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An Asymmetric Synthesis of *C*-2-*epi*-Hygromycin A

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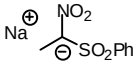
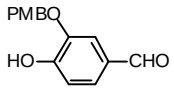
Experimental

1-Nitro-1-(phenylsulfonyl)ethane sodium salt 8



1-Nitro-1-(phenylsulfonyl)ethane[1] (4 g, 18.6 mmol) is dissolved in dry THF (20 mL), and at 0 C is added sodium hydride (60% in oil) (0.744 g, 18.6 mmol). After one hour of stirring at room temperature, the mixture is evaporated *in vacuo*, then dissolved and triturated in dichloromethane. The solid is filtrated and washed 3 times with dichloromethane to give 1-nitro-1-(phenylsulfonyl)ethane sodium salt **6** (4.4 g, 18.6 mmol) with a quantitative yield. **IR** (neat) (cm^{-1}): 1560, 1331, 1149. **^{1}H NMR** (300 MHz, $CDCl_3$): *d* (ppm) (*J* in Hz) 8.00-7.43 (m, 5H), 5.68 (q, *J* = 7.0, 1H), 1.85 (d, *J* = 7.0, 3H).

4-Hydroxy-3-(4-methoxybenzyloxy)-benzaldehyde 11

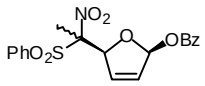


3,4-Dihydroxy-benzaldehyde is purified by filtration (elution diethyl ether). The solid (8.0 g, 58 mmol) is collected and diluted in DMSO (300 mL), and added, at 0 C, to a mixture of sodium hydride (60% dispersion in oil) (5.8 g, 140 mmol) (washed with hexane) in DMSO (250 mL) over 40 minutes. Upon addition, the ice bath is removed and the solution is stirred for 30 minutes. PMBCl (8.7 g, 56 mmol) in DMSO (26 mL) is then added, and the solution is stirred overnight. It is then poured into ice-water, acidified with a 1M solution of sulfuric acid, extracted by ethyl acetate, dried over magnesium sulfate, filtrated and evaporated *in vacuo*. The solid is recrystallized in toluene, then dissolved in boiling ethyl acetate, petroleum ether added, and filtrated on a pad of silica gel to afford a white solid **8** (7.29 g, 28 mmol) with 49% yield.

R_f = 0.5 (Heptane / diethyl ether 1/3). **M.P**. 130 C. **IR** (neat) (cm^{-1}): 3180, 1650, 1575, 1510, 1465, 1250. **^{1}H NMR** (500 MHz, $CDCl_3$): *d* (ppm) (*J* in Hz) 9.76 (s, 1H), 7.48 (d, *J* = 1.7, 1H), 7.39 (dd, *J* = 1.7, 8.1, 1H), 7.33 (d, *J* = 8.5, 2H), 7.02 (d, *J* = 8.1, 1H), 6.90 (d, *J* = 8.8, 2H), 6.45 (s, 1H), 5.06 (s, 2H), 3.79 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): *d*

(ppm) 190.9, 159.9, 151.9, 146.4, 129.9, 129.7, 127.6, 127.4, 114.6, 114.1, 110.2, 71.0, 55.3.

Benzoic acid (2*S*,5*S*)-5-(1-benzenesulfonyl-1-nitroethyl)-2,5-dihydrofuran-2-yl ester 10

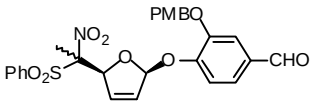


To a sonicated, degassed solution of 1-nitro-1-(phenylsulfonyl)ethane sodium salt **8** (1.922 g, 8.11 mmol) and tetrahexylammonium bromide (0.28 g, 0.64 mmol) in water (30 mL), is added a solution of cis-2,5-dibenzoxy-2,5-dihydrofuran **3** (2 g, 6.41 mmol), π-allylpalladium chloride dimer (23 mg, 0.064 mmol, 1 mol %) and (*R*,*R*)-**9** (178 mg, 0.26 mmol, 4 mol %) in dichloromethane (30 mL). The reaction is vigorously stirred at room temperature for 16 hours. The phases are separated, the organic layer dried over magnesium sulfate, filtrated and evaporated *in vacuo*. The nitrosulfone **10** (2.354 g, 5.84 mmol) is isolated pure as a white gummy solid after column chromatography (petroleum ether / ethyl acetate 7/3) with 91% yield as a 5/1 mixture of diastereoisomers (by ^{1}H NMR) with 93% enantiomeric excess (by chiral HPLC).

R_f = 0.3 (Heptane / diethyl ether 1/1); 0.52 (Heptane / diethyl ether 1/3). **IR** (neat) (cm^{-1}): 3096, 3067, 2978, 2871, 1731, 1556, 1449, 1336, 1261, 1157, 946. **^{1}H NMR** (300

MHz, $CDCl_3$): *d* (ppm) (*J* in Hz) 7.99-7.84 (m, 4H), 7.65-7.51 (m, 4H), 7.46-7.39 (m, 2H), 7.13 (d, *J* = 1.2, 1H), 6.19 (ddd, *J* = 6.0, 2.1, 1.3, 1H), 6.06 (dt, *J* = 6.1, 1.6, 1H), 5.66 (d, *J* = 1.9, 1H), 1.83 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): *d* (ppm) 164.9, 135.5, 133.6, 131.3, 130.7, 130.3, 130.0, 129.7, 129.6, 129.1, 128.5, 106.6, 102.5, 85.9, 14.2. **Anal**. Calc'd for $C_{19}H_{17}NO_7S$: C, 56.57; H, 4.25; N, 3.47. Found: C, 56.71; H, 4.54; N, 3.49. **[*a*]$_D^{20}$** = + 94.6 (*c* = 4.57, CH_2Cl_2). **HPLC** Chiracel OD column; *l* = 230 nm, 10% isopropanol in heptane; 1 mL/min; Retention times: 13.6 and 15.2 (*S* enantiomer); 18.2 and 22.6 (*R* enantiomer).

4-[(2*S*,5*S*)-5-(1-Benzenesulfonyl-1-nitroethyl)-2,5-dihydrofuran-2-yloxy]-3-(4-methoxybenzyloxy)-benzaldehyde 12

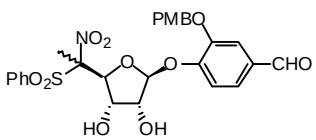


To a solution of **10** (5.24 g, 13 mmol), **11** (5.03 g, 19.5 mmol), $Pd_2dba_3.CHCl_3$ (270 mg, 0.26 mmol, 2 mol %) and (*S*,*S*)-**9** (721 mg, 1.04 mmol, 8 mol %) in dry degassed THF (26 mL, 0.5M), is added triethylamine (2.71 mL, 19.5 mmol). After 1.5 hours at 50 C, the mixture is cooled to room temperature and ethyl acetate and water are added. The organic layer is washed with brine, dried over magnesium

sulfate, filtrated and evaporated *in vacuo*. **12** (5.23 g, 9.70 mmol) is isolated pure as a white solid after column chromatography (petroleum ether / ethyl acetate 8/2 then 6/4) with 75% yield.

R_f = 0.3 (Heptane / diethyl ether 1/3); 0.75 (diethyl ether). **M.P**. 63-65 C. **IR** (neat) (cm^{-1}): 2831, 1723, 1673, 1650, 1584, 1515, 1441, 1387, 1253, 1156, 1004. **^{1}H NMR** (300 MHz, $CDCl_3$): *d* (ppm) (*J* in Hz) 9.89 (s, 1H), 7.95 (d, *J* = 6.9, 2H), 7.50-7.25 (m, 8H), 6.91 (d, *J* = 8.4, 2H), 6.41 (s, 1H), 6.21 (d, *J* = 6.0, 1H), 5.95 (d, *J* = 6.0, 1H), 5.73 (s, 1H), 5.04 (s, 2H), 3.82 (s, 3H), 1.83 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): *d* (ppm) 190.9, 159.5, 151.6, 149.6, 135.6, 135.2, 133.5, 132.1, 130.8, 130.6, 130.4, 129.8, 129.4, 129.1, 129.0, 128.1, 126.0, 117.6, 113.9, 112.5, 106.5, 85.6, 70.6, 55.2, 13.6. **Anal**. Calc'd for $C_{27}H_{25}NO_9S$: C, 60.11; H, 4.63. Found: C, 60.00; H, 4.92. **$[a]_D^{23}$** = -40.3 (*c* = 1.00, CH_2Cl_2).

4-[(2*S*,3*R*,4*S*,5*S*)-5-(1-Benzenesulfonyl-1-nitroethyl)-3,4-dihydroxy-tetrahydrofuran-2-yloxy]-3-(4-methoxybenzyloxy)-benzaldehyde

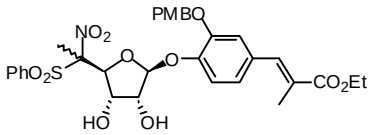


To a solution of **12** (9.37 g, 17.3 mmol) in dichloromethane (190 mL) at room temperature, is added *N*-methylmorpholine-

N-oxide (5.3 g, 45.3 mmol) then osmium tetroxide (4% solution in water) (5.5 mL, 0.86 mmol, 5 mol %). The reaction is stirred overnight, then evaporated *in vacuo*. The product (9.6 g, 16.8 mmol) is isolated pure as a white solid after column chromatography (petroleum ether / ethyl acetate 4/6) with 98% yield.

R_f = 0.32 (Diethyl ether). **M.P**. 77-79°C. **IR** (neat) (cm^{-1}): 3425, 2935, 1686, 1587, 1559, 1332, 1252, 1156, 1070, 1002. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) (*J* in Hz) 9.84 (s, 1H), 7.97 (d, *J* = 8.1, 2H), 7.74-7.32 (m, 7H), 7.09 (d, *J* = 8.4, 1H), 6.93 (d, *J* = 8.7, 2H), 5.65 (s, 1H), 5.04 (s, 2H), 4.83 (d, *J* = 7.5, 1H), 4.69 (dd, *J* = 7.4; 4.8, 1H), 4.35 (d, *J* = 4.2, 1H), 3.81 (s, 3H), 3.42 (bs, 2H), 1.77 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (ppm) 190.9, 159.6, 150.8, 149.1, 135.3, 133.3, 131.6, 131.1, 130.8, 129.4, 129.3, 129.2, 128.0, 126.2, 115.5, 115.0, 114.0, 112.4, 106.4, 104.8, 83.1, 74.8, 70.8, 60.5, 55.3, 14.3. **Anal**. Calc'd for $C_{27}H_{27}NO_{11}S$: C, 56.54; H, 4.74. Found: C, 56.45; H, 4.60. **$[\alpha]_D^{20}$** = - 48.5 (*c* = 0.24, CH_2Cl_2).

(*E*)-3{-4-[(2*S*,3*R*,4*S*,5*S*)-5-(1-Benzenesulfonyl-1-nitroethyl)-3,4-dihydroxy-tetrahydrofuran-2-yloxy]-3-(4-methoxybenzyloxy)-phenyl}-2-methyl-acrylic acid ethyl ester 13

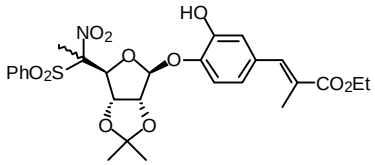


To a solution of the above (9.5 g, 16.6 mmol) in dichloromethane (83 mL, 0.2M), is added ethyl 2-(triphenylphosphoranylidene)propionate (7.9 g, 21.6 mmol) and the mixture is stirred at 45 C for one hour. It is then evaporated *in vacuo*, and **13** (10.9 g, 16.6 mmol) is isolated pure as a white solid after column chromatography (petroleum ether / ethyl acetate 1/1) with a quantitative yield.

R_f = 0.42 (Diethyl ether). **M.P**. 73-75 C. **IR** (neat) (cm^{-1}): 3386, 2931, 1702, 1609, 1560, 1514, 1331, 1244, 1157, 1006. **^{1}H NMR** (300 MHz, $CDCl_3$): *d* (ppm) (*J* in Hz) 7.98 (d, *J* = 8.3, 2H), 7.78-7.71 (m, 1H), 7.59-7.54 (m, 3H), 7.32 (d, *J* = 8.8, 2H), 6.96-6.89 (m, 5H), 5.55 (s, 1H), 4.98 (s, 2H), 4.78 (d, *J* = 7.2, 1H), 4.61 (bs, 1H), 4.29 (m, 1H), 4.27 (q, *J* = 7.2, 2H), 3.81 (s, 3H), 2.93 (bs, 2H), 2.05 (s, 3H), 1.83 (s, 3H), 1.34 (t, *J* = 7.1, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): *d* (ppm) 168.7, 159.5, 148.3, 146.0, 138.0, 135.2, 133.8, 131.2, 130.8, 129.4, 129.1, 128.5, 127.7, 123.5,

116.8, 116.4, 114.0, 106.6, 105.7, 82.9, 74.8, 71.0, 70.9, 60.9, 60.4, 55.3, 26.3, 21.0, 14.3, 14.1, 14.0. **Anal**. Calc'd for $C_{32}H_{35}NO_{12}S$: C, 58.44; H, 5.36. Found: C, 58.62 ; H, 5.45. $[\alpha]_D^{20}$ = - 44.9 (*c* = 0.40, CH_2Cl_2).

(*E*)-3{-4-[(3a*R*,4*S*,6*S*,6a*R*)-6-(1-Benzenesulfonyl-1-nitroethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yloxy]-3-(hydroxy)-phenyl}-2-methyl-acrylic acid ethyl ester

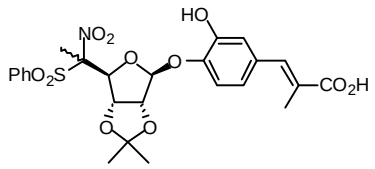


To a solution of **13** (9.6 g, 14.6 mmol) in a 1/1 mixture of THF and methanol (500 mL, 0.03M), is added *p*-toluenesulfonic acid (3.35 g, 17.5 mmol) and the mixture is stirred at 50°C for 8 hours. The mixture is then evaporated in *vacuo*. The crude is purified on a plug of silica gel (Petroleum ether / diethyl ether 1/1 then ethyl acetate pure). Triol (7.84 g, 14.6 mmol) is obtained pure as a white foam with a quantitative yield. R_f = 0.23 (Diethyl ether). The triol (7.84 g, 14.6 mmol) is then dissolved in dichloromethane (150 mL, 0.1M), 2,2-dimethoxypropane (18 mL, 146 mmol) and *p*-toluenesulfonic acid (0.28 g, 1.46 mmol) are added. After 5 minutes, ethyl acetate is added and the organic phase is washed with a saturated solution

of sodium hydrogenocarbonate and brine, dried over magnesium sulfate, filtrated and evaporated *in vacuo*. The product (7.96 g, 13.8 mmol) is isolated pure as a white solid after column chromatography (petroleum ether / diethyl ether 1/1) with 95% yield.

R_f = 0.76 (Diethyl ether). **IR** (neat) (cm^{-1}): 34.86, 2988, 1701, 1613, 1557, 1250, 1158. **^{1}H NMR** (500 MHz, $CDCl_3$): *d* (ppm) (*J* in Hz) 7.88 (dd, *J* = 1.2, 8.6, 2H), 7.74 (tt, *J* = 1.2, 7.6, 1H), 7.58 (m, 2H), 7.52 (s, 1H), 7.00 (d, *J* = 2.2, 1H), 6.95 (d, *J* = 8.5, 1H), 6.84 (dd, *J* = 8.5,2.2, 1H), 5.70 (s, 1H), 5.48 (dd, *J* = 1.5, 6.1, 1H), 5.45 (s_{large}, 1H), 5.04 (d, *J* = 1.2, 1H), 4.86 (d, *J* = 6.1, 1H), 4.22 (q, *J* = 7.1, 2H), 2.07 (d, *J* = 1.5, 3H), 1.80 (s, 3H), 1.51 (s, 3H), 1.31 (m, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): *d* (ppm) 168.7, 145.6, 143.1, 137.9, 135.7, 133.1, 131.5, 131.4, 131.0, 129.4, 129.0, 127.8, 122.5, 117.0, 113.9, 113.4, 108.0, 106.4, 89.3, 85.5, 81.0, 60.8, 26.4, 24.7, 17.7, 14.3, 14.0. **Anal**. Calc'd for $C_{27}H_{31}O_{11}NS$: C, 56.15; H, 5.41; N, 2.42; S, 5.55. Found: C, 56.30; H, 5.56; N, 2.29. **$[\alpha]_D^{23}$** = -69.8 (*c* = 1.00, CH_2Cl_2).

(*E*)-3-{4-[(3a*R*,4*S*,6*S*,6a*R*)-6-(1-Benzenesulfonyl-1-nitroethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yloxy]-3-(hydroxy)-phenyl}-2-methyl-acrylic acid 14

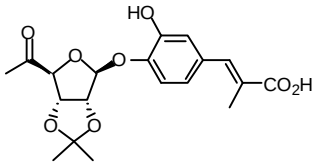


To a solution of the above product (7.96 g, 13.8 mmol) in a 1/1/1 mixture of methanol THF and water (150 mL), is added lithium hydroxide (5.8 g, 138 mmol), and the mixture is stirred at 40 C for 4 hour. After cooling to room temperature, the solution is acidified by a 5% solution of $NaHSO_3$ and extracted by ethyl acetate. The organic phase is washed brine, dried over magnesium sulfate, filtrated and evaporated *in vacuo* to afford **14** (7.6 mg, 13.8 mmol) as a white foam with a quantitative yield.

R_f = 0.53 (Diethyl ether). **IR** (neat) (cm^{-1}): 3486, 2991, 2646, 1682, 1557, 1264, 1156. **^{1}H NMR** (500 MHz, $CDCl_3$): *d* (ppm) (*J* in Hz) 7.88 (dd, *J* = 1.2, 8.6, 2H), 7.75 (tt, *J* = 1.2, 7.6, 1H), 7.65 (s, 1H), 7.58 (t, *J* = 8.1, 2H), 7.03 (d, *J* = 1.7, 1H), 6.97 (d, *J* = 8.5, 1H), 6.88 (dd, *J* = 2.0, 8.8, 1H), 5.72 (s, 1H), 5.50 (dd, *J* = 1.5, 6.1, 1H), 5.05 (d, *J* = 1.2, 1H), 4.87 (d, *J* = 6.1, 1H), 2.09 (s, 3H), 1.80 (s, 3H), 1.51 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): *d* (ppm) 173.8, 145.6, 143.5, 140.2, 135.8, 133.1,

131.0, 130.9, 129.4, 126.6, 122.9, 117.2, 113.9, 113.4, 108.0, 106.4, 89.3, 85.4, 81.0, 60.4, 26.4, 24.7, 17.7, 14.2, 13.7. **Anal**. Calc'd for $C_{25}H_{27}O_{11}NS$: C, 54.64; H, 4.95; N, 2.55. Found: C, 54.80; H, 5.02; N, 2.36. $[\alpha]_D^{23}$ = - 66.3 (*c* = 1.00, CH_2Cl_2).

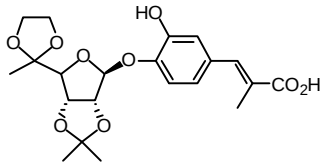
(*E*)-3-{4-[(3a*R*,4*S*,6*S*,6a*R*)-6-Acetyl-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yloxy]-3-(hydroxy)-phenyl}-2-methyl-acrylic acid 15



To a solution of **14** (284 mg, 0.517 mmol) in THF (9 mL), is added at room temperature a solution of ammonium acetate (3.12 g, 40 mmol) and titanium chloride (III) (1.03 g, 6.7 mmol) [NOTE : this reagent should be handled and kept in the glove box] in water (4.2 mL) and the mixture is stirred 3 hours. Ethyl acetate is added and the organic layer is washed by a 1M solution of sodium potassium tartrate, the aqueous phase back extracted and the combined organic phases washed with brine, dried over magnesium sulfate, filtrated and evaporated *in vacuo*. The product **15** (156 mg, 0.414 mmol) is isolated pure as a white foam after column chromatography (petroleum ether / ethyl acetate 1/1 then 1/3) with 80% yield.

R_f = 0.59 (Diethyl ether). **IR** (neat) (cm^{-1}): 3330, 2932, 2644, 1712, 1682, 1510, 1263, 1101. **^{1}H NMR** (500 MHz, $CDCl_3$): *d* (ppm) (*J* in Hz) 7.69 (s, 1H), 7.11 (d, *J* = 8.3, 1H), 7.06 (d, *J* = 2.0, 1H), 6.92 (dd, *J* = 8.5, 2.0, 1H), 5.76 (s, 1H), 5.24 (dd, *J* = 5.9, 1.0, 1H), 4.86 (d, *J* = 5.9, 1H), 4.71 (s, 1H), 2.11 (d, *J* = 1.0, 3H), 2.10 (s, 3H), 1.51 (s, 3H), 1.36 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): *d* (ppm) 206.6, 173.8, 146.9, 144.0, 140.3, 131.8, 126.8, 122.7, 117.6, 116.3, 113.4, 108.8, 91.5, 84.9, 80.3, 26.4, 26.3, 24.9, 13.8. **Anal**. Calc'd for $C_{19}H_{22}O_8$: C, 60.31; H, 5.86. Found: C, 60.51; H, 6.08. **$[a]_D^{23}$** = - 137.4 (*c* = 1.00, CH_3OH).

(*E*)-3-{4-[(3a*R*,4*S*,6*S*,6a*R*)-2,2-Dimethyl-6-(2-methyl-[1,3]dioxolan-2-yl)-tetrahydrofuro[3,4-d][1,3]dioxol-4-yloxy]-3-(hydroxy)-phenyl}-2-methyl-acrylic acid 16

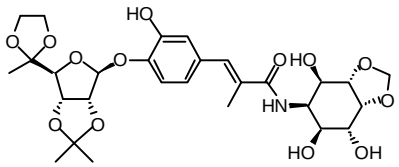


To a solution of **15** (0.5g, 1.32 mmol) in dichloromethane (13 mL), at 0°C, is added freshly distilled 1,2-bistrimethylsilyloxyethane (0.97 mL, 4 mmol) and trimethylsilyl trifluoromethanesulfonate (30 µL, 0.13 mmol). The mixture is stirred at 0 C for 6 hours. Pyridine (3 mL) and ethyl acetate are then added. The organic phase is washed with a saturated solution of sodium

hydrogenocarbonate and brine, dried over magnesium sulfate, filtrated and evaporated *in vacuo*. The ketal **16** (0.505 g, 1.20 mmol) is isolated pure as a white foam after column chromatography (petroleum ether / ethyl acetate 1/1) with 91% yield.

R_f = 0.55 (Diethyl ether). **IR** (neat) (cm^{-1}): 340, 2986, 1882, 1614, 1505, 1250, 1100. **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) (*J* in Hz) 7.65 (s, 1H), 7.03 (d, *J* = 8.1, 1H), 7.02 (s, 1H), 6.90 (d, *J* = 8.1, 1H), 5.88 (s, 1H), 4.84 (s, 2H), 4.33 (s, 1H), 4.09 (m, 2H), 4.03 (m, 2H), 2.10 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 177.6, 147.7, 143.5, 139.8, 131.5, 127.1, 122.5, 117.3, 116.4, 112.8, 108.5, 91.5, 85.4, 80.3, 65.4, 64.5, 26.5, 25.0, 20.7, 13.9. **Anal**. Calc'd for $C_{21}H_{26}O_9$: C, 59.71; H, 6.20. Found: C, 59.92; H, 6.42. **HRMS** Calc'd for $C_{21}H_{26}O_9$: 422.1577. Found: 422.1568. **$[\alpha]_D^{23}$** = - 92.2 (*c* = 1.00, CH_3OH).

(*E*)-3-{4-[(3a*R*,4*S*,6*S*,6a*R*)-2,2-Dimethyl-6-(2-methyl-[1,3]dioxolan-2-yl)-tetrahydrofuro[3,4-d][1,3]dioxol-4-yloxy]-3-(hydroxy)-phenyl}-2-methyl-*N*-((3a*S*,4*R*,6*S*,7*R*,7a*R*)-4,6,7-trihydroxy-hexahydro-benzo[1,3]dioxol-5-yl)-acrylamide 17

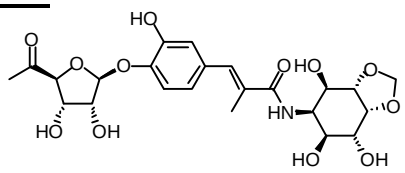


To a solution of **16** (50 mg, 118 μmol) and **6** (30 mg, 150 μmol) in DMF (2 mL) at 0 C, is added diethylcyanophosphonate (30 μL, 150 μmol) and triethylamine (28 μL, 200 μmol). After 3 h at this temperature, ethyle acetate is added and the organic phase is washed by brine, dried over magnesium sulfate, filtrated and evaporated *in vacuo*. The above amide (49 mg, 83 μmol) is isolated pure after three purifications on silica gel (preparative TLC) (Ethyle acetate / methanol 85/15) with 70% yield.

R_f = 0.25 (Ethyl acetate / methanol 85/15). **IR** (neat) (cm^{-1}): 3420, 1610, 1510. **^{1}H NMR** (500 MHz, CH_3OH-d_4): d (ppm) (*J* in Hz): 7.23 (s, 1H), 7.11 (d, *J* = 8.3, 1H), 6.92 (d, *J* = 2.0, 1H), 6.86 (dd, *J* = 2.0, 8.3, 1H), 5.81 (s, 1H), 5.23 (s, 1H), 4.93 (d, *J* = 6.1, 1H), 4.89 (dd, *J* = 1.7, 6.1, 1H), 4.79 (s, 1H), 4.50 (dd, *J* = 2.7, 6.1, 1H), 4.23 (d, *J* = 1.7, 1H), 4.20 (m, 3H), 3.92 (m, 5H), 3.80 (dd, *J* = 2.7,

2.7, 1H), 2.11 (d, *J* = 1.3, 3H), 1.49 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H). **^{13}C NMR** (125 MHz, CH_3OH-d_4): *d* (ppm) 172.8, 148.3, 145.3, 134.9, 132.3, 132.0, 122.6, 117.9, 116.8, 113.8, 109.9, 109.3, 96.1, 92.9, 87.0, 82.1, 78.1, 72.5, 71.6, 71.2, 66.7, 65.9, 50.3, 49.8, 27.1, 25.2, 23.0, 14.7. **LRMS** (ESI) Calc'd for $C_{28}H_{36}NO_{13}$ (M-H): 594.22. Found: 594.20. **[*a*]$_D^{23}$** = -44.1 (*c* = 1.00, CH_3OH).

***C*-2-*epi*-Hygromycin A 2**



To a solution of the above amide (70 mg, 117 μmol) in water (0.5 mL), is added at room temperature trifluoroacetic acid (0.6 mL). After 1 h, benzene is added and the mixture is evaporated *in vacuo*. This operation is repeated 3 times. The analog **2** (42 mg, 82 μmol) is isolated pure after purification on sephadex LH-20 (7 g) (Methanol / ethyl acetate 1/3) followed by sephadex G-10 (7 g) (water) with 70% yield.

R_f = 0.10 (Ethyl acetate / methanol 85/15). **IR** (KBr) (cm^{-1}): 3420, 1710, 1610, 1510. **^{1}H NMR** (500 MHz, CH_3OH-d_4): *d* (ppm) (*J* in Hz): 7.25 (s, 1H), 7.14 (d, *J* = 8.3, 1H), 6.93 (d, *J* = 2.0, 1H), 6.87 (dd, *J* = 2.0, 8.5, 1H), 5.56 (s, 1H), 5.22 (s, 1H), 4.78 (s, 1H), 4.50 (m, 2H), 4.43 (d, *J* = 7.3, 1H),

4.26 (d, *J* = 4.4, 1H), 4.21(dd, *J* = 3.2, 6.6, 1H), 4.17 (m, 2H), 3.96 (dd, *J* = 6.7, 6.7, 1H), 3.80 (dd, *J* = 2.8, 2.8, 1H), 2.14 (s, 3H), 2.12 (d, *J* = 1.5, 3H). **^{13}C NMR** (125 MHz, CH_3OH-d_4): d (ppm) 210.7, 172.6, 148.5, 145.7, 134.9, 132.9, 132.2, 122.6, 118.3, 118.2, 108.9, 96.2, 88.6, 78.2, 76.3, 74.2, 72.5, 71.5, 71.2, 64.3, 50.3, 26.2, 14.6. **Anal**. Calc'd for $C_{23}H_{29}NO_{12}$: C, 54.01 ; H, 5.71; N, 2.74. Found: C, 54.22; H, 5.56; N, 2.63. **LRMS** (ESI) Calc'd for $C_{23}H_{28}NO_{12}$ (M-H): 510.16. Found: 510.54. $[a]_D^{22}$ = - 60.4 (*c* = 1.00, CH_3OH).

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2. Sakai, A.; Aoyama, T.; Shioiri, T.; *Heterocycles* **2000**, *52*, 643.