Total Synthesis of (+)-Blastmycinone, (−)-Litsenolide C_1, and Related Natural Trisubstituted Lactones via Alkynyltungsten Compounds

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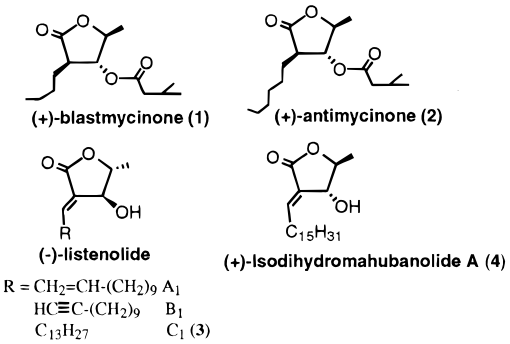
A general method for total synthesis of natural trisubstituted γ-lactones is developed on the basis of the chemistry of alkynyltungsten compounds. The key step in this approach involves the cycloalkenation of tungsten−η^1-(3*R*,4*S*)-pent-1-yne-3,4-diol with aldehydes to give tungsten−oxacarbenium salts, further leading to 3-alkylidene-4-hydroxy-5-methyl-γ-lactones upon demetalation. This synthetic sequence proceeds well for alkynylaldehydes and the MOM derivative of tungsten−η^1-(3*R*,4*S*)-pent-1-yne-3,4-diol. The resulting butyrolactone products are transformed into natural trisubstituted butyrolactones including (+)-blastmycinone, (+)-blastmycinolactol, (+)-antimycinone, NFX-2, and (+)-isodihydromahubanolide A. By using the same approach based on (*R*)-ethyl lactate, the natural (−)-litsenolide C_1 can be prepared in a few steps.

Introduction

A facile and stereocontrolled construction of functionalized butyrolactone skeletons has attracted considerable attention.[1,2] Many natural compounds exhibit potent biological activities that are attributed to their butyrolactone cores.[1,2] 3-Alkyl- or 3-alkylidene-4-oxygenated butyrolactones have been isolated from various natural sources. Scheme 1 shows two important polyketide metabolites, (+)-blastmycinone (**1**) and (+)-antimycinone (**2**), which are known to be hydrolysis products of (+)-antimycin A_3.[3] The latter is an antibiotic reagent effective against fungi and yeast. The three contiguous chiral centers in structures of **1**−**2** pose a significant challenge for synthetic chemists.[4] Also shown in Scheme 1 are

Scheme 1



natural lactones (−)-litsenolide C_1 (**3**) and (+)-isodihydromahubanolide A (**4**) which were isolated from the roots of the Japanese shrub *Litsea japonica* and the trunk wood of the Amazonian Mahuba tree, respectively.[5] Among several natural litsenolides, (−)-litsenolide C_1 is our selected target molecule for synthesis.[6a,b] Numerous methods have been developed for total synthesis of (+)-blastmycinone (**1**), (+)-antimycinone (**2**), (+) and (−)-litsenolide C_1 (**3**), and (+)-isodihydromahubanolide A (**4**) (Scheme 1). The syntheses of lactones **3**−**4** generally require longer procedures[6] than those for compounds **1**−**2**.[4] Among them, only one method involves the use of a transition-metal reagent as the key step. Mori reported[4c] the total synthesis of (+)-blastmycinone (**1**) and (+)-antimycinone (**2**) using chromium carbene reagents.

We reported that tungsten−α,δ- and -α,ϵ-alkynol species undergo cycloalkenation with aldehydes and BF_3•

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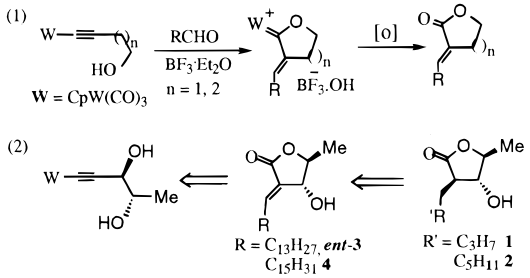
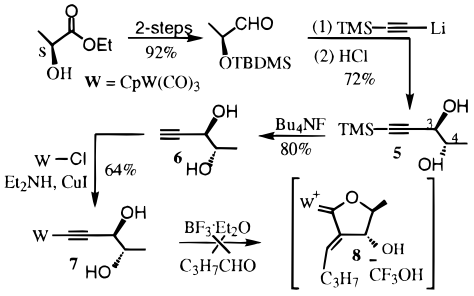
Scheme 2



Scheme 3



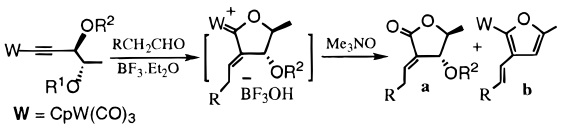
Et_2O to afford tungsten−oxacarbenium salts.[7] Oxidative demetalations of these carbenium salts afforded α-alkylidene-γ- and -ϵ-lactones (Scheme 2, eq 1). We applied this reaction to a short synthesis of natural bicyclic lactones such as mitsugashiwalactone and onikulactone.[7b] To highlight the use of this cycloalkenation reaction, we report here the total synthesis of enantiopure **1**−**4** according to the protocol shown in Scheme 2 (eq 2). In contrast with other methods, this synthetic design provides an entry to (+)-litsenolide C_1 (*ent*-**3**) and (+)-isodihydromahubanolide A (**4**), further leading to (+)-blastmycinone (**1**) and (+)-antimycinone (**2**).

Results and Discussion

We first target the enantioselective synthesis of (+)-blastmycinone (**1**) and (+)-antimycinone (**2**) which requires enantiopure (3*R*,4*S*) 4-pentyne-3,4-diol (**5**). Diol **5** is easily prepared from (*S*)-ethyl lactate by following a conventional synthesis (Scheme 3).[4c] After desilylation, the resulting chiral diol **6** was metalated with $CpW(CO)_3$ via treatment with $CpW(CO)_3Cl$ and CuI catalyst (3 mol %) in Et_2NH;[8] the yield of the resulting tungsten−η^1-(3*R*,4*S*)-pent-1-yne-3,4-diol **7** was 64%.

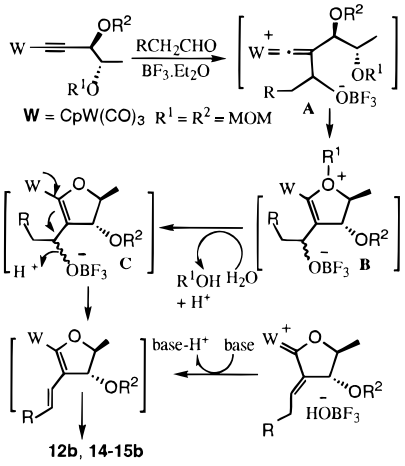
The reaction of chiral alkynyltungsten complex **7** with hexanal (1.5 equiv) and $BF_3{\cdot}Et_2O$ (1.5 equiv) in cold diethyl ether (−40 °C) failed to yield the desired oxacarbenium precipitate **8** but gave a complicated mixture of products. In this case, tungsten−diol **7** was recovered in 35% yield. Protection of the C3-alcohol of compound **7** appears to be a solution. Alkynyltungsten compounds **9**−**11** were prepared to solve the problem. Scheme 4 (entries 1−2) shows the results for cycloalkenation of compounds **9**−**10** with hexanal (2−3 equiv) and $BF_3{\cdot}Et_2O$ (1.0 equiv) in cold diethyl ether. The oxacarbenium precipitates forming in diethyl ether were collected on filtration and subsequently demetalated via treatment

Scheme 4



entry	alkynyltungsten	RCH_2CHO	products (yields)
1	R^1=H ; R^2 = MOM (**9**)	R = C_4H_9	**12a** (5%), **12b** (31%)
2	R^1=H ; R^2 = OMe (**10**)	R = C_4H_9	**13a** (6%), **12b** (31%)
3	R^1= MOM ; R^2 = MOM (**11**)	R = C_4H_9	**12a** (21%), **12b** (60%)
4	R^1= MOM ; R^2 = MOM (**11**)	R = C_2H_5	**14a** (18%), **14b** (61%)
5	R^1= MOM ; R^2 = MOM (**11**)	R = $C_{12}H_{25}$	**15a** (15%), **15b** (58%)

Scheme 5



with Me_3NO in CH_2Cl_2. The results are shown in Scheme 4. The desired α-alkylidene-γ-lactones **12a** and **13a** were obtained in low yields (5−6%) and the starting alkynyltungsten compounds **9**−**10** were recovered in 42% and 41% yields, respectively. Compared to previous tungsten−α,δ-alkynols in such reactions (Scheme 2, eq 1),[7] the presence of additional OR^2 groups (R^2 = MOM and OMe) in compounds **9**−**10** apparently decreases the acidity of $BF_3{\cdot}Et_2O$. However, the use of two MOM protecting group as in compound **11** effected the cycloalkenation to give **12a** and **12b** in 21% and 60%, respectively (entry 3). This result indicated formation of tungsten−oxacarbenium salts, but the tungsten−furyl compound **12b** was formed as the major product. This phenomenon seems to be common for those cases involving aliphatic aldehydes (entries 4−5).

Scheme 5 illustrates a mechanism to account for the high yields of tungsten−furyl complexes **12b**, **14b**, and **15b**. The two MOMO groups of alkynyltungsten compound **11** do not decrease the acidity of $BF_3{\cdot}Et_2O$ significantly and still effect the cycloalkenation to afford tungsten−allenylidenium intermediate **A**. It is unlikely that cleavage of the MOM−O bond by $BF_3{\cdot}Et_2O$ can proceed under the chosen conditions (−40 °C).[9] We proposed a direct attack of the OR^1 group at the central allenyl carbon of **A**[10] to afford oxonium species **B**. Attack of any basic species such as water facilitates removal of the R^1 group from this oxonium center, further leading

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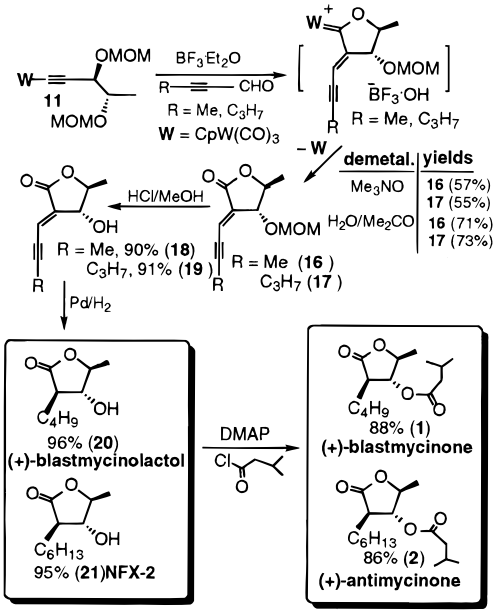
Scheme 6



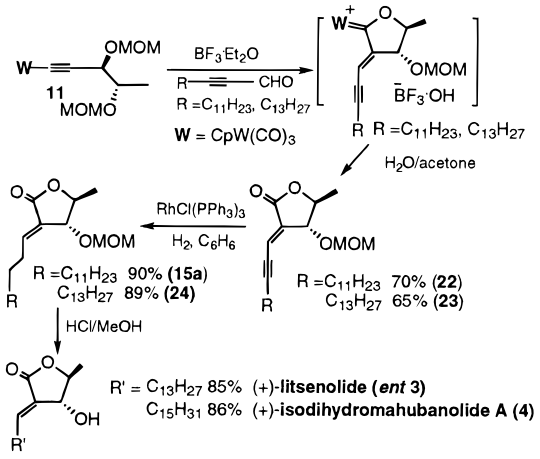
to species **C**. The proton released in this reaction cleaves the C−OBF_3^- bond to generate the desired oxacarbenium salt. This pathway can account for selective cleavage of the terminal OMOM group. The R^1OH released in conversion of **B** to **C** can be used again to cleave the R^1−O bond of species **B** to effect the reaction.

One problem in this reaction scheme is the significant amount of tungsten−η^1-furyl compounds **12b**, **14b**, and **15b** that are presumably produced on deprotonation of the allyl proton of oxacarbenium salts.[11] The acidity of this allyl proton is enhanced by the carbenium center and OR^2. We made vigorous efforts to perform demetalation of tungsten−oxacarbenium salts in neutral and acidic conditions including H_2O/air, I_2, m-CPBA, H_2O_2, or Ce(IV)-oxidation,[12] but the results were fruitless. This problem is finally circumvented by replacement of aliphatic aldehydes with alkynylaldehydes.

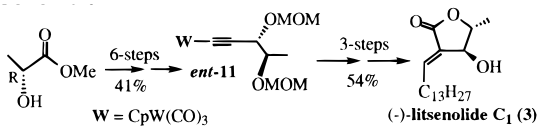
Shown in Scheme 6 is an improved synthesis of α-alkylidene-γ-lactones in a cycloalkynation of alkynyltungsten compound **11** with 2-butynal and 2-hexynal. The resulting oxacarbenium salts were subsequently demetalated with Me_3NO, yielding unsaturated lactones **16** and **17** in 57% and 55% yields, respectively. The yields of γ-lactones **16** and **17** were increased to 71 and 73%, respectively, on treatment with H_2O/acetone. Removal of the protected MOM groups of **16** and **17** was achieved by hydrolysis with HCl in MeOH to give alcohols **18** and **19** in good yields. Hydrogenation of the alcohols **18** and **19** over Pd/C catalyst ($[H_2] = 1.0$ atm) in MeOH afforded (+)-blastmycinolactol (**20**) and NFX-2 (**21**) with excellent diastereoselectivities; the yields are 96% and 95%, respectively. Hydrogenation of the trisubstituted olefins of compounds **18** and **19** proceeds preferably from the side with the hydroxy groups.[13]

These two natural alcohols were acetylated with isovaleryl chloride and DMAP in CH_2Cl_2 to give (+)-blastmycinone (**1**) and (+)-antimycinone (**2**) in 88% and 86% yields, respectively. Spectral data of trisubstituted γ-lactones **1** and **2** are identical to those reported for authentic samples.[3]

Scheme 7



Scheme 8



Our synthetic approach is also applicable to the synthesis of (+)-lisenolideC_1 (**3**) and (+)-isodihydromahubanolide A (**4**). Treatment of alkynyltungsten compound **11** with RC≡CCHO (R = $C_{13}H_{27}$, $C_{11}H_{23}$) and BF_3·Et_2O in diethyl ether formed the corresponding oxacarbenium precipitates (Scheme 7). Subsequent hydrolysis of these salts in acetone afforded the unsaturated γ-lactones **22** and **23** in 70% and 65% yields, respectively. The alkyne groups of γ-lactones **22** and **23** were selectively hydrogenated[14] by Wilkinson catalyst $RhCl(PPh_3)$ (H_2 = 1 atm, 23 °C) in benzene over 3 days. The resulting unsaturated lactones **15a** and **24** were obtained in 90% and 89% yields, respectively. Treatment of compounds **15a** and **24** with HCl in MeOH effected removal of the MOM groups to give the desired (+)-litsenolide (**3**) and (+)-isodihydromahubanolide A (**4**) in good yields. Spectral data of these two natural lactones **3** and **4** are consistent with those reported for authentic samples.[5]

The preceding chiral litsenolide C_1 (*ent*-**3**) has a configuration opposite that of the natural compound. We therefore prepared alkynyltungsten (*ent*-**11**) from commercially available (*R*)-methyl lactate by following the same sequence. Natural (−)-litsenolide-C_1 (**3**) was obtained in 22% overall yield by using such a nine-step synthesis based on (*R*)-methyl lactate. Spectral data of **3** ($[\alpha]^{25}_D = -45.0°$ ($c = 0.5$, dioxane) are consistent with those ($[\alpha]^{lit.} = -45.2°$, dioxane) of an authentic sample.[5b]

Summary. We have employed tungsten−η^1-(3*R*,4*S*)-pent-1-yne-3,4-diol for the total synthesis of natural trisubstituted γ-lactones. The key step is alkenylation of MOM derivatives of this chiral alkynyltungsten species with alkynylaldehydes and BF_3·Et_2O. The resulting oxacarbenium salts were demetalated with H_2O in acetone, affording 2-alkylidene-3-hydroxy-γ-lactones in good yields. This method provides an easy entry to (−)-litsenolide-C_1 (**3**) and (+)-isodihydromahubanolide A (**4**)

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and leads further to (+)-blastmycinone (**1**) and (+)-antimycinone (**2**).

Experimental Section

Unlessotherwise noted, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using a standard syringe, cannula, and septa apparatus. Benzene, diethyl ether, tetrahydrofuran, and hexane were dried with sodium benzophenone and distilled before use. Dichloromethane was dried over CaH_2 and distilled before use. $W(CO)_6$, sodium, dicyclopentadiene, trimethylsilylacetylene, (*S*)-ethyl lactate, and (*R*)-methyl lactate were obtained commercially and used without purification. $CpW(CO)_3Cl$ was prepared according to the literature method.[16] Spectral data of compounds **9**, **10**, **11**, **13a**, **14a**, **14b**, **15a**, and **15b** in repetitive experiments are provided in the Supporting Information.

1-Trimethylsilyl-(3*R*,4*S*)-pent-1-yne-3,4-diol (5). To a THF solution (100 mL) of trimethylsilylacetylene (5.33 g, 54.2 mmol) was added *n*-BuLi (21.7 mL, 2.5 M in hexane) at −78 °C; the mixture was stirred for 1 h before (*S*)-2-*tert*-butyldimethylsilyoxypropanal (8.50 g, 45.2 mmol) was added. The mixture was stirred for 1 h before addition of a saturated NH_4Cl solution. The organic layer was extracted with diethyl ether and concentrated to give a colorless oil. To a THF solution (50 mL) of this oil was added HCl (6 N, 30 mL), the mixture was stirred for 12 h, and the organic layer was extracted with ethyl acetate. The extract was washed with a saturated $NaHCO_3$ solution and dried over $MgSO_4$ to give a crude oil of compound **5** consisting of two diastereomers in a 13:1 ratio. Elution of this oil through a silica column (diethyl ether/hexane = 1/5) produced a pure oil of diol **5** (3.47 g, 20.2 mmol) and a 6:1 mixture of two isomers (3.13 g, 18.2 mmol). Elution of the latter over a silica column afforded pure compound **5** (2.12 g, 12.3 mmol). The combined yields were 72%. $[\alpha]^{25}_D = -13.2°$ (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): *ν*(OH) 3450 (br, s), *ν*(C≡C) 2154 (w), *ν*(C=C) 1648 (w). ^1H NMR (400 MHz, $CDCl_3$): *δ* 0.17 (s, 9H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.82 (br, 2H), 3.84 (dq, *J* = 6.0, 3.6 Hz, 1H), 4.27 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* −0.3, 17.5, 66.9, 69.9, 91.3, 103.1. MS: *m*/*z* (%): 172. HRMS: calcd for $C_8H_{16}SiO_2$ 172.0920, found 172.0923.

(3*R*,4*S*)-Pent-1-yne-3,4-diol (6). To a THF (100 mL) solution of compound **5** (4.80 g, 25.7 mmol) was added Bu_4NF (29.4 mL, 1.0 M THF), and the mixture was stirred for 2 h at 0 °C. To the solution was added a saturated NH_4Cl solution, followed by extraction with ethyl acetate and drying over $MgSO_4$. Elution of the residues through a short silica column gave the diol as a colorless oil (2.14 g, 17.9 mmol, 80%). $[\alpha]^{25}_D = -6.63°$ (*c* 0.80, $CHCl_3$). IR (neat, cm^{-1}): *ν*(OH) 3445 (br, s), *ν*(C≡C) 2144 (w), *ν*(C=C) 1645 (w). ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.25 (dd, *J* = 6.8, 1.2 Hz, 3H), 2.49 (d, *J* = 2.0 Hz, 1H), 2.61 (br, 1H), 3.18 (br, 1H), 3.90 (m, 1H), 4.29 (dd, *J* = 2.8, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 17.7, 66.5, 69.9, 74.8, 81.3. HRMS: calcd for $C_5H_8O_2$ 100.0524, found 100.0513.

$CpW(CO)_3$−[η^1-(3*R*,4*S*)-Pent-1-yne-3,4-diol] (7). To a Et_2NH solution (50 mL) of $CpW(CO)_3Cl$ (6.08 g, 16.5 mmol) were added CuI (0.28 g, 2.02 mmol) and diol **6** (1.50 g, 15 mmol); the mixtures were stirred for 4 h at 0 °C. The solution was concentrated and eluted through a silica column to afford compound **7** as a viscous oil (4.50 g, 9.62 mmol, 64%). $[\alpha]^{25}_D = -7.30°$ (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): *ν*(OH) 3452 (br, s), *ν*(C≡C) 2154 (w), *ν*(CO) 2027 (s), 1939 (s). ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.20 (d, *J* = 6.0 Hz, 3H), 3.72 (d, *J* = 6.0, 4.4 Hz, 1H), 4.32 (d, *J* = 4.4 Hz, 1H), 5.59 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 18.0, 68.5, 68.7, 70.9, 91.4, 125.8, 212.0, 228.5. MS (72 eV, *m*/*e*) 432 (M^+). Anal. Calcd for $C_{13}H_{12}WO_5$: C, 36.14; H, 2.80. Found: C, 36.02; H, 2.83.

(4*R*,5*S*)-3-[(*E*)-*n*-Butylidene-4-methoxmethoxy-5-methyltetrahydro-2-furanone] (12a). To a diethyl ether solution of alkynyltungsten compound **9** (0.56 g, 1.18 mmol) were added hexanal (165 mg, 1.65 mmol) and $BF_3{\cdot}Et_2O$ (234 mg, 1.65 mmol) at −40 °C, and the mixture was stirred for 2 h before the temperature was raised to 23 °C over 8 h. During this period, red precipitates gradually formed. These precipitates were collected on filtration and dissolved in CH_2Cl_2 (25 mL). Compound **9** was recovered in 31% yield from the diethyl ether filtrate. To the CH_2Cl_2 solution was added Me_3NO (131 mg, 1.18 mmol), and the mixture was stirred for 30 min before addition of a saturated NH_4Cl solution. The organic layer was extracted with diethyl ether, concentrated, and eluted through a silica column to give lactone **12a** (14 mg, 0.059 mmol, 5.0%) and tungsten−η^1-furyl compound **12b** (181 mg, 0.37 mmol, 31%).

Spetral data for **12a**. $[\alpha]^{25}_D = -17.3°$ (*c* 0.5, $CHCl_3$). IR (neat, cm^{-1}): *ν*(CO) 1758 (s), *ν* (C=C) 1670 (w). ^1H NMR (400 MHz, $CDCl_3$): *δ* 0.26 (t, *J* = 7.2 Hz, 3H), 1.24−1.38 (m, 7H), 1.42−1.58 (m, 2H), 2.31 (m, 2H), 3.38 (s, 3H), 4.43 (s, 1H), 4.57 (dq, *J* = 6.8, 1.6 Hz, 1H), 4.66 (dd, *J* = 7.6 Hz, 2H), 7.01 (dt, *J* = 7.6, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 13.9, 19.6, 22.4, 28.0, 29.8, 31.4, 56.0, 76.3, 80.3, 95.1, 126.6, 149.0, 169.9. HRMS: calcd for $C_{13}H_{22}O_4$ 242.1518, found 242.1507.

Spectral data for **12b**. IR (neat, cm^{-1}): *ν*(CO) 2024 (s), 1920 (s). ^1H NMR (400 MHz, $CDCl_3$): *δ* 0.90 (t, *J* = 6.8 Hz, 3H), 1.33−1.41 (m, 4H), 2.17 (m, 2H), 2.24 (s, 3H), 5.51 (s, 5H), 5.71 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.02 (s, 1H), 6.08 (d, *J* = 15.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 13.8, 13.9, 22.1, 31.9, 33.0, 91.6, 105.1, 124.8, 127.8, 142.3, 159.3, 214.4, 227.6. MS (72 eV, *m*/*z*) 496. Anal. Calcd for $C_{17}H_{16}WO_4$: C 45.99, H 4.06. Found: C 45.76, H 4.25.

(4*R*,5*S*)-3-[(*E*)-2-Butynylidene]-4-(methoxymethoxy)-5-methyltetrahydro-2-furanone] (16). This compound was prepared similarly from alkynyltungsten compound **11**, 2-butynal, and $BF_3{\cdot}Et_2O$ except that the resulting oxacarbenium salts were demetalated upon stirring its acetone solution with water for 4 h at 23 °C under air. Workup of the solution gave *γ*-lactone **16** in 71% yield. $[\alpha]^{25}_D = -13.6°$ (*c* 0.9, $CHCl_3$). IR (neat, cm^{-1}): *ν*(C≡C) 2180 (s), *ν*(CO) 1754 (s), *ν*(C=C) 1647 (m). ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.32 (d, *J* = 6.8 Hz, 3H), 2.06 (d, *J* = 2.8 Hz, 3H), 3.39 (s, 3H), 4.52 (s, 1H), 4.56 (dq, *J* = 6.8, 1.6 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 6.76 (dq, *J* = 2.8, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 5.0, 19.5, 55.8, 76.2, 76.7, 80.6, 95.9, 102.4, 124.0, 135.8, 168.9. MS (72 eV, *m*/*z*) 210 (M^+). HRMS: calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0888.

(4*R*,5*S*)-3-[(*E*)-2-Hexynylidene]-4-(methoxymethoxy)-5-methyltetrahydro-2-furanone] (17). This compound was prepared similarly from alkynyltungsten compound **11**, 2-hexynal, and $BF_3{\cdot}Et_2O$ except that the resulting oxacarbenium salts were demetalated with H_2O in acetone; the yield of *γ*-lactone **17** was 73%. $[\alpha]^{25}_D = -27.8°$ (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): *ν*(C≡C) 2216 (w), 1645 (w). ^1H NMR (400 MHz, $CDCl_3$): *δ* 0.99 (t, *J* = 7.6 Hz, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.59 (tq, *J* = 7.6, 7.2 Hz, 2H), 2.40 (dt, *J* = 7.2, 2.4 Hz, 2H), 3.40 (s, 3H), 4.51 (dd, *J* = 2.0, 1.6 Hz, 1H), 4.57 (dq, *J* = 6.8, 2.0 Hz, 1H), 4.67 (d, *J* = 7.2 Hz, 1H), 4.88 (d, *J* = 7.2 Hz, 1H), 6.81 (dt, *J* = 2.4, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 13.4, 19.4, 21.6, 22.0, 55.7, 77.1, 77.1, 80.7, 96.1, 106.8, 124.0, 135.6, 168.8. HRMS: calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1209.

(4*R*,5*S*)-3-[(*E*)-2-Butynylidene]-4-hydroxy-5-methyltetrahydro-2-furanone] (18). A MeOH (15 mL) solution of compound **16** (0.25 g, 1.19 mmol) was heated to 60 °C, and to the solution was added concentrated HCl (1.75 mL). The resulting mixture was stirred for 30 min before addition of a saturated $NaHCO_3$ solution (ca. 5 mL). The solution was extracted with CH_2Cl_2, dried over $MgSO_4$, and chromatographed over a short silica column to afford compound **18** as a colorless oil (178 mg, 1.06 mmol, 90%). $[\alpha]^{25}_D = +56.0°$ (*c* 2.1, $CHCl_3$). IR (neat, cm^{-1}): *ν*(OH) 3418 (br), *ν*(C≡C) 2210 (w), *ν*(CO) 1748 (s), *ν*(C=C) 1647 (s). ^1H NMR (400 MHz,

(15) (*R*)-Methyl lactate and (*S*)-ethyl lactate have the same reaction sequence in their transformations into enantiomerically pure organic derivatives. See: (a) Grabowski, E. J. In *Handbook of Reagents for Organic Synthesis: Reagents, Auxiliaries and Catalysts for C−C bonds*; Coates, R. M., Denmark, S. E., Eds.; Wiley: West Sussex, 1999; p 389. (b) Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768.

(16) Dub, M. *Organometallic Compounds*, 2nd ed.; Springer-Verlag: Berlin, 1966; Vol. 1.

$CDCl_3$): δ 1.36 (d, J = 6.8 Hz, 3H), 2.09 (d, J = 2.4 Hz, 3H), 2.78 (br, 1H), 4.46 (dq, J = 6.8, 2.8 Hz, 1H), 4.64 (s, 1H), 6.70 (dq, J = 2.4, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.0, 19.4, 72.8, 75.3, 81.9, 103.2, 122.6, 138.4, 168.9. HRMS: calcd for $C_9H_{10}O_3$ 166.0630, found 166.0624.

(4*R*,5*S*)-3-[(*E*)-2-Hexynylidene]-4-(hydroxy)-5-methyltetrahydro-2-furanone] (19). This compound was prepared similarly by treatment of compound **17** with HCl in hot MeOH (60 °C, 30 min); the yield of compound **19** was 91%. $[\alpha]^{25}_D$ = +66.7° (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): ν(OH) 3427 (br, s), ν(CO) 1741 (s), ν(C=C) 1644 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, J = 7.6 Hz, 3H), 1.38 (d, J = 6.4 Hz, 3H), 1.60 (tq, J = 7.6, 7.2 Hz, 2H), 2.41 (dt, J = 7.2, 2.0 Hz, 2H), 4.46 (dq, J = 6.4, 2.8 Hz, 1H), 4.65 (dd, J = 2.8, 2.0 Hz, 1H), 6.73 (m, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 19.6, 21.7, 22.0, 73.2, 76.3, 81.7, 107.6, 122.4, 138.6, 168.7. HRMS: calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0943.

(+)-Blastmycinolactol (20). To a MeOH (15 mL) solution of compound **18** (0.15 g, 0.903 mmol) was added Pd/C (10 wt %, 9.44 mg) under a hydrogen atmosphere, and the solution was sealed with a hydrogen balloon. The solution was stirred for 24 h at 23 °C before being filtered over a Celite bed. The filtrate was dried over $MgSO_4$, concentrated, and chromatographed over a short silica column to yield (+)-blastmycinolactol **20** (0.149 g, 0.890 mmol, 96%) as a colorless solid (mp 49.9−50.7 °C, cf. lit. 49.5−51.0 °C). $[\alpha]^{25}_D$ = −18.7° (*c* 1.5, $CHCl_3$; $[\alpha]^{lit.}$ = −17.1°[4b] or −19.4°,[4g] $CHCl_3$). IR (neat, cm^{-1}): ν(OH) 3422 (br), ν(CO) 1748 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.2 Hz, 3H), 1.29−1.52 (m, 7H), 1.55−1.63 (m, 1H), 1.80−1.88 (m, 1H), 2.53 (ddd, J = 8.8, 7.6, 5.2 Hz, 1H), 3.82 (dd, J = 8.8, 7.2 Hz, 1H), 4.18 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 18.1, 22.5, 28.0, 28.7, 48.5, 78.6, 80.4, 177.1. HRMS: calcd for $C_9H_{16}O_3$ 172.1099, found 172.1095.

NFX-2 (21). This compound was prepared similarly by hydrogenation of compound **19** over Pd/C catalyst in MeOH; workup of the solution gave **19** as a solid (mp 55.5−57.6 °C, cf. lit 56−58 °C) in 91% yield. $[\alpha]^{25}_D$ = −16.6° (*c* 0.8, $CHCl_3$; $[\alpha]^{lit.}$ = −15.1°,[4g] MeOH); IR (neat, cm^{-1}): ν(OH) 3475 (br), ν(CO) 1741 (s); ν(C=C) 1641 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J = 6.8 Hz, 3H), 1.20−1.38 (m, 6H), 1.39−1.53 (m, 5H), 1.56 (m, 1H), 1.80 (m, 1H), 2.53 (m, 1H), 2.75 (br, 1H), 3.81 (dd, J = 8.0, 7.6 Hz, 1H), 4.18 (dq, J = 7.6, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 18.2, 22.51, 26.6, 28.4, 29.2, 31.5, 48.5, 78.8, 80.2, 176.7. HRMS: calcd for $C_{11}H_{20}O_3$ 200.1412, found 200.1410.

(+)-Blastmycinone (1). To a CH_2Cl_2 solution (2.0 mL) of (+)-blastmycinolactol **19** (140 mg, 0.813 mmol) were added DMAP (0.397 g, 3.25 mmol) and valeryl chloride (0.59 g, 4.88 mmol); the mixture was stirred for 24 h at 23 °C. To the solution was added $NaHCO_3$; the organic layer was extracted with CH_2Cl_2 solution, dried over $MgSO_4$, and chromatographed over a silica column to afford (+)-blastmycinone **1** (0.183 g, 0.72 mmol, 88%) as a colorless oil. $[\alpha]^{25}_D$ = + 11.2° (*c* = 2.0, $CHCl_3$; $[\alpha]^{lit.}$ = + 11.3° [3] in $CHCl_3$). IR (neat, cm^{-1}): ν(C≡C) 2199 (w), ν(CO) 1784 (s), 1742 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 3H), 0.94 (d, J = 6.8 Hz, 6H), 1.30−1.43 (m, 4H), 1.44 (d, J = 6.8 Hz, 3H), 1.62 (m, 1H), 1.83 (m, 1H), 2.11 (m, 1H), 2.20 (d, J = 7.6 Hz, 2H), 2.66 (dt, J = 8.8, 5.2 Hz, 1H), 4.34 (dq, J = 6.8, 4.8 Hz, 1H), 4.92 (dd, J = 5.2, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 19.4, 22.3, 22.3, 25.7, 28.9, 29.0, 43.1, 46.4, 78.4, 79.4, 172.4, 175.9. HRMS: calcd for $C_{14}H_{24}O_4$ 256.1675, found 256.1677.

(+)-Antimycinone (2). This compound was prepared similarly from NFX-2, valeryl chloride, and DMAP; the yield of (+)-antimycinone was 85% yield. $[\alpha]^{25}_D$ = +10.6° (*c* 1.0, $CHCl_3$; $[\alpha]^{lit.}$ = + 10.8° [3]). IR (cm^{-1}): ν(CO) 1775 (s), 1741 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, J = 6.4 Hz, 3H), 0.95 (d, J = 6.8 Hz, 6H), 1.20−1.38 (m, 6H), 1.38−1.50 (m, 5H), 1.56−1.66 (m, 1H), 1.80−1.91 (m, 1H), 2.08 (m, 1H), 2.20 (d, J = 8.0 Hz, 2H), 2.66 (dt, J = 8.4, 5.6, 1H), 4.34 (dq, J = 6.8, 4.8 Hz, 1H), 4.91 (dd, J = 5.6, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.4, 22.3, 22.5, 25.7, 26.7, 28.9, 29.3, 31.5, 43.1, 46.4, 78.4, 79.4, 172.4, 175.9. HRMS: calcd for $C_{16}H_{28}O_4$ 284.1988, found 284.1977.

(4*R*,5*S*)-4-Methoxymethoxy-5-methyl-3-((*E*)-2-tetradecynylidene)tetrahydro-2-furanone (22). This compound was prepared similarly from alkynyltungsten compound **11**, tetradecynylaldehyde, and $BF_3{\cdot}Et_2O$; the resulting oxacarbenium salt was demetalated with H_2O in acetone under air. Compound **22** was obtained as an oil in 70% yield. $[\alpha]^{25}_D$ = −14.6° (*c* 2.0, $CHCl_3$). IR (neat, cm^{-1}): ν(C≡C) 2201 (w), ν(CO) 1760 (s), ν(C=C) 1646 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J = 6.8 Hz, 3H), 1.22−1.26 (m, 16H), 1.34 (d, J = 6.8 Hz, 3H), 1.35−1.42 (m, 2H), 1.52−1.60 (m, 2H), 2.41 (dt, J = 7.2, 2.4 Hz, 2H), 3.40 (s, 3H), 4.51 (br, 1H), 4.57 (dq, J = 6.8 Hz, 2.4 Hz, 1H), 4.67 (d, J = 6.8 Hz, 1H), 4.88 (d, J = 6.8 Hz, 1H), 6.81 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.5, 20.1, 22.6, 28.2, 29.0, 29.3, 29.4, 29.6, 29.6, 29.6, 31.8, 55.8, 77.0, 77.1, 80.7, 96.1, 107.1, 124.1, 135.6, 168.9. HRMS: calcd for $C_{21}H_{34}O_4$ 350.2457, found 350.2451.

(4*R*,5*S*)-3-((*E*)-2-Hexadecynylidene)-4-(methoxymethoxy)-5-methyltetrahydro-2-furanone (23). This compound was prepared similarly from alkynyltungsten compound **11**, hexadecynylaldehyde, and $BF_3{\cdot}Et_2O$; the resulting oxacarbenium salt was demetalated with H_2O in acetone under air. Compound **23** was obtained as an oil in 65%. $[\alpha]^{25}_D$ = −28.1° (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): ν(C≡C) 2360 (s), ν(CO) 1759 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, J = 6.8 Hz, 3H), 1.23 (br, 20 H), 1.34 (d, J = 6.8 Hz, 3H), 1.58 (m, 2H), 2.41 (dt, J = 6.8, 2.4 Hz, 2H), 3.40 (s, 3H), 4.51 (dd, J = 2.4, 1.6 Hz, 1H), 4.57 (dq, J = 6.8, 1.6 Hz, 1H), 4.66 (d, J = 7.2 Hz, 1H), 4.88 (d, J = 7.2 Hz, 1H), 6.81 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.5, 20.0, 22.6, 28.2, 28.9, 29.0, 29.3, 29.4, 29.6, 29.6, 29.6, 29.6, 31.9, 55.8, 77.0, 77.1, 80.7, 96.1, 107.1, 124.1, 135.6, 168.9. HRMS: calcd for $C_{23}H_{36}O_4$ 378.2770, found 378.2774.

Improved Synthesis of (4*R*,5*S*)-4-Methoxymethoxy-5-methyl-3-((*E*)-2-tetradecylidene)tetrahydro-2-furanone (15a). To a benzene solution of unsaturated lactone **22** (50 mg, 0.132 mmol) was added $RhCl(PPh_3)_3$ (31 mg, 0.031 mmol) under a hydrogen atomsphere; the reaction flask was sealed with a balloon. The mixtures were stirred at 23 °C for 3 days before filtration through a short silica column. The solution was concentrated and eluted through a preparative silica plate to afford compound **15a** as a colorless oil (46 mg, 0.119 mmol, 90%). $[\alpha]^{25}_D$ = −6.0 (*c* = 0.8, $CHCl_3$). IR (neat, cm^{-1}): ν(CO) 1762 (s), ν(C=C) 1681 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, J = 6.8 Hz, 3H), 1.21−1.25 (m, 20 H), 1.31 (d, J = 6.4 Hz, 3H), 1.33−1.50 (m, 2H), 2.31 (dt, J = 8.0, 7.2 Hz, 2H), 3.39 (s, 3H), 4.43 (s, 1H), 4.59 (dq, J = 6.4, 1.6 Hz, 1H), 4.66 (dd, J = 7.2 Hz, 2H), 7.02 (dt, J = 8.0 Hz, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.7, 22.7, 28.4, 29.3 (2 peaks), 29.5 (4 peaks), 29.6 (2 peaks), 29.7, 31.9, 55.9, 76.4, 80.3, 95.1, 126.7, 148.9, 169.5. HRMS: calcd for $C_{21}H_{38}O_4$ 354.2770, found 354.2766.

(4*R*,5*S*)-3-((*E*)-2-Hexadecylidene)-4-methoxymethoxy-5-methyltetrahydro-2-furanone (24). This compound was prepared similarly by hydrogenation of unsaturated lactone **23** with $RhCl(PPh_3)_3$; the yield of compound **24** was 89%. $[\alpha]^{25}_D$ = −12.5° (*c* = 1.0, $CHCl_3$). IR (neat, cm^{-1}): ν(CO) 1763 (s), ν(C=C) 1678 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J = 6.8 Hz, 3H), 1.21−1.25 (m, 24H), 1.31 (d, J = 6.8 Hz, 3H), 1.41−1.57(m, 2H), 2.32 (dt, J = 7.6, 7.2 Hz, 2H), 3.39 (s, 3H), 4.44 (s, 1H), 4.59 (dq, J = 6.8, 1.2 Hz, 1H), 4.66 (dd, J = 6.8 Hz, 2H), 7.02 (dt, J = 7.6, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.7, 22.7, 28.4, 29.3, 29.3, 29.3, 29.3, 29.3, 29.3, 29.5, 29.5, 29.5, 29.6, 29.9, 31.9, 56.0, 73.6, 80.3, 95.1, 126.6, 149.1, 169.6. HRMS: calcd for $C_{23}H_{42}O_4$ 382.3083, found 382.3086.

(+)-Litsenolide C_1 (*ent*-3). This compound was prepared similarly by treatment of compound **15a** with concentrated HCl in MeOH (60 °C, 30 min); the yield was 85%. $[\alpha]^{25}_D$ = +45.0° (*c* = 0.5, dioxane; compound **3** $[\alpha]^{lit.}$ = −45.° [5b]). IR (neat, cm^{-1}): ν(OH) 3401 (br), ν(CO) 1736 (s), ν(C=C) 1677 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J = 6.8 Hz, 3H), 1.24 (s, 20H), 1.32 (d, J = 6.8 Hz, 3H), 1.32−1.50 (m, 2H), 2.38 (m, 2H), 4.48 (dq, J = 6.8 Hz, 2.0 Hz, 1H), 4.53 (s, 1H), 6.98 (dt, J = 8.0, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.6,

22.6, 28.4, 29.3 (3 peaks), 29.5 (7 peaks), 31.9, 72.1, 82.7, 129.3, 148.6, 169.7. HRMS: calcd for $C_{19}H_{34}O_3$ 310.2508, found 310.2506.

(+)-Isodihydromabubanolide A. This compound was prepared similarly by hydrolysis of compound **24** with concentrated HCl in MeOH (60 °C, 30 min); the yield was 86%. $[\alpha]^{25}_D = +36.7°$ ($c = 1.0$, $CHCl_3$; $[\alpha]^{lit.} = +36.6°$ [5]). IR (neat, cm^{-1}): ν(OH) 3548 (br s), ν(CO) 1741, ν(C=C) 1682 (w). ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, $J = 6.8$ Hz, 3H), 1.23 (br m, 24H), 1.32 (d, $J = 6.4$ Hz, 1.40- 1.52 (m, 2H), 1.78 (br s, 1H), 2.38 (m, 2H), 4.48 (dq, $J = 6.4$, 2.0 Hz), 4.53 (s, 1H), 6.98 (dt, $J = 8.0$, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.7, 22.6, 28.4, 29.3 (3 peaks), 29.5 (3 peaks), 29.7 (5 peaks), 31.9, 72.2, 82.6, 129.3, 148.7, 169.7. HRMS: calcd for $C_{21}H_{38}O_3$ 338.2821, found 338.2823.

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Supporting Information Available: Syntheses and spectral data of compounds **9**−**11**, **13a**, **14a**, **14b**, **15a**, **and 15b.** This material is available free of charge via the Internet at http://pubs.acs.org.

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