Studies on the Biosynthesis of Taxol. Synthesis of Taxa-4(20),11(12)-diene-2α,5α-diol

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The synthesis of taxa-4(20),11(12)-diene-2α,5α-diol is described. An improved procedure for the intramolecular Diels−Alder cycloaddition previously reported in our synthesis of taxa-4(5),11(12)-diene has been utilized to prepare a taxoid with oxygenation in the B and C rings. It has been established previously that taxa-4(20),11(12)-dien-5α-ol is the first oxygenated intermediate on the biosynthetic pathway to Taxol. Taxa-4(20),11(12)-diene-2α,5α-diol (**5**), which has been observed in a biosynthetic conversion, is a potential candidate as the second oxygenated intermediate on the Taxol biosynthetic pathway, has been prepared to probe the intermediacy of this substance.

Introduction

The approval of Taxol (paclitaxel, **1**) as a therapeutic agent against ovarian and other types of cancer[1] has continued to elicit interest in both the synthesis and biosynthesis of this agent (paclitaxel is the generic name for Taxol, a registered trademark of Bristol-Myers Squibb; because of its greater familiarity, "Taxol" is used throughout). A diverse retinue of approaches for the synthesis of the taxane framework[2] and for Taxol itself[3] have evolved but the complexity of the fascinating structure of Taxol mandates lengthy syntheses, that result in low overall yields rendering totally synthetic approaches to this agent impractical for large-scale preparation. The Pacific yew, *Taxus brevifolia* Nutt., the initial source for commercial scale production of Taxol, grows in environmentally sensitive areas of the Pacific Northwest and has become an untenable source for Taxol production. Alternative approaches for Taxol production such as semisynthesis from 10-deacetylbaccatin III,[4] that can be isolated from the needles of the European yew *Taxus baccata*, a renewable resource, has been adopted as the current commercial method for Taxol production. However, as the drug becomes more widely adopted for other types of cancer, pressure on the yew population worldwide is expected to increase significantly. Recent interest has therefore focused on alternative biological methods for Taxol production such as emerging technologies based on the genetic manipulation of *Taxus* sp. cell cultures. To fully gain command of Taxol biosynthesis in genetically engineered *Taxus* sp. cell culture systems, a detailed understanding of the steps of Taxol biosynthesis and the identification of the associated genes is essential.

Croteau[5] and associates have isolated taxa-4(5),11(12)-diene (**3**) from a bark extract of *T. brevifolia* and demonstrated that this compound and not taxa-4(20),11(12)-diene, as had been long speculated, is the first committed intermediate in the biosynthesis of Taxol. Soon thereafter, Croteau and Williams et al.[6] reported the isolation of taxa-4(20),11(12)-dien-5α-ol (**4**) (Scheme 1) from microsomal enzymes of *Taxus* stem and cultured cells. This compound proved to be the first oxygenated intermediate in the biosynthetic pathway by in vivo incorporation experiments, and its structure was confirmed by total synthesis.[6]

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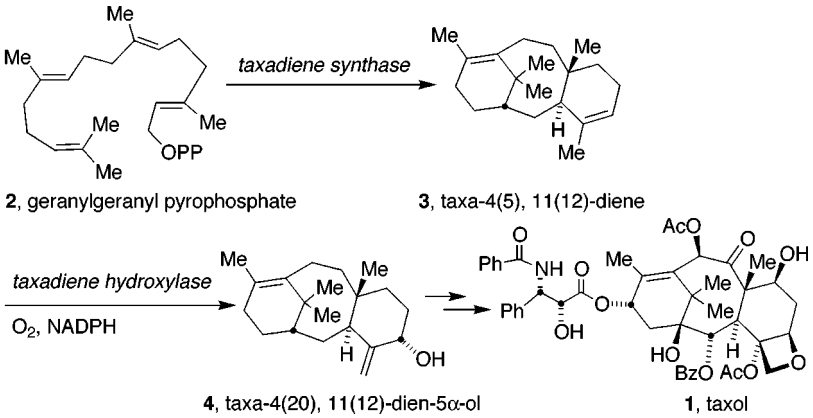
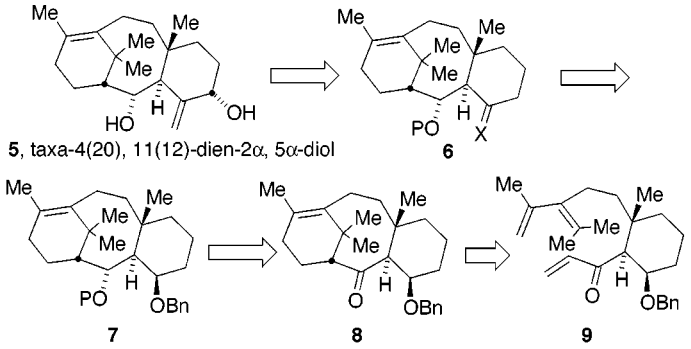
Scheme 1



Scheme 2



Synthetic tritium-labeled **3** and **4**[8b] have been employed as substrates in both *Taxus* sp. microsomes as well as using recombinant enzymes for the identification of lightly oxygenated taxoids downstream from **4**. Due to the very low yields of intermediate metabolites obtainable from these bioconversion procedures, we have been compelled to embark on synthetic routes to potential candidate metabolites as a means of aiding in the structure determination of more highly oxygenated taxoids. Based on metabolite co-occurrence,[7] we targeted taxa-4(20),11(12)-diene-2α,5α-diol and taxa-4(20),11(12)-diene-10α(or 10*β*),5α-diol as likely diol candidates. Herein, we wish to report the first synthesis of taxa-4(20),11(12)-diene-2α,5α-diol (**5**).

Results and Discussion

In 1995, our laboratory reported[8] the total synthesis of taxa-4(20),11(2)-diene (**3**), the first committed intermediate in the biosynthesis of Taxol, from readily available starting materials. We have since sought to develop a versatile synthetic method to provide gram quantities of the C-20 framework that would be amenable for the preparation of isotopically labeled congeners. We envisioned recruting an advanced intermediate from our previously reported synthesis for the preparation of taxa-4(20),11(12)-diene-2α,5α-diol (**5**). Our strategy (Scheme 2) relies on the construction of the A−B ring system of the taxane framework via an intramolecular Diels−Alder reaction similar to that originally reported by Shea and later by Jenkins.[9] A series of functional group manipulations of the C-2 ketone (**8**) prior to the allylic hydroxylation at C-5 (Taxol numbering) was considered to be an expedient route.

The synthesis started with the Diels−Alder reaction of **9** under the conditions previously reported (BF_3·Et_2O, 2 equiv, toluene, −23 °C)[7] to provide adduct **8** in 25−30% yield. The low yield of this reaction proved to be the critical bottleneck in securing multigram quantities of the taxoid ring system and was intensively investigated for improvement. After investigating the use of several catalysts and conditions for the Diels−Alder reaction, we found that by using the conditions employed by Winkler[10] (BF_3·Et_2O, 6 equiv, 0.005 M), for a substrate structurally related to **9**, the reaction yield was increased to 60%. Reduction of **8** ($LiAlH_4$, THF, 0 °C) afforded exclusively alcohol **10** in nearly quantitative yield (Scheme 3).

Initial attempts to invert the stereochemistry of **10** at C-2 under Mitsunobu reaction conditions designed for sterically hindered alcohols,[11] (Ph_3P/DEAD/4-$NO_2C_6H_4$-COOH/THF) resulted in the recovery of unreacted start-

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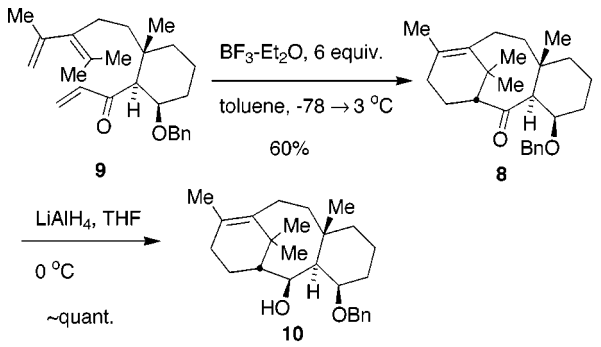
Scheme 3



ing material. Additionally, attempts to mesylate alcohol **10** under standard conditions ($MsCl/Et_3N/CH_2Cl_2$ or $NaN(TMS)_2$, MsCl, THF) were unsuccessful and only starting material was recovered, presumably as a result of the sterically demanding environment at C-2. It became clear at this point that establishing the correct stereochemistry at C-2 was a problem that needed to be solved at the earliest possible stage. During the course of synthetic studies on Taxol, Wender[12] reported the dissolving metal reduction of a substrate structurally related to **8** affording a mixture of α- and *β*-epimeric alcohols. Indeed, reduction of ketone **8** ($Na^0/EtOH/Et_2O$) resulted in a 1.3:1 separable mixture (flash column silica gel chromatography) of **10** and **11** respectively in 58% yield, along with unreacted starting material (13%). We found that when the reduction of **8** is conducted at −40 °C the ratio **10**:**11** can be reversed to 1:1.3 and the yield increased to 79% (Scheme 4).

Conversion of **11** into the corresponding TBS ether[13] (TBSOTf, 2,6-lutidine, CH_2Cl_2, 75%),[14] followed by removal of the benzyl protecting group under Birch-type reduction conditions (Na^0, NH_3, THF, −78 °C),[15] resulted in a mixture of compounds as a consequence of 1,3-silyl group migration.[16] Since we planed to unmask the hydroxyl group at C-2 after the allylic oxidation step, the selection of the appropriate protecting group was critical. Next, a MEM ether ((2-methoxyethoxy)methyl) was investigated under the premise that this group could be removed under mild conditions.[17] Reaction of **11** with MEM-Cl (DIPEA, CH_2Cl_2), afforded the corresponding MEM ether in 83% yield. This substrate was taken through a series of steps related to that shown in Scheme 5 (to a substrate corresponding to compound **17**) for the successful SEM-protected series. However, despite considerable effort, we were unable to remove the MEM ether to produce synthetically useful quantities of **5**. We also attempted to protect **11** as its 4-methoxytetrahydropyranyl ether[18] and as its *β*-trimethylsilyl ether.[19] Both tacts proved unsuccessful and only unreacted starting material was recovered from numerous attempts to protect **11** with these blocking groups.

The protecting group that proved to meet our expectations was SEM ((2-trimethylsilylethoxy)methyl) (Scheme 5). When **11** was allowed to react with SEM-Cl (Bu_4NI, DIPEA, CH_2Cl_2, reflux)[20] the corresponding SEM ether **12** was obtained in 80% yield. Removal of the benzyl protecting group (Na^0/NH_3/THF/EtOH/-78 °C) was achieved in 82% yield, followed by Dess−Martin periodinane oxidation (90%).[21] Addition of $TMSCH_2MgCl$[22] (THF, reflux) gave **15** as a single diastereomer in 97% yield, that was eliminated (KH, THF, reflux)[23] to provide taxadiene **16** in 91% yield. Since we anticipated some difficulties for the removal of the SEM protective group after the hydroxylation step, we decided to carry out the deprotection before the oxidation with SeO_2. Using the Lipshutz protocol[24] to remove the SEM group (TBAF, 4 Å molecular sieves, DMPU, 55 °C), we were able to obtain **17** in 25% yield, along with unreacted **16** (50%). When the same reaction was conducted at 80 °C, **17** was obtained in 72% yield, along with a side product identified as protodesilylated **16** in 18% yield.

The difficulties observed during the protection of the hydroxyl group at C-2 (vide supra) suggested that protection might not be required for the C-2 hydroxyl group during the hydroxylation reaction at C-5. Indeed diol **5** was obtained smoothly in 55% yield upon direct hydroxylation of **17** (SeO_2, *t*-BuOOH, AcOH, toluene).[25] The relative stereochemistry of **5** was confirmed by ^1H NMR NOE experiments. Upon irradiation of the signal corresponding to HC-5, a 0.4%, 0.5%, and 0.8% enhancement was observed for the signals of HC-2, H_3C-19, and HC-20, respectively. Irradiation of HC-2 produced a 1.3%, 0.5%, 1.3%, and 0.9% enhancement on the signals of HC-1, HC-5, H_3C-17, and H_3C-19, respectively (Table 1).

In summary, taxa-4(20),11(12)-diene-2α,5α-diol (**5**) has been efficiently prepared from the readily available ketone **9**. The synthetic methodology described here is amenable for the preparation of isotopically labeled congeners that would be required for biological studies. Microsomal bioconversion of taxa-4(20),11(12)-dien-5α-ol in *Taxus* sp. has very recently been observed to produce a metabolite identical (GC−MS) with the synthetic taxa-4(20),11(12)-diene-2α,5α-diol.[26] Possession of the synthetic material proved invaluable for securing the identity of this new natural taxoid that is produced in only minute amounts in *Taxus* sp. microsomes. The synthesis recorded here is currently being utilized to prepare radiolabeled material that will be used to probe further steps in the biosynthesis of Taxol and will be reported on in due course.

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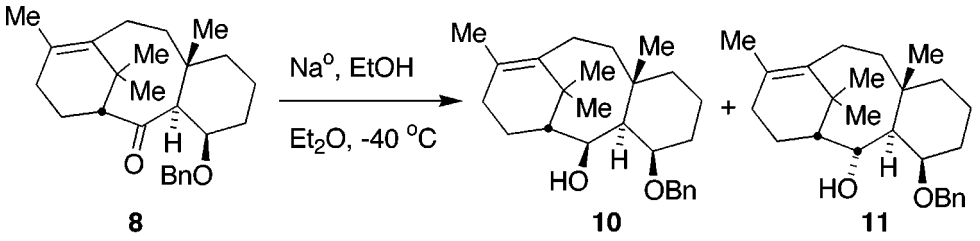
(26) Details of the isolation of **5** from *Taxus* sp. microsomes will be reported elsewhere.

Scheme 4



Scheme 5

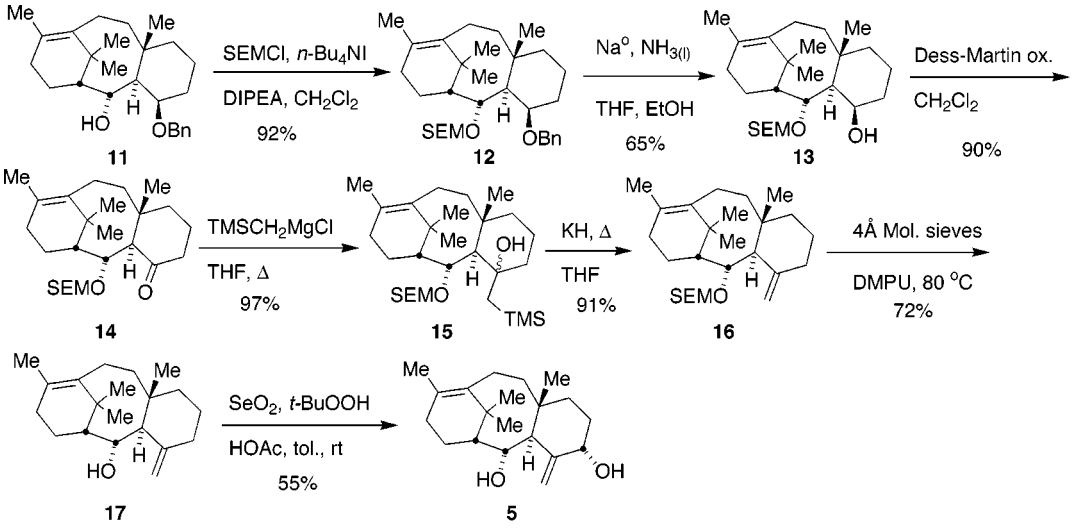
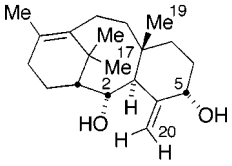


Table 1. ^{1}H NMR NOE Enhancements



5

signal irradiated	H	NOE, %
HC-5	C-2	0.4
HC-5	C-19	0.5
HC-5	C-20	0.8
HC-2	C-1	1.3
HC-2	C-5	0.5
HC-2	C-17	1.3
HC-2	C-19	0.9

Experimental

Diels−Alder Adduct 8. Boron trifluoride diethyl etherate (0.58 mL, 4.73 mmol) was added dropwise to a solution of **9** (300 mg, 0.788 mmol) in toluene (158 mL) at −78 °C. After 15 min, the dry ice/acetone bath was removed, and the stirring continued for 67 h at 3 °C. The reaction was quenched with saturated $NaHCO_3$ (50 mL), the two phases were separated, and the aqueous layer was extracted with 50% EtOAc/hexanes. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Two experiments were run in parallel. After the work up, the crude products were combined and fractionated by FCC (silica gel, 5% ether/hexanes) to provide 360 mg (60%) of **8** as a light yellow oil, which solidified upon standing. See Supporting Information for physical data.

Alcohol 11. Sodium (250 mg, 10.86 mmol) was added to a solution of ketone **8** (250 mg, 0.657 mmol) in Et_2O (22 mL) at −40 °C, followed by the addition of absolute EtOH (1.9 mL, 32.4 mmol). After 1 h, more sodium (203 mg) was added, followed by absolute EtOH, and the stirring continued for an additional 1.5 h. The reaction mixture was quenched with MeOH, acidified with 1 N HCl to pH 3, and extracted with 50% EtOAc/hexanes (3×). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was fractionated by FCC (silica gel, 5% EtOAc/hexanes) to provide 110 mg of **11** (44%) and 88 mg (35%) of the β-alcohol **10**: $R_f = 0.28$ (10% EtOAc/hexanes); IR (NaCl) ν_{max} 3516, 1454, 1082 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.29 (5H, m), 4.66(1H, d, J = 11.5 Hz), 4.27 (1H, d, J = 11.5 Hz), 4.09 (1H, m), 3.99 (1H, m), 3.91 (1H, s), 2.78 (1H, ddd, J = 13.5, 13.5, 6.0 Hz), 2.47 (1H, m), 2.43 (1H, m), 2.24−2.19 (1H, m), 2.09−2.01 (1H, m), 2.00−1.70 (6H, m), 1.77 (3H, s), 1.53 (1H, m), 1.43 (3H, s), 1.33−1.22 (3H, m), 1.12 (3H, s), 1.09 (3H, s), 1.03 (1H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 138.4, 137.0, 130.3, 128.5, 127.6, 127.3, 79.1, 70.6, 70.5, 50.5, 44.7, 40.8, 38.2 (2×), 38.1, 31.3, 30.2, 28.4, 25.5, 25.3, 25.1, 22.1, 17.9, 17.6; HRMS (FAB) m/z calcd for $C_{26}H_{38}O_2$ 382.2872, found 382.2862.

SEM Ether 12. To a mixture of alcohol **11** (55 mg, 0.144 mmol), Bu_4NI (27 mg, 0.072 mmol), and diisopropylethylamine (DIPEA) (88 μL, 0.504 mmol) in CH_2Cl_2 (1.4 mL) was added SEMCl (76 μL, 0.432 mmol) at ambient temperature. The resulting mixture was heated at 50 °C for 24 h, cooled to room temperature, and then partitionated between 50% EtOAc/hexanes and H_2O (1:1). The two phases were separated, and the organic layer was extracted with 50% EtOAc/hexanes. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was fractionated by FCC (silica gel, 2% EtOAc/hexanes) to yield 60 mg (80%) of **12**: $R_f = 0.54$ (10% EtOAc/hexanes); IR (NaCl) ν_{max} 1249, 1099, 1062, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.23 (5H, m), 4.67 (1H, d, J = 7.5 Hz), 4.44 (1H, d, J = 12 Hz), 4.40 (1H, d, J = 7.5 Hz), 4.25 (1H, d, J = 12 Hz), 3.80 (1H, d, J = 3.5 Hz), 3.71 (1H, m), 3.71−3.65 (1H, m), 3.38−3.32 (1H, m), 2.71 (1H, ddd, J = 13.5, 13.5, 5.5 Hz), 2.34 (1H, m), 2.28 (1H, dd, J = 3.5, 2 Hz), 2.01−1.61 (9H, m), 1.70 (3H, s), 1.37 (3H, s), 1.22−1.01 (3H, m), 1.07 (3H, s), 1.03 (3H, s), 1.00−0.95(1H, m), 0.93−0.76 (2H, m), −0.05 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 140.1, 136.6, 130.0, 128.2, 126.8, 126.6,

95.3, 77.5, 71.1, 65.2, 64.8, 51.7, 46.2, 41.1, 38.2, 38.1, 38.0, 31.4, 30.1, 29.8, 26.4, 25.5, 25.1, 22.2, 18.5, 18.4, 18.1, −1.2; HRMS (FAB) *m*/*z* calcd for $C_{32}H_{53}O_3Si$ (M + H) 513.3764, found 513.3745.

Alcohol 13. Sodium (80 mg, 3.48 g atm) was added portionwise to a mixture of benzyl ether **12** (48 mg, 0.094 mmol) and absolute EtOH (55 μL, 0.94 mmol), in THF (4 mL) and NH_3 (4 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 3 h and then quenched by slow addition of solid NH_4Cl. The dry ice/acetone bath was removed, and the excess ammonia was allowed to evaporate. The solid residue was dissolved in H_2O and extracted with 50% EtOAC/hexanes (3×). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was fractionated by FCC (silica gel, 5% EtOAc/hexanes) to afford 32 mg (82%) of **13**: R_f = 0.32 (10% EtOAc/hexanes); IR (NaCl) ν_{max} 3563, 1250, 1019, 860, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (1H, 1/2ABq, *J* = 6.5 Hz), 4.66 (1H, 1/2 ABq, *J* = 6.5 Hz), 4.08 (1H, br s), 3.87 (1H, m), 3.66−3.50 (2H, m), 3.35 (1H, br s), 2.70 (1H, ddd, *J* = 13.5, 13.5, 5 Hz), 2.28 (1H, m), 2.25 (1H, m), 1.99−1.60 (9H, m), 1.68 (3H, s), 1.35 (3H, s), 1.31−1.14 (3H, m), 1.07 (3H, s), 1.03 (3H, s), 1.00−0.86 (3H, m), −0.02 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 136.8, 130.8, 93.9, 78.1, 69.6, 66.2, 47.6, 44.4, 41.2, 38.3, 38.2, 38.0, 33.5, 31.3, 30.0, 25.3, 25.2, 25.0, 22.1, 18.5, 17.9, 17.6, −1.2; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{46}O_3Si$ 422.3216, found 422.3230.

Ketone 14. Dess−Martin periodinane (60 mg, 0.142 mmol) was added to a solution of **13** (30 mg, 0.071 mmol) in CH_2Cl_2 (2.4 mL) at ambient temperature. After 1h, the reaction was diluted with Et_2O (3 mL) and sat $NaHCO_3$ (3 mL), followed by the addition of $Na_2S_2O_3 \cdot 5H_2O$ (141 mg, 0.568 mmol). The resultant heterogeneous mixture was stirred for 15 min and then extracted with CH_2Cl_2 (3×); the organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was fractionated by FCC (silica gel, 10% EtOAc/hexanes) to provide 27 mg (90%) of **14** as a colorless oil, which solidified upon standing: R_f = 0.21 (10% EtOAc/hexanes); IR (NaCl) ν_{max} 1716, 1031, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (1H, 1/2 ABq, *J* = 7.5 Hz), 4.63 (1H, 1/2 ABq, *J* = 7.5 Hz), 3.99 (1H, dd, *J* = 6.0, 2.5 Hz), 3.67−3.60 (1H, m), 3.57−3.50 (1H, m), 2.93 (1H, d, *J* = 6 Hz), 2.62 (1H, ddd, *J* = 13.5, 13.5, 6 Hz), 2.43−2.33 (2H, m), 2.21−2.13 (2H, m), 2.05−1.90 (3H, m), 1.88−1.83 (3H, m), 1.76 (3H, s), 1.70−1.62 (1H, m), 1.52 (2H, t, *J* = 6.5 Hz), 1.36 (3H, s), 1.22 (1H, dd, *J* = 13.5, 4.5 Hz), 1.13 (3H, s), 1.07 (3H, s), 0.96−0.87 (2H, m), 0.16 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 212.4, 135.7, 131.2, 94.6, 76.7, 65.5, 57.3, 50.9, 42.0, 41.4, 39.5, 38.1, 37.7, 30.6, 29.5, 26.8, 24.0, 22.4, 22.1, 21.1, 18.4, 17.9, −1.2; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{45}O_3Si$ (M + H) 421.3138, found 421.3125.

Alcohol 15. To a solution of ketone **14** (25 mg, 0.059 mmol) in THF (2.5 mL) was added a 1 M solution of $TMSCH_2MgCl$ in Et_2O (0.6 mL, 0.59 mmol) at 0 °C. The resulting mixture was refluxed for 3 h, cooled to ambient temperature, quenched with saturated NH_4Cl, and extracted with 50% EtOAc/hexanes (3×). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was fractionated by FCC (silica gel, 10% EtOAc/hexanes) to provide 29 mg (97%) of **15** as a single diasteromer: R_f = 0.60 (10% EtOAc/hexanes); IR (NaCl) ν_{max} 3550, 1246, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (1H, 1/2 ABq, *J* = 6.5 Hz), 4.68 (1H, 1/2 ABq, *J* = 6.5 Hz), 4.05 (1H, br s), 3.69−3.57 (2H, m), 3.29 (1H, d, *J* = 2.5 Hz), 2.70 (1H, ddd, *J* = 15, 15, 6 Hz), 2.31−2.24 (1H, m), 2.19−2.12 (1H, m), 2.18 (1H, d, *J* = 14 Hz), 2.04−1.76 (8H, m), 1.68 (3H, s), 1.64−1.57(1H, m), 1.42 (3H, s), 1.40−1.32 (1H, m), 1.17−1.05 (2H, m), 1.11 (3H, s), 1.08 (3H, s), 1.02−0.94 (1H, m), 0.95 (2H, m), 0.65 (1H, d, *J* = 14 Hz), 0.05 (9H, s), 0.02 (9H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 136.9, 130.0, 94.4, 81.1, 76.4, 66.5, 49.5, 47.7, 42.1, 41.5, 40.3, 38.9, 38.1, 35.5, 32.2, 29.8, 25.5, 24.9, 24.8, 21.8, 19.2, 18.7, 18.5, 1.4, −1.2; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{56}O_3Si_2$ 508.3768, found 508.3788.

Taxadiene 16. A solution of alcohol **15** (28 mg, 0.055 mmol) in THF (2.0 mL) was treated with excess of KH (35% oil, approximately 50 mg) at reflux temperature for 1 h. The reaction mixture was cooled to ambient temperature and quenched by careful addition of MeOH and then extracted with 50% EtOAc/hexanes (3×). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was fractionated by FCC (silica gel, hexanes to 5% EtOAc/hexanes) to afford 21 mg (91%) of **16** as a light yellow oil: R_f = 0.60 (10% EtOAc/hexanes); IR (NaCl) ν_{max} 1636, 1249, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (1H, dd, *J* = 2.5, 1 Hz), 4.81 (1H, d, *J* = 2.5 Hz), 4.68 (1H, 1/2 ABq, *J* = 7 Hz), 4.64 (1H, 1/2 ABq, *J* = 7 Hz), 3.97 (1H, dd, *J* = 4.5, 1 Hz), 3.64−3.60 (2H, m), 2.77 (1H, d, *J* = 4.5 Hz), 2.69 (1H, ddd, *J* = 23.5, 18, 4.5 Hz), 2.44−2.32 (1H, m), 2.18−2.09 (2H, m), 1.96−1.83 (4H, m), 1.80−1.68 (3H, m), 1.78 (3H, s), 1.65−1.58 (2H, m), 1.40 (3H, s), 1.40−1.33 (1H, m), 1.11 (1H, m), 1.08 (3H, s), 0.96−0.91 (2H, M), 0.94 (3H, S), 0.02 (9H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 149.0, 136.3, 130.8, 110.8, 93.9, 77.4, 65.7, 50.7, 48.2, 40.7, 40.6, 38.4, 38.3, 38.1, 30.8, 30.1, 26.2, 24.5, 23.7, 23.5, 22.4, 18.4, 18.3, −1.2; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{46}O_2Si$ 418.3267, found 418.3260.

Taxa-5(20),11(12)-dien-2α-ol (17). A 1M solution of TBAF in THF (240 μL, 0.24 mmol) was added to the SEM ether **16** (20 mg, 0.048 mmol) and the mixture concentrated in vacuo. The residue was dissolved in dry DMPU (0.5 mL), and 4 Å molecular sieves (40 mg) were added. The resulting mixture was heated at 80 °C for 18 h and cooled to ambient temperature, and the molecular sieves wereremoved by filtration. The filtrate and washings were combined, diluted with H_2O, and extracted with 50% Et_2O/hexanes (3×). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was fractionated by FCC (silica gel, 2% EtOAc/hexanes) to give 10 mg (72%) of alcohol **17**: R_f = 0.28 10% EtOAc/hexanes; IR (NaCl) ν_{max} 3482, 1636, 1461, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (1H, br s), 4.74 (1H, m), 3.94 (1H, ddd, *J* = 8, 6, 2.5 Hz), 2.64 (1H, d, *J* = 6 Hz), 2.58−2.50 (1H, m), 2.44−2.34 (1H, m), 2.23−2.13 (3H, m), 2.05−1.82 (4H, m), 1.73 (3H,s), 1.78−1.66 (1H, m), 1.64−1.46 (4H, m), 1.37 (3H, s), 1.36−1.33 (1H, m), 1.10 (3H, s), 1.07 (3H, s), 1.05−1.02 (1H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 151.4, 136.5, 130.1, 112.1, 69.2, 54.5, 51.0, 42.1, 39.3, 38.9, 37.7, 32.2, 30.7, 29.4, 27.0, 23.9, 22.3, 22.0, 21.3, 17.6; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{32}O$ 288.2453, found 288.2457.

Taxa-5(20),11(12)-diene-2α,5α-diol (5). A 1M solution of *t*-BuOOH in toluene (90 μL, 0.09 mmol) was added to a mixture of taxadiene **17** (9 mg, 0.03 mmol), SeO_2 (Aldrich, 99.9%) (1.7 mg, 0.015 mmol), and 1 M AcOH/toluene (30 μL, 0.03 mmol) in toluene (0.5 mL) at ambient temperature. The stirring was continued for 18 h at that temperature, and then the reaction was diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was fractionated by FCC (silica gel, 40% EtOAc/hexanes) to yield 5 mg (55%) of **5** as a white solid: R_f = 0.25 (50% EtOAc/hexanes); IR (NaCl) ν_{max} 3320, 1636, 1461, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (1H, m), 4.88 (1H, br s), 4.37 (1H, m), 3.94 (1H, m), 2.94 (1H, d, *J* = 5.5 Hz), 2.60−2.54 (1H, m), 2.46−2.34 (1H, m), 2.21−2.09 (2H, m), 2.10−1.93 (3H, m), 1.91−184 (1H, m), 1.75 (3H, s), 1.73−1.64 (2H, m), 1.56 (1H, ddd, *J* = 15, 10, 5.5 Hz), 1.45−1.36 (2H, m), 1.37 (3H, m), 1.08 (3H, s), 1.07 (3H, s), 1.04 (1H, dd, *J* = 1.0, 6.5 Hz); ^{13}C NMR (400 MHz, $CDCl_3$ δ 154.0, 135.8, 130.6, 109.2, 70.7, 69.5, 54.6, 48.4, 41.9, 39.5, 38.0, 37.8, 31.0, 30.7, 29.4, 26.9, 24.1, 22.6, 21.8, 17.5; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2390.

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Supporting Information Available: ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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