Stereoselective Total Synthesis of (3*R*,8*S*)-Falcarindiol, a Common Polyacetylenic Compound from Umbellifers

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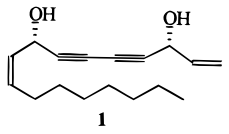
The first stereoselective total synthesis of (3*R*,8*S*)-falcarindiol (**1**) from L-tartaric acid and D-xylose is reported, via the Cadiot−Chodkiczwicz reaction, to couple 1-bromoalkyne (**2**) with 3(*R*)-(*tert*-butyldiphenylsilyloxy)-1-penten-4-yne (**3**).

Several polyacetylenes have been isolated from Umbelliferae and the closely related Araliaceae.[1] Their biological properties make them of interest to plant pathologists and pharmacologists. Falcarindiol (**1**) is a toxic polyacetylenic compound commonly occurring in umbellifers and in many Araliaceae plant species.[2] Antimicrobial tests showed growth inhibitory effects against *Escherichia coli* DC2 (MIC = 2.5 μg mL^{-1}), methicillin-sensitive *Staphylococcus aureus* K147 (MIC = 12.5 μg mL^{-1}), methicillin-resistant *S. aureus* SAP0017 (MIC = 25.0 μg mL^{-1}), and *Bacillus subtilis* Vernon (MIC = 12.5 μg mL^{-1}).[3] It was further proved that falcarindiol (**1**) had antiproliferative activity;[4] the ED_{50} against MK-1 cell growth was 3.2 μg mL^{-1}.



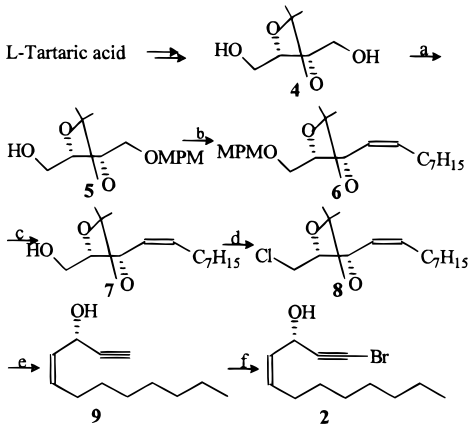
1

The first report of falcarindiol (**1**) was in 1966,[5] and it was determined to be heptadeca-1,9(*Z*)-diene-4,6-diyne-3,8-diol in 1969.[6] The absolute configuration was determined to be 3*R*,8*S*.[7] To our knowledge, no total synthesis of this compound has been reported. We carried out the stereoselective total synthesis of **1** to verify the structure and absolute configuration and to do more research on its pharmacological activities. Herein, we report details of this work.

Retrosynthetic analysis for falcarindiol (**1**) revealed that it could be obtained from **2** and **3**, which are prepared from cheap chiral templates L-tartaric acid and D-xylose, respectively. In our approach to the total synthesis of **1**, we took advantage of the Cadiot−Chodkiczwicz reaction[8] to couple of **2** with **3**.

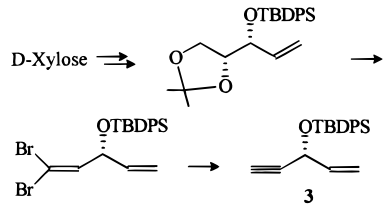
1-Bromoalkyne **2** was synthesized as outlined in Scheme **1**. The readily available 2,3-isopropylidenedioxy-L-threitol (**4**), prepared from L-tartaric acid according to known procedure,[9] was converted into monosubstituted *p*-methoxybenzyl (MPM) ether **5**. Swern oxidation of **5** and subsequent Wittig reaction with *n*-$C_7H_{15}CH{=}PPh_3$ afforded *Z*-isomer **6** (no E-isomer was found from TLC and ^{1}H NMR). Deprotection of **6** with DDQ[10] in a $CH_2Cl_2-H_2O$ system provided alcohol **7**, which was smoothly transformed to chloride **8** using PPh_3 and CCl_4.[11] Treatment of **8** with LDA in THF[12] gave terminal alkyne **9**, which was reacted with NBS and $AgNO_3$[13] to afford the 1-bromoalkyne compound **2**.

Scheme 1[a]

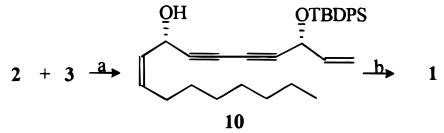


[a] Key: (a) MPMCl, NaH, THF−DMF; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, (ii) $CH_3(CH_2)_7PPh_3^+Br^-$, KO-*t*-Bu, THF, −78 °C; (c) DDQ, $CH_2Cl_2-H_2O$ (20:1); (d) PPh_3, CCl_4, reflux; (e) LDA, THF, −78 °C; (f) NBS, $AgNO_3$, acetone.

Scheme 2



Scheme 3[a]



[a] Key: (a) CuCl, $NH_2OH{\cdot}HCl$, aqueous $EtNH_2$, MeOH; (b) TBAF, THF.

3(*R*)-(*tert*-Butyldiphenylsilyloxy)-1-penten-4-yne **3** was obtained according to Scheme 2.[14] Using the Cadiot−Chodkiczwicz reaction, fragment **2** was coupled with **3**. After deprotection of the *tert*-butyldiphenylsilyl (TBDPS) group, falcarindiol (**1**) was obtained (Scheme 3). The $[\alpha]_D$ value and other spectral data of synthetic **1** were in agreement with the reported data.[3] Thus, we report a stereospecific synthesis of falcarindiol (**1**) from L-tartaric acid and D-xylose. The overall yield was 10.5% starting from **4**.

Experimental Section

General Experimental Procedures. Infrared spectra (IR) were recorded on a Nicolet Magna IR 750 spectrometer. NMR

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were run on a Bruker AMX-400 MHz or a Gemini-300 MHz instrument with TMS as internal standard and $CDCl_3$ as solvent. Optical rotation values were measured on a Perkin-Elmer 241 polarimeter at 25 °C. EIMS spectra were obtained on a Varian MAT-711 or HP-5989A spectrometer. HREIMS were recorded on a Finnigan MAT spectrometer. Column chromatography was performed on silica gel, 200−300 mesh, from Qing Dao, China.

(2*S*,3*S*,4*Z*)-1-*p*-Methoxybenzyloxy-2,3-isopropylidenedioxydodeca-4-ene (6). Dimethyl sulfoxide (4.70 mL, 65.88 mmol), dissolved in CH_2Cl_2 (10 mL), was added to a solution of oxalyl chloride (2.90 mL, 32.94 mmol) in CH_2Cl_2 (50 mL) at −78 °C. After 15 min, a solution of **5** (6.20 g, 21.96 mmol) in CH_2Cl_2 (10 mL) was added and the mixture stirred for 30 min. Triethylamine (15 mL, 110 mmol) in CH_2Cl_2 (10 mL) was added, and the resulting mixture was stirred for another 10 min and then allowed to warm to room temperature. The resulting mixture was poured into H_2O and extracted with CH_2Cl_2. The extract was washed with 1% HCl, H_2O, and saturated NaCl, dried ($MgSO_4$), and concentrated to give the corresponding aldehyde, which was directly used for the next reaction.

To a solution of octyltriphenylphosphonium bromide (12.00 g, 26.35 mmol) in THF (150 mL) was added potassium *tert*-butoxide (26 mL, 1 M in THF, 26 mmol) at room temperature. After being stirred for 1 h, the mixture was cooled to −78 °C. To this mixture was added a solution of the above aldehyde in THF (20 mL), and the whole mixture was stirred for another 2 h. Stirring was continued overnight at room temperature. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated. Column chromatography of the residue (petroleum ether/ethyl acetate, 20:1) gave the desired *Z*-isomer **6** (5.14 g, 64.6% from **5**) as a colorless oil: $[\alpha]_D = -8.7°$ (*c* 1.05, $CHCl_3$); IR (film) ν_{max} 3320, 2990, 2960, 2930, 2860, 1710, 1612, 1460, 1350, 1514, 1250, 1063, 822 m^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.23 (d, 2H, J = 8.5 Hz, Ph), 6.85 (d, 2H, J = 8.5 Hz, Ph), 5.63 (dt, 1H, J = 10.8, 7.6 Hz, H-5), 5.35 (dd, 1H, J = 10.8, 9.1 Hz, H-4), 4.59 (m, 1H, H-3), 4.51 (s, 2H, $PhCH_2O$), 3.82 (m, 1H, H-2), 3.79 (s, 3H, CH_3O), 3.51 (m, 2H, H-1), 2.03 (m, 2H, H-6), 1.41 (s, 2 × 3H, $C(CH_3)_2$), 1.30 (m, 2H, H-7), 1.22 (m, 8H, H-8 → H-11), 0.87 (t, 3H, J = 6.7 Hz, H-12); EIMS *m*/*z* 376 [M^+], 361, 318, 272, 210, 121 (100), 97, 77, 59; anal. C 73.09%, H 9.65%, calcd for $C_{23}H_{36}O_4$, C 73.37%, H 9.64%.

(2*S*,3*S*,4*Z*)-2,3-Isopropylidenedioxydodeca-4-en-1-ol (7). To a stirred solution of **6** (1.90 g, 5.24 mmol) in CH_2Cl_2 (25 mL) and H_2O (1.25 mL, 1/20 of CH_2Cl_2) was added DDQ (1.78 g, 7.86 mmol). After the solution was stirred for 2 h, saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$ and NaCl, dried ($MgSO_4$), and concentrated. Column chromatography of the residue (petroleum ether/ethyl acetate, 50:1 → 20:1) gave **7** (1.09 g, 81.3%) as a colorless oil: $[\alpha]_D = -8.6°$ (*c* 0.95, $CHCl_3$); IR (film) ν_{max} 3450, 2990, 2930, 2860, 1650, 1512, 1379, 1236, 1057, 856 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.69 (dt, 1H, J = 10.8, 7.6 Hz, H-5), 5.37 (dd, 1H, J = 10.8, 9.1 Hz, H-4), 4.69 (m, 1H, H-3), 3.71 (X of ABX, 1H, H-2), 3.54 and 3.81 (AB of ABX, 2H, J_{AB} = 3.3 Hz, $J_{AX} = J_{BX}$ = 12.0 Hz, H-1), 2.10 (m, 2H, H-6), 1.42 (s, 2 × 3H, $C(CH_3)_2$), 1,34 (m, 2H, H-7), 1.26 (m, 8H, H-8 → H-11), 0.88 (t, 3H, J = 6.7 Hz, H-12); EIMS *m*/*z* 256 [M^+], 241, 196, 181, 155, 124 (100), 109, 97, 81, 59, 55; anal. C 70.53%, H 11.05%, calcd for $C_{15}H_{28}O_3$, C 70.27%, H 11.01%.

(2*R*,3*S*,4*Z*)-1-Chloro-2,3-isopropylidenedioxydodeca-4-ene (8). To a solution of **7** (2.31 g, 9.01 mmol) in CCl_4 (40 mL) was added triphenylphosphine (4.73 g, 18.02 mmol) and the mixture refluxed for 12 h. The reaction mixture was cooled to room temperature, poured into petroleum ether (200 mL), and left at 0 °C overnight. The mixture was filtered and concentrated, and column chromatography of the residue (petroleum ether/ethyl acetate 100:1) gave **8** (2.25 g, 91.1%) as a colorless oil: $[\alpha]_D = -9.6°$ (*c* 1.15, $CHCl_3$); IR (film) ν_{max} 2990, 2960, 2930, 2860, 1760, 1680, 1458, 1373, 1223, 1061, 899, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.72 (dt, 1H, J = 10.8, 7.6 Hz, H-5), 5.37 (dd, 1H, J = 10.8, 9.1 Hz, H-4), 4.69 (m, 1H, H-3), 3.88 (X of ABX, 1H, H-2), 3.61 (AB of ABX, 2H, J_{AB} = 4.3 Hz, $J_{AX} = J_{BX}$ = 11.9 Hz, H-1), 2.12 (m, 2H, H-6), 1.45 and 1.46 (s, 2 × 3H, $C(CH_3)_2$), 1.36 (m, 2H, H-7), 1.28 (m, 8H, H-8 → H-11), 0.87 (t, 3H, J = 6.7 Hz, H-12); EIMS *m*/*z* 274 [M^+], 259, 239, 196, 181, 97, 85(100); anal. C 65.52%, H 9.93%, calcd for $C_{15}H_{27}ClO_2$, C 65.55%, H 9.90%.

(3*S*,4*Z*)-Dodec-4-en-1-yn-3-ol (9). *n*-Butyllithium (22 mL, 2.15 M in hexane, 46.92 mmol) was added to a solution of diisopropylamine (6.60 mL, 46.92 mmol) in THF (80 mL) at 0 °C. After being stirred for 30 min, the mixture was cooled to −78 °C. To this mixture was added a solution of **8** (2.15 g, 7.82 mmol) in THF (20 mL). Stirring was continued for 4 h, and the reaction was then warmed to room temperature and stirred overnight. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated. Column chromatography of the residue (petroleum ether/ethyl acetate, 20:1) gave **9** as a colorless oil (820 mg), and 200 mg of **8** was recovered (64.1%): $[\alpha]_D = 122.9°$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3311, 2960, 2930, 2860, 2117, 1660, 1466, 1018, 654 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 5.56 (m, 2H, H-4, H-5), 5.13 (dd, 1H, J = 2.2 Hz, 7.3 Hz, H-3), 2.49 (d, 1H, J = 2.2 Hz, H-1), 2.11 (m, 2H, H-6), 1.36 (m, 2H, H-7), 1.27 (m, 8H, H-8 → H-11), 0.86 (t, 3H, 6.7 Hz, H-12); EIMS *m*/*z* 179 [$M^+ - 1$], 162, 151, 137, 109, 95, 81 (100), 68, 55; HREIMS *m*/*z* 179.1448 (calcd for $C_{12}H_{19}O$, 179.1437).

(3*S*,4*Z*)-1-Bromododec-4-en-1-yn-3-ol (2). *N*-Bromosuccinimide (760 mg, 4.24 mmol) and $AgNO_3$ (100 mg, 0.57 mmol) were added to a solution of **9** (510 mg, 2.83 mmol) in acetone (20 mL) at room temperature. After being stirred for 3 h, the mixture was poured into saturated aqueous Na_2SO_3 and extracted with ether. The extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated. Column chromatography of the residue (petroleum ether/ethyl acetate, 50:1) gave **2** (580 mg, 79.1%) as a colorless oil: $[\alpha]_D = 77.4°$ (*c* 0.90, $CHCl_3$); IR (film) ν_{max} 3427, 2960, 2930, 2860, 2187, 1726, 1645, 1626, 1466, 1248, 980, 740, 660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.54 (m, 2H, H-4, H-5), 5.15 (d, 1H, J = 7.3 Hz, H-3), 2.10 (m, 2H, H-6), 1.36 (m, 2H, H-7), 1.27 (m, 8H, H-8 → H-11), 0.89 (t, 3H, J = 6.7 Hz, H-12); EIMS *m*/*z* 257/259 [$M^+ - 1$], 242, 161 (100), 146, 133, 109, 95, 81, 67, 55; HREIMS *m*/*z* 257.0545 (calcd for $C_{12}H_{18}BrO$, 257.0542).

(3*R*,8*S*)-3-(*tert*-Butyldiphenylsilyoxy)falcarindiol (10). To a solution of CuCl (4 mg, 0.038 mmol), $NH_2OH{\cdot}HCl$ (16 mg, 0.225 mmol), 65% $EtNH_2$ (0.8 mL) in MeOH (1 mL) at 0 °C were added successively **3** (240 mg, 0.75 mmol) and **2** (176 mg, 0.68 mmol) in MeOH (1 mL). After being stirred for 30 min, the mixture was treated with H_2O and extracted with ether. The extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated. Column chromatography of the residue (petroleum ether/ethyl acetate, 20:1) gave **10** (218 mg, 64.3%) as a slightly yellow oil: $[\alpha]_D = 108.8°$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3311, 2960, 2930, 2860, 2150, 1970, 1860, 1464, 1427, 1112, 821, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69 (m, 4H, SiPh), 7.39 (m, 6H, SiPh), 5.83 (ddd, 1H, J = 17.0, 10.1, 5.4 Hz, H-2), 5.56 (m, 2H, H-9, H-10), 5.27 (dt, 1H, J = 17.0, 1.3 Hz, H-1a), 5.18 (d, J = 8.1 Hz, H-8), 5.12 (dt, 1H, J = 10.1, 1.3 Hz, H-1b), 4.83 (br d, J = 5.4 Hz, H-3), 2.10 (m, 2H, H-11), 1.38 (m, 2H, H-12), 1.30 (m, 8H, H-13 → H-16), 1.10 (s, 9H, $SiC(CH_3)_3$), 0.89 (t, 3H, J = 6.7 Hz, H-17); EIMS *m*/*z* 441 [$M^+ - C(CH_3)$], 384, 286, 231 (100), 199, 83, 55, 43; HREIMS *m*/*z* 498.2926 (calcd for $C_{33}H_{42}SiO_2$, 498.2956).

Falcarindiol (1). TBAF (0.6 mL, 1 M in THF, 0.60 mmol) was added to a solution of **10** (60 mg, 0.12 mmol) in THF (5 mL) at 0 °C. After being stirred for 3 h, the mixture was treated with saturated aqueous NH_4Cl and extracted with ethyl acetate. The extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated. Column chromatography of the residue (petroleum ether/ethyl acetate, 5:1) gave **1** (26 mg, 83.9%) as a slightly yellow oil: $[\alpha]_D = 211.7°$ (*c* 0.65, $CHCl_3$) [lit.[14] $[\alpha]_D = 219.4°$ (*c* 4.6, $CHCl_3$)]; IR (film) ν_{max} 3338, 2960, 2930, 2860, 2231, 2150, 1709, 1464, 1263, 1119, 1018, 933 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.93 (ddd, 1H, J = 17.0,

10.1, 5.4 Hz, H-2), 5.51 (m, 2H, H-9, H-10), 5.47 (dt, 1H, J = 17.0, 1.2 Hz, H-1a), 5.25 (dt, J = 10.1, 1.2 Hz, H-1b), 5.19 (d, 1H, J = 8.1 Hz, H-8), 4.92 (br d, J = 5.4 Hz, H-3), 2.10 (m, 2H, H-11), 1.38 (m, 2H, H-12), 1.30 (m, 8H, H-13 → H-16), 0.89 (t, 3H, J = 6.7 Hz, H-17); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.8 (C-2), 134.6 (C-10), 127.7 (C-9), 117.3 (C-1), 79.9 (C-4), 78.3 (C-7), 70.3 (C-5), 68.7 (C-6), 63.5 (C-3), 58.6 (C-8), 31.8 (C-11), 29.3 (C-12), 29.2 (C-13), 29.1 (C-14), 27.7 (C-15), 22.6 (C-16), 14.1 (C-17); EIMS m/z 259 [$M^+ - 1$], 215, 157, 129 (100), 91, 77, 55, 43; HREIMS m/z 259.1697 (calcd for $C_{17}H_{23}O$, 259.1699).

References and Notes

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