JOC*Article*

A Facile Synthesis of Enantiopure Tricyclic Furanyl and Pyranyl Derivatives via Tungsten-Mediated Cycloalkenation and Diels−Alder Reaction

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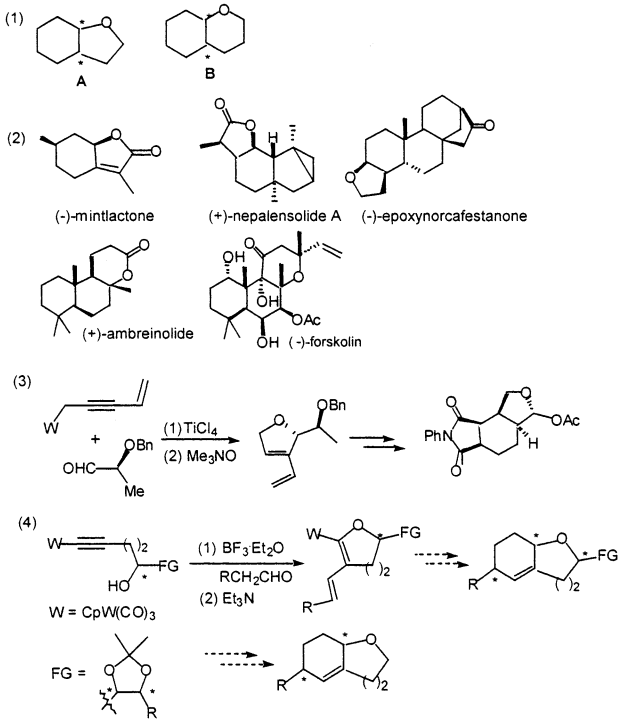
We report the synthesis of chiral furanyl and pyranyl dienes **1** and **2** based on cycloalkenation of chiral tungsten alkynol complexes. These two dienes bear a chiral 1,3-dioxolane group to control diastereoselective Diels−Alder reactions with electron-deficient olefins. The chiral 1,3-dioxolane substituents of the cycloadducts were degraded into hydrogen atoms to make these molecules possess common furan and pyran rings. Dienes **1** and **2** are good building blocks for enantiopure forms of tricyclic oxygen compounds.

Introduction

Enantiopure tricyclic furanyl and pyranyl derivatives with the frameworks **A** and **B** are often encountered in many naturally occurring compounds, particularly on terpenoids.[1] Scheme 1 shows several representatives with interesting biological activities.[1] The bicyclic ether frameworks **A** and **B** are also useful building blocks for complex bioactive molecules.[2] Synthesis of these bicyclic ether derivatives has attracted considerable attention.[2,3] The synthetic methods are quite diversified and lengthy. Furthermore, most previous studies have focused on the synthesis of racemic forms.[2,3] [4 + 2]-Cycloaddition of heterocyclic dienes with electron-deficient olefins is a useful method for synthesis of complex molecules.[4] One example is depicted in eq 3 (Scheme 1) which shows a facile synthesis of furanyl diene via [3 + 2]-cycloaddition of tungsten−vinylpropargyl complex with (2*S*)-2-(benzyloxy)propanal.[3e] This chiral diene is a good building block for chiral tricyclic furanyl derivatives through its diastereoselective Diels−Alder reaction with dienophile. Recently, we reported that treatment of alkynyltungsten compounds with $RCH_2CHO/BF_3{\cdot}Et_2O$ complex formed oxacarbenium salts[5] (Scheme 1, eq 4), further yielding tungsten-furanyl diene[5] efficiently. In this report, we describe a short synthesis of enantiomeric bicyclic ethers **A** based on this tungsten-mediated cyclization with the protocol shown in Scheme 1. The oxacyclic diene is

SCHEME 1



(1) For representative examples, see the following: (a) Flegel, M.; Adam, K.-L.; Becker, H. *Phytochemistry* **1999**, *52*, 1633. (b) Finnegan, R. A.; Djerassi, C. *J. Am. Chem. Soc.* **1960**, *82*, 4342. (c) Astudillo, L.; Gonzalez, A.; Galindo, A.; Mansilla, T. *Tetrahedron Lett.* **1997**, *38*, 6737 (d) Hijfte, L. V.; Vandewalle, M. *Tetrahedron* **1984**, *40*, 4371. (e) Carda, M.; Marco, J. A. *Tetrahedron* **1992**, *48*, 9789. (f) Talwar, K. K.; Singh, I. P.; Kalsi, P. S. *Phytochemistry* **1992**, *31*, 336. (g) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107. (h) Ohloff, G.; Vial, C.; Wolf, H. R.; Job, K.; Jejou, E.; Polonsky, J.; Lederer, E. *Helv. Chim. Acta*. **1980**, *63*, 205. (i) Maji, S. K.; Mukhopadhyaya, S. K.; Mukherjee, D.; Dutta, P. C. *J. Chem. Soc., Perkin Trans 1* **1980**, 2511.

(2) (a) Medebielle, M. *Tetrahedron Lett.* **1996**, *37*, 5119. (b) Backvall, J.-E.; Anderson, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 6374. (c) Takacs, J. M.; Weidner, J. J.; Newson, P. W.; Takacs, B. E.; Chidambaram, R.; Shoemaker, R. *J. Org. Chem*. **1995**, *60*, 3473. (d) Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1995**, *60*, 3473. (e) Itami, K.; Palmgren, A.; Backvall, J.-E. *Tetrahedron Lett*. **1998**, *39*, 1223.

(3) (a) Breitmaire, E.; Potthoff, B. *Chem. Ber.* **1986**, *119*, 3204 (b) Breitmaire, E.; Reffer, U. *Synthesis* **1989**, 623. 3204. (c) Cornwall, P.; Dell, C. P.; Knight, D. W. *J. Chem. Soc., Perkin Trans*. 1 **1993**, 2395. (d) Arrayas, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 6185. (e) Pei, C. C.; Liu, R. S. *Org. Lett*. **2001**, *3*, 1295.

(4) Review article of Diels−Alder reaction, see: Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 513.

(5) (a) Liang, K.-W.; Li, W.-T.; Lee, G.-H.; Peng, S.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **1997**, *119*, 4404. (b) Li, W.-T.; Lai, F.-C.; Lee, G.-H.; Peng, S.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **1998**, *120*, 4520.

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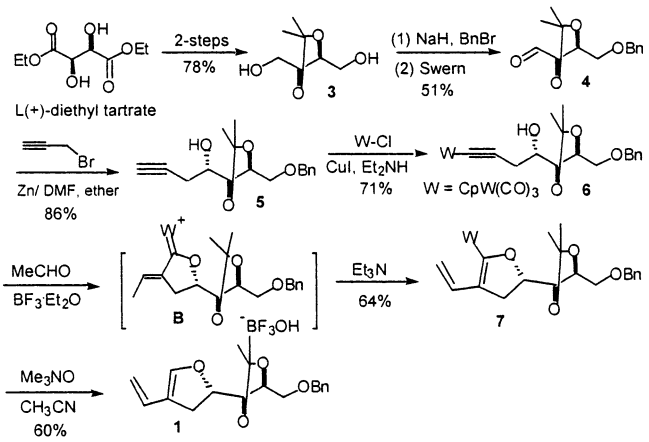
SCHEME 2



designed to bear a chiral dioxolane group. This substituent has roles in synthetic applications: (1) it controls the diastereoselectivity of [4 + 2]-cycloaddition and (2) it is easily degradable into a common functionality after cycloaddition.

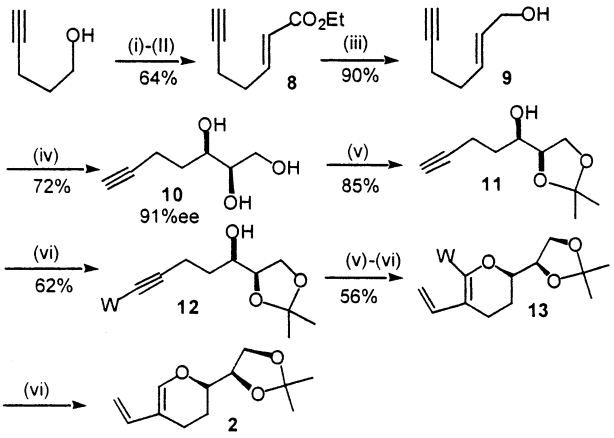
Results and Discussion

Scheme 2 shows the synthesis of chiral tungsten−alkynol **6** for the cyclization. The starting chiral diol **3** was prepared in two steps from L(+)-diethyl tartrate as described in the literature.[6] This diol was subsequently transformed into chiral alkynyl alcohol **5** according to method reported by Wu,[7] and the protocol is shown in Scheme 2. Treatment of alkynol **5** with $CpW(CO)_3Cl$ (1.1 equiv) and CuI catalyst (11.0 mol %) in Et_2NH effected metalation,[5] yielding tungsten−alkynol species **6** in 71% yield. Treatment of complex **6** with excess acetaldehyde in the presence of $BF_3{\cdot}Et_2O$ (1.5 equiv) in cold diethyl ether (−40 °C) produced a yellow oil, presumably a tungsten−oxacarbenium salt **B**.[5] Subsequent treatment of this salt with Et_3N (2.0 equiv) afforded tungsten−furanyl diene **7** in an overall yield of 64%. Hydrodemetalation of dienyl complex **7** with Me_3NO[3e] in CH_3CN gave the desired chiral diene **1** in 60% yield.

Scheme 3 shows a protocol for the synthesis of chiral tungsten−alkynol species **2**. Carbon elongation of 4-pentyn-1-ol was achieved by conventional methods including Swern oxidation, Wittig reaction, and Dibal reduction.

Asymmetric dihydroxylation of alcohol **9** with AD-mix-β[8] afforded chiral triol **10** in 72% yield with 91% ee. Triol **10** is present as a solid form, and crystallization from ether/hexane increased its ee value to 96% with a yield of 61%. Treatment of triol **10** with $Me_2C(OMe)_2$ and *p*-TSA catalyst (3.0 mol %) gave the dioxolane derivative **11**, which was converted to chiral tungsten−alkynol **12** by $CpW(CO)_3Cl$, Et_2NH, and CuI catalyst (11 mol %).

SCHEME 3[a]



[a] Conditions: (i) Swern oxidation, (ii) $(EtO)_3PCH_2CO_2Et$, (iii) Dibal-H, (iv) AD-mix β, $MeSO_2NH_2$, $BuOH/H_2O$, (v) $Me_2C(OMe)_2$, *p*-TSA/acetone, (vi) $CpW(CO)_3Cl$, CuI, Et_2NH, (v) MeCHO, $BF_3{\cdot}Et_2O$, Et_3N, (vi) Me_3NO, CH_3CN.

Compound **12** was smoothly converted to chiral diene **2**, using tungsten-mediated cycloalkenation as mentioned above.

Table 1 shows the Diels−Alder reaction of oxacyclic diene **1** with various reactive dienophiles. The dioxolane group of diene **1** effects diastereoselective Diels−Alder reaction under ambient conditions; the results are shown in Scheme 3. The reaction of diene **1** with maleic anhydride, maleic imide, and *N*-phenyl maleimide proceeded smoothly at 23 °C to give only one diastereomeric product **14**−**16** (dr > 20, entries 1−3). Crystallization from diethyl ether/hexane afforded the cycloadducts **14**−**16** in yields of 84−87%. This stereoselectivity is remarkable, because four isomers are likely to occur. Elucidation of the structures of cycloadduct **14** relies on the proton NOE map, which reveals that the H^3 proton is cis to the H^2 and H^4 protons but trans to the H^1-proton (Chart 1). This infers that the olefin approaches the diene in endo mode and opposite the chiral dioxolane group. In the presence of $Zn(OTf)_2$ (3.0 equiv), 1,4-benzoquinone and 1,4-naphthoquinone reacted with diene **1** at 23 °C to give cycloadducts in 8.2:1 and 13.1:1 diastereomeric mixtures, respectively, and finally gave pure **17** and **18** in respective yields of 76% and 79% after crystallization. It is fruitless to determine stereochemistry of the minor diastereomer of **17** and **18**, because their NMR resonances are largely overlapped with those of its major isomer. $BF_3{\cdot}Et_2O$ also effected cycloaddition of **1** with ethyl glyoxalate to give pure cycloadduct **19** in 85% yield after crystallization. The ^1H NOE map of compound **19** is shown in Supporting Information. Although the ee value of pyranyl diene **2** is 96%, its Diels−Alder cycloadducts **20**−**24** have ee values exceeding 98% (Merck, chiralsphere column) because of purification by crystallization.

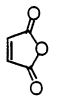
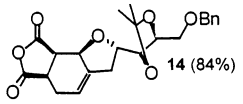
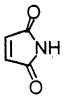
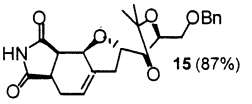
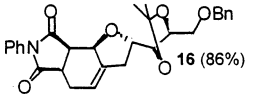
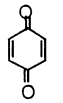
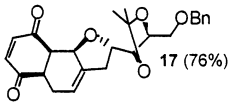
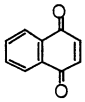
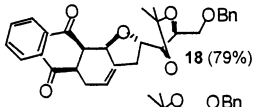
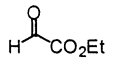
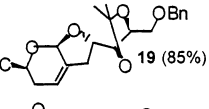
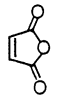
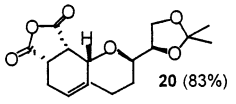
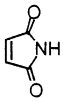
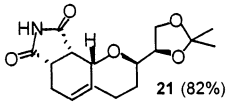
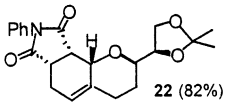
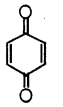
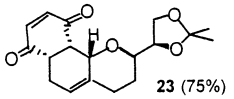
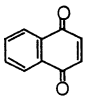
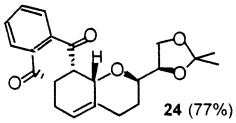
Table 1 also shows the results for the cycloaddition of chiral pyranyl diene **2** with the same olefins. Using the same approach, the cycloadducts **20**−**22** were obtained in yields of 82−83% after crystallization (entries 7−9). Again, the chiral dioxolane group of diene **2** has a pronounced effect on diastereoselectivity. In the presence of $Zn(OTf)_2$, pure 1,4-benzoquinone and 1,4-naphthoquinone adducts **23**−**24** were obtained in 8.1:1 and 11.1:1

(6) (a) Palomo, C.; Oiarbide, M.; Landa, A.; Esnal, A.; Linden, A. *J. Org. Chem*. **2001**, *66*, 4180. (b) Inouye, M.; Fujimoto, K.; Furusyo, M.; Nakazumi, H. *J. Am. Chem. Soc.* **1999**, *121*, 1452.

(7) Wu, W.-L.; Yao. Z.-J.; Li, J. C.; Xia, Y.; Wu, Y.-L. *J. Org. Chem.* **1995**, *60*, 3257.

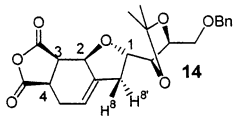
(8) (a) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 5. 448. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispimo, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H.; Morikawa, K.; Wang, Z.; Xu, D.; Zhang, X. *J. Org. Chem*. **1992**, *57*, 2786. (c) Crispimo, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z.; Xu, D.; Sharpless, K. B. *J. Org. Chem*. **1993**, *58*, 3785.

TABLE 1. Cycloaddition of Chiral Dienes 1−2 with Olefins

	diene	dienophile	condition	product (yield)[a]
(1)	**1**		CH_2Cl_2, 23 °C, 12 h	 **14** (84%)
(2)	**1**		toluene, 23 °C, 12 h	 **15** (87%)
(3)	**1**		toluene, 23 °C, 12 h	 **16** (86%)
(4)	**1**		CH_2Cl_2, $Zn(OTf)_2$, 0 °C, 24 h	 **17** (76%)
(5)	**1**		CH_2Cl_2, $Zn(OTf)_2$, 0 °C, 24 h	 **18** (79%)
(6)	**1**		CH_2Cl_2 $BF_3{\cdot}Et_2O$ 0 °C, 12 h	 **19** (85%)
(7)	**2**		CH_2Cl_2, 23 °C, 12 h	 **20** (83%)
(8)	**2**		toluene, 55 °C, 12 h	 **21** (82%)
(9)	**2**		toluene, 55 °C, 12 h	 **22** (82%)
(10)	**2**		CH_2Cl_2, $Zn(OTf)_2$, 0 °C, 24 h	 **23** (75%)
(11)	**2**		CH_2Cl_2, $Zn(OTf)_2$, 0 °C, 24 h	 **24** (77%)

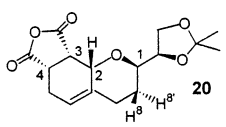
[a] The yields were reported after purification from crystallization from ether/hexane.

CHART 1



14

irradiation	Intensities
H^2 (δ 4.47)	H^3 (4.5 %), H^1 (0 %), $H^{8'}$ (1.8 %)
H^3 (δ 3.47)	H^2 (4.1 %), H^4 (5.0 %)
H^1 (δ 3.67)	H^2 (0 %), $H^{8'}$ (1.1 %), H^8 (4.2 %)

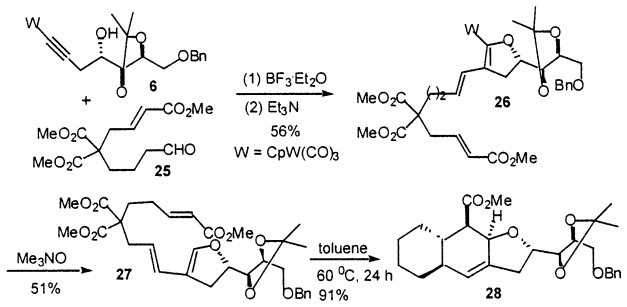


20

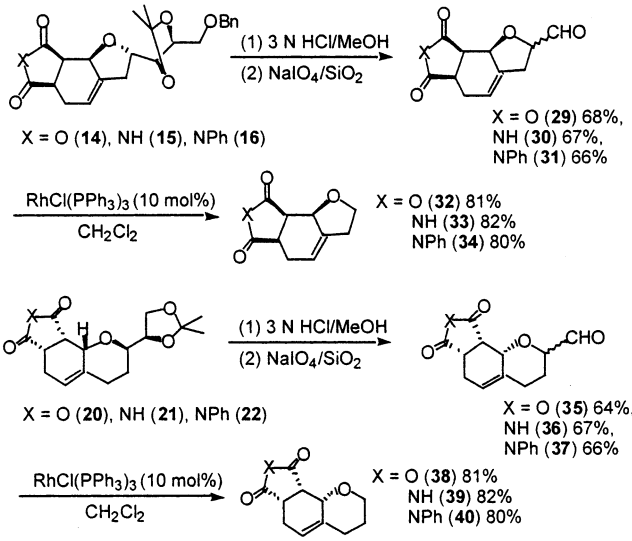
irradiation	Intensities
H^2 (δ 4.61)	H^3 (4.5 %), H^1 (0 %),
H^3 (δ 3.21)	H^2 (4.1 %), H^4 (4.8 %)
H^1 (δ 3.83)	H^2 (0 %), $H^{8'}$ (4.3 %), H^8 (1.0 %)

diastereomeric mixtures (entries 10−11). Crystallization of these mixtures gave pure **23** and **24** in respective yields of 75% and 77%. Determination of the stereochemistry relies on the NOE map of the maleic anhydride adduct **20** shown in Chart 1. Again, the observed stereoselectivities are attributed to endo-facial cycloaddition and the steric effect of a chiral dioxolane group.

SCHEME 4



SCHEME 5



This new approach is applicable to the intramolecular Diels−Alder reaction,[4] as shown in Scheme 4. Sequential treatment of chiral tungsten−alkynol **6** with aldehyde **25** and $BF_3{\cdot}Et_2O$ (1.5 equiv) in cold diethyl ether (−40 °C), followed by the addition of Et_3N, gave chiral tungsten−furanyl species **26** in 56% yield. Hydrodemetalation of complex **26** with Me_3NO in CH_3CN gave chiral oxacyclic diene **27** in 51% yield. Heating diene **27** at 60 °C in toluene for 24 h gave tricyclic furan **28** (dr > 20) in 91% yield. The structure of furan **28** was elucidated based on proton NMR NOE spectra. The trans-annulated configuration is consistent with those expected from the literature.[4,9,10]

Scheme 5 shows a convenient method for degradation of the dioxolane group of cycloadducts into a hydrogen atom to make these chiral molecules possess a common structure. Hydrolysis of compounds **14**−**16** with HCl (3.0 N)/MeOH mixtures at 0 °C for 4 h led to formation of the corresponding diols, which were subsequently oxidatively cleaved by $NaIO_4$/silica[11] to afford aldehyde derivatives **29**−**31** in yields of 62−65% after purification

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on a silica column. Column chromatography of these samples also led to epimization of the aldehyde carbon to form two diastereomers (ca. 3:1 ratio). Treatment of compounds **29**−**31** with $RhCl(PPh_3)_3$ catalyst (1.0 equiv)[12] in CH_2Cl_2 (23 °C) led to decarbonylation and the efficient formation of tricyclic furan derivatives **32**−**34** efficiently. This degradation method can be also applicable to related pyran derivatives **20**−**22**. Aldehydes **35**−**37**and their decarbonylation products **38**−**40** were obtained in reasonable yields via HCl hydrolysis, followed by catalytic decarbonylation using $RhCl(PPh_3)_3$ catalyst.

In summary, we report a short synthesis of chiral furanyl and pyranyl dienes **1** and **2** based on organotungsten chemistry. Synthesis of related oxacyclic dienes in the literature reports requires a lengthy procedure even for their racemic forms. The dienes bear a chiral 1,3-dioxolane group to effect diastereoselective Diels−Alder reaction. The chiral 1,3-dioxolane groups of the cycloadducts were easily degradable into hydrogen atoms. Dienes **1** and **2** are good building blocks for enantiopure forms of tricyclic oxygen compounds.

Experimental Sections

Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe, cannula, and septa apparatus. Toluene, diethyl ether, tetrahydrofuran, and hexane were dried with sodium benzophenone and distilled before use. Dichloromethane was dried over CaH_2 and distilled before use. $W(CO)_6$, $BF_3{\cdot}Et_2O$, L(+)-diethyl tartrate, AD-mix-β, maleic anhydride, maleic imide, *N*-phenyl maleimide, 1,4-benzoquinone, and 1,4-naphthoquinone were obtained commercially and used without purification. Proton NOE-spectra were measured on the basis of spatial (through-space) effect. The measurement follows the procedure described in the literature.[13] Mass data of tungsten compounds were reported according to ^{184}W. Chiral diol **3** was prepared by the method as described in the literature.[7]

Synthesis of 5-Benzyloxymethyl-2,2-dimethyl-[1,3]-dioxolane-4-carbaldehyde (4). To a THF solution of sodium hydride (*n*-hexane, prewashed, 1.30 g, 60%, 32.4 mmol) was added compound **3** (5.00 g, 30.9 mmol) at 0 °C, and the mixture was stirred for 1 h before addition of benzyl bromide (4.98 g, 29.3 mmol). The resulting solution was stirred for 12 h at room temperature and then quenched with a saturated NH_4Cl solution. The organic layer was extracted with diethyl ether, dried with $MgSO_4$, concentrated, and purified by flash chromatography to afford a benzyl ether derivative (4.67 g, 18.5 mmol, 60%) as a colorless oil.

To a CH_2Cl_2 solution of oxalyl chloride (3.1 g, 24.6 mmol) at −78 °C was added dropwise DMSO (3.60 g, 46.3 mmol) at −60 °C for 30 min, and to this mixture was added benzyl ether. The mixture was stirred for 30 min before addition of Et_3N. The resulting solution was stirred for 30 min at −60 °C and then warmed to 25°C for 2 h. It was washed with brine several times and concentrated at reduced pressure to afford the compound **4** as a pale yellow colored oil (3.93 g, 15.7 mmol, 85%). IR (neat, cm^{-1}): 1720 (s), 1620 (w). $[\alpha]^{23}_D = +16.8$ (c = 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.67 (s, 1H), 7.25 (m, 5H), 4.51 (s, 2H), 4.15 (m, 2H), 3.57 (t, J = 4.0 Hz, 2H), 1.40 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.6, 137.6, 128.4, 128.4, 127.7, 127.6, 127.6, 111.6, 82.0, 76.1, 73.6, 69.8, 26.8, 26.1. HRMS (70 eV): calcd for $C_{14}H_{18}O_4$, 250.1387; found, 250.1384.

Synthesis of 1-(5-Benzyloxymethyl-2, 2-dimethyl-[1, 3]-dioxolan-4-yl)-but-3-yn-1-ol (5). To a mixed solvent (Et_2O−DMF, 1:1, 40 mL) of compound **4** (3.93 mmol, 15.7 mmol) and propargyl bromide (3.71 g, 31.4 mmol) was added zinc powder (3.01 g, 47.1 mmol) at 23 °C. The mixture was stirred for 10 h at 25 °C and combined with diethyl ether (150 mL), and the resulting solution filtered. The filtrate was washed with saturated ammonium chloride. The organic layer was dried with $MgSO_4$, concentrated, and chromatograghed over a silica column to give compound **5** as a pale gray oil (3.92 g, 13.5 mmol, 86%). IR (neat, cm^{-1}): 3280(br,vs), 1620(w). $[\alpha]^{23}_D$ = −5.7 (c 0.7, $CHCl_3$). ^1H NMR($CDCl_3$, 400 MHz): δ 7.32 (m, 5H), 4.55 (m, 2H), 4.09 (q, J = 6.0 Hz, 1H), 3.57−3.77 (m, 4H), 3.08 (br, 1H), 2.41−2.62 (m, 2H), 2.02 (t, J = 3.2 Hz, 1H), 1.38 (m, 6H). ^{13}C NMR($CDCl_3$, 100 MHz): δ 137.3, 128.4, 128.4, 127.8, 127.8, 127.6, 109.4, 80.5, 80.3, 78.3, 73.7, 70.6, 70.1, 64.8, 26.8, 26.8, 24.0. HRMS (70 eV): calcd for $C_{17}H_{22}O_4$, 290.1514; found, 290.1517.

Synthesis of Tungsten Alkynol Compound (6). To an Et_2NH solution (15 mL) of $CpW(CO)_3Cl$ (5.48 g, 14.8 mmol) and CuI (0.28 g, 1.49 mmol) was added compound **5** (3.92 g, 13.5 mmol). The mixture was stirred for 4 h, concentrated, and chromatographed over a silica column to afford compound **6** as an orange oil (5.97 g, 9.59 mmol, 71%). IR (neat, cm^{-1}): 3380 (br,vs), 1978 (s), 1945 (s), 1618 (w). $[\alpha]^{23}_D = -4.5$ (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36 (m, 5H), 5.57 (s, 5H), 4.60 (m, 2H), 4.22 (m, 1H), 3.83 (t, J = 7.6 Hz, 1H), 3.60−3.75 (m, 4H), 2.72 (t, J = 4.8 Hz, 1H), 2.56 (m, 1H), 1.40 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 229.1, 212.0, 212.0, 137.9, 128.0, 128.0, 127.4, 127.4, 127.3, 122.4, 109.1, 91.2, 78.7, 78.1, 73.3, 71.0, 70.5, 61.3, 27.6, 26.8, 26.8. HRMS (70 eV): calcd for $C_{25}H_{26}O_7W$, 622.1237; found, 622.1243.

Synthesis of Tungsten Furanyl Diene (7). To a diethyl ether solution (15 mL) of compound **6** (1.50 g, 2.41 mmol) at −78 °C was added acetaldehyde (3.0 mL) and $BF_3{\cdot}OEt_2$ (0.29 mL, 2.89 mmol), and the solution was stirred for 5 h. The solution was dried in vacuo, redissolved in CH_2Cl_2 (12 mL), and treated with Et_3N (1.5 mL). The mixture was stirred for 30 min at 23 °C, concentrated, and filtered over a basic aluminum oxide bed to give compound **7** as an orange oil (1.00 g, 1.54 mmol, 64%). IR (neat, cm^{-1}): 2002 (s), 1945 (s), 1621 (w). $[\alpha]^{23}_D = -16.4$ (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31 (m, 5H), 6.29 (dd, J = 10.8 Hz, J = 17.8 Hz, 1H), 5.21 (s, 5H), 4.78 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 15.8 Hz, 1H), 4.54 (s, 2H), 4.50 (m, 1H), 4.11 (m, 1H), 3.72 (t, J = 8.2 Hz, 1H), 3.66 (m, 1H), 3.53 (m, 2H), 2.74 (m, 1H), 1.37−1.43 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 227.0, 215.3, 215.3, 150.2, 138.0, 134.1, 130.1, 128.2, 128.2, 127.6, 127.6, 127.4, 109.0, 107.4, 91.4, 82.5, 79.1, 78.7, 73.3, 70.9, 33.9, 27.1, 27.0. HRMS (70 eV): calcd for $C_{27}H_{28}O_7W$, 648.1322; found, 648.1223.

Synthesis of 4-Benzyloxymethyl-2,2-dimethyl-5-(vinyl-2,3-dihydro-furan-2-yl)-[1,3]-dioxolane (1). To an acetonitrile solution (20 mL) of compound **7** (1.00 g, 1.54 mmol) at 23 °C was added anhydrous Me_3NO (0.60 g). The mixture was stirred for 4 h, filtered through $MgSO_4$, concentrated, and chromatographed over a silica column to give compound **1** as a colorless oil (0.29 g, 0.93 mmol, 60%). IR (neat, cm^{-1}): 1621-(w). $[\alpha]^{23}_D = +32.0$ (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33 (m, 5H), 6.42 (dd, J = 10.8 Hz, J = 17.2 Hz, 1H), 6.34 (s, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.81 (d, J =17.2 Hz, 1H), 4.58 (m, 2H), 4.09 (m, 1H), 3.94 (t, J = 6.8 Hz, 1H), 3.65 (m, 1 H), 3.58 (m, 2 H), 2.66−2.84 (m, 2 H), 1.43 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.2, 138.0, 128.5, 128.3, 128.3, 127.7, 127.7, 127.6, 116.4, 110.4, 109.8, 82.6, 78.6, 78.6, 73.5, 70.7, 31.1, 27.1, 27.1. HRMS (70 eV): calcd for $C_{19}H_{24}O_4$, 316.1732; found, 316.1714.

Synthesis of Hept-2-en-6-yonic Acid Ethyl Ester (8). To a THF (250 mL) solution of oxalyl chloride (6.65 g, 51.6 mmol) was added dropwise DMSO (4.10 mL, 4.51 g, 57.8 mmol) at −78 °C, and the mixtures were stirred at −78 °C for 20

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min. To this resulting white suspension was added a THF (10 mL) solution of 4-pentyl-1-ol (2.0 g, 23.8 mmol), and the mixtures were stirred at −78 °C for 1 h before treatment with triethylamine (18.0 mL, 13.1 g, 0.129 mol). The reaction was stirred at −60 °C for 45 min, warmed to 23 °C, and stirred for an additional 1 h. The mixtures were filtered, the filtercake was washed with THF, and the filtrate was stored under nitrogen at 0 °C.

A suspension of sodium hydride (hexane-prewashed, 54.2 mmol) in THF (70 mL) was cooled to 0 °C, and neat triethyl phosphonoacetate (12.4 g, 55.4 mmol) was added dropwise over 5 min. The solution was stirred at 0 °C for 45 min and then added to the filtrate described above. The solution was stirred at 0 °C for 1 h, combined with ethyl ether (150 mL), washed with ammonium chloride and then with 1 N HCl, and finally washed with sodium bicarbonate. The organic layer was dried with $MgSO_4$, filtered, concentrated, and chromatographed over a silica column to afford **8** as a yellow oil (3.37 g, 22.1 mmol, 93%). IR (neat, cm^{-1}): 2221 (m), 1700 (s), 1620 (w). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.93 (dt, J = 16.0, 6.8 Hz, 1H), 5.85 (d, J = 15.6 Hz, 1H), 4.18 (q, J = 6.0 Hz, 2H), 2.36−2.42 (m, 2H), 2.31−2.33 (m, 1H), 1.97 (m,1H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.3, 146.2, 122.4, 82.6, 69.3, 60.2, 30.9,17.3, 14.2. HRMS (70 eV): calcd for $C_9H_{12}O_2$, 152.0843; found, 152.0821.

Synthesis of Hept-2-en-6-yn-1-ol (9). A THF (100 mL) solution of compound **8** (3.20 g, 21.0 mmol) was stirred at 0 °C, and to this solution was added diisobutylaluminum hydride (1.0 M in hexane, 46.6 mL, 46.6 mmol) over a period of 30 min. The mixture was stirred at 0 °C for 2 h, quenched by ammonium chloride, extracted with EtOAc, concentrated, and purified by flash chromatography to give **9** as a pale yellow oil (2.07 g, 18.8 mmol, 85%). IR (neat, cm^{-1}): 2221 (m), 1650 (w). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.68 (m, 2H), 4.05 (m, 2H), 2.23 (m, 4H), 1.93 (d, J = 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 130.7, 84.0, 69.0, 63.6, 31.3, 18.7. HRMS (70 eV): calcd for $C_7H_{10}O$, 110.0795; found, 110.0643.

Synthesis of Hept-1,2,3-triol (10). To a mixed (*t*-BuOH and water, 1:1, 50 mL) solvent of compound **9** (2.07 g, 18.8 mmol) at 0 °C was added AD-mix-β (26.4 g) and benzenesulfonamide (1.79 g), and the mixture was stirred at 0 °C for 27 h. The solution was quenched with sodium sulfite, extracted with EtOAc, and concentrated to afford **10** as a white solid (1.95 g, 13.6 mmol, 72%). IR (neat, cm^{-1}): 3467 (br, vs), 2310 (m). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.10−4.58 (br, 3H), 3.46−3.67 (m, 4H), 2.26 (m, 2H), 2.10 (t, J = 2.4 Hz, 1H), 1.64 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 84.0, 74.0, 70.5, 63.9, 43.1, 31.9, 14.7. HRMS (70 eV): calcd for $C_7H_{12}O_3$, 144.0842; found, 144.0846.

Synthesis of 1-(2,2-Dimethyl-[1,3]-dioxolan-4-yl)-pent-4-yn-1-ol (11). To an anhydrous acetone solution (40 mL) of compound **10** (1.95 g, 13.6 mmol) was added *p*-toluenesulfonic acid (80 mg, 0.41 mmol), and the solution was cooled to −60 °C and combined with 2,2-dimethoxypropane. The solution was stirred for 4 h, quenched by saturated sodium carbonate, and extracted with diethyl ether. The etherate solution was dried over $MgSO_4$, concentrated, and purified by flash chromatography to afford **9** as a pale yellow oil (2.12 g, 11.5 mmol, 85%). IR (neat, cm^{-1}): 2221 (m), 1648 (w). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.03 (m, 2H), 3.77 (m, 1H), 3.66 (m, 1H), 2.39 (m, 2H), 1.96 (t, J = 2.8 Hz, 1H), 1.62 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 109.5, 83.8, 78.7, 70.7, 68.8, 66.0, 32.5, 26.6, 25.2, 14.7. HRMS (70 eV): calcd for $C_{10}H_{16}O_3$, 184.1121; found, 184.1193.

Synthesis of 2-(5-Benzyloxymethyl-2,2-dimethyl-[1,3]-dioxolan-4-yl)-2,3,5,5a,8a,8b-hexahydro-1,7-dioxa-*as*-indacene-6,8-dione (14). To a toluene solution (0.5 mL) of compound **1** (100 mg, 0.32 mmol) was added maleic anhydride (30 mg, 0.35 mmol), and the solution was stirred at 60 °C for 1 h. The mixture was concentrated and chromatographed with a silica column to afford compound **14** as a white solid. Crystallization from ether/hexane afforded a colorless crystalline solid (110 mg, 0.28 mmol, 87%). $[\alpha]^{23}_D$ = −25.8 (c = 1.0, $CHCl_3$). IR (neat, cm^{-1}): 1778 (s), 1642 (w), 1620 (w). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29 (m, 5H), 5.54 (s, 1H), 4.56 (m, 2H), 4.47 (m, 1H), 4.34 (m, 1H), 3.97 (d, J = 2.0 Hz, 2H), 3.56−3.68 (m, 2H), 3.47 (m, 1H), 2.71 (m, 1H), 2.62 (d, J = 7.2 Hz, 2H), 2.41 (m, 2H), 1.39 (m, 6H). ^{13}C NMR($CDCl_3$, 100 MHz): δ 171.9, 169.4, 138.0, 137.6, 135.6, 128.3, 127.8, 127.8, 127.6, 118.4, 109.8, 79.5, 79.5, 78.7, 73.5, 73.5, 70.7, 44.1, 41.8, 32.7, 27.1, 27.0, 26.7. HRMS (70 eV): calcd for $C_{23}H_{26}O_7$, 414.1744; found, 414.1771.

(11) Synthesis of 8-(2,2-Dimethyl-[1,3]-dioxolan-4-yl)-2-phenyl-4,6,7,8,9a,9b-hexahydro-3a*H*-9-oxa-2-aza-cyclopenta[*a*]naphthalene-1, 3-dione (22). To a CH_2Cl_2 solution (1.0 mL) of compound **2** (60 mg, 0.29 mmol) was added N-phenyl maleimide (50 mg, 0.31 mmol), and the solution was stirred at room temperature for 12 h. The mixture was concentrated and chromatographed with a silica column to afford compound **22** as a white solid. Crystallization from ether/hexane gave a crystalline solid (90 mg, 0.23 mmol, 82%). $[\alpha]^{23}_D$ = +4.5 (c = 1.0, $CHCl_3$). IR (neat, cm^{-1}): 1720 (s), 1640-(w), 1622 (w); ^1H NMR($CDCl_3$, 400 MHz): δ 7.16−7.42 (m, 5H), 5.59 (s, 1H), 4.66 (d, J = 7.2 Hz, 1H), 4.16 (m, 1H), 3.96 (m, 3H), 3.52 (t, J = 8.8 Hz, 1H), 3.17 (t, J = 7.2 Hz, 1H), 2.77 (dd, J = 15.6, 6.8 Hz, 1H), 2.46 (dt, J = 15.2, 5.2 Hz, 1H), 2.29 (dt, J = 12.4, 3.2 Hz, 1H), 2.15 (m, 1H), 1.78 (m, 1H), 1.64 (m, 1H), 1.38−1.43 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.6, 175.5, 139.0, 132.3, 129.2, 129.1, 128.7, 126.5, 126.5, 118.4, 109.6, 78.1, 73.1, 69.9, 65.8, 44.9, 39.1, 28.4, 28.4, 26.6, 25.4, 23.6. HRMS (70 eV): calcd for $C_{22}H_{25}NO_5$, 383.1742; found, 383.1773.

(12) Synthesis of 1,3-Dioxo-2-phenyl-1,2,3,3a,4,6,7,8,9a,-9b-decahydro-9-oxa-2-aza-cyclopenta[*a*]naphthalene-8-carbaldehyde (37). To a methanol solution (2.0 mL) of compound **22** (90 mg, 0.23 mmol) was added dropwise 3 N HCl (50 mL) at 0 °C, and the solution was warmed to 23 °C. The solution was quenched with 20% NaOH solution, extracted with EtOAc, and chromatographed over a silica column to afford a diol derivative as a white solid (50 mg, 0.15 mmol). $NaIO_4$ (2.57 g, 12 mmol) was dissolved in H_2O (5 mL) and mixed with SiO_2 (10 g), and this slurry was dried in vacuo for 12 h at 23 °C. To a CH_2Cl_2 solution (5 mL) of the diol derivative prepared above was added this $NaIO_4$/silica gel mixture (1.0 g) at 0 °C, the slurry was stirred for 1 h and filtered, and the silica cake was washed with diethyl ether. The combined filtrate was concentrated and chromatographed with a silica column to afford compound **37** as a white solid (50 mg, 0.15 mmol, 66%). $[\alpha]^{23}_D$ = −18.5 (c = 1.0, $CHCl_3$). IR (neat, cm^{-1}): 1720 (s), 1640 (w), 1622 (w). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.87 (s, 1H), 7.21−7.45 (m, 5H), 5.62 (m, 1H), 4.50 (d, J = 7.6 Hz, 1H), 4.39 (t, J = 6.4 Hz, 1H), 3.58 (t, J = 8.0 Hz, 1H), 3.43 (m, 1H), 3.22 (t, J = 7.6 Hz, 1H), 2.86 (dd, J = 16.8, 6.0 Hz, 1H), 2.25 (m, 2H), 2.02 (m, 1H), 1.93 (m, 1H). ^{13}C NMR($CDCl_3$, 100 MHz): δ 203.4, 177.8, 175.0, 135.5, 132.0, 129.1, 129.1, 128.5, 126.4, 126.4, 119.6, 79.1, 69.1, 44.0, 37.9, 27.4, 24.4, 21.7. HRMS (70 eV): calcd for $C_{18}H_{17}NO_4$, 311.1231; found, 311.1232

(13) Synthesis of 2-Phenyl-4,6,7,8,9a,9b-hexahydro-3a*H*-9-oxa-2-aza-cyclopenta[*a*]naphthalene-1, 3-dione (40). To a CH_2Cl_2 solution (2.0 mL) of the compound **37** (50 mg, 0.16 mmol) was added $RhCl(PPh)_3$ (112 mg, 0.16 mmol), and the mixture was stirred at 23 °C for 24 h. The color of the solution turned from red to yellow. The solution was concentrated and chromatographed on a silica column to afford compound **40** as a white solid (39.1 mg, 0.14 mmol, 86%). To a CH_2Cl_2 solution of the compound **37** (0.05 g, 0.16 mmol, 1.0 equiv) was added Wilkinson's catalyst $RhCl(PPh)_3$ (148 mg, 0.2 mmol), and the mixture was stirred at room temperature for 24 h. The color of the solution turned from red to yellow. The solution was concentrated at and chromatographed on a silica column to afford compound **40** as a white solid (39.13 mg, 0.14 mmol, 86%). $[\alpha]^{23}_D$ = −12.35 (c = 1.0, $CHCl_3$). IR (neat, cm^{-1}): 1728 (s), 1651 (w), 1620 (w). ^1H NMR ($CDCl_3$,

400 MHz): δ 7.15−7.44 (m, 5H), 5.58 (m, 1H), 4.65 (s, 1H), 4.51 (t, J = 7.6 Hz, 1H), 3.77 (q, J = 6.2 Hz, 1H), 3.52 (m, 1H), 3.22 (m, 1H), 2.78 (m, 1H), 2.45 (dd, J = 12.6, 4.2 Hz, 1H), 2.20 (m, 2H), 1.91 (m, 1H), 1.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.7, 175.5, 138.1, 132.3, 129.2, 129.2, 129.1, 127.1, 127.1, 118.0, 73.1, 69.9, 41.7, 34.9, 32.1, 26.4, 23.6. HRMS (70 eV): calcd for $C_{17}H_{17}NO_3$, 283.1293; found, 283.1281.

Supporting Information Available: Spectral data of compounds **2**, **12-13**, **15**−**21**, **23**−**36**, and **38**−**39** in repetitive experiments and ^{1}H and ^{13}C NMR spectra of compounds **1-40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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