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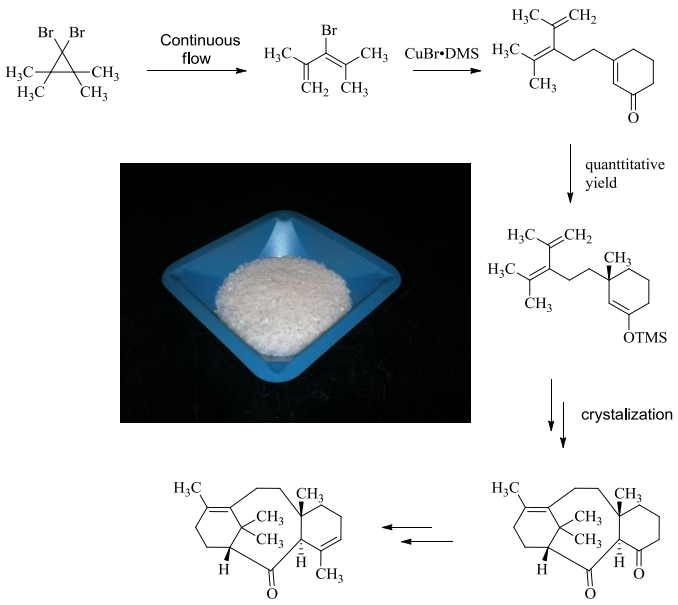
Continuous flow
CuBr•DMS
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crystalization
OTMS

Route Optimization and Synthesis of Taxadienone.

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Keywords: Taxadienone, continuous flow reactor, copper catalyzed addition, Diels-Alder reaction, Negishi coupling.

Abstract

Early process development toward the scalable production of taxadienone on a decagram scale is described. A continuous flow reactor was employed to safely run a potentially hazardous cyclopropane ring opening. The route featured two copper mediated additions, a Diels-Alder reaction, and a palladium-catalyzed Negishi coupling to construct the final structure.

INTRODUCTION

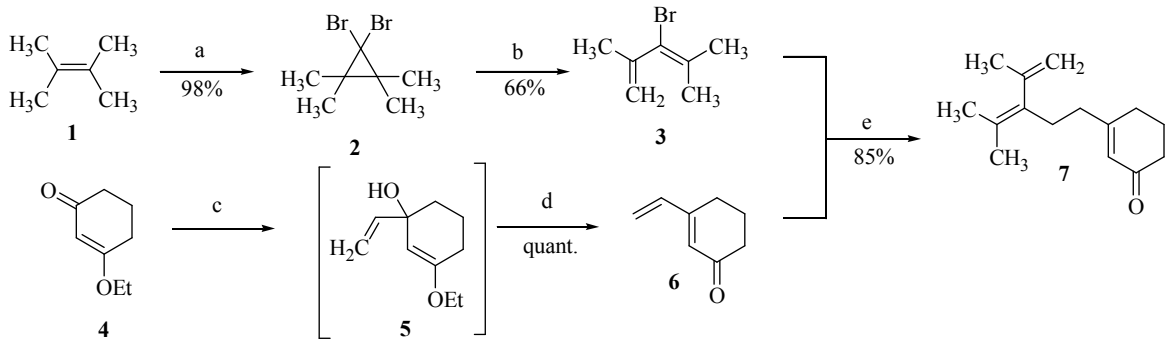
Paclitaxel is a promising anti-cancer drug with a broad range of therapeutic action.[1] The compound is produced semi-synthetically and its supply relies on cell culture production. Therefore, several synthetic routes were developed to meet the demand on scale as well as gain access to different analogues. Recently, a promising new strategy has been described in Baran's group.[2] The proposed route to synthetic paclitaxel relies on the stepwise oxidation of the C_{20}-

structure of taxadienone which marks taxadienone as a center block intermediate in the production of paclitaxel and analogues.

RESULTS AND DISCUSSION

The present work describes early process development toward the production of taxadienone **(+)-16** (Schemes 1 and 2) using Baran's route as a point of inception. The commercially available olefin **1** served as a starting material in the preparation of bromodiene **3** via a two-step procedure (Scheme 1), in which dibromide **2** did not have to be isolated and the reaction was performed in a one-pot fashion.

Scheme 1. Preparation of **7**.



Reagents and Conditions: (a) $CHBr_3$, tBuOK, heptanes, 0 °C, quant; (b) $PhNMe_2$, 10 min, 150 °C; (c) 1 M vinylmagnesium bromide in THF, MTBE, 0 °C to room temperature, 1 h; (d) SiO_2, DCM; (e) **3**, **6**, *sec*-BuLi, CuBr•DMS, THF, -78 °C to -20 °C, 3 h.

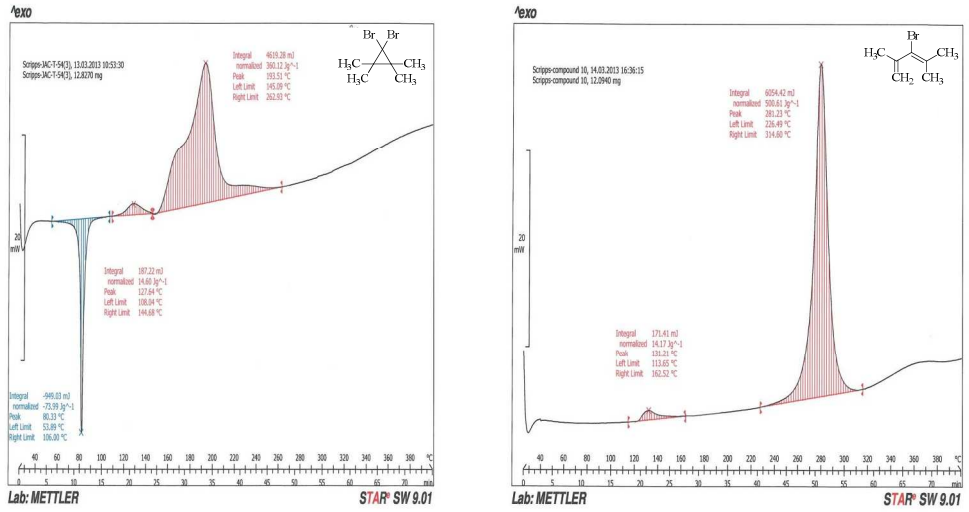
Initially, the same strategy was adopted in our studies. The reaction of a carbene with the olefin **1** was performed in heptanes at 0 ºC with the olefin **1** taken in excess as reported.[3,4] The volatiles were removed under reduced pressure and the mixture was heated to 150 °C for 1 h. The reaction output was improved as follows:

- the level of heptanes was decreased to 3 volumes;

- the volume of *N,N*-dimethylaniline was decreased to 1.5 volumes relative to bromoform;
- the amount of olefin was decreased **1** from 2.0 to 1.5 equivalents.

In order to continue with the reaction scale-up, a safety assessment of dibromide **2** and the bromodiene **3** was performed (see Figure 1). The DSC analysis revealed that the second part of the reaction is highly energetic. The dibromide **2** has an on-set temperature of 145 °C with energy of 360 J/g. The bromodiene **3** has an on-set temperature of 226 °C with energy 500 J/g. These results were against our standard process safety practice, which suggests at least 100 °C margin of safety (MOS) from the operating temperature of 150 °C for a safe chemical operation and therefore deemed unsafe for standard batch operations.[5]

Figure 1. DSC Data for compounds **2** and **3**.



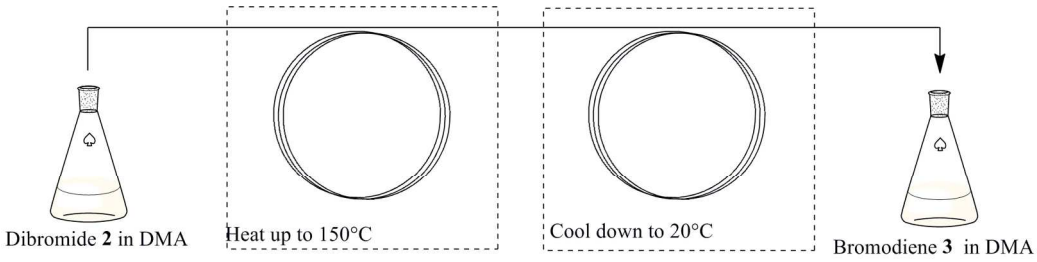
Based on these observations, we decided to isolate dibromide **2** and perform the second part (conversion of **2** to **3**) as a separate stage. Upon scale-up, the exotherm was controlled by the

slow addition of bromoform (over 4 h) to a slurry of olefin **1** and potassium *tert*-butoxide (*t*BuOK) at –9 to 0 °C. Reaction between the olefin and carbene is instantaneous, so the *in situ* generated carbene was expected not to accumulate. The excess of olefin **1** was further reduced to 10 mol %. An attempt to remove the side product, potassium bromide, by filtration was unsuccessful even when filtration aids were employed. Hence, the salts were removed by aqueous wash. Dibromide **2** was found to be sensitive to water at high pH. Thus, aqueous workup conditions which properly buffer against *t*BuOK are important to prevent discoloration and preserve yield.

After successful scale-up of **2**, efforts were concentrated on a safe procedure to produce **3** due to the high energy exhibited by DSC analysis. The conversion of **2** to **3** at a lower temperature (100 °C) took 30 h to reach completion. A screening of reaction time (10, 20, 40 min) and the required volume of *N,N*-dimethylaniline (1, 2 and 3 volumes) showed that efficient conversion of **2** to **3** can be achieved in 10 min at 150 °C, and the optimum amount of *N,N*-dimethylaniline is 2 volumes. These conditions should be amendable to the use of continuous processing. Therefore, we employed a continuous flow reactor (CFR), which is a common solution for fast and potentially hazardous reactions (Figure 2). The reaction occurred inside Hastelloy tubing, which was placed in an oven. The pump speed was correlated with the reactor tube dimensions to permit a desired residence time for the starting material inside the tube. The reaction mixture upon leaving the oven was cooled in a separate heat exchange loop. The reaction was performed on 490 g scale of dibromide **2** using a 125 mL reaction tube, which allowed increasing the flow up to 10 mL/min. Processing was complete in 3.5 h. The engagement of the CFR in the production of compound **(+)-16** effectively addressed our safety concerns and minimized the

reaction time for this step. The required time from start to finish was 5 h, whereas in the batch mode the reaction would require more than two days.

Figure 2. The Flow Chemistry Setup.



The preparation of conjugated ketone **6**[6] from commercially available compound **4** is shown in Scheme 1. The first part is a Grignard reaction to form **5**, which is followed by elimination of a molecule of EtOH on a silica gel plug to form **6**. The reaction solvent, diethyl ether, was replaced with MTBE without any issues. The reaction time was decreased from the reported 14 h to 1 h with a quantitative yield.

Preparation of **7** (Scheme 1) in diethyl ether proceeded with 50% yield only if freshly prepared CuBr•DMS complex was used.[7] Literature suggests that THF is a good solvent for copper mediated additions as well.[8,9] Thus, when diethyl ether was replaced by THF, the reaction was complete in 2 h. Moreover, running the reaction in THF made it possible to use commercially available CuBr•DMS complex, which had failed earlier in our studies.

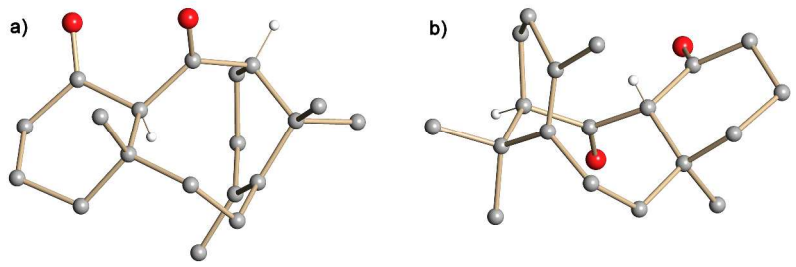
Preparation of (-)-**9** is shown in Scheme 2. Although successful on small scale, the literature conditions[10] failed upon attempted scale-up. It was speculated that the likely cause of this problem was brief exposure of the highly acidic reaction mixture to atmospheric moisture during the quench. Implementation of a reverse quench allowed the reaction to be scaled up with a consistently quantitative yield. When the reaction was performed in an alternative solvent, such

as THF, conversion was poor. The enantiomeric (*ee*) purity of compound (-)-**9** was determined by hydrolysis of the TMS ether to ketone **10** using 2 N HCl and analysis by chiral HPLC. The observed *ee* varied from 92.9 to 94.2 %.

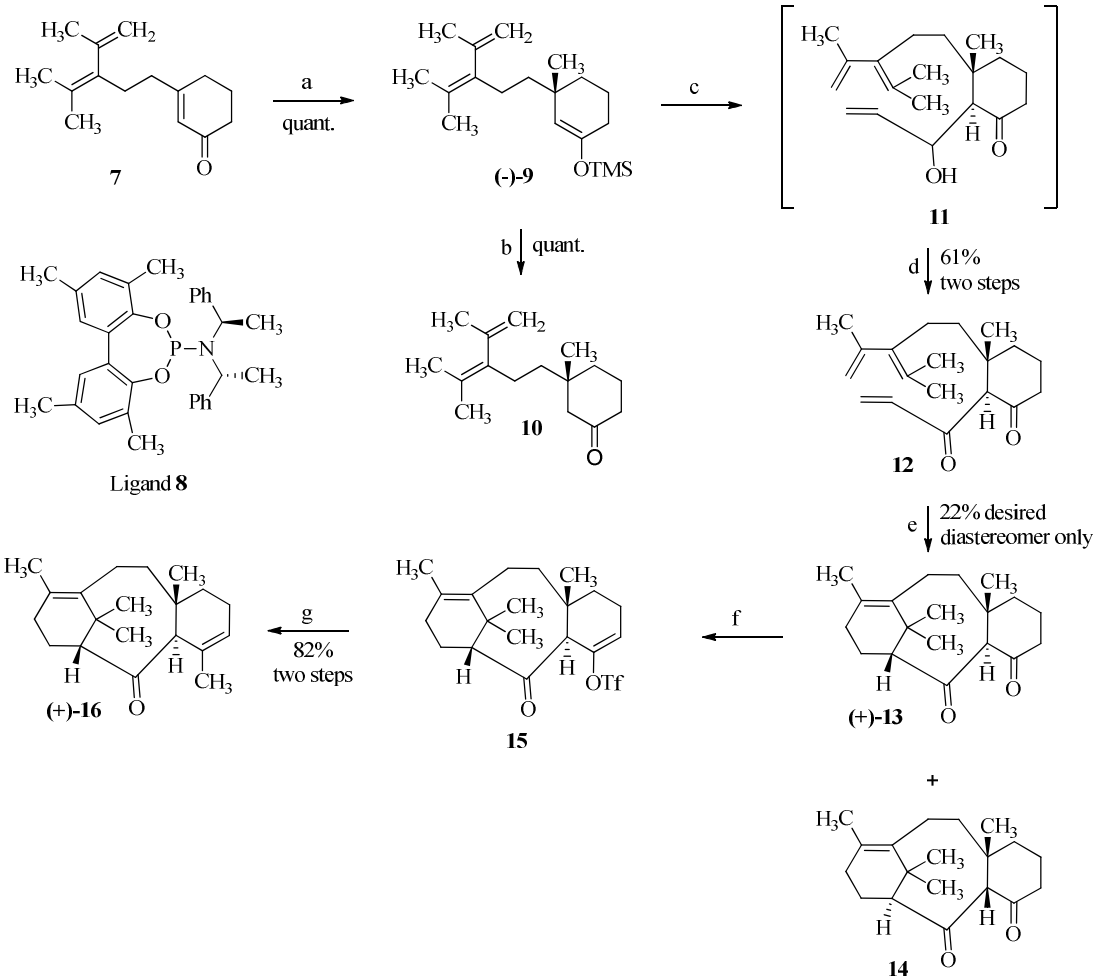
Preparation of **12** (Scheme 2) was repeated as described[2] with the following modifications to meet the scale requirements. Overall, the reaction is a two-step procedure consisting of an aldol reaction between **(-)-9** and acrolein catalyzed by gadolinium(III) triflate[11] to form **11** followed by Jones' oxidation of the alcohol to the diketone **12** affording overall 61% yield for two steps. In order to avoid the retro aldol reaction of **11** during the workup, the reaction was quickly concentrated in portions, which were diluted with acetone and taken into the next oxidation step. It is worth noting that acrolein diethoxy acetal can also be used and can be hydrolyzed in water using camphorsulfonic acid. The product, acrolein, is distilled from the reaction as a mixture in ethanol and water, which are the solvents used in the aldol reaction.

Modifications in the purification of **(+)-13, t**he Diels-Alder reaction product,[12] were critical to obtain high quality material. The crude material after silica plug purification was contaminated with several co-eluting impurities, which would not purge in the next step and were difficult to remove by silica column chromatography. To our delight, we found that the desired product **(+)-13** can successfully be crystallized from heptanes.

Figure 3. Ball-and-stick views of **(+)-13**. [13]



Scheme 2. Preparation of taxadienone.



Reagents and Conditions: (a) (i) copper (I) 2-thiophenecarboxylate (CuTC), ligand **8**, 2 M Me_3Al in heptane, diethyl ether, 14 h, -30 °C; (ii) TEA, TMSCl, 3 h; (b) THF, 2 N HCl; (c) acrolein, $Gd(OTf)_3$, water, ethanol, toluene; (d) Jones reagent, acetone, 0 °C; (e) BF_3•OEt_2, DCM, 0 °C; (f) $PhNTf_2$, KHMDS, THF, 0 °C; (g) Me_2Zn, $Pd(PPh_3)_4$, 0 °C to room temperature.

This crystallization step was essential to obtain taxadienone **(+)-16** in high quality. Single crystal X-ray data analysis confirmed the structure and the absolute stereochemistry of **(+)-13** (Figure 3). Hydrogen atoms were omitted for clarity except two most stereochemically important ones.

A Negishi coupling was employed to prepare of **(+)-16** via a two step procedure.[2] The triflate **15** was prepared using *N*-phenyl-bis(trifluoromethanesulfonimide) and potassium bis(trimethyl-

silyl)amide in a quantitative yield. Azeotropic drying by distillation while adding fresh THF was done to ensure moisture would not interfere with the next step. The Negishi reaction between triflate **15** and dimethylzinc using tetrakis(triphenylphosphine)palladium(0) as a catalyst[14] afforded the product **(+)-16** in 82% yield after crystallization from methanol.

CONCLUSIONS

The reported route[2] to taxadienone **(+)-16** was successfully optimized and scaled-up to decagram quantity. Thermal hazards associated with the production of bromodiene **3** were addressed by employing a continuous flow reactor. Two cuprate additions to form a desired enantiomer of **(-)-9** were executed in good yield. The crystallization of **(+)-13** at the penultimate step proved to be a decisive factor for obtaining taxadienone **(+)-16** of high quality.

EXPERIMENTAL SECTION

Chiral analysis of ketone **8** was performed on Waters 2695 system equipped with a Daicel Chiral OJ-H, 4.6×250 mm, 5μm column at 25 °C with hexanes as mobile phase with the flow rate 0.5 mL/min using Waters 2487 dual wavelength detector at 220 nm.

1,1-Dibromo-2,2,3,3-tetramethylcyclopropane (**2**). A mixture of butene **1** (147 g, 1.75 mol, 1.10 equiv), heptanes (1.2 L), and potassium tert-butoxide (196.0 g, 1.75 mol, 1.10 equiv) at –9 °C was treated with bromoform (401 g, 1.59 mol, 1.00 equiv) over 2 h at –9 to 2 °C range. The addition funnel was rinsed with heptanes (10 mL), and the mixture was stirred at room temperature for 2 h. After this time, 50% saturated sodium bicarbonate solution (500 mL) was added. The mechanical stirrer was stopped and phase separation occurred. The aqueous layer was separated and extracted with heptanes (2 × 250 mL). The organic layers were combined and

concentrated under reduced pressure to afford dibromide **2** (440 g, 98% yield) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): 1.26 (s).

3-Bromo-2,4-dimethylpenta-1,3-diene (**3**). Continuous flow reactor (CFR) setup is shown on Figure 1. A GC oven was equipped with a 5/16" Hastelloy tube (total volume 125 mL). A mixture of dibromide **2** (440 g, 1.72 mol, 1.00 equiv) and *N,N*-dimethylaniline (0.9 L) was pumped into CFR using an HPLC pump. [The flow rate was set to 10 mL/min to achieve 12.5 min residence time in the reactor at 150 °C.] Upon exiting the CFR, the mixture was cooled to 20 °C, diluted with MTBE (2 L), and treated with HCl (4 N, 2 × 2 L). The organic layer was separated and concentrated under reduced pressure to afford **3** (200 g, 66% yield) as a yellow oil. The material was stored over sodium hydroxide pellets. ^{1}H NMR (500 MHz, $CDCl_3$): 5.04 (m, 1H), 4.91 (m, 1H), 1.89 (m, 6H), 1.81 (s, 3H).

3-Vinylcyclohex-2-enone (**6**). A mixture of **4** (75 g, 0.53 mol, 1.00 equiv) and MTBE (0.5 L) at 0 °C was treated with vinylmagnesium bromide (1 M, 0.59 L, 0.59 mol, 1.10 equiv) over 40 min at 0 °C to 10 °C range. The addition funnel was rinsed with MTBE (10 mL) and the mixture was stirred at room temperature for 1 h. After this time, the mixture was cooled to 0 °C and saturated ammonium chloride solution (0.2 L) was added. The mechanical stirrer was stopped and phase separation occurred. The aqueous layer was separated, extracted with MTBE (2 × 0.1 L). The organic layers were combined, concentrated under reduced pressure, and passed through a silica plug (500 g, eluent: dichloromethane). The fractions containing product were concentrated under reduced pressure to afford **6** (65.3 g, quantitative yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 6.50 (dd, J = 17.5, 10.5 Hz, 1H), 5.96 (s, 1H), 5.69 (d, J = 17.5 Hz), 5.47 (d, J = 10.5 Hz), 5.30 (s, 1H), 2.47 (m, 1H), 2.43 (m, 2H), 2.06 (m, 2H).

Preparation of CuBr•DMS complex. A suspension of Cu(0) metal powder (40 g, 0.63 mol, 1.00 equiv) and DMSO (0.6 L) at 100 °C was treated with benzyl bromide (215 g, 1.26 mol, 2.00 equiv) over 1 h at 90 to 100 °C range. The addition funnel was rinsed with DMSO (10 mL) and the mixture was stirred at 120 °C for 5 h. After this time, the mixture was cooled to 0 °C and water (1.2 L) was added. The suspension was stirred for 30 min and precipitate was allowed to settle. The aqueous layer was decanted and acetone (0.6 L) was added. The suspension was stirred for 30 min at room temperature. The precipitate was removed by filtration and dried in a vacuum oven at room temperature to afford CuBr•DMS complex (67.3 g, 52% yield) as a white solid.

3-(4-Methyl-3-(prop-1-en-2-yl)pent-3-en-1-yl)cyclohex-2-enone (**7**). A mixture of bromide **3** (127 g, 0.72 mol, 1.55 equiv) and THF (2.0 L) at –70 °C was treated with *sec*-butyllithium (1.4 M in cyclohexane, 500 mL, 0.70 mol, 1.50 equiv) over 40 min at –63 °C to –70 °C range. The reaction was stirred for 0.5 h and was treated with CuBr•DMS complex (105 g, 0.51 mol, 1.1 equiv) over 20 min at –61 °C to –70 °C range. The reaction was stirred for 0.5 h and treated with trimethylsilyl chloride (101 g, 0.93 mol, 2.00 equiv) over 15 min at –65 °C to –70 °C range. The reaction was stirred for 0.5 h and was treated with a mixture of **6** (57.0 g, 0.47 mol, 1.00 equiv) in THF (40 mL) over 15 min at –65 °C to –70 °C range. The reaction was stirred for 2 h and was deemed complete by TLC (heptanes/ethyl acetate 3:1 (v/v)). The reaction was quenched by slow addition of acetic acid (60 mL) followed by water (12 mL). The contents of the flask were transferred to a 5-L beaker, containing saturated sodium carbonate (2 L), and stirred for 0.5 h. After this time, the mixture was filtered and the mother liquor was allowed to phase separate. The aqueous layer was separated, extracted with MTBE (2 × 0.1 L). The organic layers were combined, concentrated under reduced pressure, and passed through a silica column (570 g, 0 to

20% ethyl acetate in hexanes). The fractions containing product were concentrated under reduced pressure to afford **7** (85.2 g, 85% yield) a yellow oil. [Care should be taken during solvent evaporation, since **7** is volatile.] ^{1}H NMR (500 MHz, $CDCl_3$): 5.88 (t, J = 1 Hz, 1H), 4.96 (dd, J = 2.5, 1 Hz, 1H), 4.57 (m, 1H), 2.35 (m, 2H), 2.30-2.23 (m, 6H), 1.98 (m, 2H), 1.76 (t, J = 1 Hz, 3H), 1.67 (s, 6H).

(S)-Trimethyl((3-methyl-3-(4-methyl-3-(prop-1-en-2-yl)pent-3-en-1-yl)cyclohex-1-en-1-yl)oxy)silane ((-)-**9**). A mixture of copper(I)-thiophene-2-carboxylate (1.31 g, 6.9 mmol, 0.05 equiv), ligand **8** (6.81 g, 13.7 mmol, 0.1 equiv), **7** (30.0 g, 137 mmol, 1.00 equiv), and diethyl ether (0.6 L) at –40 °C was treated with trimethylaluminum (2 M in hexanes, 96 mL, 0.19 mol, 1.40 equiv) over 40 min at –35 °C to –40 °C range and stirred for 14 h. After this time, THF (0.6 L) was added over 20 min at –35 °C to –40 °C range. The reaction was stirred for 0.5 h and was treated with trimethylsilyl chloride (25.7 g, 0.24 mol, 1.72 equiv) over 15 min at –35 °C to –40 °C range. The reaction was stirred for 0.5 h and was treated with triethylamine (57.2 g, 0.57 mol, 4.12 equiv) over 15 min at –35 °C to –40 °C range. The reaction was stirred for 2 h allowing the temperature to rise to room temperature and was deemed complete by TLC (heptanes/ethyl acetate 3:1 (v/v)). The reaction was concentrated to 1/3 volume, poured into a suspension of florisil (150 g) and heptanes (1.5 L), stirred for 0.5 h and filtered. The filtrate was concentrated under reduced pressure and passed through a florisil plug (450 g, eluent: heptanes). The fractions containing product were concentrated under reduced pressure to afford **(-)-7** (85.2 g, quantitative yield) as a yellow oil. The product was used without additional purification.

Determination of enantiomeric purity of **(-)-9**. A mixture of **(-)-9** (100 mg) and THF (4 mL) was treated with 3 N HCl (2 mL) over 15 min at room temperature. The reaction was deemed complete by TLC (heptanes/ethyl acetate 3:1 (v/v)) and ketone **10** was formed. The reaction

mixture was portioned between ethyl acetate (20 mL) and water (2 mL). The organic layer was separated, dried over magnesium sulfate and concentrated under reduced pressure. The residue was analyzed by chiral HPLC.

(2S,3S)-2-Acryloyl-3-methyl-3-(4-methyl-3-(prop-1-en-2-yl)pent-3-en-1-yl)cyclohexanone (**12**). *Preparation of acrolein solution in ethanol/water.* A mixture of acrolein diethyl acetal (168 g, 1.29 mol), water (48 mL), and camphorsulfonic acid (10 g) was charged to a distillation flask, stirred for 30 min to form a homogenous solution, and was distilled under atmospheric pressure at 65 to 70 °C. The receiving flask was charged with 60 mg of hydroquinone. The NMR assay showed that the mixture contained 77.8 g of acrolein. The acrolein mixture at 0 °C was treated with a solution of **(-)-9** (25 g, 82 mmol, 1 equiv) in toluene (65 mL) followed by gadolinium(III) triflate (9.86 g, 16.3 mmol, 0.2 equiv). The reaction was stirred for five days at 0 °C. After this time, the reaction was concentrated down to 60 mL and diluted with acetone (600 mL). Jones' reagent (100 mL, 2.1 M; made from 26.7 g CrO_3, 23 mL conc. H_2SO_4 and 100 mL H_2O) at 0 °C was treated with the above mentioned acetone solution at 0 °C to 15 °C range. The excess of Jones' reagent was quenched with isopropanol (~10 mL). The flask contents were diluted with water (100 mL) to obtain a homogenous solution and acetone was removed under reduced pressure. (CAUTION: Acrolein is present). The product was extracted with ethyl acetate (3 × 300 mL). The organic layers were combined, concentrated under reduced pressure, and passed through a silica column (500 g, 0 to 20% ethyl acetate in heptanes). The fractions containing product were concentrated under reduced pressure to afford **12** (19.0 g, 61% yield) as a yellow oil. The material is an inseparable mixture of two diastereomers of **12** and ketone **10**.

(4aS,6R,12aS)-9,12a,13,13-Tetramethyl-1,2,3,7,8,11,12,12a-octahydro-6,10-methanobenzo-[10]annulene-4,5(4aH,6H)-dione (**(+)-13**). A mixture of boron trifluoride etherate (34.9 g, 0.25

mmol, 3.65 equiv) and dichloromethane (3 L) at 0 °C was treated with a solution of **12** (19.4 g, 67.3 mmol, 1.00 equiv) in dichloromethane (2 L) over 1.5 h using an FMI pump at 0 to 5 °C range. The reaction was stirred for 4.5 h at 0 °C, quenched with saturated sodium carbonate solution (1 L), and stirred for 0.5 h. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 300 mL). The organic layers were combined, concentrated under reduced pressure and passed through a silica column (500 g, 0 to 20% ethyl acetate in heptanes). The product containing fractions were concentrated under reduced pressure. The material was crystallized from heptanes to afford **(+)-13** (4.3 g, 22% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): 4.22 (s, 1H), 2.89 (m, 1H), 2.52 (m, 1H), 2.45 (d, J = 8.5 Hz, 1H), 2.34 (m, 1H), 2.22 (m, 2H), 2.04–1.90 (m, 8H), 1.75 (m, 1H), 1.69 (m, 1H), 1.44 (m, 1H), 1.35(m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 209.9, 206.8, 137.1, 131.5, 64.0, 61.9, 44.0, 39.5, 39.4, 38.4, 37.5, 29.4, 28.8, 25.4, 24.9, 24.0, 22.2, 21.0, 17.8.

(4aS,6R,12aS)-9,12a,13,13-Tetramethyl-5-oxo-1,2,4a,5,6,7,8,11,12,12a-decahydro-6,10-methanobenzo[10]annulen-4-yl trifluoromethanesulfonate (**15**). A mixture of **(+)-13** (4.80 g, 16.6 mmol, 1.00 equiv), *N*-phenylbis(trifluoromethanesulfonimide) (11.9 g, 33.3 mmol, 2.00 equiv), and THF (380 mL) at 0 °C was treated with 1 M solution of KHMDS in THF (25.0 mL, 25.0 mmol, 1.50 equiv) over 15 min at 0 to 5 °C range. The reaction was stirred for 1 h at 0 °C and was quenched with saturated sodium carbonate solution (200 mL). The flask contents were transferred into a separatory funnel containing heptanes (400 mL). The layers were separated and the organic layer was washed with potassium hydroxide (3 N, 2 × 200 mL). The organic layer was separated and concentrated under reduced pressure. The residual water was removed by azeotropic co-distillation with THF (2 × 200 mL). The crude material was used in the next step.

(4aS,6R,12aS)-4,9,12a,13,13-Pentamethyl-1,4a,6,7,8,11,12,12a-octahydro-6,10-methano-benzo[10]annulen-5(2H)-one (**(+)-16**). A mixture of the crude triflate **15**, tetrakis(triphenyl-phosphine)palladium(0) (1.92 g, 1.66 mmol, 0.1 equiv) at 0 °C was treated with 1.2 M solution of dimethylzinc in toluene (99.9 mL, 83.2 mmol, 5.00 equiv) over 15 min at 0 to 5 °C range. The reaction was stirred for 1 h at 0 °C and was warm up to room temperature. The reaction was stirred for 3 days. After this time, the reaction was quenched by carefully pouring the contents of the reaction flask to a separatory funnel containing 1 M HCl (100 mL). (CAUTION: GAS EVOLUTION!). The product was extracted with heptanes (2 × 200 mL). The organic layers were combined, concentrated under reduced pressure, and passed through a silica column (120 g, 0 to 20% ethyl acetate in heptanes). The fractions containing product were concentrated under reduced pressure. The material was crystallized from methanol to afford **(+)-16** (3.94 g, 82% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): 5.55 (d, J = 6.5 Hz, 1H), 3.31 (d, J = 0.5 Hz, 1H), 2.58 (m, 1H), 2.51 (m, 2H), 2.26 (m, 1H), 2.10 (m, 2H), 2.00 (m, 2H), 1.81 (m, 5H), 1.48 (m, 3H), 1.32 (m, 2H), 1.21 (m, 4H), 1.09 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 218.0, 136.8, 133.35, 130.6, 124.8, 64.9, 55.9, 43.5, 40.7, 38.5, 37.3, 28.9, 28.3, 27.6, 23.7, 23.6, 22.1, 21.8, 20.6, 18.7; HRMS (ESI) m/z cald for $C_{20}H_{31}O^+$ $[M+H]^+$ 286.2375, found 287.2375; $[\alpha]_D^{25}$ = + 70 ° (*c* 0.27, $CHCl_3$).

ASSOCIATED CONTENT

Supporting Information.

The NMR spectra of corresponding compounds **2–7, 9–16,** and X-ray data for **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

[1] Itokawa, H; Lee, K.-H. *Taxus: The Genus Taxus*; Taylor & Francis: London and New York, 2003.
[2] Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nature Chem.* **2012**, *4*, 21.
[3] Magnus, P.; Westwood, N.; Spyvee, M.; Frost, C.; Linnane, P.; Tavares, F.; Lynch, V. *Tetrahedron* **1999**, *55*, 6435.
[4] Laurent, A.; Villava-Serin, N. P.; Forgione, P.; Wilson, P. D.; Smil. D. V.; Fallis, A. G. Fallis et al., *Can J. Chem.* **2004**, *82*, 215.
[5] Barnhart, R.; Ironside, M. D.; Vogt, P. F. *Org. Process Res. Dev.* **2011**, *15*, 1407.
[6] Petersson, M. J.; Marchal, C.; Loughlin, W. A.; Jenkins, I. D.; Healy, P. C.; Almesaker, A. *Tetrahedron* **2007**, *63*, 1395.
[7] Park, I-H; So, M. S.; Park, K. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 1515.
[8] Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019.
[9] Lipshutz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283.
[10] Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647.
[11] Kobayashi, S.; Hachiya, I.; Yamanoi, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2342.
[12] Funel, J. A.; Abele, S. *Angew. Chem. Int. Ed.* **2013,** *52*, 3822.
[13] Color scheme: C grey, O red, H white. Hydrogen atoms were omitted for clarity except two most stereochemically important ones.
[14] Reeder, M. R.; Gleaves, H. E.; Hoover, S. A.; Imbordino, R. J.; Pangborn, J. J. *Org. Process Res. Dev.* **2003**, *7*, 696.