Total Synthesis of Natural Bicyclic Lactones (+)-Dihydrocanadensolide, (±)-Avenociolide, and (±)-Isoavenociolide via Tungsten−π-Allyl Complexes

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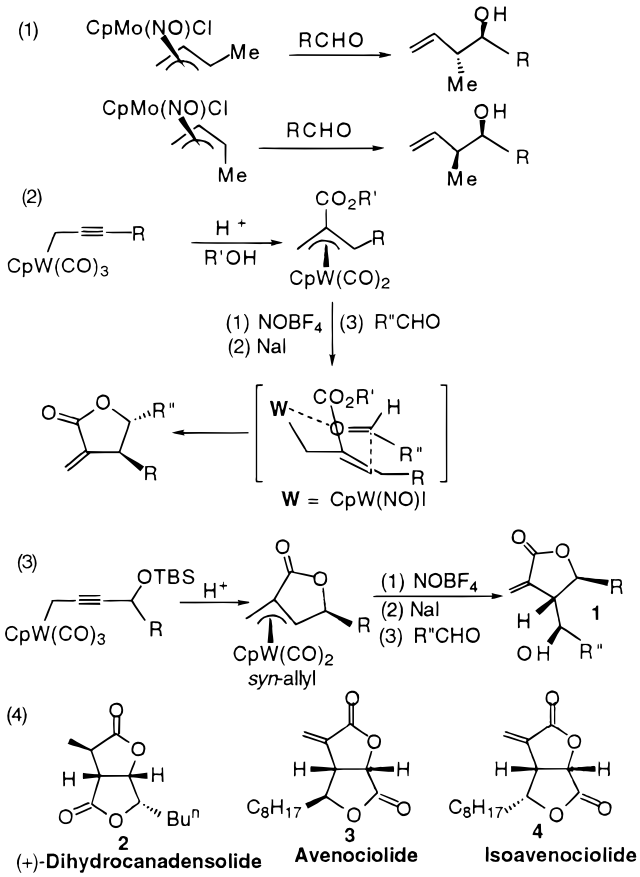
A synthetic method using tungsten−π-allyl compounds is developed for total syntheses of natural bislactones including (+)-dihydrocanadensaolide (**2**), (±)-avenociolide (**3**), and (±)-isoavenociolide (**4**). Syntheses of these natural compounds are based on a common intermediate, *trans*-α-methylene butyrolactones bearing an anti-homoallylic alcohol. The kep steps in the syntheses involve an intramolecular alkoxycarbonylation of propargyltungsten complexes to yield tungsten−π,γ-lactonyl species, followed by condensation of their CpW(NO)I(π-allyl) derivatives with suitable aldehydes. This new method is very efficient for the synthesis of (±)-avenociolide (**3**) and (±)-isoavenociolide (**4**). Total syntheses of compounds **3** and **4** require only six and three steps, respectively, on the basis of chloropropargyl derivatives.

Introductions

Allylation of organic carbonyl compounds with allylmetal complexes is a very important tool in organic synthesis.[1,2] Faller reported[3] that CpMo(NO)Cl(π-allyl) complexes condensed with aldehyde via a chairlike transition state, yielding homoallylic alcohol with excellent diastereoselectivities (Scheme 1, eq 1). We applied this method to the syntheses of *trans*-α-methylene butyrolactones[4] via alkoxycarbonylation of propargyltungsten compounds (eq 2) to yield tungsten−π-allyl complexes, followed by condensation of their CpW(NO)I(π-ally) derivatives with aldehydes. We extended this synthetic sequence to intramolecular alkoxycarbonylation[5] of propargyltungsten compounds as shown in eq 3, ultimately proceeding to *trans*-α-methylene butyrolactones bearing an anti-homoallylic alcohol **1**. Recently, we reported that compound **1** serves as an useful intermediate for total synthesis of natural monocyclic α-methylene butyrolactones including (−)-methylenolactocin,[6] (±)-protolichesterinic acid, and (±)-rocellaric acid.[7] In this paper, we demonstrate the use of compound **1** as an intermediate for total syntheses of natural bislactones[8] including (+)-dihydrocanadensolide **2**, (±)-avenociolide **3**, and (±)-isoavenociolide **4**. Dihydrocanadensolides **2** was isolated as a mold metabolite of *Penicillum canadense*[9,10]

Scheme 1



with biological activity, and a first total synthesis was described by Mulzer.[11,12] Avenaciolide (**3**) and isoavenaciolide (**4**) are secondary metabolites isolated from *As-*

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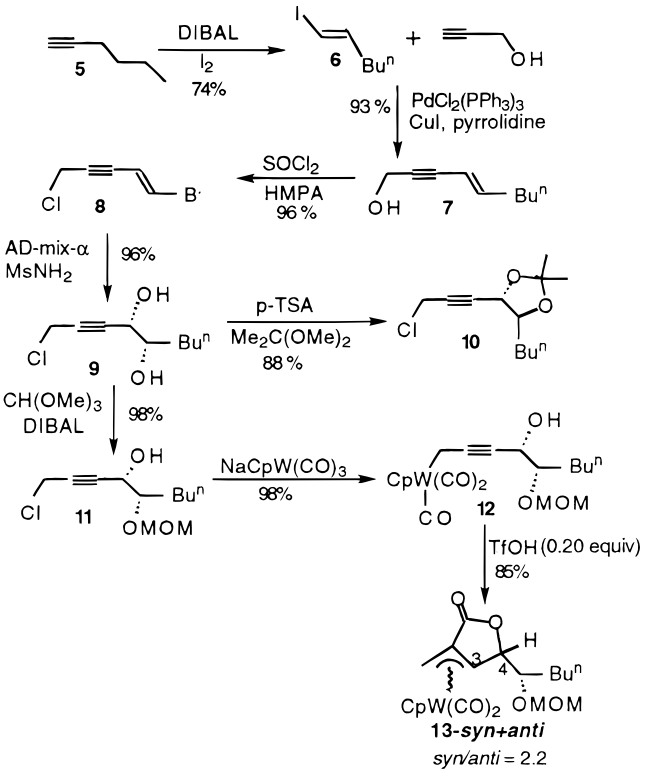
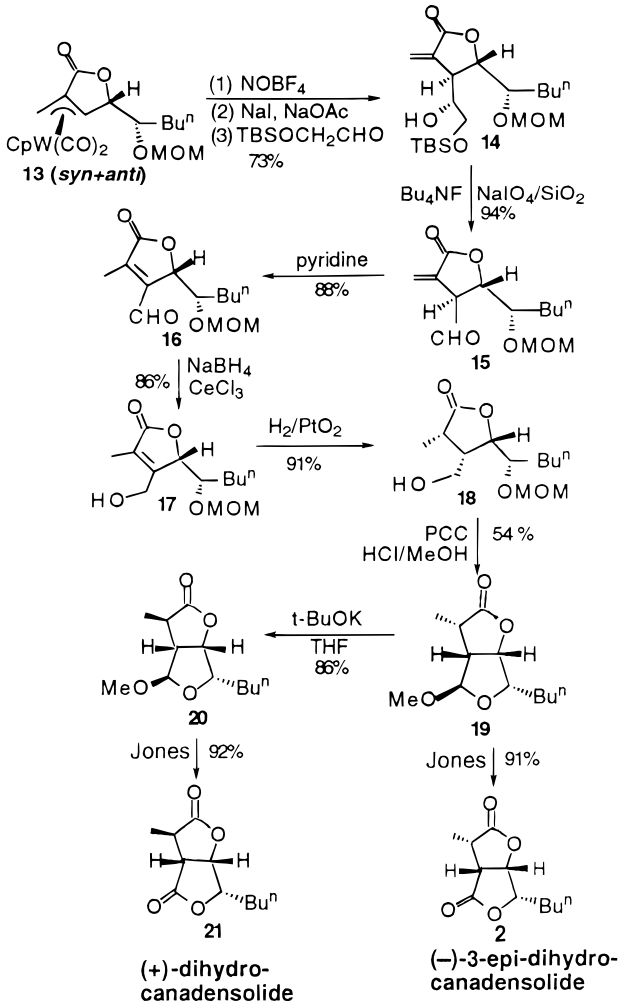
Scheme 2



pergillus and *Penicillium*;[13] total syntheses of these two compounds have attracted considerable attention[14] because of their diverse and potent biological activities. In this paper, we report total syntheses of these three bislactones based on tungsten−π-allyl complexes; this synthetic protocol is highly efficient, particularly for avenociolide **3** and isoavenociolide **4**, because it requires only a few steps from the starting chloropropargyl derivative.

Total Synthesis of (+)-Dihydrocanadeinsolide. Shown in Scheme 2 are the syntheses of organic substrates designed for organotungsten compounds. Treatment of 1-hexyne **5** with DIBAL, followed by I_2-oxidation, gave the iodoalkene derivative **6** in 74% yield. Palladium-catalyzed coupling of the propargyl alcohol and **6** in pyrrolidine[15] in the presence of CuI catalyst yielded the alcohol **7** in 93%. Chlorination of the alcohol **7** with thionyl chloride in HMPA gave a 96% yield of chloropropargyl derivative **8.** Asymmetric cis-dihydroxylation of **8** over AD-mix-α catalysts[16] produced the (+)-diol **9** in 96% yield. The enantiomeric excess of the diol was determined to be 97% by analysis of its cyclic ketal (−)-**10** on a chiral HPLC column (Merck, Chiraspher). Protection of the diol group of **9** with $CH(OMe)_3$, followed by DIBAL-treatment to induce asymmetric ring cleavage,[17] afforded the (+)-methoxymethyl ether **11** in 98% yield. Metalation of (+)-chloropropargyl compound **11** with $NaCpW(CO)_3$ gave a 98% yield of (−)-propargyltungsten compound **12**. Treatment of **12** with triflic acid catalyst (20 mol %) induced an intramolecular alkoxycarbonylation reaction[12] to yield an 85% yield of tungsten−π-allyl complex **13** as a mixture of syn and anti isomers (syn/anti = 2.2). The two isomers are distinguishable by the magnitude of the J_{34} coupling constant; the value is 3.0 Hz for the syn isomer and 0 Hz for the anti isomer.[5a] It is unnecessary to separate the two diastereomers **13-syn** and **13-anti** because their CpW(NO)I derivatives will give the same diastereomeric product[12] in condensation with aldehydes.

Scheme 3



Scheme 3 shows a synthetic protocol to use tungsten−π-allyl complex **13** for enantiomeric synthesis of (+)-dihydrocanadensolide **2**. Sequential treatment of the syn and anti mixtures (syn/anti = 2.2) of **13** with $NOBF_4$ (1.0 equiv), NaI, and NaOAc yielded the CpW(NO)I(π-allyl) derivative[3] of **13** that reacted in situ with $TBSOCH_2CHO$ to afford *trans*-α-methylene butyrolactone **14** in

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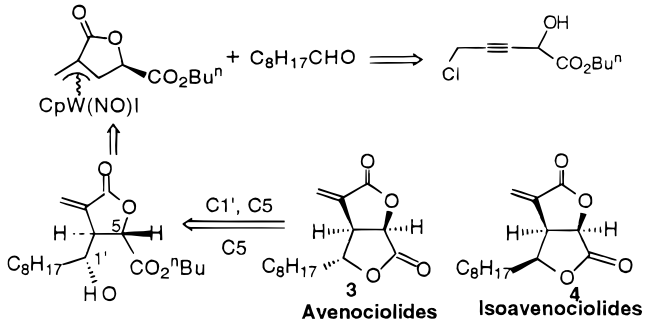
Scheme 4

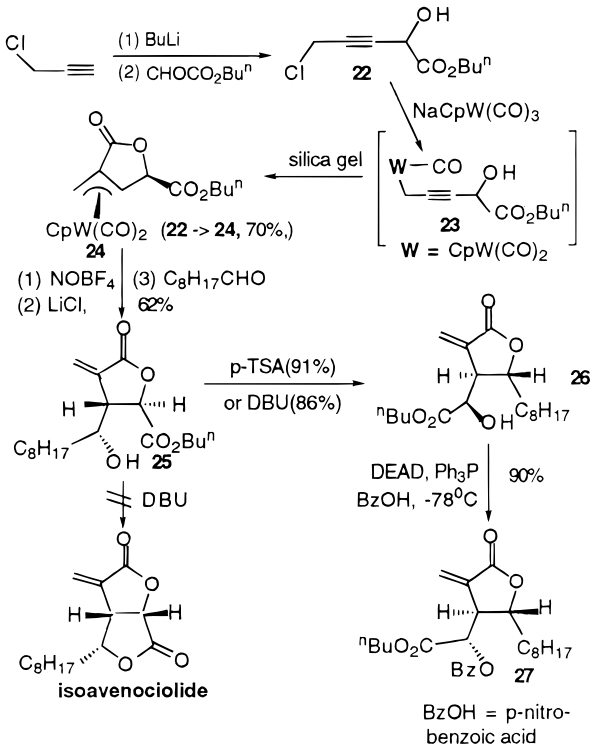


73% yield. After removal of the siloxy group, the diol group of **14** was oxidatively cleaved by $NaIO_4/SiO_2$ to give the aldehyde **15.** The trans configuration of **15** seems to be a problem to achieve a 5,5-bislactone structure. Compound **15** was thus treated with pyridine to give a furanone **16** in 88% yield. Reduction of the aldehyde **15** with $NaBH_4/CeCl_3$ afforded the alcohol **17** in 86% yield. Hydrogenation (1.0 atm) of **17** over PtO_2 catalyst delivered the trisubstituted γ-lactone **18** in 91% yield. The stereochemistry of **18** is established by proton NOE spectra that show a cis arrangement for the three substituents. PCC-oxidation of the alcohol **18** afforded an aldehyde that was subsequently heated in a HCl/MeOH mixture to give a tetrahydrofuranyl ether **19** in overall 54% yield. The stereochemistry of **19** is again confirmed by proton NOE-difference spectra. Epimerization of **19** with *t*-BuOK in THF gave the more stable isomer **20** in 86% yield. Finally, Jones oxidation of compound **20** afforded a 91% yield of the desired (+)-dihydrocanadensolide **2**. Spectral data of **2** $[[\alpha]^{25}_D = +29.8$ ($c = 0.1$, $CHCl_3$)] in this synthesis is virtually identical to those reported in the literature[9,10] $[[\alpha]^{25}_D = +30.1$ ($c = 0.1$, $CHCl_3$)]. A similar oxidation on bicyclic furanyl ether **19** delivered the (−)-3-*epi*-dihydrocanadensolide **21** $[[\alpha]_D = -20.3$ ($c = 0.50$, $CHCl_3$)] in 92% yield. Spectral data of the 3-epimer **21** are also identical to those reported in the literature[12] ($[\alpha]_D = -20.6$ ($c = 1.3$, $CHCl_3$)].

Total Synthesis of Avenociolide and Isoavenociolide. Avenociolide (**3**) and isoavenociolide (**4**) have distinct bislactone structures from that of dihydrocanadensolide (**2**). Total synthesis of **3** and **4** in racemic forms can also be achieved from tungsten−π-allyl complexes according to the retrosynthesis in Scheme 4. A major task here is that it requires to complete two inversions of stereochemistries at the C1′ and C5 carbons for avenociolide (**3**) and an inversion of stereochemistry at the C5 carbon for isoavenociolide (**4**).

As shown in Scheme 5, the starting chloropropargyl derivative **22** is readily available from chloropropargyl anion and *n*-butyl glyoxalate.[18] Metalation of **22** with $CpW(CO)_3Na$ (1.3 equiv) yielded propargyltungsten complex **23**, which was not isolated because of its chemical reactivity. Elution of this tungsten species through a silica column led to intramolecular alkoxycarbonylation, giving tungsten−*syn*-π-allyl complex **24** in a overall 70% yield. The syn configuration of **24** is indicated by the coupling constant $J_{34} = 3.1$ Hz.[5a,b] Sequential addition of $NOBF_4$ (1.0 equiv) and LiCl (2.0 equiv) to **4** in CH_3CN generated its CpW(NO)Cl derivative,[3] which reacted in

Scheme 5



situ with $C_8H_{17}CHO$ to yield *trans*-α-methylene butyrolactone **25** in 62% isolated yield. For compound **25**, the anti configuration at the secondary alcohol is inferred from the structure of its transacylation product **26** that has a trans configuration (vide infra). We first aim at the synthesis of isoavenociolide **4** because it can be easily achieved from γ-lactone **25** via epimerization at its C(5) carbon. Compound **25** was thus heated in toluene for 7 h with the DBU catalyst (0.30 equiv), but to induce an unexpected transacylation reaction, yielding a new α-methylene butyrolactone **26** in 86% yield. Compound **26** also has a trans configuration on the lactonyl ring according to the proton NOE effect. Under the same conditions, *p*-TSA catalyst (0.20 equiv) also gave compound **26** in 91% yield. If ^{t}BuOK (0.15 equiv) was used in the reaction, compound **26** and a mixture of unknown species were formed upon heating in THF (60 °C) for 6 h. Hence, we sought to invert the configuration at the CH(OH) carbon of **26** since it is a more stable form than its transacylation isomer **25**. Epimerization of this secondary alcohol proceeded smoothly according to Mitsunobu reaction,[19] sequentially giving **27** and **28** in 90% and 89%, respectively. We envision that isoavenociolide **4** is readily achieved from **28** via a base-catalyzed transacylation equilibrium. To our disappointment, heating a mixture of DBU (0.2−2.0 equiv) and **28** in toluene at reflux for 72 h did not show any sign of chemical reaction, and the starting material **28** was recovered exclusively. We then attempt to achieve this transacylation with acid catalyst but to give surprising results. Heating **28** with excess p-TSA·H_2O (2.0 equiv) in toluene in a sealed tube (150 °C, 4 h) produced the desired avenaciolide **3** in 65% yield together with isoavenaciolide **2** in 5% yield. Formation of avenaciolide **3** from **28** indicates an inversion of

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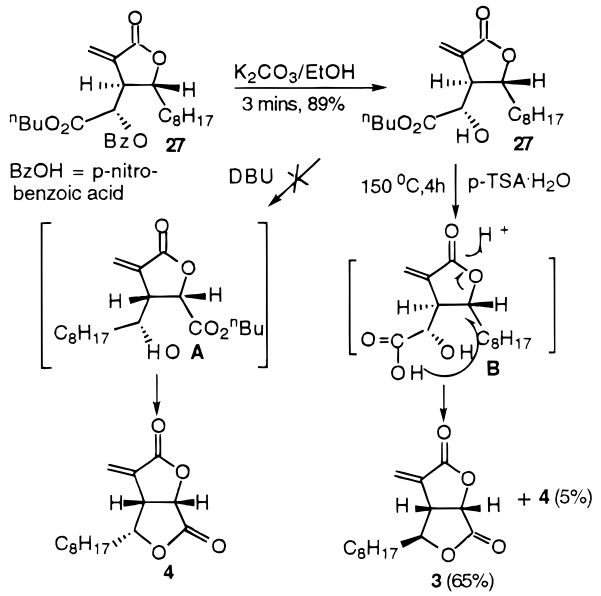
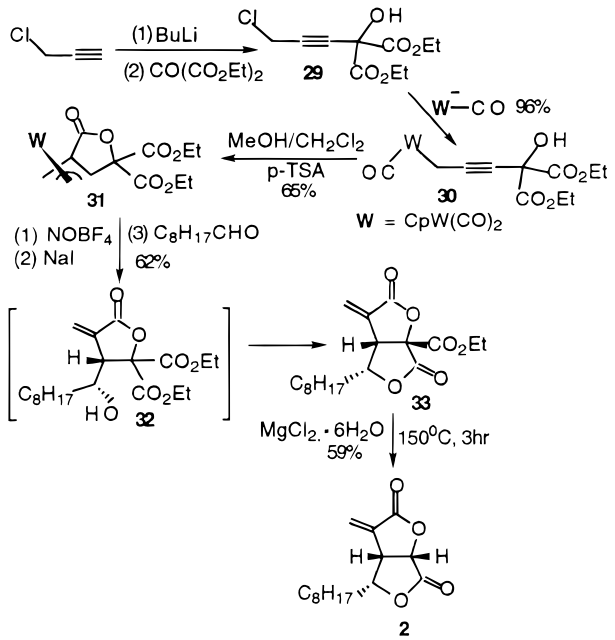
Scheme 6



Scheme 7



stereochemistry at the *C*H(C_8H_{17}) carbon of **28**. According to an early Burk's work,[14d] formation of **3** can be rationalized to proceed from intramolecular attack of the acid group of intermediate **B** at its C(5)-carbon to invert its stereoconfiguration,[14c–d] ultimately yielding avenaciolide **3** (Scheme 6). Spectral data of avenociolide **3** were consistent with those reported in the literature.[13,14]

Although we were unsuccessful in obtaining isoavenociolide **4** in the preceding synthesis, we sought to find an alternative approach to the synthesis of isoavenaciolide **4** using tungsten−π-allyl complexes. The whole synthesis shown in Scheme 7 requires only three steps from chloropropargyl species **9**.[20] Treatment of **9** with $CpW(CO)_3Na$ (2.0 equiv) in THF at 23 °C gave the expected propargyltungsten species **30**, which was purified on a deactivated alumina column; the overall yield was 96%. Subsequent treatment of propargyltungsten species **30** with *p*-TSA·H_2O (1.0 equiv) in a MeOH/CH_2Cl_2 mixture (volume ratio = 1/10) to effect intramolecular alkoxycarbonylation,[5a,b] yielding tungsten−π-allyl complex **31** in 65% yield. Further conversion of **31** to its CpW(NO)I derivative is achieved through sequential treatment with $NOBF_4$ (1.0 equiv) and NaI (2.0 equiv). Reaction of this species in situ with $C_8H_{17}CHO$ gave a 62% yield of bislactone species **33** which was presumbly produced via lactonization of the primary compound **32**. Decarboxylation of **33** proceeded smoothly through heating its dimethylacetamide solution (150 °C, 3 h) containing $MgCl_2·6H_2O$ (5.0 equiv)[21] to yield the desired isoavenaciolide **4** in 59% yield. ^1H and ^{13}C NMR data of isoavenociolide **4** in this synthesis were identical to those of authentic sample.[14]

We reported here an extented work on the synthetic utility of tungsten−π-allyl complexes. Previously, we demonstrated the use of these organotungsten compounds for the synthesis of natural monocyclic α-methylene butyrolactone.[6,7] In this paper, these allyl complexes are proved useful for total syntheses of naturally occurring bislactones such as (+)-dihydrocanadensolide (**2**), (±)-avenociolide (**3**), and (±)-isoavenociolide (**4**). The overall synthetic sequence for racemic avenociolide and isoavenociolide is considered to be the most efficient one among the known methods.[14]

Experimental Section

General procedures and spectroscopic methods are described elsewhere.[5a,b] $NaCpW(CO)_3$ was prepared by stirring of $[CpW(CO)_3]_2$ with sodium amalgam in THF for 8 h, and it was used in situ.

Synthesis of 1-Iodo-1-hexene (6). To a hexane solution of 1-hexyne (13.1 g, 160 mmol) was added DIBAL (1.0 M, 160 mL, 160 mmol) at −40 °C, and the solution was stirred for 20 min and gradually warmed to 23 °C in a period of 4 h. After an additional stirring for 2 h at 23 °C, the solution was heated at 50 °C for 4 h and then cooled to −40 °C. To this cooled solution was added dropwise a THF solution of I_2 (41.0 g, 160 mmol), the solution was warmed to 23 °C and stirred for 12 h. To the resulting solution was added 20% H_2SO_4 (72 mL), and the organic layer was extracted with hexane. The extract was washed sequentially with an aqueous solution of $Na_2S_2O_3$ (2.0 M, 10 mL), $NaHCO_3$ (1.5 M, 10 mL) and NaCl (10 mL). The extract was dried over $MgSO_4$, and eluted through a silica column to give iodo compound **6** as an oil (25 g, 119 mmol, 74.4%): IR (neat, cm^{-1}) ν(C=C) 1610 (w); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 6.9 Hz, 3H), 1.31 (m, 4H), 2.02 (m, 2H), 5.94 (d, J = 13.3 Hz, 1H), 6.46 (dt, J = 13.3, 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 21.85, 30.34, 35.59, 74.28, 146.37; HRMS calcd for $C_6H_{11}I$, 209.9905, found 209.9900.

Synthesis of Non-4-en-2-yn-1-ol (7). To a pyrrolidine solution (30 mL) of iodo compound **1** (6.73 g, 32.1 mmol) were added $PdCl_2(PPh_3)_2$ (0.90 g, 1.28 mmol) and CuI (0.44 g, 2.56 mmol), and the mixture was stirred for 10 min before addition of propargyl alcohol (3.73 mL, 64.1 mmol) at 0 °C. The mixture was stirred for 2 h and quenched with a saturated solution of NH_4Cl (60 mL) and HCl (2.0 N, 60 mL). The organic layer was extracted with ethyl acetate, dried over $MgSO_4$, and eluted through a silica column to afford alkynol **7** (4.10 g, 29.7 mmol, 92.7%): IR (neat, cm^{-1}) ν(OH) 3328(vs), ν(C≡C) 2245(m); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J = 7.0 Hz, 3 H), 1.24 (m, 4 H), 1.98 (m, 2 H), 3.56 (bs, 1 H), 4.24 (d, J = 3.4 Hz, 2H), 5.38 (dt, J = 16.1, 1.6 Hz, 1H), 6.03 (dt, J = 16.1, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 21.9, 30.5, 32.4, 50.8, 83.9, 85.6, 108.7, 145.0; HRMS calcd for $C_9H_{14}O$ 138.1045, found 138.1047.

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Synthesis of 1-Chloro-non-4-en-2-yne (8). To a diethyl ether solution (11 mL) of alkynol **2** (3.70 g, 26.8 mmol) and HMPA (11.0 mL) was added $SOCl_2$ (32.1 mL) at 0 °C, and the mixture was stirred for 3 h before addition of water (10 mL). To this solution was added $NaHCO_3$ solution, and the organic layer was extracted with diethyl ether, dried over $MgSO_4$, and eluted through a silica column to give chloropropargyl compound **8** as a colorless oil (4.05 g, 23.9 mmol, 96.6%): IR (neat, cm^{-1}) ν(C≡C) 2221(w), ν(C═C) 1624(w); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.2 Hz, 3H), 1.33 (m, 4H), 2.10 (m, 2H), 4.24 (d, J = 2.0 Hz, 2H), 5.49(dt, J = 16.0, 0.8 Hz, 1H), 6.19 (dt, J = 16.0, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 22.0, 30.6, 31.2, 32.7, 82.0, 85.2, 108.4, 146.7; HRMS calcd for $C_9H_{13}Cl$ 156.0706, found 156.0705.

Synthesis of (+)-(4*S*,5*S*)-1-Chloronon-2-yne-4,5-diol (9). To a *tert*-butyl alcohol solution (46 mL) of AD-mix-α (12.25 g) was added an aqueous solution (46 mL) of $MeSO_2NH_2$ (0.97 g, 10.2 mmol) and chloropropargyl compound **9** (1.60 g, 10.2 mmol), and the mixture was stirred for 27 h in the absence of light. To this solution was added Na_2SO_3 (13.2 g) at 0 °C, and the mixture was stirred for 2 h before it was concentrated in vacuo. The organic layer was extracted with ethyl acetate, and the extract was washed with an aqueous NaCl solution, dried over $MgSO_4$, and eluted through a short silica bed to yield the diol **4** (1.87 g, 9.80 mmol, 96%): $[\alpha]_D$ = +15.5 (c = 0.35, $CHCl_3$); IR (neat, cm^{-1}) ν(OH) 3443(vs), ν(C≡C) 2214 (w); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 7.3 Hz, 3H), 1.27−1.64 (m, 6H), 3.22 (bs, 2H), 3.59 (m, 1H), 4.19 (d, J = 1.7 Hz, 2H), 4.27 (dt, J = 6.6, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 22.6, 27.5, 30.2, 32.1, 66.0, 74.6, 80.8, 84.9; HRMS calcd for $C_9H_{15}ClO_2$ 190.0761, found 190.0761.

Synthesis of (−)-(4*S*,5*S*)-4-Butyl-5-(3-chloroprop-1-ynyl)-2,2-dimethyl[1,3]dioxolane (10). To an acetone solution (7.0 mL) of the diol **9** (0.381 g, 2.0 mmol) were added *p*-toluenesulfonic acid (30 mg, 0.16 mmol) and 2,2-dimethoxypropane (7 mL), and the mixtures were heated under reflux. To this mixture was added a saturated $NaHCO_3$ (10 mL) solution, and the solution was extracted with diethyl ether. The extract was dried over $MgSO_4$ and eluted through a silica column to obtain compound **10** as a colorless oil (0.41 g, 1.76 mmol, 88%): $[\alpha]_D$ = −41.3 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν(C≡C) 2260(w), ν(C═C) 1624(w); ^1H NMR ($CDCl_3$, 400 MHz) δ, 0.90 (t, J = 7.2 Hz, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.35−1.62 (m, 6H), 3.99 (dt, J = 8.0, 6.0 Hz, 1H), 4.15 (d, J = 1.6 Hz, 1H), 4.23 (dt, J = 8.0, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 13.8, 22.6, 26.1, 27.0, 27.7, 30.1, 32.0, 70.4, 81.2, 81.3, 83.2, 109.8; HRMS calcd for $C_{12}H_{19}ClO_2$ 230.1074, found 230.1072.

Synthesis of (+)-(4*S*,5*S*)-1-Chloro-5-methoxymethoxynon-2-yn-4-ol (11). To a CH_2Cl_2 solution of the diol **9** (1.50 g, 7.87 mmol) and camphorsulfonic acid (72 mg, 0.31 mmol) was added $CH(OMe)_3$ (1.72 mL, 15.6 mmol), and the mixture was stirred for 1 h before it was cooled to −78 °C. To this solution was added DIBAL-H (1.0 M in hexane, 78.4 mL, 78.4 mmol), and the mixture was stirred for 1 h before it was warmed to 0 °C. To this solution was added an aqueous HCl solution (1 N, 60 mL), and the organic layer was extracted ethyl acetate. The extract was washed with HCl (1.0 N, 20 mL) and NaCl (2.0 M, 20 mL), dried over $MgSO_4$, and concentrated. Elution of the residues through a silica column afforded compound **11** as a colorless oil (1.81 g, 7.72 mmol, 98%): $[\alpha]_D$ = +17.5 (c = 0.7, $CHCl_3$); IR (neat, cm^{-1}) ν(OH) 3412(w), ν(C≡C) 2260(w); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.2 Hz, 3H), 1.32 (m, 4H), 1.57 (m, 1H), 1.70 (m, 1H), 3.42 (s, 3H), 3.55 (m, 1H), 4.15 (d, J = 1.6 Hz, 2H), 4.32(dt, J = 5.6, 1.6 Hz, 1H), 4.67(d, J = 7.6 Hz), 4.79(d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 22.2, 27.0, 29.9, 30.1, 55.3, 64.2, 79.9, 81.3, 85.1, 96.6; HRMS calcd for $C_{11}H_{19}ClO_3$ 234.1023, found 234.1021.

Synthesis of (−)-Propargyltungsten Compound 12. $[CpW(CO)_3]_2$ (4.62 g, 6.94 mmol) was stirred with Na/Hg (8.30 g, 20% Na content) in THF (60 mL) for 6 h, and to this solution was added chloroalkynol **11** (1.81 g, 7.72 mmol) at 0 °C. The mixture was stirred for 23 °C for 9 h, and the solution was concentrated and filtered through a basic alumina column to afford **12** as a viscous yellow oil (4.20 g, 7.56 mmol, 98%): $[\alpha]_D$ = −41.3; IR (neat, cm^{-1}) ν(OH) 3444(vs), ν(CO) 2022(s), 1931-(s); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 6.8 Hz, 3H), 1.34 (m, 4H), 1.59 (m, 1H), 1.78 (m, 1H), 1.99 (d, J = 2.4 Hz, 2H), 3.09 (bs, 1H), 3.43 (s, 3H), 3.50 (m, 1H), 4.37 (dt, J = 5.5, 2.4 Hz, 1H), 4.70(d, J = 6.8 Hz, 1H), 4.82 (d, J = 6.8 Hz, 1H), 5.51 (s, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −33.1, 13.8, 22.6, 27.2, 30.9, 55.6, 65.4, 78.1, 83.5, 92.4, 95.7, 97.3, 216.5, 228.5. Anal. Calcd for $C_{19}H_{24}WO_6$: C, 42.88; H, 4.53. Found: C, 42.85; H, 4.51.

Synthesis of Tungsten−π-Allyl Complex (13). To a CH_2Cl_2 solution (80 mL) of propargyltungsten complex (4.20 g, 7.56 mmol) was added triflic acid (0.133 mL, 1.51 mmol) at −60 °C, and the mixture was stirred for 30 min before treatment with a saturated $NaHCO_3$ solution The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and eluted through a silica column to give allyltungsten compound **13** as a mixture of syn and anti isomers (3.57 g, 6.71 mmol, 85%):. IR (neat, cm^{-1}) ν(CO) 1953(s), 1874(s), 1700(s); ^1H NMR ($CDCl_3$, 400 MHz) syn form, δ, 0.92 (t, J = 7.6 Hz, 3H), 1.20−1.90 (m, 6H), 1.50 (d, J = 3.6 Hz, 1H), 3.22 (d, J = 4.0 Hz, 1H), 3.42 (d, J = 3.6 Hz, 1H), 3.43 (s, 3H), 3.73 (m, 1H), 4.70 (t, J = 7.2 Hz, 2H), 4.95 (dd, J = 8.8, 4.0 Hz, 5.39 (s, 5H), anti form, δ, 0.91 (t, J = 7.6 Hz, 3H), 1.20−1.90 (m, 6H), 1.50 (d, J = 3.6 Hz, 3H), 3.11−3.16 (m, 2H), 3.37 (s, 3H), 3.46 (s, 1H), 4.69 (d, J = 4.4 Hz, 1H), 4.70 (s, 2H), 5.34 (s, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) *syn*-form, 13.8, 21.3, 22.5, 27.2, 30.8, 55.7, 63.2, 69.4, 81.9, 83.2, 93.8, 96.4, 175.2, 219.8, 224.4, anti form, 13.8, 21.0, 22.6, 27.2, 29.6, 55.9, 63.2, 68.7, 79.3, 83.8, 93.8, 96.8, 175.6, 219.2, 225.2. Anal. Calcd for $C_{19}H_{24}WO_6$: C, 42.88; H, 4.54. Found: C, 42.67; H, 4.66.

Synthesis of (+)-*trans*-α-Methylenebutyrolactone 14. To a CH_3CN solution of tungsten−π-allyl complex **13** (2,60 g, 4.89 mmol) was added $NOBF_4$ (571 mg, 4.89 mmol) at 0 °C, and the mixture was stirred for 20 min before addition of LiCl (415 mg, 9.78 mmol). After being stirred for 20 min at 0 °C, this solution was added to NaOAc (802 mg, 9.78 mmol) and $CHOCH_2OTBS$ (2.54 g, 14.7 mmol), and the mixture was stirred for 8 h at 23 °C. To this solution was added MeOH (1.0 mL), and the mixture was stirred for 30 min. Diethyl ether (200 mL) was added to the solution to precipitate the undesired salt, and the filtrate was dried over $MaSO_4$, concentrated, and eluted through a silica column to yield compound **14** as an oil (1.39 g, 3.59 mmol, 73.3%): $[\alpha]_D$ = + 20.0 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν(OH) 3358, ν(CO) 1751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 6 H), 0.87−0.91 (bs, 12 H), 1.31 (m, 4 H), 1.59 (m, 2H), 2.62 (bs, 1H), 3.32 (m, 1H), 3.52 (s, 3H), 3.54 (m, 1H), 3.63 (dd, J = 10.4, 4.0 Hz, 1H), 3.77 (m, 1H), 4.56 (t, J = 2.8 Hz, 1H), 4.57 (d, J = 7.6 Hz, 1H), 4.67 (d, J = 7.6 Hz, 1H), 5.67 (d, J = 2.0 Hz, 1H), 6.29 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.6, 13.8, 18.3, 22.6, 25.7, 27.5, 30.1, 43.6, 59.9, 63.4, 72.8, 78.8, 79.3, 96.1, 123.2, 135.4, 170.2; HRMS calcd for $C_{20}H_{38}SiO_6$ 402.2438, found 402.2435.

Synthesis of Compound 15. To a THF solution (30 mL) of compound **14** was added a THF solution of Bu_4NF (1.0 M, 1.86 mL), and the solution was stirred for 3 h. To this solution was added a saturated NH_4Cl solution (0.6 mL) to form a precipitate that was removed by filtration, and the filtrate was dried over MgSO, and eluted through a silica column to yield a colorless oil (380 mg, 1.32 mmol, 85% yield). To a CH_2Cl_2 (50 mL) solution of this diol (300 mg, 1.04 mmol) was added $NaIO_4$/silica (3.00 g, 20 wt %, 1.50 mmol), and the mixture was stirred for 1 h before filtration through a short $MgSO_4$ bed. The silica bed was washed twice with CH_2Cl_2, and the CH_2Cl_2 layer was combined with the filtrate and concentrated in vacuo to give the aldehyde **15** in 94% yield (250 mg, 0.98 mmol): $[\alpha]_D$ = −14.5 (c = 0.5, $CHCl_3$); IR (neat, cm^{-1}) ν(CO) 1767(s), 1708(s); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 6.9 Hz, 3H), 1.32 (m, 4H), 1.58 (m, 2H), 3.30 (s, 3H), 3.60 (dt, J = 9.9, 3.3 Hz, 1H), 3.86 (dd, J = 6.2, 3.3 Hz, 1H) 4.60 (dd, J = 6.9 Hz, 2H), 5.01 (t, J = 3.4 Hz, 1 H), 5.86 (d, J = 2.7 Hz, 1H), 6.43 (d, J = 2.7 Hz, 1H), 9.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 13.8, 22.6, 27.5, 29.8, 56.1, 75.7, 78.3, 96.5, 124.6, 131.1, 168.2, 194.9; HRMS calcd for $C_{13}H_{20}O_5$ 256.1311, found 256.1308.

Synthesis of Compound 16. To a $CHCl_3$ solution (20 mL) of the aldehyde **15** (250 mg, 0.98 mmol) was added pyridine (0.60 mL), and the mixtures were stirred at 0 °C for 2 h before addition of a saturated NH_4Cl solution. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and eluted through a short silica bed to give the unsaturated aldehyde **16** (220 mg, 0.86 mmol, 88%): $[\alpha]_D = +20.1$ ($c = 0.8$, $CHCl_3$); IR (neat, cm^{-1}) ν(CO) 1767(s), 1688(s); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, $J = 6.8$ Hz, 3 H), 1.33 (m, 4 H), 1.70 (m, 2H), 2.25 (d, $J = 2.4$ Hz, 3 H), 3.16 (s, 3H), 3.95 (dt, $J = 7.2$, 1.2 Hz, 1 H), 4.43 (dd, $J = 7.6$, 2H), 5.13 (dd, $J = 2.4$, 1.2 Hz, 1H), 10.14(s, 1H); ^{13}C NMR (CDCl3, 100 MHz) δ 9.4, 13.9, 22.6, 27.7, 31.9, 55.6, 76.8, 81.5, 97.0, 139.9, 149.8, 173.0, 186.2; HRMS calcd for $C_{13}H_{20}O_5$ 256.1309, found 256.1311

Synthesis of Compound 17. To a MeOH solution (2.0 mL) of the aldehyde **16** (120 mg, 0.47 mmol) was added $CeCl_3.H_2O$ (174 mg, 0.47 mmol), and the mixture was stirred for 10 min. To this solution was added $NaBH_4$ (36 mg, 0.95 mmol) at 0 °C, and the mixture was stirred for 1 h before quenching with water (3 mL). The solution was neutralized with HCl (2.0 N), and the organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and eluted through a short silica bed to yield the alcohol **17** (103 mg, 0.40 mmol, 85.2%): $[\alpha]_D = -21.3$ ($c = 1.3$, $CHCl_3$); IR (neat, cm^{-1}) ν(OH) 3398(vs), ν(CO) 1763(vs); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, $J = 6.4$ Hz, 3 H), 1.20−1.50 (m, 6 H), 1.87 (s, 3 H), 3.34 (s, 3 H), 4.01 (m, 1H), 4.49 (d, $J = 14.8$, 2H), 4.70 (d, $J = 6.4$ Hz, 2H), 5.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.7, 13.8, 22.4, 27.8, 30.3, 55.8, 57.3, 77.9, 82.0, 97.3, 125.5, 158.5, 173.9; HRMS calcd for $C_{13}H_{22}O_5$ 258.1467, found 258.1466.

Synthesis of Trisubstituted γ-Lactone 18. To a prevacuated two-neck vessel charged with MeOH (10 mL) were added compound **17** (150 mg, 0.58 mmol) and PtO_2 (13.2 mg, 0.058 mmol), and the solution was filled with hydrogen with a balloon. The mixture was stirred for 48 h before it was filtered through a Celite bed. The filtrate was concentrated to yield compound **17** as a colorless oil (138 mg, 0.53 mmol, 91%): $[\alpha]_D = -8.1$ ($c = 1.0$, $CHCl_3$); IR (neat, cm^{-1}) ν(OH) 3459(s), ν(CO) 1761(s); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, $J = 7.6$ Hz, 3H), 1.31 (d, $J = 7.2$ Hz, 3H), 1.20−1.70 (m, 6H), 2.38 (m, 1H), 2.78 (dq, $J = 7.6$, 7.2 Hz, 1H), 3.72 (dd, $J = 3.2$, 1.6 Hz), 3.85 (dd, $J = 12.0$, 3.2 Hz, 1H), 3.93 (q, $J = 6.0$ hz, 1H), 4.37 (t, $J = 5.6$ Hz, 1H), 4.77 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.3, 13.8, 22.6, 27.1, 31.1, 38.1, 42.9, 56.1, 57.3, 75.5, 82.3, 96.6, 179.1; HRMS calcd for $C_{13}H_{24}O_5$ 260.1624, found 260.1620.

Synthesis of Tetrahydrofuranyl Ether 19. The PCC reagent (183 mg, 0.85 mmol) was placed in vacuo for 3 h and dissolved in CH_2Cl_2 (20 mL). To this solution was added compound **18** (138 mg, 0.53 mmol), and the mixtures were stirred for 3 h. The solution was filtered through a short silica bed, and the bed was eluted with ethyl acetate to afford an aldehyde (89 mg, 0.35 mmol, 65%). To a MeOH solution (3.0 mL) of this aldehyde (89 mg, 0.35 mmol) was added concentrated HCl solution (0.035 mL), and the mixture was heated at 70 °C for 30 min. After removal of MeOH in vacuo, to the solution was added water (3.0 mL), and the mixture was neutralized with a saturated $NaHCO_3$ solution. The organic layer was extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$, and eluted through a silica column to give bicyclic tetrahydrofuranyl ether **19** (66 mg, 0.29 mmol, 83%): $[\alpha]_D = -48.3$ ($c = 0.13$, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν(CO) 1771(vs). ^1H NMR ($CDCl_3$, 600 MHz) δ 0.90 (t, $J = 7.2$ Hz, 3H), 1.31 (d, $J = 7.5$ Hz, 3H), 1.37 (m, 4H), 1.70 (m, 2H), 2.86 (dq, $J = 11.2$, 7.2 Hz, 1H), 2.99 (dd, $J = 11.2$, 6.4 Hz, 1H), 3.31 (s, 3H), 4.00 (dt, $J = 6.4$, 2.8 Hz, 1H), 4.81 (dd, $J = 6.4$, 2.8 Hz, 1H), 4.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.7, 13.9, 22.7, 27.9, 28.3, 35.5, 50.3, 54.7, 79.9, 81.5, 103.3, 178.3; HRMS calcd for $C_{12}H_{20}O_4$ 228.1362, found 228.1359.

Epimerization of 19 to Compound 20. To a THF solution (10 mL) was added ^{t}BuOK (74 mg, 0.066 mmol), and 1.0 mL of this solution was added to a THF solution (4.0 mL) of compound **19** (30 mg, 0.13 mmol). The mixture was stirred for 2.5 h, added to $NaHSO_3$ (0.50 mL), and finally neutralized with $NaHCO_3$ solution. The organic layer was extracted with CH_2Cl_2, and the extract was washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated. Elution of the residues through a preparative SiO_2-TLC afford compound **20** in 86% yield (25.8 mg, 0.113 mmol): $[\alpha]_D = -38.8$ ($c = 0.25$, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν(CO) 1778(vs); ^1H NMR ($CDCl_3$, 600 MHz) δ 0.85 (t, $J = 7.2$ Hz, 3H), 1.29−1.36 (m, 7H), 1.62 (m, 2H), 2.49 (dq, $J = 7.2$, 4.4 Hz, 1H), 2.61 (dd, $J = 7.2$, 4.4 Hz, 1H), 3.30 (s, 3H), 3.92 (dt, $J = 6.8$, 3.6 Hz, 1H), 4.81 (s, 1H), 4.85(dd, $J = 6.8$, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 17.2, 22.6, 28.2, 28.2, 38.4, 55.9, 54.4, 79.4, 81.4, 108.6, 179.22; HRMS calcd for $C_{12}H_{20}O_4$ 228.1362, found 228.1361.

Synthesis of (+)-Dihydrocanadensolide (3). To an acetone solution of bicyclic tetrahydrofuranyl ether **20** (30 mg, 0.13 mmol) was added Jones reagent (ca. 0.20 mmol) at 23 °C, and the resulting solution was stirred for 2 h before quenching with 2-propanol. To this mixture was added water (2.0 mL), and the solution was concentrated and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and eluted through a preparative SiO_2 plate to afford (+)-dihydrocanadensolide **3** as a colorless solid (25.1 mg, 0.12 mmol, 91%): mp 93−94 °C (lit.[9,10] mp 94 °C); $[\alpha]_D = +29.8$ ($c = 0.35$, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν(CO) 1779(s); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, $J = 7.60$ Hz, 3H), 1.36−1.46 (m,7H), 1.80 (m, 2H), 3.04 (dq, $J = 7.6$, 1.2 Hz, 1H), 3.12(dd, $J = 6.4$, 1.2 Hz, 1H), 4.53 (m, 1H), 5.09 (dd, $J = 6.4$, 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 17.1, 22.4, 27.4, 28.5, 38.3, 48.9, 78.3, 82.4, 174.7, 176.8; HRMS calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1047.

Synthesis of (−)-3-*epi*-Dihydrocanadensolide (21). To an acetone solution of bicyclic tetrahydrofuranyl ether **19** (30 mg, 0.13 mmol) was added Jones reagent (ca. 0.20 mmol) at 23 °C, and the resulting solution was stirred for 2 h before quenching with 2-propanol. To this mixture was added water (2.0 mL), and the solution was concentrated and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and eluted through a preparative SiO_2 plate to afford (−)-3-*epi*-dihydrocanadensolide **21** (25.4 mg, 0.12 mmol, 92%): $[\alpha]_D = -20.2$ ($c = 0.50$, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν(CO) 1778(s), 1764(s); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, $J = 7.2$ Hz, 3H), 1.37−1.47 (m,-7H), 1.84 (m, 2H), 3.04 (dq, $J = 10.4$, 8.4 Hz, 1H), 3.43 (dd, $J = 10.4$, 6.4 Hz, 1 H), 4.49 (m, 1 H), 5.00 (dd, $J = 6.4$, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.8, 13.8, 22.4, 27.4, 28.4, 36.6, 44.6, 77.9, 81.57, 172.1, 176.2. Anal. Calcd for $C_{11}H_{16}O_4$: 212.1049. Found 212.1043.

Synthesis of 5-Chloro-2-hydroxypent-3-ynoic Acid Butyl Ester (22). To a solution of propargyl chloride (1.74 mL, 24 mM) in ether (25 mL) at −78 °C under nitrogen was added *n*-BuLi (1.6 M in hexane, 13.8 mL, 22.0 mmol) dropwise, and the mixture was stirred at −78 °C for 15 min. To this acetylide solution was added a freshly prepared butyl glyoxalate (2.6 g, 20 mmol) in ether (10 mL) dropwise over 10 min. at −78 °C. The reaction mixture was stirred for further 1 h at −78 °C and quenched with dropwise addition of acetic acid (1.5 mL, 26 mmol) at −78 °C. The resulting mixture was allowed to warm to 0 °C, and 15 mL of brine was added. The organic layer was extracted with ethyl acetate, dried over $MgSO_4$, concentrated, and purified on a silica gel column (10% ethyl acetate in hexane) to afford compound **22** as colorless oil (1.23 g, 6.7 mmol, 30%): IR (neat, cm^{-1}) ν(OH) 3465(vs), ν(CO) 1746(s).; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, $J = 7.3$ Hz, 3H), 1.41 (m, 2H), 1.67 (m, 2H), 4.14 (d, $J = 1.7$ Hz, 1H), 4.24 (m, 2H), 4.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 18.9, 29.9, 30.4, 61.4, 66.9, 80.3, 81.7, 169.9; HRMS calcd for $C_9H_{13}ClO_3$ 204.0553, found 204.0550.

Synthesis of Tungsten-π-Allyl Complex (24). To an ice-cold $NaCpW(CO)_3$ solution (6.5 m M) in THF (30 mL) was added a THF (5 mL) solution of the chloropropargyl derivative **22** (1.02 g, 5.0 mmol), and the mixture was stirred over 8 h at 23 °C. The solution was filtered through a short pad of basic alumina with THF as a eluent. The combined filterate was concentrated under reduced pressure and purified on a silica gel column (1:1 ether−hexane) to yield tungsten−π-allyl complex **24** as a yellow oil (1.76 g, 3.50 mmol, 70%): IR (neat, cm^{-1}) ν(CO) 1950(s), 1898(s), 1764(s), 1746(s); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (m, 3H), 1.37 (m, 2H), 1.48 (d, $J = 3.7$ Hz, 1H), 1.67 (m, 2H), 3.08 (d, $J = 3.8$ Hz, 1H), 3.62 (d, $J = 4.8$ Hz, 1H), 4.12 (d, $J = 2.2$ Hz, 1H), 4.25 (m, 2H), 5.36 (s, 5H),

5.58 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 18.9, 19.1, 20.8, 30.5, 59.5, 65.9, 76.4, 86.7, 94.2, 167.4, 174.8, 219.3, 223.4. Anal. Calcd for $C_{17}H_{18}WO_6$: C, 40.66; H, 3.61. Found: C, 40.58; H, 3.77.

Synthesis of *trans*-α-Methylene Butyrolactone (25). To a solution of the tungsten−π-allyl complex **24** (1.50 g, 3.00 mmol) in acetonitrile (15 mL) at 0 °C under nitrogen was added $NOBF_4$ (350 mg, 3.01 mmol), and the mixture was stirred at 0 °C for 30 min. LiCl (254 mg, 6 mmol) was then added to the reaction mixture, and the solution was stirred for addition 30 min at 0 °C before addition of nonaldehyde (1.55 mL, 9.0 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 8 h and then quenched with MeOH (3 mL), concentrated, and purified on a silica gel column (30% ethyl acetate in hexane) to afford compound **25** as a colorless oil in 62% yield (633 mg, 1.86 mmol): IR (neat, cm^{-1}) ν(OH) 3482(s), ν(CO) 1772(s), 1760(s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (t, J = 6.6 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H), 1.10−1.70 (m, 18 H), 3.07 (m, 1H), 3.72 (m, 1H), 4.14 (t, J = 6.3 Hz, 2H), 4.83 (d, J = 2.5 Hz, 1H), 5.73 (s, 1H), 6.35 (d, J = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 14.1, 18.9, 22.6, 25.7, 29.1, 29.2, 29.4, 29.5, 30.4, 31.8, 33.2, 49.0, 65.9, 72.9, 76.1, 125.7, 132.9, 169.6, 169.9; HRMS calcd for $C_{19}H_{32}O_5$ 340.2250, found 340.2252.

Transacylation of γ-Lactone 25 to γ-Lactone 26. A mixture of α-methylene butyrolactone **25** (340 mg, 1.0 mmol) and *p*-TSA (38 mg, 0.21 mmol) in toluene (15 mL) was heated at 130 °C for 7 h. The reaction mixture was cooled to 23 °C, concentrated, and purified on a silica gel column (30% ethyl acetate) in hexane to afford the trans-acylation product **26** (310 mg, 0.91 mmol, 91%):. IR (neat, cm^{-1}), ν(OH) 3482(vs), ν(CO) 1765(s), 1760(s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 6.7 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 1.10−1.70 (m, 18H), 3.06 (m, 2H), 4.17−4.30 (m, 3H), 4.45−4.50 (m, 1H), 5.50 (d, J = 2.3 Hz, 1H), 6.33 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz) δ 13.6, 14.0, 19.0, 22.8, 24.8, 29.1, 29.3, 29.4, 30.4, 31.8, 36.1, 47.7, 66.4, 71.8, 79.8, 124.2, 134.3, 169.7, 172.5; HRMS calcd for $C_{19}H_{32}O_5$ 340.2250, found 340.2255.

Synthesis of γ-Lactone 27. To a solution of the substrate **26** (170 mg, 0.5 mM), triphenylphosphine (262 mg, 1.0 mmol), and *p*-nitrobenzoic acid (167 mg, 1.0 mmol) in THF (4 mL) at −78 °C under nitrogen was added DEAD (174 mg, 1.0 mmol) dropwise, and the mixture was slowly warmed to 23 °C over 2 h. The mixture was stirred for 5 h. The reaction mixture was concentrated and eluted on a silica gel column (10% ethyl acetate in hexane) to afford γ-lactone **27** (220 mg, 0.90 mmol, 90%) as a colorless oil: IR (neat, cm^{-1}) ν(CO) 1767(s), 1738(s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 6.7 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H), 1.2−1.7 (m, 18H), 3.30−3.40 (m, 1H), 4.10−4.30 (m, 2H), 4.66−4.72 (m, 1H), 5.42 (d, J = 3.4 Hz, 1H), 5.85 (d, J = 2.0 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 8.13 (d, J = 8.8 Hz, 2H), 8.28 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 14.1, 19.0, 22.1, 24.7, 29.2, 29.3, 29.5, 30.5, 31.7, 36.3, 45.4, 66.3, 74.7, 78.3, 123.7, 125.3, 131.1, 133.8, 134.6, 151.1, 163.8, 167.3, 168.9; HRMS calcd for $C_{26}H_{35}O_8N$ 489.2363, found 489.2367.

Synthesis of γ-Lactone 28 A mixture of the *p*-nitrobenzoate **28** (147 mg, 0.30 mmol) and freshly fused K_2CO_3 (21 mg, 0.15 mmol) in dry ethanol (3 mL) was stirred at 23 °C for 3 min and quenched with a saturated NH_4Cl solution. The organic layer was extracted with ethyl acetate. The extract was dried over $MgSO_4$, concentrated, and purified on a silica gel column (30% ethyl acetate in hexane) to afford compound **28** (91 mg, 2.68 mmol, 89%): IR (neat, cm^{-1}) ν(CO) 1770, 1760; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (t, J = 6.7 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3 H), 1.10−1.70 (m, 18 H), 3.08 (bs, 1 H), 3.20 (d, J = 3.2 Hz, 1H), 4.10−4.25 (m, 2 H), 4.33 (bs, 1H), 4.45−4.50 (m, 1H), 5.76 (d, J = 2.2 Hz, 1H), 6.34 (d, J = 2.5 Hz, 1H); ^{13}CNMR (100 MHz) δ 13.6, 14.1, 19.1, 22.7, 24.7, 29.2, 29.3, 29.4, 30.47, 31.9, 36.2, 47.7, 66.5, 72.1, 78.3, 124.1, 135.4, 169.6, 172.7; HRMS calcd for $C_{19}H_{32}O_5$ 340.2250, found 340.2245.

Synthesis of Avenociolide 3. A mixture of γ-lactone **28** (68 mg, 0.20 mmol) and *p*-TSA·H_2O (76 mg, 0.40 mmol) in d_8-toluene (0.60 mL) in a sealed NMR tube was heated at 150 °C for 4 h. The reaction mixture was concentrated and eluted on a preparative silica plate (50% ethyl acetate in hexane) to afford avenaciolide **3** (34 mg, 0.13 mmol 65%) and isoavenociolide **4** (2.8 mg, 1.05 × 10^{-2} mmol, 5%). Spectral data for **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 6.7 Hz, 3H), 1.20−1.60 (m, 15 H), 1.70−1.90 (m, 2H), 3.55 (m, 1H), 4.40 (m, 1H), 5.04 (d, J = 8.5 Hz, 1H), 5.86 (d, J = 2.0 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.7, 24.9, 29.2, 29.4, 31.8, 36.3, 44.3, 74.4, 85.3, 126.3, 134.7, 167.6, 169.8; HRMS calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1516.

Synthesis of Chloropropargyl Compound 29. To a solution of propargyl chloride (2.35 mL, 32.5 mmol) in 50 mL of ether at −78 °C under nitrogen was added *n*-BuLi (1.6 M in hexane, 18.7 mL, 30 mmol) dropwise at −78 °C over a period of 30 min. To this stirring acetylide solution at −78 °C was added a ether solution of diethyl ketomalonate (4.35 g, 25.0 mmol) in a period of 10 min. The mixture was slowly allowed to warm to −60 °C over 3.0 h and quenched by a dropwise addition of acetic acid (2 mL, 35 mmol) at −60 °C. The resulting mixture was slowly warmed to 23 °C, and water (50 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic solution was dried over $MgSO_4$, concentrated, and purified on a silica gel column (10% ethyl acetate in hexane) to yield the alcohol **29** as a colorless oil (2.5 g, 10.1 mmol, 40%): IR (neat, cm^{-1}) ν(OH) 3460(vs), ν(CO) 1747(s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, J = 7.6 Hz, 6H), 4.18 (s, 2H), 4.32 (q, J = 7.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 29.8, 63.9, 72.6, 79.9, 81.6, 166.8; HRMS calcd for $C_{10}H_{13}ClO_5$ 248.0452, found 248.0448.

Synthesis of Propargyltungsten Complex 30. To a THF solution (40 mL) of $NaCpW(CO)_3$ (ca. 8.0 mmol) at 0 °C was added dropwise a solution (THF, 5 mL) of chloropropargyl derivative **29** (995 mg, 4.0 mmol), and the mixture was stirred at 23 °C for 12 h. The reaction mixture was filtered through a deactivated basic alumina with THF as a eluent, and concentration of the filterate yielded propargyltungsten **30** as a yellow viscous solid (2.10 g, 3.84 mmol, 96%): IR (neat, cm^{-1}) ν(OH) 3391(vs), ν(CO) 2016(s), 1913(s), 1740(s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, J = 7.0 Hz, 6H), 1.95 (s, 2H), 4.31 (q, J = 7.0 Hz, 4H), 5.56 (s, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −33.4, 14.1, 63.4, 86.7, 90.7, 92.8, 98.2, 168.1, 191.2, 216.5, 228.9. Anal. Calcd for $C_{18}H_{18}WO_8$: C, 39.58; H, 3.32. Found: C, 39.55; H, 3.40.

Synthesis of Tungsten-π-Allyl Complex 31. To a CH_2Cl_2 (15 mL) solution of the propargyltungsten complex **30** (1.64 g, 3.00 mmol) were added *p*-TSA (570 mg, 3.00 mmol) and methanol (2.43 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The reaction mixture was warmed to 23 °C and stirred for an additional 2 h. The resulting reaction was recooled to 0 °C and quenched with 25 mL of a saturated $NaHCO_3$ solution. The organic layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers was dried, evaporated, and purified on a silica gel column (1:1 ether/hexane) to afford tungsten−π-allyl complex **31** in 65% yield (1.07 g, 1.95 mmol): IR (neat, cm^{-1}), ν(CO) 1962(s), 1885(s), 1775(s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28−1.37 (m, 6H), 1.63 (d, J = 3.72 Hz, 1H), 3.17 (d, J = 3.78 Hz, 1H), 3.72 (s, 1H), 4.16−4.50 (m, 4H), 5.37 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.2, 58.8, 62.8, 63.5, 85.1, 89.6, 94.5, 165.1, 165.9, 173.6, 216.9, 222.3. Anal. Calcd for $C_{18}H_{18}WO_8$: C, 39.58; H, 3.32. Found: C, 39.33; H, 3.45.

Synthesis of Bislactone 33. To a solution of the tungsten−π-allyl complex **32** (900 mg, 1.65 mmol) in acetonitrile (8.5 mL) at 0 °C was added solid $NOBF_4$ (193 mg, 1.65 mmol) under nitrogen and the mixture stirred at 0 °C for 30 min. To this mixture at 0 °C was added NaI (494 mg, 3.30 mmol), and the solution was stirred for further 30 min at 0 °C. To the above mixture was added nonaldehyde (703 mg, 4.94 mmol) at 0 °C, and the mixture was allowed to warm to 23 °C and stirred for 24 h. The reaction was quenched with MeOH (1.6 mL) and evaporated under reduced pressure. The crude product was purified on a silica column (30% ethyl acetate in hexane) to afford bislactone (346 mg, 1.02 mmol, 62%): IR (neat), ν(CO) 1790 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 6.7 Hz, 3H), 1.20−1.80 (m, 17H), 4.01 (m, 1H), 4.34 (q, J = 7.0 Hz, 2H), 4.87 (m, 1H), 5.90 (d, J = 2.3 Hz, 1H), 6.63 (d, J = 2.8

Hz, 1H); ^{13}C NMR (100 MHz) δ 13.7, 13.6, 22.4, 25.9, 28.9, 29.1, 31.5, 31.6, 46.6, 63.4, 80.6, 82.3, 129.6, 130.0, 164.9, 166.6, 167.7; HRMS calcd for $C_{18}H_{26}O_6$ 338.1729, found 338.1730.

Synthesis of Isoavenociolide 4. To a solution of bislactone **33** (68 mg, 0.2 mmol) in dimethylacetamide (0.6 mL) was added $MgCl_2 \cdot 6H_2O$ (203 mg, 1.0 mmol), and the solution was heated at 150 °C for 3 h. After removal of solvent under reduced pressure at 70 °C, to the residue was added water (0.5 mL), and the organic product was extracted with ethyl acetate. The extracts were dried over $MgSO_4$ and concentrated. Elution of the residue through a short silica bed yield isoavenaciolide **4** as a colorless solid (mp 99 °C, 28 mg, 0.105 mmol, 52%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 7 Hz, 3H), 1.20−1.80 (m, 14H), 3.98 (m, 1H), 4.74 (m, 1H), 5.10 (d, J = 8.8 Hz, 1H), 5.86 (d, J = 2.2 Hz, 1H), 6.60 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz) δ 14.1, 22.7, 26.1, 29.0, 29.2, 29.4, 31.8, 32.4, 41.8, 74.9, 80.6, 129.0, 130.9, 130.9, 167.9, 170.1; HRMS calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1521.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **2**, **3**, **4**, and **6**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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