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Enantioselective Synthesis of an Oxa-Taxane Derivative *via* Tandem Intramolecular [2+2] Cycloaddition and [3, 3]-Sigmatropic Rearrangement of Allenyl Ether

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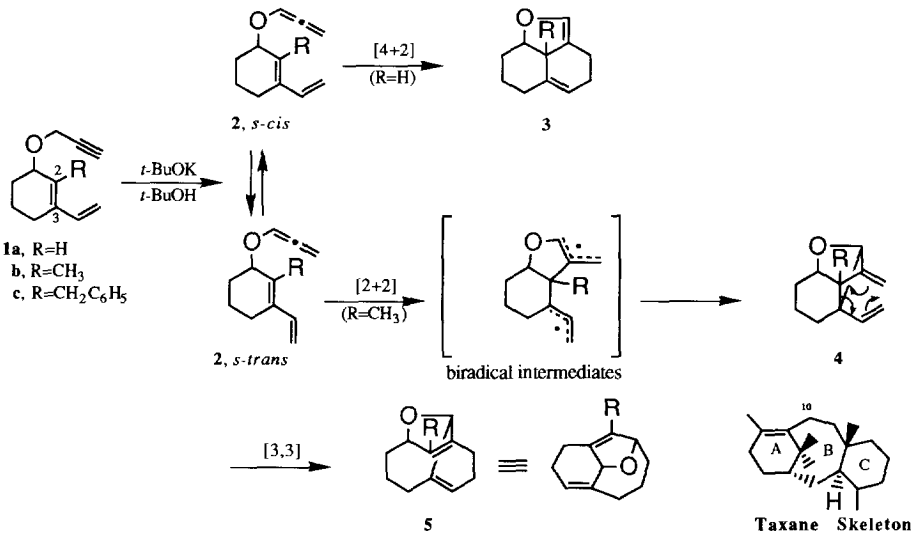
Abstract: A novel construction of the oxa-taxane skeleton *via* the intramolecular cycloaddition of allenyl ether is described.

Taxol, the family of taxane diterpenoids, was originally isolated from the Pacific yew tree (*Taxus brevifolia*) in 1964.[1] These compounds exhibit potent antitumor activities by inhibiting mitosis through an enhancement of the polymerization of tublin and consequent stabilization of microtubules.[2] The taxane diterpenes have a unique tricyclo [9, 3, 1, $0^{3,8}$] pentadecane skeleton and are the most challenging targets in synthetic organic chemistry. Studies of taxol and other taxane diterpenoids have been summarized in several reviews.[3]

Recently, the total synthesis of taxol was achieved by R. A. Holton[4] and K. C. Nicolaou[5] at almost the same time. The former adapted a linear synthetic route, which involved annulation of ring C onto the AB intermediate (AB to ABC approach), while the latter adapted a convergent route, where the coupling of A- and C-ring fragments was followed by cyclization to form the B-ring (AC to ABC approach). Increased interest in the antitumor potential of taxol, coupled with the synthetic challenge offered by a molecule of taxol, has attracted the attention of many synthetic chemists, and structure-activity studies will help to clarify the mode of action of taxane diterpenes.

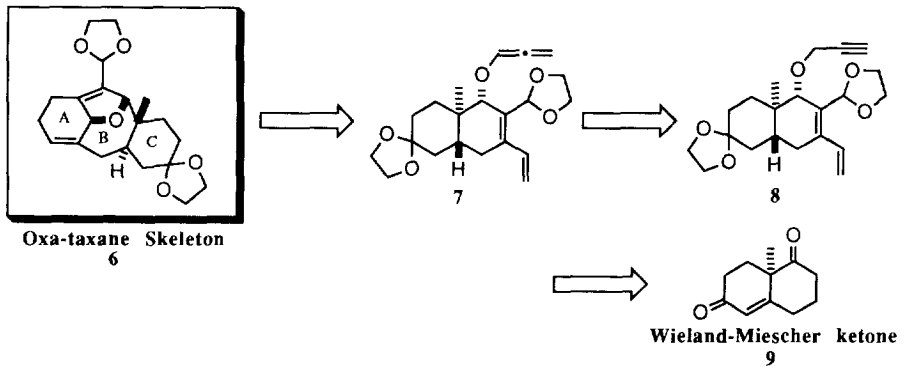
Previously, we developed the tandem [2+2] cycloaddition-[3, 3]-sigmatropic rearrangement of allenyl ethers and semicyclic dienes to produce a bicyclo [n, 3, 3, 1] ring system.[6,7] During the course of our study, we found dramatic substituent effects in the intramolecular cycloaddition of allenyl ethers **1**.[6] The key feature of those effects was the switching of the reaction pathway depending on a substituent at the C-2 position. The substituents at the C-2 position would sterically disfavor the *s-cis* conformation of **2** and preclude any normal [4+2] cycloaddition. Consequently, the base-catalyzed reaction of **1a** (R=H) exclusively afforded the [4+2] adducts **3**, however, the compounds **1b-1c** bearing a substituent at the C-2 position resulted in the novel products **5**. The formation of **5** can be explained by a [2+2] cycloaddition of **2** followed by the [3, 3]-sigmatropic rearrangement (Cope rearrangement). Presumably, the [2+2] cycloaddition of the allenyl ether **2**, which was formed by the base-catalyzed isomerization of **1**, afforded the intermediate **4** through a stepwise biradical intermediate (Scheme 1). This reaction can be characterized by special advantages including procedural simplicity, mild reaction conditions, high efficiency, and the predictable stereochemistry of the product. The obtained bicyclo ring system corresponds to the A and B rings of the taxane skeleton, and the application of this reaction to bicyclic allenyl ether affords the functionalized oxa-taxane skeleton, which can be a precursor of taxane derivatives.

Scheme 1



As a means of demonstrating the usefulness of our synthetic strategy for the taxane skeleton, we herein report the enantioselective synthesis of the oxa-taxane skeleton *via* the tandem intramolecular [2+2] cycloaddition-[3, 3]-sigmatropic rearrangement, whilst describing the full details of previously undisclosed data for the cycloaddition reactions of allenes.[7] Retrosynthetic analysis of the taxane skeleton is shown in Scheme 2: the

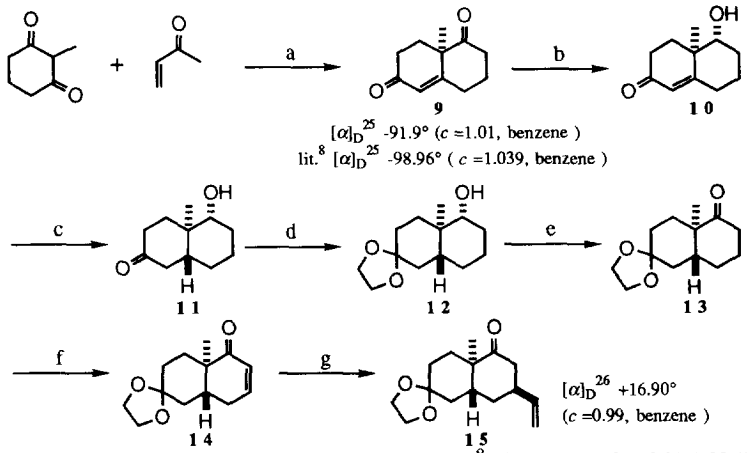
Scheme 2



synthesis of **6** possessing an oxa-taxane skeleton should be achieved by our tandem intramolecular [2+2] cycloaddition and [3, 3]-sigmatropic rearrangement of the bicyclic allenyl ether **7**, which would be obtained from readily available optically pure Wieland-Miescher ketone.

The optically pure (8a*R*)-(-)-Wieland-Miescher ketone **9**, which was prepared by Harada's method,[8] was used as the starting material (Scheme 3). Repeated recrystallization effected the purification of **9** which had a slightly lower optical purity ($[\alpha]_D^{25}$ -91.9° (*c*=1.01, benzene)) than reported in the literature[8] ($[\alpha]_D^{25}$ -98.96° (*c*=1.039, benzene)). The chemoselective reduction of **9** with $NaBH_4$ quantitatively afforded **10**, which was subjected to conjugate reduction of the enone moiety of **10**. The protection of the ketone group of **11** gave the 1, 3-dioxolane **12** in a quantitative yield. After oxidation of **12** with PDC in a quantitative yield, the obtained ketone **13** was converted to the enone **14** by selenylation at the α-position of the ketone followed by oxidative

Scheme 3



Reagents and Conditions: a) The same as Harada's method.[8]; b) $NaBH_4$, EtOH, 0 °C (100%); c) Li, *liq*. NH_3 (76%); d) $(CH_2OH)_2$, *p*-TsOH, benzene, Dean-Stark, 80 °C (100%); e) PDC, CH_2Cl_2 (100%); f) i) LDA, THF, -78 °C, then PhSeCl (100%); ii) 15% H_2O_2, Py, CH_2Cl_2, 0 °C (100%); g) CuI, $CH_2CHMgBr$, THF, -78 °C (88%).

elimination. The enone **14** was treated with vinylmagnesium bromide in the presence of copper (I) iodide to afford **15** in 88% yield. Then, the structure of the vinyl ketone **15** was confirmed by NOE correlation between the angular methyl proton and the C-7' methine proton as shown in Figure 1.

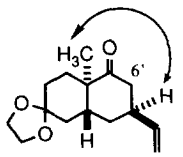
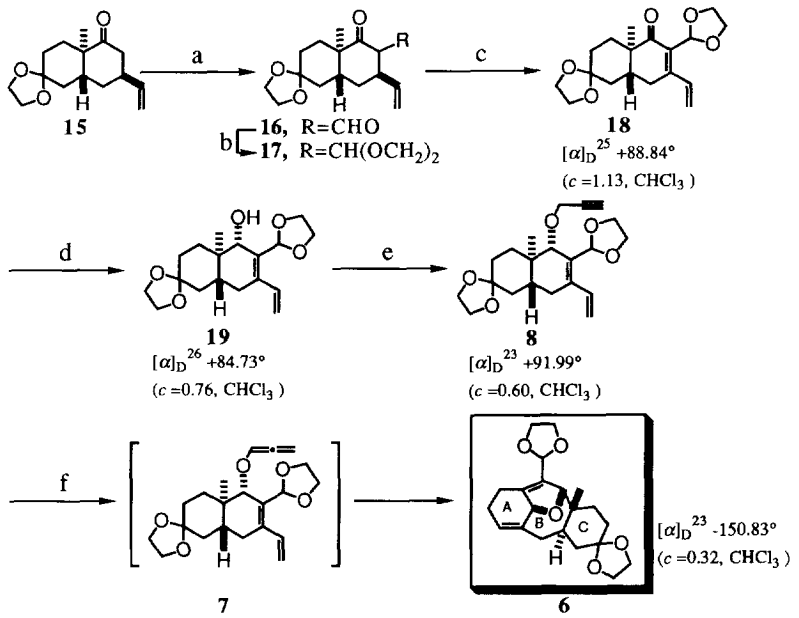


Figure 1

As mentioned above, the substituent at the C-6' position of the bicyclic allenyl ether which corresponds to the C-2 substituent of **1** (R_1 in Scheme 1) plays a crucial role in controlling the reaction pathway and in the introduction of the substituent, which enables the *s-trans* conformation of **2**, leading to the tandem [2+2] cycloaddition-[3, 3]-sigmatropic rearrangement. The C-2 position corresponds to the C-10 position in the taxane skeleton and the appropriate conversion of the C-2 substituent is necessary for successful taxane synthesis. The alkoxy substituent (*i.e.*, methoxy group) at the C-2 position is considered to be one of the most suitable substituents, since this can be directly converted to oxygen functionality at the C-10 position in the taxane skeleton. Against all our expectations, the propargyl ether possessing methoxy group at the C-6' position afforded the furan product through the intramolecular [4+2] cycloaddition and consecutive elimination of methanol.[9]

Next, the formyl group was introduced into the C-6' position of **15**. The propargyl ether **8**, which has a protected formyl group (*i.e.*, a 1, 3-dioxolane group), was prepared (Scheme 4). Treatment of **15** with ethyl formate in the presence of sodium hydride gave the β-keto aldehyde **16** (56%) as a keto-enol tautomer, which was then converted to **17** by the standard procedure.[10] The compound **18**, which has a tetra-substituted olefin, was synthesized from **17** by selenylation and oxidative elimination in a moderate yield. The selective 1, 2-reduction of the dienone **18** by DIBAL-H afforded **19** in 43% yield, while the consecutive propargylation in a two-phase system with Bu_4NHSO_4 gave **8** in 57% yield. Treatment of **8** with *t*-BuOK in *t*-BuOH resulted in a smooth isomerization to the allenyl ether **7**, which was directly converted to the [2+2] cycloaddition-[3, 3]-sigmatropic rearrangement product **6** ($[\alpha]_D^{23}$ -150.83° (*c*=0.32, $CHCl_3$)) in a quantitative yield.[11]

Scheme 4



Reagents and Conditions: a) NaH, THF, 0 °C, then HCO_2Et (56%); b) [=d) in Scheme 3] (68%); c) [=f) in Scheme 3] (15%); d) DIBAL-H, ether (43%); e) 50% NaOH, propargyl bromide, Bu_4NHSO_4, rt. (57%); f) *t*-BuOK, *t*-BuOH (100%).

Thus, we accomplished the synthesis of an optically active oxa-taxane compound by the use of optically pure Wieland-Miescher ketone. Further study on the cleavage of the oxa-taxane **6** for the synthesis of the enantiomerically pure taxane skeleton is now in progress.

EXPERIMENTAL

The melting points were measured with a Yanaco micromelting point apparatus and were uncorrected. The ^1H NMR spectra were taken with a JEOL JNM-GX 270 or Hitachi R-1500 spectrometer with TMS as an internal standard; chemical shifts are expressed in δ values. The ^{13}C NMR spectra were determined with a JEOL JNM-GX 270 spectrometer with TMS as an internal standard. IR spectra were obtained with a JASCO A-100 infrared spectrophotometer. Mass spectra were determined on a JEOL-D 300 or a DX 300 spectrometer. Elemental analyses were performed on a Yanagimoto MT2 CHN recorder. Each reaction was monitored by TLC (Kieselgel 60 F_{254} plates). Column chromatography was done with E. M. Merck kieselgel 60 (70-230 mesh) as the stationary phase.

All experiments dealing with air- and moisture-sensitive compounds were conducted under atmosphere of dry argon. All solvents were purified before use: ether and THF were distilled from sodium benzophenone ketyl; benzene and CH_2Cl_2 were distilled from calcium hydride.

(4a*R*,5*R*)-5-Hydroxy-4a-methyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (10). To a stirred solution of Wieland-Miescher ketone (**9**) (5 g, 28. 1 mmol), which was prepared by Harada's method,[8] in EtOH (40 ml) was added dropwise a suspension of $NaBH_4$ (300 mg, 7.94 mmol) in EtOH (60 ml) over 2 h with stirring at 0 °C. After the reaction mixture was stirred for 10 min at 0 °C, the resulting mixture was quenched by the addition of AcOH (3 ml). After dilution with water, EtOH was removed in vacuo. The residue was extracted twice with $CHCl_3$ and the combined organic layers were neutralized with saturated

$NaHCO_3$, washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=3:1) gave 5.0 g (100%) of **10** as colorless needles: mp 45-48 °C (from ethyl acetate/ether); ^1H NMR ($CDCl_3$, 60 MHz) δ 5.80 (br s, 1H), 3.55-3.43 (m, 1H), 2.52-1.64 (m, 11H), 1.21 (s, 3H); IR (KBr, cm^{-1}) 3400, 2940, 2850, 1650, 1610; Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.33; H, 8.97; $[\alpha]_D^{26}$ -198.5° (*c*=0.93, benzene).

(4a*R*,5*R*,8a*R*)-Octahydro-5-hydroxy-4a-methyl-2(1*H*)-naphthalenone (11). Liquid ammonia (300 ml) was poured into a three-necked flask at -78 °C. Lithium (1.155 g, 0.166 mol) was added in small portion. After 30 min, the lithium was dissolved and the solution of **10** (10 g, 55.5 mmol) in THF (130 ml) was added dropwise. After the reaction mixture was stirred for 30 min at -78 °C, ammonium chloride was added and the ammonia was allowed to evaporate. The residue was added to 5% HCl (160 ml), extracted twice with ether and the combined organic layers were neutralized with saturated $NaHCO_3$, washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=3:1) gave 7.68 g (76%) of **11** as colorless needles: mp 84-85 °C (from ether); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.29 (dd, *J*=11.22, 4.62 Hz, 1H), 2.49-2.30 (m, 2H), 2.27-2.12 (m, 3H), 1.82-1.71 (m, 2H), 1.64-1.22 (m, 7H), 1.04 (d, *J*=0.66 Hz, 3H); IR (KBr, cm^{-1}) 3300, 2920, 2850, 1710; Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.49; H, 9.90; $[\alpha]_D^{27}$ -52.96° (*c*=1.08, benzene).

(4'a*R*,5'*R*,8'a*R*)-Octahydro-4'a-methyl-spiro[1,3-dioxolane-2,2'(1'*H*)-naphthalen]-5'-ol (12). To a solution of **11** (3.1192 g, 17.1 mmol) in anhydrous benzene (75 ml) were added ethylene glycol (2.863 ml, 51.34 mmol) and small amount of *p*-TsOH and the resulting mixture was refluxed for 4 h with a Dean-Stark apparatus. After cooling to room temperature, the reaction mixture was washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=4:1) gave 3.87 g (100%) of **12** as colorless needles: mp 101-103 °C (from ether); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.95-3.94 (m, 4H), 3.27 (dd, *J*=11.04, 4.12 Hz, 1H), 1.85 (dd, *J*=12.87, 3.46 Hz, 1H), 1.75-1.64 (m, 4H), 1.60-1.26 (m, 7H), 1.21-1.12 (m, 2H), 0.84 (d, *J*=0.66 Hz, 3H); IR (KBr, cm^{-1}) 3470, 2970, 2920, 2850; Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.79. Found: C, 68.91; H, 9.70; $[\alpha]_D^{24}$ -15.7° (*c*=0.75, benzene).

(4'a*R*,8'a*R*)-Hexahydro-4'a-methyl-spiro[1,3-dioxolane-2,2'(1'*H*)-naphthalen]-5'(3'*H*)-one (13). To a stirred mixture of **12** (610 mg, 2.70 mmol) and $MgSO_4$ in absolute CH_2Cl_2 (50 ml) was added PDC (1.93 g, 5.13 mmol). The reaction mixture was stirred for 2 d at room temperature. The resulting mixture was filtered through silica gel with CH_2Cl_2. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=4:1) gave 605 mg (100%) of **13** as colorless crystals: mp 34 °C (from petroleum ether); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.98-3.89 (m, 4H), 2.70-2.57 (m, 1H), 2.26-2.19 (m, 1H), 2.07-1.98 (m, 1H), 1.85 (dt, *J*=12.20, 3.30 Hz, 1H), 1.77-1.51 (m, 8H), 1.46-1.41 (m, 1H), 1.13 (s, 3H); IR (neat, cm^{-1}) 2940, 2860, 1710, 1110, 1080; Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.50; H, 8.92; $[\alpha]_D^{25}$ +76.41° (*c*=1.17, benzene).

(4'a*R*,8'a*R*)-4',4'a,8',8'a-Tetrahydro-4'a-methyl-spiro[1,3-dioxolane-2,2'(1'*H*)-naphthalen]-5'(3'*H*)-one (14). To a stirred solution of LDA (39.81 mmol) at -78 °C, prepared from diisopropylamine (5.6 ml, 39.81 mmol) and butyllithium (1.5 M in hexane, 26.54 ml, 39.81 mmol) in dry THF (120 ml), was added a solution of **13** (5.95 g, 26.54 mmoi) in dry THF (60 ml). After stirring for 30 min, the reaction mixture was added dropwise to a solution of phenylselenenyl chloride (7.6 g, 39.81 mmol) in dry THF (30 ml), and the mixture was stirred for 10 min at 0 °C. The reaction mixture was poured into saturated NH_4Cl

and extracted twice with ether. The combined organic layers were neutralized with saturated $NaHCO_3$, washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=5:1) gave the α-selenyl ketone. Consecutively, the α-selenyl ketone was dissolved in CH_2Cl_2 (120 ml) and pyridine (30 ml) and 15% H_2O_2 (13 ml) were added. After the reaction mixture was stirred for 30 min at room temperature, the resulting mixture was poured into water and extracted twice with ether and the combined organic layers were washed with brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=4:1) gave 5.9 g (100% overall yield from **13**) of **14** as colorless needles: mp 81-82 °C (from ether/petroleum ether); IR (KBr, cm^{-1}) 2930, 2900, 2850, 1650; Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.22; H, 8.18; $[\alpha]_D^{25}$ +51.9° (*c*=0.967, $CHCl_3$).

(4'a*R*,7'*S*,8'a*R*)-7'-Ethenylhexahydro-4'a-methyl-spiro[1,3-dioxolane-2,2'-(1'*H*)-naphthalen]-5'(3'*H*)-one (15). To a stirred solution of cupper (I) iodide (15 mg) and dimethyl sulfide (0.4 ml) in dry THF (6 ml) was added vinylmagnesium bromide (1.0 M in THF, 4.59 ml, 4.59 mmol) at -78 °C. After 10 min, a solution of **14** (500 mg, 2.249 mmol) in dry THF (1 ml) was added dropwise and the mixture was stirred for 30 min at -78 °C. The resulting mixture was quenched by acetic acid and poured into water and extracted twice with ether. The combined organic layers were neutralized with saturated $NaHCO_3$, washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=4:1) gave 495 mg (88%) of **15** as colorless needles: mp 54-55 °C (from ethyl acetate); ^1H NMR ($CDCl_3$, 270 MHz) δ 5.80 (ddd, *J*=17.16, 10.56, 5.44 Hz, 1H), 5.07 (ddd, *J*=10.56, 1.32, 1.32 Hz, 1H), 5.03 (ddd, *J*=17.16, 1.32, 1.32 Hz, 1H), 3.97-3.89 (m, 4H), 2.90-2.87 (m, 1H), 2.81 (dd, *J*=14.51, 6.60 Hz, 1H), 2.37 (ddd, *J*=14.51, 1.97, 1.97 Hz, 1H), 2.05 (tt, *J*=12.70, 3.13 Hz, 1H), 1.92 (td, *J*=13.19, 5.28 Hz, 1H), 1.74-1.59 (m, 4H), 1.44 (tm, *J*=13.60 Hz, 2H), 1.13 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$, ppm) 214.6 (s), 140.9 (d), 115.3 (t), 108.4 (s), 64.2 (t), 64.1 (t), 47.2 (s), 40.4 (t), 37.9 (d), 36.8 (t), 36.5 (d), 31.9 (t), 30.4 (t), 29.8 (t), 14.9 (q); IR (KBr, cm^{-1}) 2950, 2930, 2875, 1700; Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.83; H, 8.81; $[\alpha]_D^{26}$ +16.90° (*c*=0.994, benzene).

(4'a*R*,7'*R*,8'a*R*)-7'-Ethenyloctahydro-4'a-methyl-5'-oxo-spiro[1,3-dioxolane-2,2'(1'*H*)-naphthalene]-6'-carboxaldehyde (16). A 100 ml round bottomed flask was charged with sodium hydride (60% dispersion in mineral oil) (734 mg, 18.74 mmol). The sodium hydride was washed three times with anhydrous hexane and then was suspended in ethyl formate (5 ml). To a stirred suspension was added dropwise ethyl formate (20 ml) and **15** (1.15 g, 4.59 mmol) at 0 °C and the reaction mixture was stirred for 1 h at 0 °C. Then ethylene glycol dimethyl ether (28 ml) was added at 0 °C and the mixture was stirred for 4 h at 0 °C. The resulting mixture was quenched by 5% HCl and poured into water and extracted twice with ether. The combined organic layers were neutralized with saturated $NaHCO_3$, washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=5:1) gave 714 mg (56%) of **16** as colorless cubes: mp 71.5-72.5 °C (from ether/petroleum ether); IR (KBr, cm^{-1}) 2980, 2950, 2880, 1620, 1580; Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.04; H, 7.98; $[\alpha]_D^{26}$ -53.23° (*c*=0.789, $CHCl_3$).

(4'a*R*,7'*R*,8'a*R*)-6'-(1,3-Dioxolan-2-yl)-7'-ethenylhexahydro-4'a-methyl-spiro[1,3-dioxolane-2,2'(1'*H*)-naphthalen]-5'(3'*H*)-one (17). To a solution of **16** (151 mg, 0.54 mmol) in anhydrous benzene (10 ml) were added ethylene glycol (0.1 ml, 1.74 mmol) and small amount of *p*-TsOH and the resulting mixture was refluxed for 1 h with a Dean-Stark apparatus. After cooling to room temperature, the

reaction mixture was washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=5:1) gave 106 mg (68%) of **17** as colorless needles: mp 158-159 °C (from ethyl acetate); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.78 (ddd, *J*=17.16, 10.23, 9.57 Hz, 1H), 5.13 (ddd, *J*=17.16, 1.98, 0.66 Hz, 1H), 5.07 (ddd, *J*=10.23, 1.98, 0.66 Hz, 1H), 5.05 (d, *J*=7.59 Hz, 1H), 3.98-3.77 (m, 8H), 3.16-3.07 (m, 1H), 3.00 (dd, *J*=7.59, 5.61 Hz, 1H), 2.13 (tt, *J*=12.77, 2.97 Hz, 1H), 1.99 (td, *J*=13.20, 4.62 Hz, 1H), 1.90-1.81 (m, 1H), 1.76-1.66 (m, 4H), 1.47-1.38 (m, 2H), 1.19 (d, *J*=0.66 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$, ppm) 212.5 (s), 136.4 (d), 117.4 (t), 108.4 (s), 101.9 (d), 65.0 (t), 64.4 (t), 64.2 (t), 64.1 (t), 52.5 (d), 47.9 (s), 43.2 (d), 38.4 (d), 36.8 (t), 34.2 (t), 30.4 (t), 29.3 (t), 14.5 (q); IR (KBr, cm^{-1}) 2960, 2850, 1710, 1110, 1080; Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.04; H, 8.02; $[\alpha]_D^{25}$ +81.62° (*c*=0.713, $CHCl_3$).

(4'a*R*,8'a*R*)-6'-(1,3-Dioxolan-2-yl)-7'-ethenyl-4',4'a,8',8'a-tetrahydro-4'a-methyl-spiro [1,3-dioxolane-2,2'(1'*H*)-naphthalene]-5'(3'*H*)-one (18). To a stirred solution of LDA (0.093 mmol) at -78 °C, prepared from diisopropylamine (0.013 ml, 0.093 mmol) and butyllithium (1.5 M in hexane, 0.062 ml, 0.093 mmol) in dry THF (1 ml), was added a solution of **17** (20 mg, 0.062 mmol) in dry THF (1 ml). After stirring for 30 min, the reaction mixture was added dropwise to a solution of phenylselenenyl chloride (17.8 mg, 0.093 mmol) in dry THF (1 ml) and the mixture was stirred for 10 min at 0 °C. The reaction mixture was poured into saturated NH_4Cl and extracted twice with ether. The combined organic layers were neutralized with saturated $NaHCO_3$, washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=8:1) gave the α-selenyl ketone. Consecutively, the α-selenyl ketone was dissolved in CH_2Cl_2 (5 ml) and pyridine (3 ml) and 15% H_2O_2 (1.5 ml) were added. After the reaction mixture was stirred for 30 min at room temperature, the resulting mixture was poured into water and extracted twice with ether and the combined organic layers were washed with brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=5:1) gave 2.98 mg (15% overall yield from **17**) of **18** as colorless crystals: mp 114-116 °C (from petroleum ether); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.25 (dd, *J*=16.82, 11.22 Hz, 1H), 5.95 (s, 1H), 5.71 (dd, *J*=16.82, 0.83, Hz, 1H), 5.48 (dd, *J*=11.22, 0.83 Hz, 1H), 4.00-3.86 (m, 8H), 2.54-1.59 (m, 9H), 1.04 (s, 3H); IR (KBr, cm^{-1}) 2950, 2880, 1680, 1080, 950; Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 64.92; H, 7.29; $[\alpha]_D^{25}$ +88.84° (*c*=1.13, $CHCl_3$).

(4'a*R*,5'*S*,8'a*R*)-6'-(1,3-Dioxolan-2-yl)-7'-ethenyl-3',4',4'a,5',8',8'a-hexahydro-4'a-methyl-spiro[1,3-dioxolane-2,2'(1'*H*)-naphthalen]-5'-ol (19). To a solution of **18** (36.5 mg, 0.11 mmol) in dry ether (2 ml) was added a 0.93 M solution of DIBAL-H (0.18 ml, 0.17 mmol) at 0 °C. The mixture was stirred for 90 min at 0 °C and then 2 g of wet NaF was added. After 30 min, the reaction mixture was filtered and the organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=2:1) gave 16.5 mg (43%) of **19** as a colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.74 (dd, *J*=17.48, 10.88 Hz, 1H), 5.81 (s, 1H), 5.35 (d, *J*=17.48 Hz, 1H), 5.20 (d, *J*=10.88 Hz, 1H), 4.26 (br s, 1H), 4.16-4.05 (m, 2H), 4.01-3.86 (m, 6H), 3.41 (d, *J*=3.95 Hz, 1H), 2.13 (dm, *J*=16.83 Hz, 1H), 2.00 (dt, *J*=13.20, 3.46 Hz, 1H), 1.89 (dd, *J*=11.54, 2.97 Hz, 1H), 1.81-1.38 (m, 6H), 0.85 (s, 3H); IR (neat, cm^{-1}) 3550, 2940, 2880, 1100, 1080; HRMS ((+) FAB) *m/z* 322.1761 (M^+, calcd for $C_{18}H_{26}O_5$ 322.1780); $[\alpha]_D^{26}$ +84.73° (*c*=0.76, $CHCl_3$).

(4'a*R*,5'*S*,8'a*R*)-6'-(1,3-Dioxolan-2-yl)-7'-ethenyl-3',4',4'a,5',8',8'a-hexahydro-4'a-methyl-5'-(propinyl-3-oxy)-spiro-1,3-dioxolane-2,2'(1'*H*)-naphthalene (8). To a solution of **19** (7.8 mg, 0.024 mmol) and small amount of Bu_4NHSO_4 in 50% aqueous sodium hydroxide (1 ml) was

added propargyl bromide (0.013 ml, 0.15 mmol) and the mixture was then stirred at room temperature for 48 h. After the reaction mixture was diluted with ether, the organic layer was washed successively with water, 10% HCl, and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate=5:1) gave 5.0 mg (57%) of **8** as a colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.90 (dd, *J*=17.49, 10.89 Hz, 1H), 5.64 (s, 1H), 5.31 (d, *J*=17.49 Hz, 1H), 5.15 (d, *J*=10.89 Hz, 1H), 4.37 (dd, *J*=15.18, 2.31 Hz, 1H), 4.30 (dd, *J*=15.18, 2.31 Hz, 1H), 4.18-4.05 (m, 2H), 3.99-3.85 (m, 6H), 2.42 (t, *J*=2.31 Hz, 1H), 2.17-2.11 (m, 1H), 1.97 (dt, *J*=13.37, 3.30 Hz, 1H), 1.89-1.47 (m, 7H), 0.89 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$, ppm) 137.9 (s), 133.9 (d), 130.7 (s), 115.7 (t), 108.6 (s), 101.6 (d), 87.1 (d), 80.4 (s), 73.9 (s), 64.9 (t), 64.3 (t), 64.2 (t), 60.9 (t), 37.6 (s), 37.0 (t), 35.8 (d), 35.7 (t), 30.8 (t), 30.5 (t), 10.8 (q); IR (neat, cm^{-1}) 3300; HRMS ((+) FAB) *m/z* 361.2007 (M^++H, calcd for $C_{21}H_{29}O_5$ 361.2021); $[\alpha]_D^{25}$ +91.99° (*c*=0.60, $CHCl_3$).

(4'a*S*,6'*S*,6'a*R*,10'a*R*)-12'-(1,3-Dioxolan-2-yl)-2',6',6'a,7',8',10',10'a,11'-octahydro-6'a-methyl-spiro[1,3-dioxolane-2,9'(4'a*H*)-[3*H*-6,4]methanodibenz[*b*,*e*]oxepin] (6). To a solution of **8** (9 mg, 0.025 mmol) in *t*-BuOH (2 ml) was added a solution of *t*-BuOK (17 mg, 0.15 mmol) in *t*-BuOH (2 ml). The reaction mixture was refluxed for 2.5 h. After the reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure. The residue was subjected to chromatography on silica gel (hexane/ethyl acetate=5:1) to give 6.2 mg (100%) of **6** as a colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.12 (s, 1H), 5.51-5.48 (m, 1H), 4.84 (s, 1H), 4.20 (s, 1H), 3.94 (s, 4H), 4.12-3.85 (m, 4H), 2.62-2.55 (m, 1H), 2.40-2.02 (m, 5H), 1.87-1.25 (m, 7H), 0.90-0.82 (s, 3H); IR ($CHCl_3$, cm^{-1}) 2940, 1095; LRMS ((+) FAB) *m/z* 361(M^+), 287, 73: HRMS ((+) FAB) *m/z* 361.2031 (M^++H, calcd for $C_{21}H_{29}O_5$ 361.2024); $[\alpha]_D^{23}$ -150.83° (*c*=0.32, $CHCl_3$).

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11. The structural determination of the oxa-taxane **6** was based on the comparison of its spectroscopic data (^{1}H NMR, ^{13}C NMR, etc.) with those of another [2+2], [3, 3] adducts, a structure of which was exclusively determined by a single-crystal X-ray analysis.[6]

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