Solid-Supported Total Synthesis

A Total Synthesis of Epothilones Using Solid-Supported Reagents and Scavengers**

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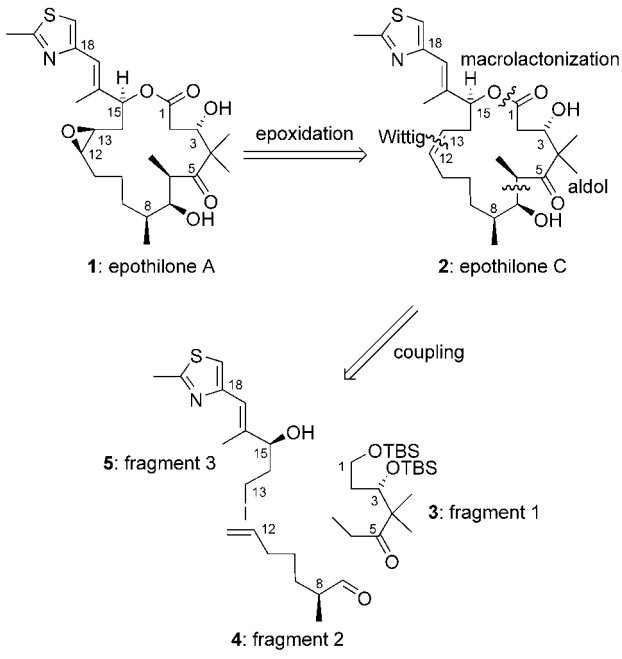
The epothilone natural products[1] exhibit extraordinary cytotoxic biological activity by promoting GTP-independent tubulin polymerization. This mode of action inhibits the growth of tumors by inducing mitotic arrest, followed by cell apoptosis. Mechanistic investigations have revealed that the epothilones bind competitively to the same, or overlapping, sites in β-tubulin as taxol.[2] However, certain epothilones exhibit a higher activity than taxol, even against multiple-drug-resistant cells, and are more soluble in water, making them interesting drug candidates.

Several total syntheses of both natural and analogous epothilones have been reported reported since the disclosure of their biological importance.[3–12] However, as a result of the complexity of these molecules, all previous synthetic programs have required extensive silica-gel chromatography to provide material free from contaminating by-products. Although acceptable in the research laboratory, such processes cannot be efficiently accommodated within larger-scale production, nor are they appropriate for the high-throughput preparation of libraries of analogues, in which speed and simplicity of operation are important criteria.

In recent years we have begun to explore the utility of commercially available immobilized reagents and scavengers[13] in the synthesis of drugs and natural products.[14] The combined application of these tools has been shown to provide versatile methods for molecular conversion and elimination of impurities, thereby offering the opportunity to avoid conventional approaches to reaction quenching, extraction, and purification.

Herein we describe how immobilized reagents and scavengers have been employed in a multistep sequence leading to epothilones A (**1**) and C (**2**), avoiding frequent use of conventional workup and purification procedures, including flash-column chromatography, recrystallization, and distillation (Scheme 1).

Our approach to the 16-membered macrocycle is similar to several previously published syntheses in that it utilizes a stereoselective union of three fragments by lithium aldol (C6–C7) and Wittig (C12–C13) reactions, followed by macrolactonization (C1–C15) to provide epothilone C (**2**; Scheme 1).[7,8,15] Epoxidation can then be applied to the



Scheme 1. Synthetic plan.

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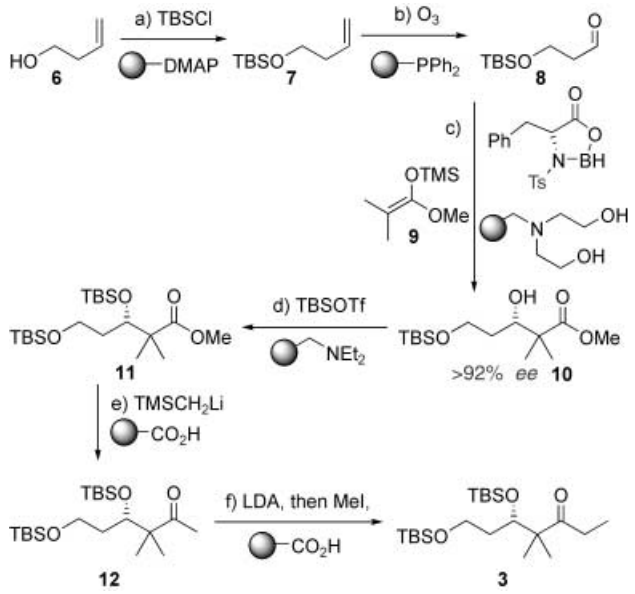
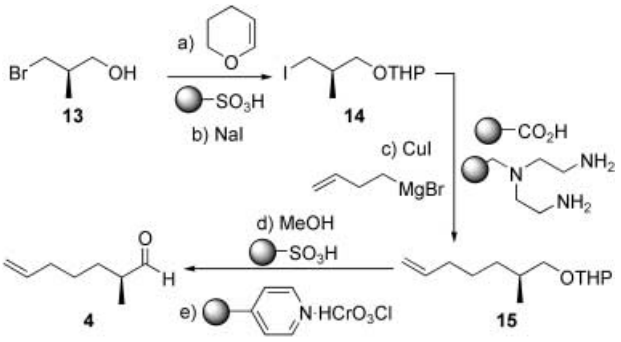
C12–C13 double bond to complete the synthesis of epothilone A (**1**).[5]

The stereogenic center in fragment 1 (**3**) was efficiently installed by using Kiyooka's asymmetric Lewis acid catalyzed Mukaiyama aldol methodology between readily accessible aldehyde **8** and silyl enol ether **9**[16] in a similar manner to the groups of Mulzer and Taylor.[10,11] Sulfonamide-protected D-phenylalanine in combination with borane gave optimal results, providing the desired alcohol adduct **10** in >92% *ee* (Scheme 2).[17] The reaction was quenched by the addition of a small amount of water and Amberlite IRA-743, a boron-specific scavenging resin, allowing efficient separation of the desired product and quantitative recovery of the amino acid. A silyl protecting group was introduced by using *tert*-butyldimethylsilyl triflate in the presence of basic diethylaminomethyl polystyrene. Ester **11** was converted into ethyl ketone fragment 1 (**3**) by the single addition of (trimethylsilylmethyl)lithium followed by monoalkylation. Both steps were quenched by a supported carboxylic acid to neutralize the reactions and scavenge the lithium ions.[10]



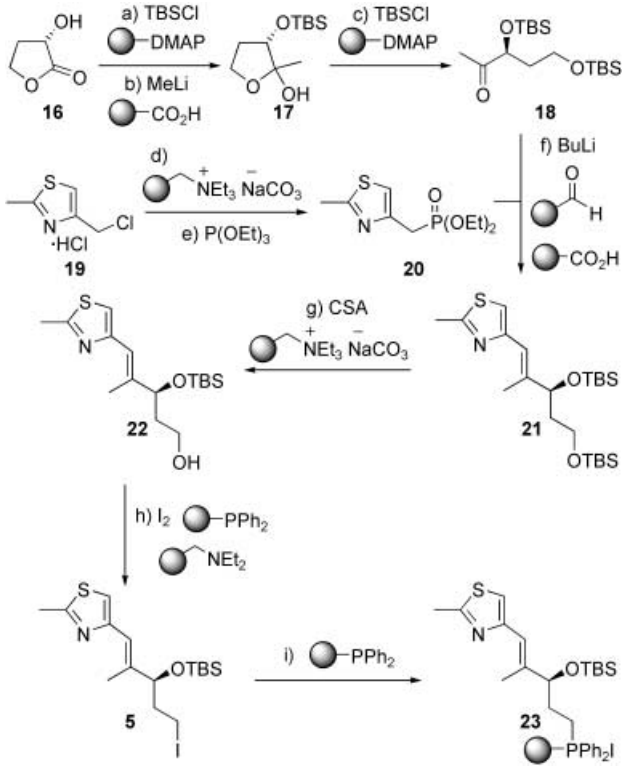
Scheme 2. Synthesis of fragment 1.[18] a) TBSCl (1.4 equiv), PS DMAP (2.0 equiv, 1.49 mmol g^{-1}), CH_2Cl_2, room temperature, 2.5 h, 96%; b) O_3, CH_2Cl_2, −78 °C, 20 min, then PS PPh_3 (1.5 equiv, 3.3 mmol g^{-1}), −78 °C→RT, 12 h, 93%; c) *N*-Ts-D-phenylalanine (1.2 equiv), BH_3·THF (1.05 equiv, 1.5 M), CH_2Cl_2, 0 °C→RT, 1 h, then **8** (1.0 equiv), −94 °C, 15 min, then **9** (1.0 equiv), −94 °C→−78 °C, 105 min, then H_2O (5 equiv), Amberlite IRA-743 (1.3 equiv), −78 °C→RT, 6 h, 93% (92% of *N*-Ts-D-phenylalanine recovered); d) TBSOTf (2.0 equiv), diethylaminopolystyrene (5.0 equiv, 3.2 mmol g^{-1}), CH_2Cl_2, 0 °C→RT, 165 min, then MeOH (25 equiv), room temperature, 1 h, 100%; e) (trimethylsilylmethyl)lithium (2.2 equiv, 1.0 M pentane), pentane, 0 °C, 195 min, then MeOH (50 equiv), 0 °C→RT, 5 h, then Amberlite IRC-50 (2.5 equiv, ~5.0 mmol g^{-1}), room temperature, 75 min, 100%; f) LDA (2.3 equiv), THF, −78 °C→−15 °C, 30 min, then MeI (3.1 equiv), −78 °C→−40 °C, 2 h, then Amberlite IRC-50 (12 equiv, ~5.0 mmol g^{-1}), room temperature, 2 h, 94%. TBS = *tert*-butyldimethylsilyl, PS = polymer-supported, DMAP = 4-dimethylaminopyridine, Tf = trifluoromethanesulfonyl, LDA = lithium diisopropylamide, Ts = *para*-toluenesulfonyl, TMS = trimethylsilyl.

Synthesis of aldehyde fragment 2 (**4**) utilized a popular strategy that allowed access from a commercially available "(*R*)-Roche ester" derivative. Protection of (*R*)-(−)-3-bromo-2-methyl-1-propanol (**13**) as the tetrahydropyranyl acetal was achieved with polymeric sulfonic acid catalysis and was followed by a Finkelstein halide exchange to provide the more reactive primary iodide **14** (Scheme 3). Workup required addition of diethyl ether and silica gel to bind any remaining dissolved inorganic salts prior to filtration. CuI-mediated substitution with 3-butenylmagnesium bromide, followed by Amberlite IRC-50 acidic quench and a trisamine copper scavenge, yielded desired alkene **15**. Acid-catalyzed deprotection in methanol and oxidation of the corresponding alcohol with pyridinium chlorochromate on alumina, provided fragment 2 (**4**).



Scheme 3. Synthesis of fragment 2. a) 3,4-Dihydropyran (1.02 equiv), PS TsOH (0.05 equiv, 4.2 mmol g^{-1}), neat, 30 min, 100%; b) NaI (3 equiv), 2-butanone, 75 °C, 1 h, then Et_2O, silica-gel filtration, 96%; c) CuI (1.0 equiv), 3-butenylmagnesium bromide (4.0 equiv), THF, −10 °C→0 °C, 2 h, then Amberlite IRC-50 (3.0 equiv, ~5.0 mmol g^{-1}) and PS trisamine (3.0 equiv, 4.36 mmol g^{-1}), room temperature, 24 h, 97%; d) MP-TsOH (0.04 equiv, 4.2 mmol g^{-1}), MeOH, RT, 7 h 30 min, 97%; e) pyridinium chlorochromate on Al_2O_3 (3.0 equiv, 1.0 mmol g^{-1}), CH_2Cl_2, room temperature, 3.5 h, 80%. MP = macroporous polymer.

A precedented, convergent route was applied to the formation of thiazole fragment 3 (**5**). A commercially available lactone derivative of malic acid was used to provide the necessary stereochemistry at C15. Silyl protection of *S*-(−)-α-hydroxy-γ-butyrolactone (**16**) was followed by the addition of 1 equivalent of methyllithium to give lactol **17**, which was subsequently trapped as the open-chain ketone **18** upon the formation of a second TBS ether (Scheme 4).[6] In parallel, the hydrochloride salt of 4-chloromethyl-2-methylthiazole (**19**) was deprotonated with polymer-supported carbonate, before heating with excess triethylphosphite to yield phosphonate **20**. The residual triethylphosphite was subsequently removed under reduced pressure.[6] Deprotonation of phosphonate **20** with butyllithium, followed by a Horner–Wadsworth–Emmons olefination with ketone **18** provided thiazole adduct **21**. An excess of the phosphonate anion was used, which was later scavenged by a polymeric benzaldehyde equivalent, followed by the addition of silica gel to bind the polar phosphorus by-products. This provided the desired *E*-trisubstituted olefin **21** after simple filtration. Selective deprotection of the primary hydroxy group was effected in



Scheme 4. Synthesis of fragment 3. a) TBSCl (1.4 equiv), PS DMAP (2.0 equiv, 1.49 mmol g^{-1}), CH_2Cl_2, RT, 1 h 30 min, 97%; b) MeLi (1.05 equiv), THF, −78 °C, 1 h, then Amberlite IRC-50 (20 equiv, ~10 mmol g^{-1}), 98%; c) TBSCl (1.48 equiv), PS DMAP (2.0 equiv, 1.49 mmol g^{-1}), CH_2Cl_2, room temperature, 2.5 h, 98%; d) PS carbonate (2 equiv, 3.5 mmol g^{-1}), MeOH, room temperature, 45 min, 98%; e) triethylphosphite (1.2 equiv), neat, 160 °C, 3.5 h, 84%; f) **20** (3.5 equiv), *n*BuLi (3.5 equiv), THF/hexanes, −78 °C, then **18** (1.0 equiv), −78 °C→RT, 1.5 h, then PS benzaldehyde (5.0 equiv, 1.2 mmolg-1) and Amberlite IRC-50 (10 equiv, ~5 mmol g^{-1}), 105% by mass w.r.t. ketone **18**; g) CSA (1.5 equiv), MeOH/CH_2Cl_2 (1:1), 0 °C, 2.5 h, then PS carbonate (2.2 equiv, 3.5 mmol g^{-1}), 2 h, 104%; h) iodine (4.0 equiv), PS PPh_3 (5.0 equiv, 3.3 mmol g^{-1}), imidazole (6.0 equiv), MeCN/Et_2O (3:1), then diethylaminomethylpolystyrene (8.0 equiv, 3.2 mmol g^{-1}), Amberlite IRC-50 (13.0 equiv, ~5 mmol g^{-1}), toluene, room temperature, 105 min, 73%; i) PS PPh_3 (1.0 equiv, 3.3 mmol g^{-1}), toluene, 90 °C, 18 h. CSA = 10-camphorsulfonic acid.

acidic solution and quenched by a polymer-supported carbonate, before conversion of the resulting alcohol **22** into iodide **5** by treatment with polymer-supported triphenylphosphane and iodine. The corresponding resin-bound phosphonium iodide salt **23** of fragment 3 was then formed, in preparation for Wittig coupling, by heating iodide **5** with polymer-supported triphenylphosphane in toluene. This final "catch" step also permitted separation from minor phosphorus contaminants that had remained following the olefination coupling.

Aldol coupling between fragments 1 (**3**) and 2 (**4**) generates two new stereocenters, so a highly diastereoselective process was required. Coupling at C6–C7 has been extensively investigated on a wide variety of substrates, and shown to be highly sensitive to proximal and remote functionality in both fragments.[9,19] Our approach, although bearing close analogy to those already published, incorporates a novel fragment combination of ketone **3** and aldehyde **4**.[20] The use of freshly prepared lithium diisopropylamide in THF reliably gave excellent selectivity (>13:1) for the desired anti-Felkin–Anh adduct **24**,[21] with an excess of the aldehyde required to force the reaction to completion. After quenching with acetic acid, diamine polymer was added to scavenge excess acid and aldehyde fragment from the crude reaction mixture. Protection of aldol adduct **24** followed by ozonolysis, using polymer-supported triphenylphosphane to reduce the ozonide, efficiently gave aldehyde **25** in preparation for Wittig coupling with fragment 3 (**5**).

Treatment of immobilized phosphonium salt **23** with excess sodium bis(trimethylsilyl)amide followed by washing with dry THF allowed the isolation of the corresponding salt-free ylide.[22] Coupling of aldehyde **25** with this ylide installed the necessary *cis* olefin exclusively (Scheme 5). Selective primary alcohol deprotection yielded **26**, which after a two-step oxidation with catalytic TPAP in the presence of NMO[23] followed by polymer-supported chlorite, gave the corresponding carboxylic acid.[24] Selective removal of the allylic TBS ether by using excess TBAF[25] provided hydroxy acid **27** in readiness for macrolactonization.[8]

Macrolactonization of linear hydroxy acid **27** proceeded under Yamaguchi conditions, using a polymer-supported DMAP equivalent, to furnish the required 16-membered lactone.[8,12] Polymeric sulfonic acid resin was used not only to remove both TBS protecting groups, but also to protonate the thiazole nitrogen atom and to capture the natural product as an ion-exchanged salt. Unbound impurities were removed by washing the resin with dichloromethane, before subsequent release of epothilone C by using a basic solution of ammonia in methanol. Having obtained the natural product as a mixture containing over 90% of the desired diastereoisomer, the material was then finally purified by flash column chromatography to provide pure epothilone C (**2**). Epoxidation of epothilone C has been shown to proceed with facial selectivity to provide a formal synthesis of epothilone A (**1**).[3]

In summary, we have demonstrated the scope and utility of supported reagents and scavenging techniques within a multistep synthesis by stereoselectively providing epothilone C in 29 steps overall and with a longest linear sequence of only 17 steps from commercially available materials.[26] The high selectivity and overall efficiency is comparable with the best of the previous conventional syntheses. As epothilone C is the most challenging target that has been synthesized by using solid-phase reagent and scavenging techniques, we hope that this will encourage their future integration alongside conventional methods for application within general synthesis programs.

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Keywords: aldol reaction · antitumor agents · natural products · polyketides · polymers

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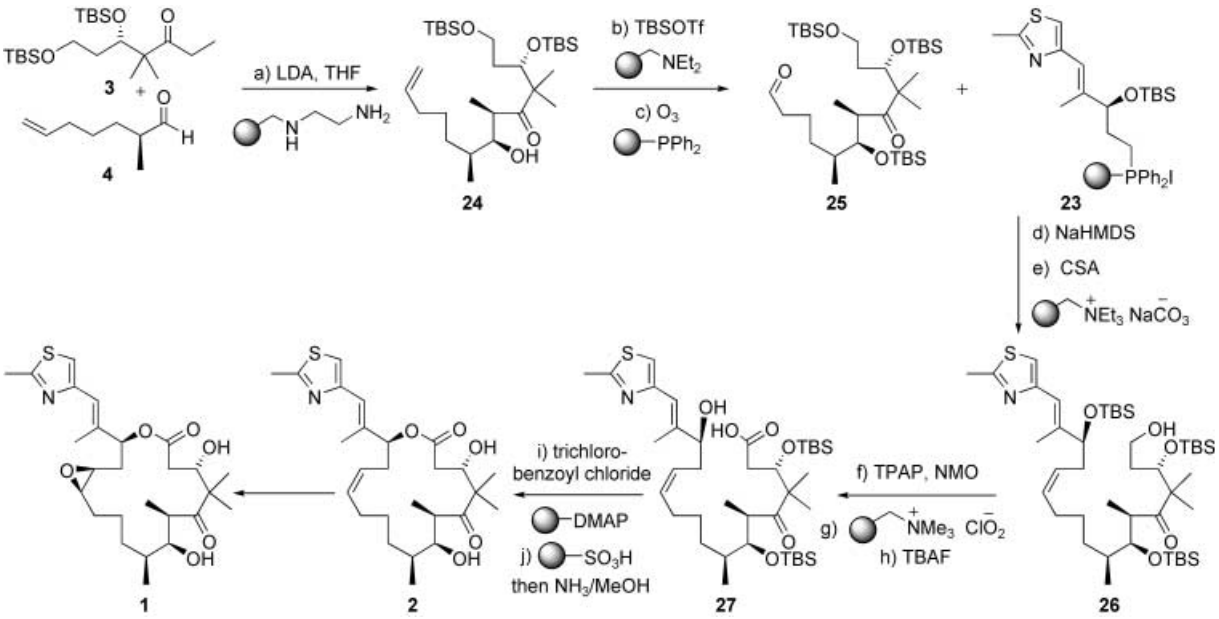

Scheme 5. Fragment coupling and cyclization. a) LDA (1.6 equiv), THF, −78 °C→−40 °C, 1.5 h, then aldehyde **4** (1.5 equiv), −78 °C, 20 min, then AcOH (5 equiv), −78 °C→RT, 30 min, then PS diamine (4.8 equiv, 3.0 mmol g^{-1}), room temperature, 2 h, 100% (13.5:1); b) TBSOTf (1.5 equiv), diethylaminopolystyrene (3.0 equiv, 3.2 mmol g^{-1}), CH_2Cl_2, 0 °C→RT, 205 min, then MeOH (3.0 equiv), room temperature, 2 h, 99%; c) O_3, CH_2Cl_2, −78 °C, 20 min, then PS PPh_3 (5.0 equiv, 3.3 mmol g^{-1}), −78 °C→RT, 15 h, 100%; d) phosphonium salt **23** (2.5 equiv), NaHMDS (10.0 equiv), THF, room temperature, 15 min, then THF wash, then aldehyde **25** (1.0 equiv), −78 °C→−40 °C, 15 min, 93%; e) CSA (1.0 equiv), $MeOH/CH_2Cl_2$ (1:1), 0 °C, 4 h, 99%; f) TPAP (0.05 equiv), NMO (1.5 equiv), CH_2Cl_2, 0 °C→RT, 3 h 10 min, then Et_2O through silica pad, 93%; g) PS chlorite (2 equiv, ~0.5 mmol g^{-1}), PS dihydrogenphosphate (3 equiv, ~0.5 mmol g^{-1}), 2-methyl-2-butene (5 equiv, 2 M in THF), *t*BuOH/H_2O (1:2), room temperature, 6 h, 99%; h) TBAF (6 equiv, 1 M in THF), THF, room temperature, 12 h, 95%; i) 2,4,6-trichlorobenzoylchloride (10.0 equiv), triethylamine (12 equiv), room temperature, 50 min, then added to PS DMAP (20 equiv), THF/toluene (1:25), 80 °C, 2.5 h; j) PS TsOH (12 equiv, 1.5 mmol g^{-1}), CH_2Cl_2, 1 h, then CH_2Cl_2 and Et_2O wash, then release with NH_3 (2 M in MeOH), 81% (over two steps), k) reference [4]. HMDS = bis(trimethylsilyl)amide, NMO = 4-methylmorpholine *N*-oxide, TBAF = tetrabutylammonium fluoride, TPAP = tetra-*N*-propylammonium perruthenate.

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[17] Enantiomeric excess determined by ^{1}H NMR spectroscopy (Mosher esters).
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[20] It was necessary to perform a filtration through silica gel to remove baseline impurities from ketone fragment 1 (**3**) prior to the aldol coupling.
[21] The same reaction also proceeded well in diethyl ether, although the selectivity appeared to be more capricious, varying from 10:1 to as high as >30:1.
[22] M. H. Bolli, S. V. Ley, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2243.
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[24] T. Takemoto, K. Yasuda, S. V. Ley, *Synlett* **2001**, 1555.
[25] It proved to be necessary to perform an aqueous workup to remove the excess TBAF from the reaction.
[26] Although no attempt was made to recycle or regenerate the immobilized reagents, owing to the scale of this particular synthesis, recycling remains an option for larger-scale processes.

