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Practical syntheses of the C12–C21 epothilone subunit via catalytic asymmetric reductions: Itsuno–Corey oxazaborolidine reduction and asymmetric Noyori hydrogenation

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Abstract—Two practical catalytic asymmetric reductions to introduce the epothilone C15 stereocenter are described (Itsuno–Corey reduction and Noyori hydrogenation).

The epothilones (**1**, Fig. 1) have proven to be the most promising group of antimitotic agents among the new classes of compounds that have activity similar to that of paclitaxel, that is microtubule stabilization.[1,2] Their interesting biological properties, especially their effectiveness against multi-drug resistant cancer cell lines,[2–4] have inspired numerous synthetic and semisynthetic efforts.[4–9] The chemotherapeutic potential held by the epothilones has sustained a continued interest in the development of novel and practical synthetic routes toward these promising antitumor macrolides.

As part of a program initiated to study the binding site of the epothilones through affinity labeling on tubulin, we targeted the total synthesis of these molecules and analogues that could be used as biochemical tools.

Herein we report two unique stereoselective syntheses of key intermediates **2** and **3** that are important building blocks for the total syntheses of the epothilones.[5–10] The stereochemistry at C15 of **2** was set by two different asymmetric reductions utilizing ketones **4** and **5**. Both approaches rely on well precedented chemistry, known to be amenable for large-scale enantioselective reductions. The Itsuno–Corey reduction[11] utilizes oxazaborolidines as chiral catalysts and Noyori asymmetric hydrogenations are carried out in the presence of BinapRu-catalysts.[12]

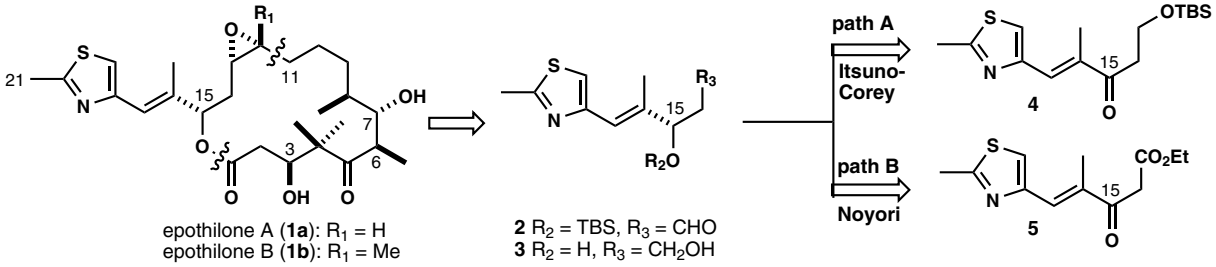

Figure 1. Structures of epothilones A and B and retrosynthetic analysis.

Keywords: Epothilones; Antitumor agents; Asymmetric catalysis; Itsuno–Corey reduction; Noyori reduction.
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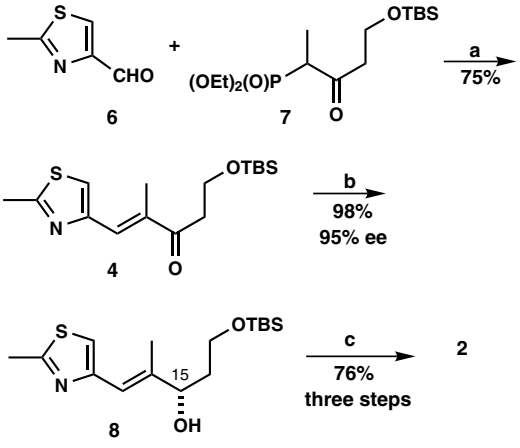
The asymmetric synthesis of aldehyde **2** from enone **4** via the Itsuno–Corey method is outlined in Scheme 1. With a goal to create a useful handle to modify the aryl region, we utilized a strategically functionalized β-keto-phosphonate **7**[13] in a modified Horner–Wadsworth–Emmons reaction[14] with commercially available aldehyde **6** to access enone **4** exclusively in 75% yield (Scheme 1). The C15 asymmetric center was then introduced by the reduction of this enone using (*R*)-*B*-Me-CBS-oxazaborolidine,[11] which provided allylic alcohol **8** in 98% yield and 95% ee (as determined by chiral HPLC).[15] Protection of **8** using TBSOTf provided the corresponding bis-silyl ether in 94% yield. Selective deprotection of the primary TBS ether functionality,[16,17] followed by Dess–Martin oxidation of the corresponding alcohol, furnished aldehyde **2**.[18]

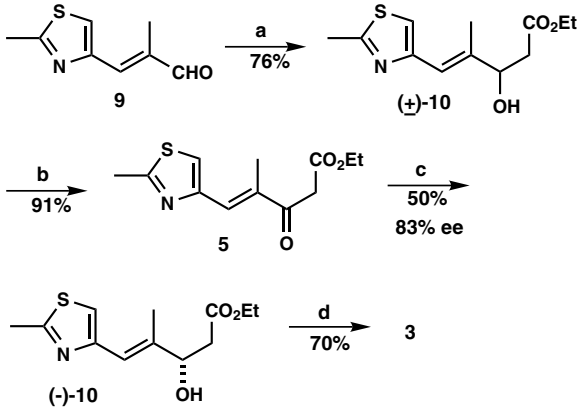
The optimized conditions for the Itsuno–Corey reduction involved removing toluene from the commercially available catalyst and the addition of CH_2Cl_2 and $BH_3{\cdot}Me_2S$ at 0 °C. The optimum amount of catalyst was found to be 50 mol%. The enone **4** was added to the reaction mixture using a syringe pump. When the reaction was scaled up to 33 mmol, the enone addition took 15 h. At that scale, the enantiomeric excess was 92%.

The second route toward the synthesis of building block **3** is shown in Scheme 2. Reaction of aldehyde **9**[19] with the lithium enolate of ethyl acetate furnished alcohol (±)-**10** in 76% yield. Oxidation with activated MnO_2 (10 wt%) provided a 91% yield of the desired β-ketoester **5**, which was subjected to Noyori reduction.

The Noyori reduction needed to be optimized for reaction time, temperature, pressure, and catalyst loading. The best results were obtained at room temperature with 15 mol% catalyst, and a pressure range of 50.5–48.5 psi for 2 h. Longer reaction times and higher temperatures



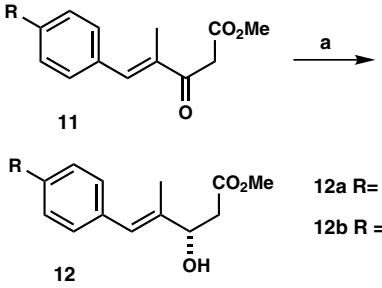
Scheme 1. Reagents and conditions: (a) $Ba(OH)_2{\cdot}8H_2O$ (freshly activated), THF, 45 min, rt, then **6** in THF–H_2O (40:1), 0 °C, 1 h, then rt, 45 min; (b) (*R*)-2-Me-CBS-oxazaborolidine (0.5 equiv), $BH_3{\cdot}Me_2S$ (1.5 equiv), CH_2Cl_2, 0 °C, then **4**, 0 °C, 2 h, then ethanolamine, rt, 16 h; (c) i. TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 15 min, 94%, ii. HF (48% aq), glass splinters, MeCN–Et_2O (1:1), 0 °C, 2 h, 82%, iii. Dess–Martin periodinane (1.3 equiv), CH_2Cl_2, rt, 1 h, 98%.



Scheme 2. Reagents and conditions: (a) LDA, THF, −78 °C, EtOAc, 10 min; (b) MnO_2, $CHCl_3$, 0 °C, 2 h; (c) $RuBr_2$–(*S*)-BINAP, H_2, MeOH, 50 psi, rt, 2 h; (d) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, then rt, 2 h.

yielded over-reduced product that was difficult to separate from the desired reaction product. The optimized conditions yielded a 1:1 mixture of the starting material and the product with only a trace of over-reduced compound (reduction of the ketone and the double bond). The product was easily separated from the starting material by column chromatography. The enantiomeric excess of (−)-**10** was 83% ee, as determined by chiral HPLC.[15] Reduction of the methyl ester of **5** to the methyl ester of (−)-**10** under similar conditions gave an ee of 80%. Conversion to the known diol **3** was accomplished with DIBAL-H in 70% yield.[10]

We also investigated the Noyori reduction with epothilone building blocks **11** in which the thiazole moiety was replaced by a phenyl ring (Scheme 3). It is of interest to note that the chemical yields (86–89%) and the enantiomeric excesses (89–94%) of these reactions were significantly improved compared to the reduction of **5**.[15] We were able to increase the reaction times without observing much of the double bond reduced products (<5%). The results indicate that the presence of the thiazole moiety is promoting the reduction of the enone double bond and is also responsible for lowering the enantiomeric excess of this reaction. This could be due to the ability of the heteroatoms in the thiazole moiety to coordinate with the catalyst,[20] promoting side reactions.



Scheme 3. Reagents and conditions: (a) $RuBr_2$–(*S*)-BINAP, H_2, MeOH, 50 psi, rt, R = Ph, 5 h, R = 4-FC_6H_4, 3 h.

Asymmetric ruthenium catalyzed reductions of β-ketoesters, that also contain di- and tri-substituted double bonds in the molecule, have been described before.[21,22] The reductions were selective for the ketone moiety and provided the alcohols in excellent yields and enantiomeric excesses.[21,22] The Noyori reduction of γ,δ-unsaturated β-ketoesters such as **10**–**12** has apparently not been investigated before.[23] Our results suggest that selective reduction of the ketone can be achieved in the presence of a tri-substituted enone double bond unless functional groups are present in the molecule, such as the thiazole moiety, that promote side reactions.

In summary, we have developed two asymmetric syntheses for the C12–C21 epothilone building block featuring two highly versatile and enantioselective catalytic asymmetric reductions, the Itsuno–Corey oxazaborolidine-mediated reduction and the Noyori hydrogenation to introduce the C15 epothilone stereocenter.[24] The strategies developed in this synthesis are currently being applied toward the construction of analogues that would assist in mapping the binding site of the epothilones on tubulin protein.

Acknowledgements

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