 90%; b) TBSOTf, 2,6-lutidine, 0 °C to room temp., 4 h, 91%; c) H_2, Pd/C (10%), MeOH, room temp., 6 h, 82%; d) MsCl, Et_3N, 0 °C, 30 min; NaI, acetone, 50 °C, 3 h, 81% (2 steps); e) Zn–Cu, 1,2-dibromoethane, TMSCl, DMA, TMSOTf; then $Pd(PPh_3)_4$, **25**, benzene, 65 °C, 85%; f) LiOH, H_2O_2, THF/H_2O (4:1), room temp., 3 h, 78%; g) $i Pr_2EtN$, HBTU, DMF, room temp., 3 h, h) TBAF; i) LiOH, THF/H_2O (7:1), room temp., 5 h; j) 2,4,6-$Cl_3PhCOCl$, Et_3N, THF, room temp., 30 min, then DMAP, toluene, room temp., 3 h; k) HF–pyridine, CH_3CN, room temp., 6 h.

TBS group was successful for **129b** and **129d** using TBAF at 0 °C. Unfortunately, **129a** and **129c** proved problematic. Hence, the vinyl iodide **25** was prepared with a TES protecting group rather than a TBS group. Deprotection of **129a** and **129c** with a C15 TES group in place of the TBS group was possible using TBAF/AcOH. Standard synthetic manipulations provided a series of 4-aza epothilone D derivatives **131**.

V. Conclusions

Since the discovery of the epothilone class of anticancer agents in 1993, substantial work has been done in the areas of chemistry, biology, and medicine to further understand and improve upon the activities of these molecules. Numerous total and partial syntheses have been completed and countless analogues have been developed, some of which are far more potent than their parent compounds. Several of these compounds are now in clinical trials as research groups continue to strive for new and more powerful methods to eradicate cancer or, at least, to slow its life-threatening progress.

Acknowledgments

The authors wish to express their gratitude to Tapestry Pharmaceuticals for financial support of our research program.

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Received: February 21, 2006