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Facile synthesis of enantiopure tricyclic furanyl derivatives via tungsten-mediated cycloalkenation reactions and Diels–Alder reactions

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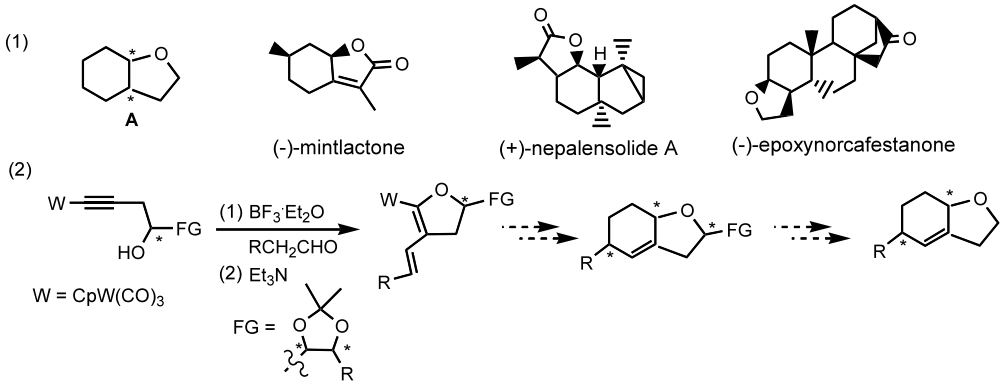
Abstract—Chiral furanyl diene **1** is easily prepared from cycloalkenation of chiral tungsten alkynol with acetaldehyde, followed by demetalation with Me_3NO. This diene bears a chiral 1,3-dioxolane group to control diastereoselective Diels–Alder reactions with electron-deficient olefins. The chiral 1,3-dioxolane substituent of the cycloadducts was degraded to a hydrogen atom to make these molecules possess a common furanyl functionality.

Enantiopure tricyclic furanyl derivatives with framework **A** are commonly encountered in many naturally occurring compounds, particularly in the family of terpenoids.[1] Scheme 1 shows several representatives that show interesting biological activities.[1] The bicyclic ether framework **A** is also a useful building block for complex bioactive molecules.[2] A short synthesis of these ether derivatives has attracted considerable attention.[2,3] The synthetic methods are quite diverse and require long procedures. Furthermore, most investigation focused on synthesis of racemic forms.[2,3] [4+2]-Cycloaddition of heterocyclic dienes with electron-deficient olefins is a useful synthetic method for many complicated molecules.[4] Previously, we reported that treatment of alkynyltungsten compounds with $RCH_3CHO/BF_3{\cdot}Et_2O$ complex formed oxacarbenium salts[6] (Scheme 1, Eq. (2)), further yielding a tungsten–furanyl diene[7] efficiently. In this work, we report a facile synthesis of enantiomeric bicyclic ethers **A** based on this tungsten-mediated cyclization with the protocol shown in Scheme 1. The oxacyclic diene is designed to bear a chiral dioxolane group to control diastereoselectivity of [4+2]-cycloaddition, and such a chiral substituent is readily removed from the resulting cycloadducts.

Scheme 2 shows the synthesis of chiral tungsten–alkynol **5** for the cyclization, The starting chiral diol **1**



Scheme 1.

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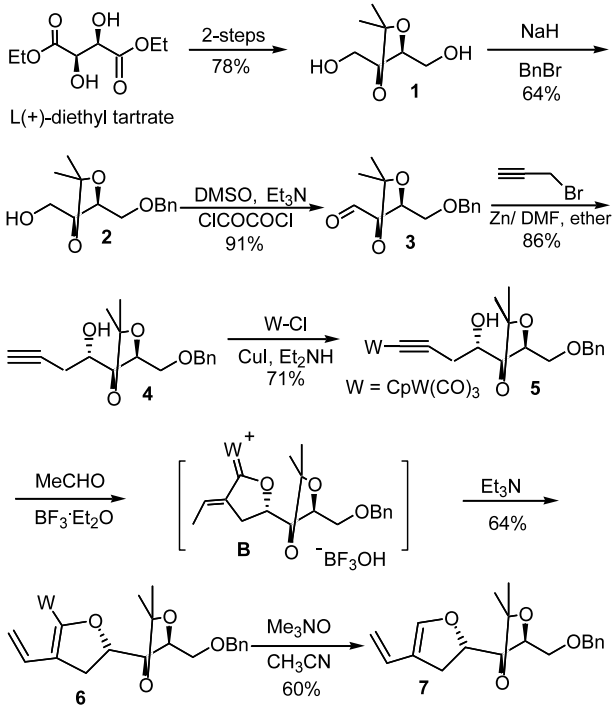
was prepared in two steps from L(+)-diethyl tartrate according to the literature.[8] Alkylation of **1** with benzyl bromide, followed by Swern oxidation, afforded aldehyde **3** in an overall yield 58%. Propargylation of chiral aldehyde **3** proceeded with excellent diastereoselectivity (dr >25) on treatment with propargyl zinc bromide in DMF/ether and anti-alcohol **4** was obtained in 86% yield.[5] Treatment of alkynol **4** with $CpW(CO)_3Cl$ (1.0 equiv.) and CuI catalyst (11 mol%) in Et_2NH effected metallation,[6,7] yielding tungsten–alkynol species **5** in 71% yield. Treatment of complex **5** with excess acetaldehyde in the presence of $BF_3{\cdot}Et_2O$ in cold diethyl ether (−78°C) produced a yellow oil, presumably tungsten–oxacarbenium salt **B**. Subsequent treatment of this salt with Et_3N (2.0 equiv.) afforded tungsten–furanyl diene **6** in 64% overall yield. Hydrodemetalation of dienyl complex **6** with Me_3NO in CH_3CN yielded the desired chiral diene **7** in 60% yield.[9]

The dioxolane group of diene **7** effects diastereoselective Diels–Alder reaction upon treatment with various electron-deficient olefins under ambient conditions; the results are shown in Scheme 3. The reaction of diene **7** with maleic anhydride, maleimide and *N*-phenyl maleimide proceeds smoothly at 23°C to afford one diastereomeric product **8**–**10** exclusively (dr >20). In the presence of $Zn(OTf)_2$ (3.0 equiv.), 1,4-benzoquinone and 1,4-naphthoquinone reacted with diene **7** at 23°C to afford cycloadducts **11** and **12** efficiently. Structural elucidation of these cycloadducts relies on proton NOE spectra that show the H^3 proton to be cis to H^2 and H^4 protons but trans to the H^1-proton, respectively. This information indicates that the olefin approaches the diene in an endo mode and opposite the chiral dioxolane group.



Scheme 2.

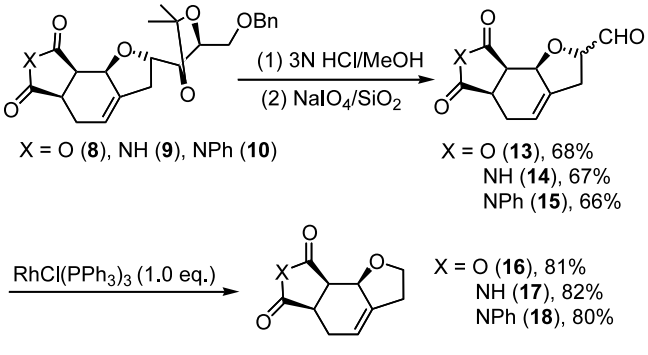
olefins	conditions	products (yields)[a]
(1)	toluene 23 °C, 12 h	**8** (84%)
(2)	toluene 23 °C, 12 h	**9** (87%)
(3)	toluene 23 °C, 12 h	**10** (86%)
(4)	CH_2Cl_2, $Zn(OTf)_2$,, 0 °C, 24 h	**11** (84%)
(5)	CH_2Cl_2, $Zn(OTf)_2$,, 0 °C, 24 h	**12** (85%)

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

Scheme 3. Diels–Alder reaction of diene **7** with olefins.

Scheme 4 shows a convenient method for degradation of the dioxolane group of cycloadducts **8**–**10** into an aldehyde or a hydrogen atom. Hydrolysis of compounds **8**–**10** with HCl (3.0 M)/MeOH mixtures at 23°C for 4 h led to formation of the corresponding diols that were subsequently oxidatively cleaved with $NaIO_4$/silica to afford aldehyde derivatives **13**–**15** in 66–68% yields after purification 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 **13**–**15** with $RhCl(PPh_3)_3$ catalyst (1.0 equiv.) in CH_2Cl_2 (23°C) led to decarbonylation to form tricyclic furan derivatives **16**–**18** efficiently.[10] HPLC-analysis of compounds **16**–**18** shows the ee values of these compounds to exceed 98%.[11,12]

In summary, we present a facile synthesis of chiral furanyl diene **1** based on tungsten-mediated cycloalke-



Scheme 4.

nation. Synthesis of furanyl diene requires a long procedure according to literature methods.[3] The diene bears a dioxolane group to control diastereoselectivity of Diels–Alder reactions. This stereodirecting group is readily removed using conventional method. This synthetic approach provides a short synthesis of enantiopure tricyclic furan.

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11. Determination of the ee values of compounds of **16**–**18** is performed on a Merck Chiralsphere column (diisopropyl ether/hexane = 1/15–1/5).
12. Spectral data: Spectral data for compound **16**: $[\alpha] = -13.7$ (*c* 1.0, $CHCl_3$); ^1H ($CDCl_3$, 400 MHz): δ 5.68 (br s, 1H), 4.52 (m, 1H), 4.18 (m, 1H), 3.98 (m, 1H), 3.37 (t, $J = 8.8$ Hz, 1H), 3.02 (m, 1H), 2.70 (m, 1H), 2.55 (m, 1H), 2.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.7, 174.8, 131.7, 117.3, 79.9, 73.7, 42.7, 38.3, 31.3, 22.9; MS (70 eV, *m*/*e*): 194 (M^+). Anal. calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19; Found: C, 61.78; H, 5.17. Compound **17**: $[\alpha] = -15.2$ (*c* 1.0, $CHCl_3$); ^1H ($CDCl_3$, 400 MHz): δ 5.80 (br s, 1H), 4.67 (m, 1H), 4.42 (t, $J = 6.8$ 1 Hz, 1H), 3.74 (t, $J = 7.2$ Hz, 1H), 3.53 (m, 1H), 3.18 (m, 1H), 2.79 (s, 1H), 2.63 (m, 1H), 2.34 (m, 1H), 2.10 (m, 1H); ^{13}C NMR $CDCl_3$, 100 MHz: δ 178.7, 174.1, 137.3, 117.4, 79.0, 75.9, 43.0, 40.0, 32.2, 24.9; MS (70 eV, *m*/*e*): 193 (M^+). Anal. calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; Found: C, 62.12; H, 5.79. Compound **18**: $[\alpha] = -23.7$ (*c* 1.0, $CHCl_3$); ^1H ($CDCl_3$, 400 MHz): δ 7.17–7.48 (m, 5H), 5.78 (m, 1H), 4.65 (m, 1H), 4.50 (m, 1H), 3.72 (m, 1H), 3.66 (q, $J = 8.8$ Hz, 1H), 3.52 (t, $J = 7.2$ Hz, 1H), 3.24 (m, 1H), 2.91 (m, 1H), 2.61 (m, 1H), 2.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.0, 175.0, 137.9, 131.9, 128.3, 127.6, 126.6, 117.3, 79.0, 75.4, 42.4, 39.4, 32.2, 25.0; MS (70 eV, *m*/*e*): 269 (M^+). Anal. calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; Found: C, 71.32; H, 5.60%.