A Formal Total Synthesis of Epothilone A: Enantioselective Preparation of the C1−C6 and C7−C12 Fragments[1]

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Our continued interest in the anticancer agent paclitaxel is driven by the desire to understand the structural features and spatial arrangement necessary for tubulin binding[2] and stabilization of microtubule dynamics.[3] The recently reported class of natural products, epothilone, now provides us with compounds structurally distinct from taxol and taxol analogues but with similar biological activity. In addition, epothilones have much greater activity against multi-drug resistant cell lines.[4] After independently determining the relative stereochemistry of epothilone A we reported our synthetic approach, Figure 1, which includes a late-stage macrocyclic olefin metathesis.[5] Our initial publication presented an enantioselective preparation of thiazole fragment **C** and the successful application of a ring-closing olefin metathesis reaction to an epothilone model system. Concurrently, three other synthetic groups reported similar approaches to epothilone A all of which have culminated in total synthesis.[6−10] Herein we report the details of our independent, enantioselective preparation of the ketone fragment **B** and aldehyde **A**.

Ketone **B** has been prepared from a sequence which is highlighted by a samarium-mediated Reformatsky reaction[11] originally developed by Molander, Scheme 1. The sequence begins with racemic alcohol **2** readily prepared in one step from propionaldehyde and 3-methyl-2-butenylmagnesium chloride. Enzymatic resolution in methyl *tert*-butyl ether using Altus Biologics[12] Chiro-CLEC-PC(which is reusable without significant loss of activity) provided an efficient route to gram quantities of (*R*)-**2** after purification and deacylation. The enantioselectivity of the resolution at 47% conversion was determined to be >20:1 by Mosher ester methodology[13] and chiral capillary gas chromatography (see Experimental Section for details). The enantiomeric excess was found to be dependent upon percent conversion (97% ee at 15% conversion and 92% ee at 48% conversion). The unreacted alcohol **2** can be easily recycled by a two-step oxidation−reduction sequence. Acylation of the secondary hydroxyl occurred readily with bromoacetyl bromide in the presence of *N*,*N*-dimethylaniline to provide ester **3** in excellent yield. Ozonolytic cleavage of the terminal olefin yielded the necessary Reformatsky precursor which under exposure to freshly prepared SmI_2 provided the lactone **4** in quantitative yield with >20:1 diastereose-

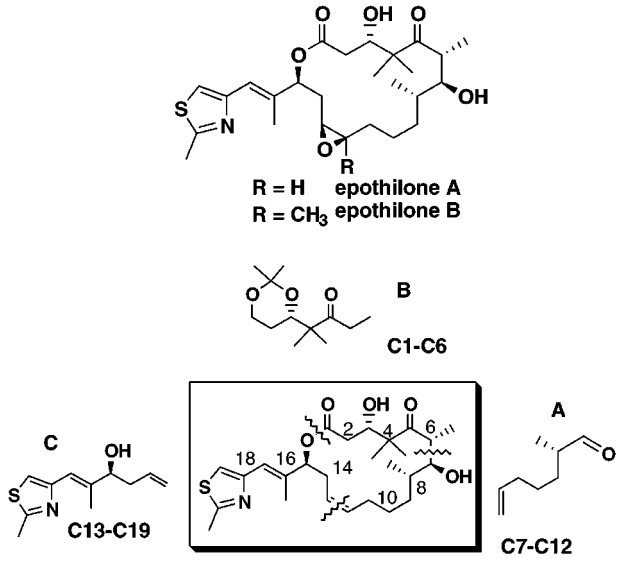

Figure 1. Connectivity analysis of desoxy-epothilone A.

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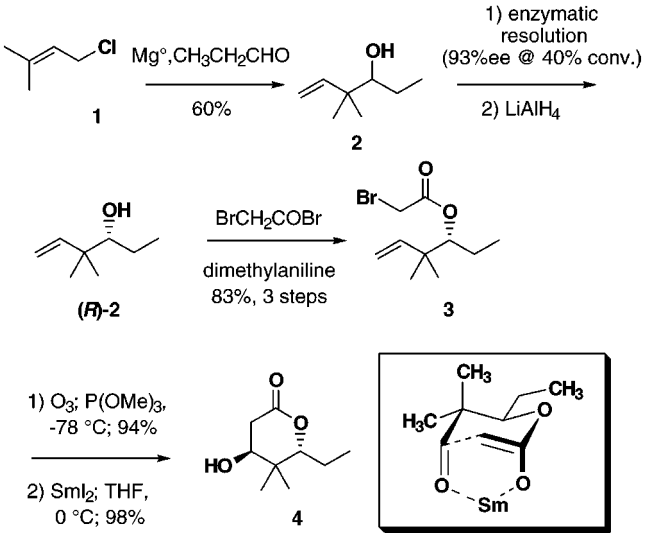
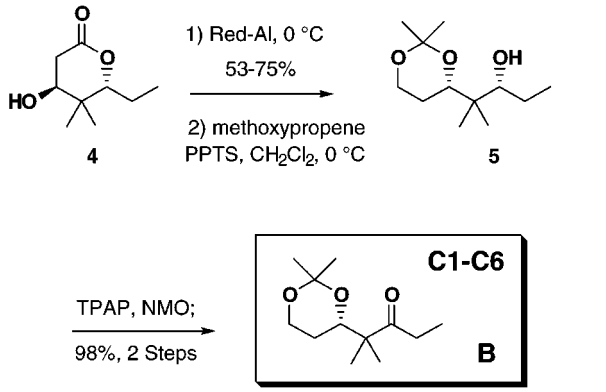
Scheme 1



Scheme 2



lectivity. The selectivity of this intramolecular condensation can be rationalized by consideration of the chelated transition state shown.

The enantioselective preparation of ketone **B** was completed by a three-step sequence from lactone **4**, Scheme 2. Exposure of the lactone to Red-Al followed by protection of the resulting triol without purification provided the alcohol **5**. The yields of the reduction step appeared to be dependent upon reaction scale. Kinetic conditions (−15 °C) are necessary for the selective acetonide formation. When the reaction is carried out in refluxing methylene chloride, exclusive protection of the internal 1,3-diol occurs. Oxidation of the secondary alcohol with TPAP then provided the desired ketone **B** in quantitative yield.

The synthesis of aldehyde **A** uses the well-precedented chemistry developed in the Evans' laboratory.[14] Schinzer has previously reported a similar route to this intermediate starting from commercially available 6-heptenoic acid.[8] However, the exorbitant cost of 6-heptenoic acid (>$5000/mol) created a need for a practical, alternative source of this starting material. Our independent route was developed starting from 1,7-octadiene (<$50/mol). The diene was selectively epoxidized using *m*-CPBA at 0 °C. With careful control of stoichiometry and temperature, the monoepoxide could be obtained in reasonable yield (76%). The epoxide was subjected to periodic acid-based oxidative cleavage to provide 6-heptenal in 79%

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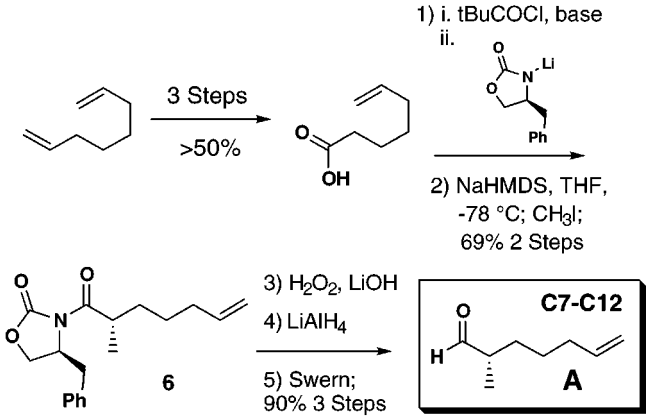
Scheme 3



yield, Scheme 3. Oxidation to the carboxylic acid was accomplished with sodium chlorite to provide the desired 6-heptenoic acid. The mixed anhydride, generated by exposure of the acid to pivaloyl chloride, was then treated with the lithium amide of Evans' auxiliary to provide the heptenoyl imide in excellent yield. The sodium enolate was generated with sodium hexamethyldisilazide at low temperature which was followed by alkylation with methyl iodide to provide the imide **6** with a high degree of diastereocontrol, >20:1. The low temperature conditions presumably generated exclusively the *Z*-enolate which based on the steric encumbrance of the neighboring benzyl substituent directed alkylation to the α-face. The chiral auxiliary was removed by basic hydrolysis, and the resulting acid was reduced with lithium aluminum hydride. Oxidation of the resulting primary alcohol under Swern conditions provided aldehyde **A** in excellent yield with high enantiomeric excess.

Herein we have reported practical routes to two synthetic precursors to epothilone A. Our independent preparation of each of three precursors (**A**, **B**, **C**) coupled with the recently published work from the Schinzer group[8] represents a formal total synthesis of epothilone A. Our effort is now focused on the use of this concise route for the preparation of analogues, particularly compounds with altered conformational properties. These novel compounds have the potential to provide important information concerning the conformation of the epothilones while bound to microtubules. The details of these synthetic efforts as well as our independent completion of the synthesis of the natural product will be presented in a subsequent publication.

Experimental Section

General Methods. Chiro-CLEC-PC (dry) enzyme was obtained from Altus Biologics, Cambridge, MA. When appropriate, reactions were performed under an atmosphere of nitrogen or argon with flame-dried glassware. Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone ketyl. CH_2Cl_2 was dried by distillation from CaH_2. All purchased reagents were of reagent grade quality and were used without further purification. GC analysis was accomplished using a gas chromatograph with a flame ionization detector.

(*R*)-Alcohol 2. Racemic alcohol **2** (5.00 g, 0.30 mmol) and vinyl acetate (6.30 mL, 7.81 mmol) were added to a stirring solution of ChiroCLEC-PC (dry) enzyme (206 mg) in *tert*-butyldimethyl ether (30 mL) at room temperature. The progress of the reaction was monitored via ^1H NMR or GC. After 40% conversion was obtained, the solution was carefully concentrated and the oil was chromatographed with pentane−Et_2O (gradients

to 3% Et_2O) to yield the acetate as a colorless oil (because of volatility the bulk material was taken directly to the reduction without complete removal of solvent). This particular sample was shown to be 93% ee by chiral GC: t_R (*S*)-OAc 6.483 min; t_R (*R*)-OAc 6.874 min (Cyclodex B column, 30 m length, 0.25 mm i.d., J & W Scientific, Folsom, CA); $[\alpha]^{23}_D = +39.5$; ^{1}H NMR ($CDCl_3$) δ 5.80 (dd, $J = 9.8$ Hz, $J = 11.5$ Hz, 1 H), 4.97 (m, 2 H), 4.71 (dd, $J = 2.5$ Hz, $J = 10.8$ Hz, 1 H), 2.05 (s, 3 H), 1.56 (m, 1 H), 1.38 (m, 1 H), 0.97 (s, 6H), 0.81 (t, $J = 7.34$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.10, 144.54, 112.41, 81.00, 40.81, 23.18, 22.75, 20.94, 10.84; HRMS (CI) calcd for $[M + H]^+$, 171.1385, obsd 171.1361; IR (neat) 3085, 2972, 2937, 2879, 1740, 1370, 1240 cm^{-1}. The acetate was dissolved in anhydrous diethyl ether, and lithium aluminum hydride (0.83 g, 21.8 mmol) was added in small portions at −20 °C. After 30 min the reaction was carefully quenched with solid $Na_2SO_4 \cdot 10H_2O$ and stirred at room temperature until the white aluminum salts precipitated. The mixture was filtered, and the salts were washed with additional diethyl ether. The combined organic washings were carefully concentrated, and the residue was chromatographed with pentane−Et_2O (gradients to 3% Et_2O) to yield alcohol (***R***)-**2** as a colorless oil (because of volatility the bulk material was taken directly to the acylation without complete removal of solvent): $[\alpha]^{23}_D = +31.7$; ^{1}H NMR ($CDCl_3$) δ 5.82 (dd, $J = 10.9$ Hz, $J = 17.4$ Hz, 1 H), 5.06 (m, 2 H), 3.16 (ddd, $J = 1.9$ Hz, $J = 4.9$ Hz, $J = 10.3$ Hz, 1 H), 1.62 (m, 1 H), 1.45 (d, $J = 5.2$ Hz, 1 H), 1.21 (m, 1 H), 1.04 (t, $J = 3.8$ Hz, 3 H), 1.04 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 145.53, 113.18, 80.02, 41.70, 24.30, 23.14, 22.09, 11.57; HRMS (CI) calcd for $[M + H^+]$ 129.1279, obsd 129.1274; IR (neat) 3459, 3083, 2966, 2876, 1216 cm^{-1}.

(*R*)-Bromoacetate 3. Dimethylaniline (4 mL, 31 mmol) and bromoacetyl bromide (2.70, 31.2 mmol) were added slowly to a stirring solution of alcohol (***R***)-**2** (from above) in Et_2O (30 mL) at 0 °C. The solution became green upon addition of the bromoacetyl bromide, and a green precipitate was formed. Stirring was continued at room temperature for 24 h. After consumption of (***R***)-**2** (monitored by TLC), the reaction mixture was diluted with water and extracted three times with diethyl ether. The organic layer was washed alternate times with NaOH (2 N) and HCl (2 N) until the aqueous layer was no longer cloudy upon addition of NaOH. The organic layer was then dried over $MgSO_4$ and concentrated. Chromatography (gradients to 5% Et_2O) yielded bromoacetate **3** (3.23 g, 83% for three steps based upon 40% conversion in enzyme resolution) as a yellow oil: $[\alpha]^{23}_D = +25.8$; ^{1}H NMR ($CDCl_3$) δ 5.85 (dd, $J = 11.2$ Hz, $J = 17.0$ Hz, 1 H), 5.05 (m, 2 H), 4.81 (dd, $J = 2.5$ Hz, $J = 10.7$ Hz, 1 H), 3.88 (s, 2H) 1.66 (m, 1 H), 1.52 (m, 1 H), 1.05 (s, 6 H), 0.90 (t, $J = 7.3$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.29, 144.07, 112.92, 83.46, 41.03, 25.94, 23.13, 22.78, 10.80; IR (neat) 3084, 2972, 2879, 1734, 1279 cm^{-1}.

(3*S*,2*R*)-Lactone 4. Ozone was bubbled into a stirring solution of bromoacetate **3** (2.91 g, 11.7 mmol) in CH_2Cl_2 (140 mL) at −78 °C until the solution became blue and **3** was consumed (by TLC). Nitrogen was then bubbled through the solution until the blue color dissipated. The reaction was quenched with trimethylphospite (3.6 g, 29 mmol), and the reaction was stirred at room temperature for 24 h. The solution was concentrated and chromatographed with pentane−diethyl ether (gradients to 20% Et_2O) to yield the intermediate aldehyde (2.75 g, 94%) as a clear pale yellow oil: $[\alpha]^{23}_D = +20.9$; ^{1}H NMR ($CDCl_3$) δ 9.53 (s, 1 H), 5.13 (dd, $J = 3.2$ Hz, $J = 9.9$ Hz, 1 H), 3.83 (s, 2 H), 1.60 (m, 2 H), 1.10 (s, 1 H), 1.09 (s, 1 H), 0.92 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.35, 167.03, 79.64, 50.16, 25.43, 22.96, 18.56, 17.84, 10.50; HRMS (FAB) calcd for $[M + H^+]$ 251.0283, obsd 251.0297; IR (neat) 2975, 2880, 1731, 1277 cm^{-1}. A solution of the aldehyde (1.77 g, 7.05 mmol) in THF (3 mL) was added slowly to a stirring solution of freshly prepared[11] SmI_2 in THF (153 mL, 15.3 mmol) at 0 °C. The solution was titrated with additional SmI_2 until a deep blue color persisted. The solution was stirred for 5 min until consumption of the aldehyde was complete (monitored by TLC). The reaction was quenched with oxygen, and the mixture was concentrated to a green-yellow solid, dissolved in EtOAc, and separated with water and $NaHCO_3$. The aqueous layer was washed two additional times with EtOAc. An insoluble material was isolated by filtration, dissolved in 1 N HCl (100 mL), and extracted with additional portions of ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ and brine and then concentrated to give a pale yellow oil which was chromatographed with pentane−Et_2O (gradients from 1:1 to 100% Et_2O) to yield lactone **4** (∼20:1 mixture of diastereomers) (1.19 g, 98%) as a low-melting pale yellow solid: $[\alpha]^{23}_D = +38.7$; ^{1}H NMR ($CDCl_3$) δ 4.39 (dd, $J = 4.1$ Hz, $J = 8.6$ Hz, 1H), 3.75 (s, 1 H), 2.85 (dd, $J = 4.8$ Hz, $J = 18.7$ Hz, 1 H), 2.60 (dd, $J = 2.4$ Hz, $J = 18.7$ Hz, 1 H), 1.59 (m, 2 H), 1.10 (t, $J = 7.3$ Hz, 3 H), 1.07 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.09, 84.42, 72.43, 36.64, 36.38, 22.52, 22.06, 18.79, 10.89; HRMS (CI) calcd for $[M + H^+]$ 173.1178, obsd 173.1171; IR (neat) 3437, 2970, 2973, 2880, 1710, 1249 cm^{-1}.

(3*S*,5*R*)-Acetonide 5. To a stirring solution of lactone **4** (1.76 g, 10.2 mmol) in THF (1 mL) at 0 °C was added Red-Al (65% in toluene) (6.8 mL, 22.5 mmol). The solution was stirred at room temperature for 24 h. The reaction was quenched with H_2O (1 mL), 2 N NaOH (1 mL), and anhydrous Na_2SO_4 (20 g) and allowed to stir for 30 min. The solution was then filtered over a bed of $MgSO_4$ and washed through numerous times with EtOAc, the organic layers were then concentrated to provide the triol as a colorless solid (0.96 g, 53%).

2-Methoxypropene (1.35 mL, 13.9 mmol) and PPTS (cat.) were added to a stirring solution of the triol (0.56 g, 3.23 mmol) in DMF (10 mL) at −15 °C. The solution was stirred at −15 °C for 48 h, the reaction was quenched with saturated $NaHCO_3$, and the resulting mixture was extracted with Et_2O (5 × 50 mL). The organic layer was washed with water, dried with $MgSO_4$, concentrated, and filtered through a bed of silica gel to yield the acetonide **5** (0.68 g, 100%) as a pale yellow oil: $[\alpha]^{23}_D = +31.5$; ^{1}H NMR ($CDCl_3$) δ 3.91 (m, 3H), 3.38 (dd, $J = 2.4$ Hz, $J = 10.4$ Hz, 1 H), 1.75 (m, 1 H), 1.51 (m, 1 H), 1.48 (s, 3 H), 1.38 (s, 3 H), 1.33 (m, 2 H), 0.99 (t, $J = 7.4$ Hz, 3 H), 0.90 (s, 3 H), 0.72 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 98.44, 81.23, 78.00, 60.20, 40.27, 29.78, 25.37, 24.16, 20.67, 19.29, 14.42, 11.20; HRMS (FAB) calcd for $[M + H^+]$ 217.1804, obsd 173.1171; IR (neat) 3448, 2963 cm^{-1}.

(*S*)-Ketone B. A solution of acetonide **5** (6.75 g, 3.12 mmol) in CH_2Cl_2 (1.5 mL) with 3 Å MS (cat.) was stirred for 15 min at room temperature. *N*-Methylmorpholine *N*-oxide (0.89 g, 7.02 mmol) and TPAP (cat.) were added, and this mixture was stirred for 2.5 h until consumption of **5** was complete (monitored by TLC). The reaction mixture was then filtered through silica gel with diethyl ether and concentrated to yield ketone **B** (0.66 g, 99%) as a clear colorless oil: $[\alpha]^{23}_D = +10.5$; ^{1}H NMR ($CDCl_3$) δ 3.93 (m, 3 H), 2.50 (q, $J = 7.2$ Hz, 2 H), 1.60 (m, 1 H), 1.40 (s, 3 H), 1.32 (s, 3 H), 1.12 (s, 3 H), 1.06 (s, 3 H), 1.00 (t, $J = 7.1$, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.85, 98.34, 73.92, 59.99, 50.56, 31.70, 29.72, 25.27, 21.02, 19.06, 18.97, 7.87; HRMS (CI) calcd for $[M + H^+]$ 215.1647, obsd 215.1643; IR (neat) 2973, 2940, 2876, 1706, 1372, 1198, 1105 cm^{-1}.

6-Heptenoic Acid. 1,7-Octadiene (2 mL, 13 mmol) was added to a stirred solution of sodium acetate (1.1 g, 13.3 mmol) and *m*-chloroperbenzoic acid (2.55 g, 12.3 mmol) in methylene chloride at 0 °C. The mixture was stirred for 2.5 h, and the reaction was then quenched by the addition of saturated aqueous solution of sodium bicarbonate (10 mL) and sodium thiosulfate (1 mL). The aqueous layer was separated and washed with additional portions of methylene chloride (2 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash chromatography (silica gel; 15% ether in pentane) to yield the monoepoxide (1.27 g, 76%). To a THF (3 mL) solution of the monoepoxide (708 mg, 5.6 mmol) was added a solution of periodic acid (1.44 g, 6.7 mmol) in water (3 mL) at 0 °C. The mixture was stirred for 3 h at this temperature and then extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium thiosulfate solution (2 × 10 mL) and then dried over $MgSO_4$. Concentration in vacuo provided 6-heptenal (498 mg, 79%): ^{1}H NMR ($CDCl_3$) δ 9.76 (t, $J = 1.8$ Hz, 1H), 5.79 (m, 1 H), 5.04−4.93 (td, $J = 7.2$ Hz, $J = 1.8$ Hz, 2 H), 2.11−2.03 (m, 2 H), 1.70−1.60 (m, 2 H), 1.48−1.40 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 202.6, 138.2, 114.8, 43.7, 33.4, 28.3, 21.4; HRMS (FAB) calcd for $[M + H^+]$ 113.0966, obsd 113.0966; IR (neat) 3075, 2927, 1727, 1640 cm^{-1}. 6-Heptenal (56 mg, 0.5 mmol) was dissolved in a mixture of *tert*-butyl alcohol (10 mL) and 2-methyl-2-butene (5 mL). To this solution was added, an aqueous solution of sodium chlorite (225 mg, 2 mmol) and sodium phosphate (138 mg, 1 mmol) in distilled water (4 mL). The reaction mixture was then stirred vigorously for 30 min at

room temperature. The mixture was then diluted with ethyl acetate (80 mL) and washed with water (2 × 10 mL). The combined aqueous layers were washed with additional portions of ethyl acetate, and the combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The crude material was purified by chromatography (silica gel, 5% diethyl ether in hexane) to provide 6-hepenoic acid as a colorless oil (38 mg, 60%).

Acknowledgment. Altus Biologics is thanked for a generous gift of Chiro-CLEC-PC. We gratefully acknowledge support from the University of Notre Dame. R.E.T. is a recipient of a National Science Foundation Early Career Award.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **2**−**5** and ketone **B** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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