Synthesis of Epothilones: Stereoselective Routes to Epothilone B

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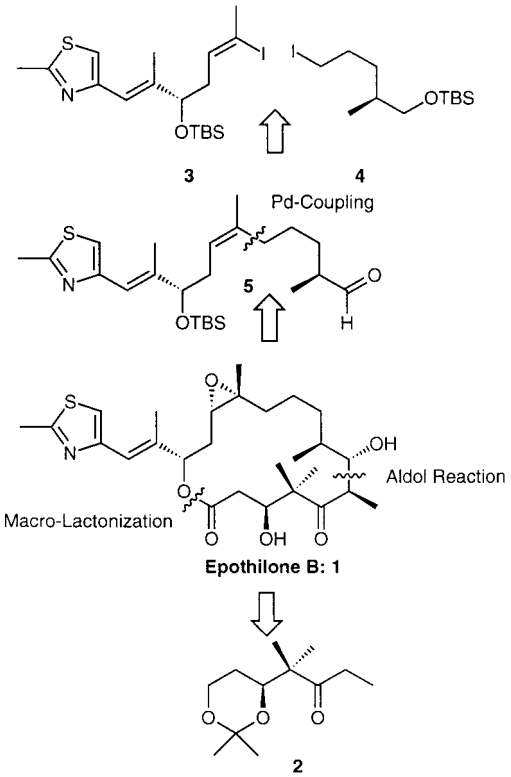
Received 15 May 1998

Abstract: In connection with our studies of the total syntheses of epothilones we report our efforts on the syntheses of epothilone B using a macro-lactonization and a metathesis approach. Key reaction for the solution of the acyclic stereoselection is a stereoselective aldol reaction.

In light of their powerful anti-tumor activity, epothilones, a new family of natural products isolated by the research groups of Höfle and Reichenbach at the Gesellschaft für Biotechnologische Forschung (GBF), in Braunschweig, Germany, have created tremendous excitement in the scientific community.[1]

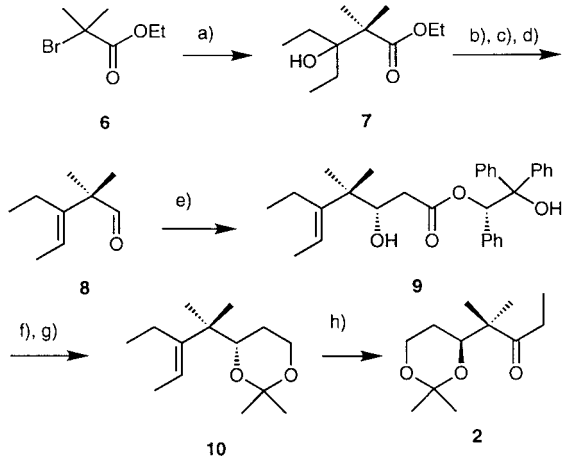
Due to their impressive biological profile,[2] multiple efforts towards the synthesis of epothilones appeared almost simultaneously in the literature.[3] Three groups described total syntheses of epothilone A[4] shortly after these initial studies, and two described total syntheses of epothilone B.[5] In addition, a flood of papers appeared presenting partial solutions towards the synthesis of epothilones.[6] Many derivatives have been synthesized as well and their biological profiles have been tested.[7]

In this report, we wish to present our recent investigations along these lines focusing on two novel routes to approach epothilone B. The first approach uses macro-lactonization as the ring closing step (the retrosynthetic analysis is shown in Scheme 1),[4d] and the second uses metathesis for ring closure following our epothilone A strategy.[4c,7e]



Scheme 1. Retrosynthetic Analysis of Epothilone B

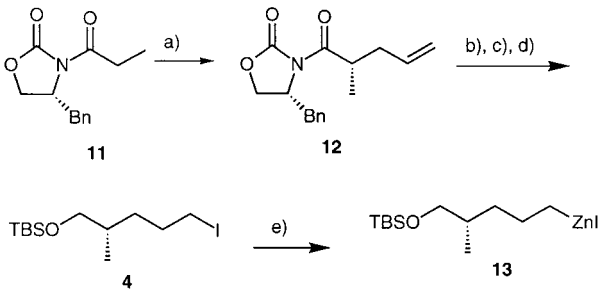
As shown in Scheme 1, the two major fragments **2** and **5** are coupled by an aldol reaction and are finally cyclized *via* macro-lactonization to obtain **1**. Key aldehyde **5** was obtained by a palladium-mediated coupling[8] of fragments **3** and **4**, which were obtained by efficient routes. In contrast to our early studies, we have used an alternative strategy to synthesize key fragment **2**, which avoids large scale borane chemistry and offers crystalline intermediates with the possibility to obtain higher optical purity.



Scheme 2. a) Zn, 3-propanone, THF/B(OMe)$_3$ (1:1), 20 h, r .t., 49%; b) P_4O_{10}, benzene, 15 min, reflux, 70%; c) LAH, THF, 3 h, reflux, 58%; d) Swern oxidation, 63%; e) (*S*)-HYTRA (2.0 eq), LDA (2.0 eq), THF, -78 °C, then aldehyde **10**, THF, -78 °C, 90 min, 75%, 96% de; f) LAH, Et_2O, 24 h, r.t., 90%; g) acetone, pTsOH (0.2 eq), pyridine (0.15 eq), $CuSO_4$ (1.5 eq), 90 %; h) O_3, CH_2Cl_2, -78 °C, then PPh_3, -78 °C -> r.t., 85 %

Zinc-mediated coupling of **6** with 3-pentanone yielded ester **7**.[9] Subsequent transformation into aldehyde **8** and aldol coupling with (*S*)-HYTRA [(*S*)-(-)-2-hydroxy-1,2,2-triphenyl acetate][10] yielded **9** in very high optical purity (de = 96%). Ester cleavage, reduction, protection, and finally, ozonolysis gave the desired ethyl ketone **2**.

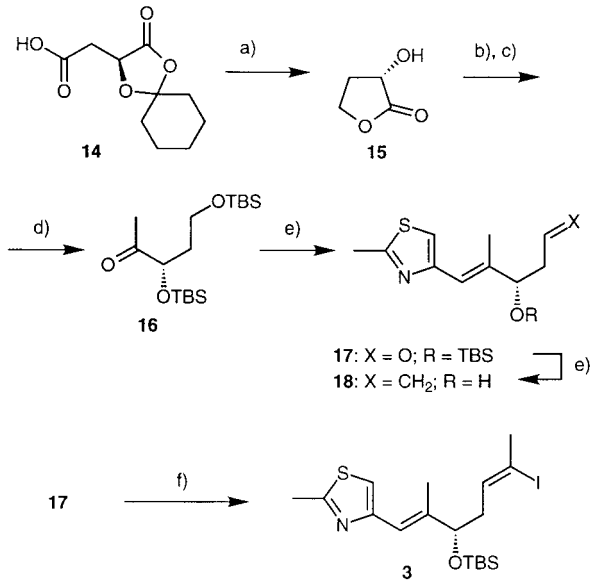
The alkyl fragment **4** required for our desired palladium coupling was synthesized using Evans' procedure.[11]



Scheme 3. a) NaHMDS (1.05 eq), THF, -78 °C, 1h, then allyl iodide (3.0 eq), -78 °C, 4h, 61%; b) LAH, Et_2O, 0 °C -> r.t.; c) TBSCl (1.3 eq), imidazole (2.6 eq), DMF, 24 h, r.t., 80% (for 2 steps); d) BH_3·THF, THF, 1h, r.t., then ICl (1.0 eq), MeOH, NaOAc, 30 min r.t., 60%; e) alkyl iodide **4** (1.5 eq), Zn/Cu couple (2.3 eq), benzene/dimethyl acetamide (10:1), 2 h, reflux, then Pd coupling

Starting from compound **11**, a diastereoselective allylation gave **12** (ratio: 20:1), which was transformed into **4** by a one-pot hydroboration/ iodination sequence after cleavage of oxazolidinone from **12**.[12]

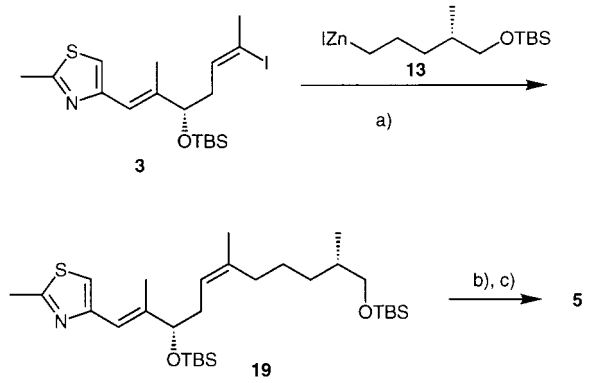
The key thiazole fragments **3** and **18** were obtained by very efficient reactions starting from (*S*)-malic acid.[13,14]



Scheme 4. a) 1. $BH_3{\cdot}SMe_2$ (2.85 eq), $B(OMe)_3$ (2.85 eq), THF, 24 h, r.t., 2. pTsOH (0.1 eq), CH_2Cl_2, 24 h, r.t., 72%; b) TBSCl (1.1 eq), imidazole (2.2 eq), DMF, 24 h, r.t., 93%; c) MeLi (1.1 eq), THF, -78 °C, 3h; d) TBSCl (1.1 eq), imidazole (2.2 eq), DMF, 24 h, r.t., 78% (for 2 steps); e) ref. 4c; f) $Ph_3P{=}C(Me)I$ (2.0 eq), THF, -30 °C, 15 min, 54%

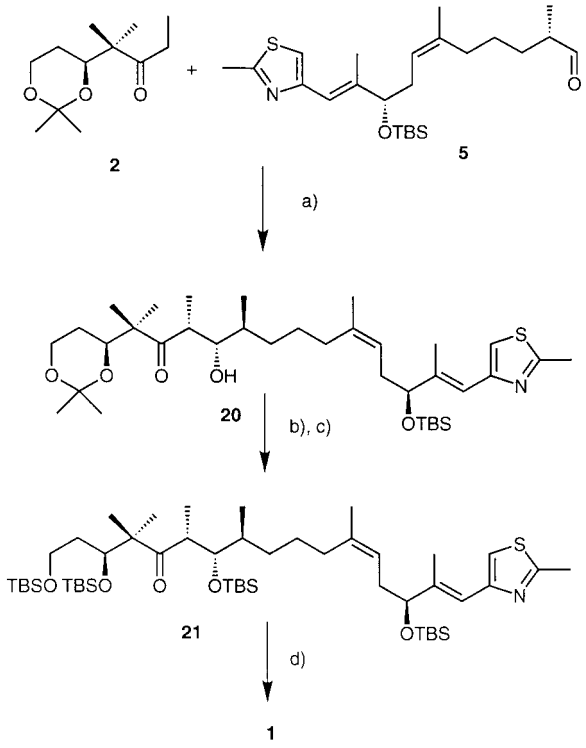
Starting from **14,**[14a] lactone **15** was obtained after borane reduction and acid-catalyzed cyclization. Silylation, addition of methyllithium, and further silylation gave functionalized ketone **16**, which was transformed into aldehyde **17** as previously described.[4c] Further elaborations by Wittig reactions gave key intermediates **3** and **18**.[15]

Coupling of intermediates **3** and **13**[16] by palladium catalysis[8] gave compound **19** in a stereochemically homogeneous form containing the desired trisubstituted double bond moiety of epothilone B. Deprotection and Dess Martin periodinane oxidation yielded key aldehyde **5** in high overall yield.



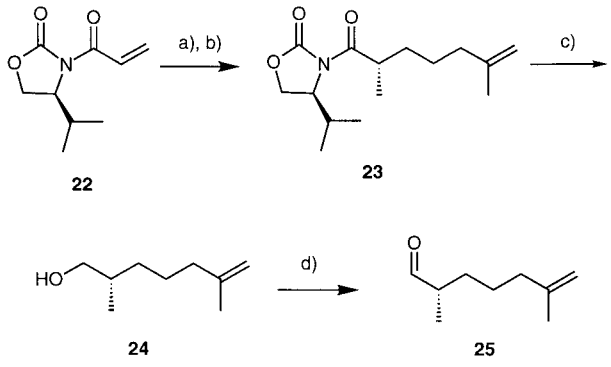
Scheme 5. a) alkyl iodide **4** (1.5 eq), Zn/Cu couple (2.3 eq), benzene/dimethyl acetamide (10:1), 2 h, reflux, then **3**, $Pd(PPh_3)_4$ (4 mol-%), 60 °C, 30 min, 84%; b) CSA (1.05 eq), $MeOH/CH_2Cl_2$ (1:1) 0 °C-> r.t., 2 h, 99%; c) Dess-Martin periodinane, CH_2Cl_2, r.t., 97%

Coupling of the enolate of **2**, which was preformed with LDA in THF at low temperature, with aldehyde **5** gave the required aldol product in 94% isolated yield with the desired *anti*-Felkin *syn* isomer **20** as the major product (9:1).[17] Deprotection and trisilylation of the triol provided compound **21** which is identical to the compound published by Nicolaou in his total synthesis of epothilone B.[4d]



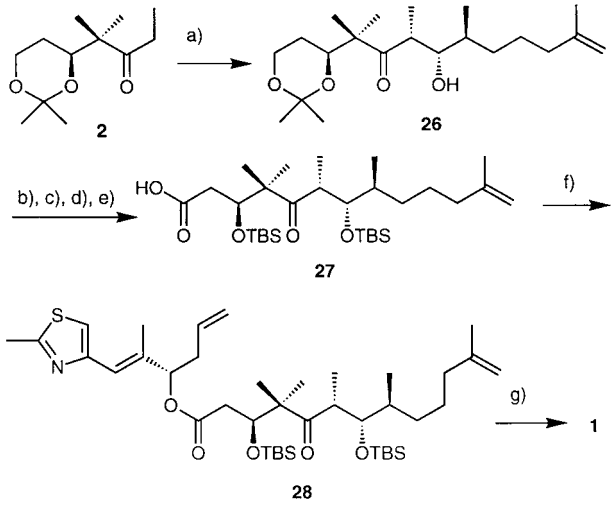
Scheme 6. a) ethyl ketone **2** (2.0 eq), LDA (1.96 eq), THF, -78 °C, 1h, then aldehyde **5** (1.0 eq), 15 min, -78 °C, 94 % (9:1); b) PPTS (1.0 eq), MeOH, 72 h, r.t., 86%; c) TBSOTf (4.5 eq), 2,6-lutidine (7.5 eq), CH_2Cl_2, 2h, 0 °C, 95%; d) ref. 3d

Our second epothilone B synthesis is based on our epothilone A approach[4c] using three key fragments, which were combined by an aldol reaction that proceeds with remarkable stereocontrol, and then by ring closure *via* olefin metathesis. Key aldehyde **25** was also synthesized using Evans' protocol as shown in Scheme 7.[18]



Scheme 7. a) $(CH_2{=}C(CH_3)CH_2CH_2)_2CuMgBr$ (1.1 eq), LiI (1.1 eq), TMSCl (2.2 eq), THF, -78 °C, 5 h, 60%; b) NaHMDS (1.1 eq), THF, -78 °C, 30 min, then MeI (5.0 eq), -78 °C, 11h, 87%; c) LAH, Et_2O, 0 °C -> r.t., 3 h, 94%; d) Dess-Martin periodinane (1.3 eq), CH_2Cl_2, r.t., 5 min, 80%

Ethyl ketone **2** and aldehyde **25** were coupled by an aldol reaction under kinetically controlled conditions yielding the desired *anti*-Felkin *syn* aldol product **26** with high facial selectivity (10:1).[19] Following our deprotection/protection and oxidation protocol from the epothilone A strategy[4c] we obtained the acid **27** (4 steps, 67% from **26**). Esterification with thiazole segment **18** gave ester **28** which is identical to Danishefsky's key intermediate in his epothilone B synthesis based on the metathesis approach.[7e]



Scheme 8. a) 1. LDA (0.98 eq), THF, -78 °C, 1 h, 2. aldehyde **25** (1.0 eq), -78 °C, 30 min, 68% + 7% other diastereoisomer (-> 10:1); b) PPTS (0.6 eq), MeOH, r.t., 36 h, 88%; c) TBSOTf (4.5 eq), 2,6-lutidine (7.5 eq), CH_2Cl_2, -50 °C -> +10 °C, 4 h; d) CSA (0.2 eq), MeOH/CH_2Cl_2(1:1), 0 °C, 5 h, 84 % (over 2 steps); e) PDC (9.0 eq), DMF, r.t., 34 h, 91%; f) thiazole **18** (1.0 eq), DCC (1.1 eq), DMAP (0.15 eq), CH_2Cl_2, r.t., 61%; g) Ref. 7e

In summary, we have presented two formal total syntheses of epothilone B. Our macro-lactonization approach represents the best and most efficient solution to epothilone B to date as it provides an especially convergent synthesis and demonstrates the power of palladium-mediated couplings and aldol technology towards stereoselective C,C bond formations. The acyclic stereocontrol of the configurations at C-6 and C-7 has been easily resolved using our fragments in the key aldol reaction.

Acknowledgment. We are indebted to the Novartis Pharma AG, Basel, for generous support.

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(17) *Experimental procedure for the aldol reaction:* A solution of **2** (64 mg, 0.3 mmol) in THF (500 µl) was added to a freshly prepared solution of LDA [*n*-BuLi (118 µl, 2.5 m solution in hexanes, 0.294 mmol, 0.98 eq) was added to a solution of diisopropylamine (41.6 µl, 0.294 mmol) in THF (500 µl) at 0 °C] dropwise at - 78 °C. The solution was stirred for 1 h at -78 °C. A solution of **5** (65 mg, 0.15 mmol, 0.5 equiv) in THF (600 µl) was added dropwise and stirring was continued for 20 min at -78 °C. The mixture was quenched by dropwise addition of satd. NH_4Cl solution (2 ml). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×5 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (pentane / Et_2O 10:1) afforded 83 mg (85 %) of **20** and 9 mg (9.5 %) of its corresponding Felkin diastereoisomer (ratio 9:1 by HPLC).
Spectroscopic data for compound **20**: $[\alpha]_D^{20}$ -2.5 (c = 1.0, $CHCl_3$), $[\alpha]_{546}^{20}$ -2.7 (c = 1.0, $CHCl_3$); IR: 3505, 2931, 1686, 1472, 1373, 1255, 1098, 837, 777 cm^{-1}; UV (MeOH): λ_{max} = 209, 249 nm; MS (EI, 70 eV) m/z 650 (M^+, 3), 436(5), 282 (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.91(s, 1H), 6.45 (s, 1H), 5.12 (t, ^3J = 6.8 Hz, 1H), 4.08 (t, ^3J = 6.2 Hz, 1H), 4.04 (dd, ^3J = 11.8 Hz, ^3J = 2.5 Hz, 1H), 3.96 (dt, ^2J = 11.9 Hz, ^3J = 2.7 Hz, 1H), 3.86 (ddd, ^2J = 11.7 Hz, ^3J = 5.4 Hz, ^3J = 1.7 Hz, 1H), 3.49 (s br, 1H, -OH), 3.36 (d, ^3J = 9.3 Hz, 1H), 3.27 (dq, ^3J = 7.0 Hz, ^3J = 1.4 Hz, 1H), 2.71 (s, 3H), 2.34 -2.14 (m, 2H), 2.06 - 1.93 (m, 2H), 1.99 (d, ^4J = 1.2 Hz, 3H), 1.82 - 1.71 (m, 1H), 1.67 (d, ^4J = 1.1 Hz, 3H), 1.66 - 1.42 (m, 3H), 1.40 (s, 3H), 1.37 - 1.22 (m, 2H), 1.33 (s, 3H), 1.20 (s, 3H), 1.16 - 1.05 (m, 1H), 1.09 (s, 3H), 1.02 (d, ^3J = 7.0 Hz, 3H), 0.88 (s, 9H, -Si^{t}Bu), 0.82 (d, ^3J = 6.8 Hz, 3H), 0.04 (s, 3H, -$SiMe_2$), 0.00 (s, 3H, -$SiMe_2$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 222.8, 164.3, 153.3, 142.5, 136.9, 121.4, 118.7, 114.9, 98.5, 79.1, 74.7, 74.4, 59.9, 51.6, 41.3, 35.4, 35.3, 33.0, 32.4, 29.8, 25.9, 25.2, 25.2, 23.5, 21.6, 19.2, 19.0, 18.6, 18.2, 15.4, 13.9, 9.3, -4.7, -4.9; Anal. calcd. for $C_{36}H_{63}NO_5SSi$ (650.0): C 66.46, H 9.69, N 2.15, S 4.99, found C 66.37, H 9.34, N 2.42, S 4.72.

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(19) Spectroscopic data for compound **26**: $[\alpha]_D^{20}$ -23.3 (c = 1.0, $CHCl_3$), $[\alpha]_{546}^{20}$ -28.1 (c = 1.0, $CHCl_3$); IR: 3508, 2969, 1685, 1373, 1197, 1107, 971 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$):δ (ppm) = 4.72 - 4.64 (m, 2H), 4.06 (dd, ^2J = 11.8 Hz, ^3J = 2.5 Hz, 1H), 3.96 (dt, ^2J = 11.9 Hz, ^3J = 2.7 Hz, 1H), 3.86 (ddd,^3J = 11.7 Hz, ^3J = 5.4 Hz, ^3J = 1.6 Hz, 1H), 3.50 (s, 1H, OH), 3.37 (d, ^3J = 9.3 Hz, 1H), 3.29 (dq, ^3J = 7.0 Hz, ^3J = 1.2 Hz, 1H), 2.09 - 1.94 (m, 2H), 1.82 - 1.48 (m, 4H), 1.71 (s, 3H), 1.41 (s, 3H), 1.40 - 1.31 (m, 2H), 1.33 (s, 3H), 1.21 (s, 3H), 1.16 - 1.05 (m, 1H), 1.09 (s, 3H), 1.02 (d, ^3J = 7.0 Hz, 3H), 0.84 (d, ^3J = 7.0 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 222.9, 146.2, 109.5, 98.4, 74.7, 74.3, 59.8, 51.5, 41.2, 38.2, 35.3, 32.6, 29.7, 25.1, 24.7, 22.3, 21.5, 19.0, 18.5, 15.3, 9.2; MS (EI, 70 eV) m/z 354 (M^+, 3), 339 (6), 296 (9), 278 (5), 214 (6), 197 (10), 185 (26), 156 (84), 141 (28), 127 (26), 123 (65), 115 (78), 82 (100); Anal. calcd. for $C_{21}H_{38}O_4$ (354.5): C 71.15, H 10.80, found C 71.21, H 10.88.