Supporting Information

Synthesis and Biological Evaluation of C-Aromataxane Derivatives as P-Glycoprotein-Mediated Multi Drug Resistance Reversal Agents

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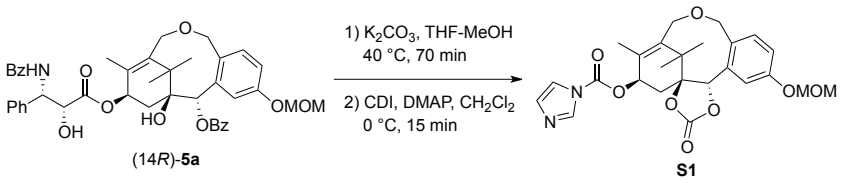
(14*R*)-Imidazolecarbonyloxy-1,2-carbonate S1

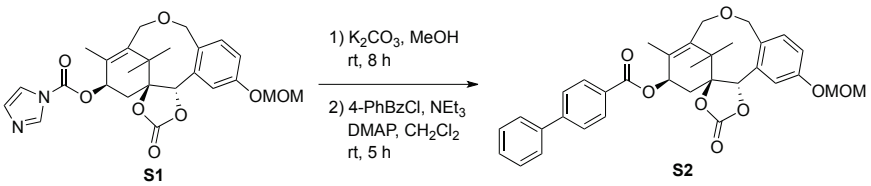


To a solution of (14*R*)-**5a** (15.2 mg, 24.1 mmol) in THF (0.50 mL,) was added KOH (1.50 mL, 0.80 M in methanol) at 0 ˚C. After being stirred at 40 ˚C for 70 min, the reaction mixture was quenched with 1 M aqueous HCl at 0 ˚C. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4. After removal of the solvent in vacuo, the crude 1,2,14-triol was used for the next reaction without further purification.

To a solution of the 1,2,14-triol in CH_2Cl_2 (1.00 mL) was added carbonyl diimidazole (39.0 mg, 0.24 mmol, 10.0 equiv.) and a catalytic amount of DMAP at 0 ˚C under argon. After being stirred at 0 ˚C for 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 ˚C. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2.0% methanol in $CHCl_3$) to afford the (14*R*)-imidazolecarbonyloxy-1,2-carbonate **S1** (10.5 mg, 21.7 mmol, 90% in 2 steps) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.34 (d, *J* = 2.9 Hz, 1H), 7.31 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.05 (s, 1H), 7.00 (dd, *J* = 2.9, 8.2 Hz, 1H), 6.27 (s, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.20 (d, *J* = 6.8 Hz, 1H), 4.85 (d, *J* = 14.5 Hz, 1H), 4.54 (d, *J* = 14.5 Hz, 1H), 4.41 (d, *J* = 13.1 Hz, 1H), 4.31 (d, *J* = 13.1 Hz, 1H), 3.96 (dd, *J* = 4.8, 9.7 Hz, 1H), 3.52 (s, 3H), 3.02 (dd, *J* = 9.7, 15.5 Hz, 1H), 2.93 (dd, *J* = 4.8, 15.5 Hz, 1H), 1.61 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H); FT-IR (Neat) 2957, 1808, 1760 1502, 1473, 1393, 1317, 1288, 1241, 1206, 1153, 1041, 999, 928, 754 cm^{-1}; HRMS (ESI-TOF) calcd for $[C_{25}H_{28}N_2O_8+H]^+$ 485.1924, found 485.1944.

(14*R*)-Hydroxy-1,2-carbonate 2-77.



To a solution of **S1** (6.3 mg, 12.9 mmol) in THF (0.40 mL) and H_2O (0.8 mL) was added K_2CO_3 (40.0 mg, 0.29 mmol, 22.5 equiv) at 0 ˚C under argon. After being stirred for 8 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 ˚C, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was used for next reaction without further purification.

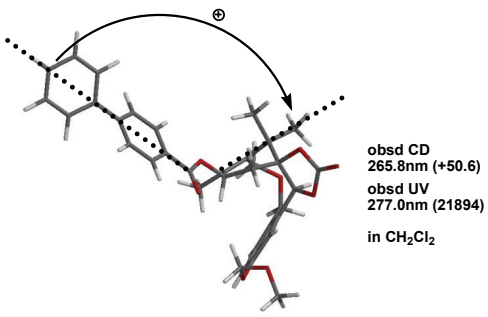
To a solution of the crude allylic alcohol in CH_2Cl_2 (0.50 mL) was added triethylamine (0.20 mL), a catalytic amount of DMAP and 4-phenylbenzoyl chloride (28.0 mg, 0.129 mmol, 10.0 equiv.) at 0 ˚C under argon. After

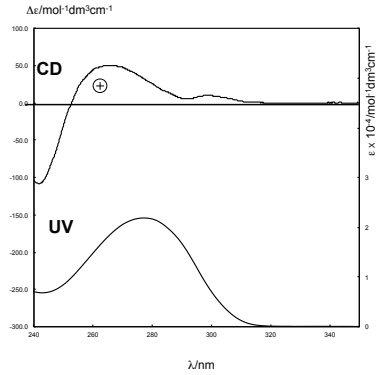
being stirred for 5.5 h at room temperature, the reaction mixture was quenched with H_2O at 0 °C. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative TLC (50% ethyl acetate in hexane) to afford the (14*R*)-(phenyl benzoyloxy)-1,2-carbonate **S2** (3.9 mg, 7.19 mmol, 83%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.40 (d, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 2.9 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 2.9, 8.2 Hz, 1H), 6.29 (s, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.25 (d, *J* = 6.8 Hz, 1H), 4.86 (d, *J* = 14.5 Hz, 1H), 4.55 (d, *J* = 14.5 Hz, 1H), 4.42 (d, *J* = 13.0 Hz, 1H), 4.33 (d, *J* = 13.0 Hz, 1H), 4.07 (dd, *J* = 4.8, 9.7 Hz, 1H), 3.55 (s, 3H), 3.03 (dd, *J* = 9.7, 15.0 Hz, 1H), 2.21 (dd, *J* = 4.8, 15.0 Hz, 1H), 1.61 (s, 3H), 1.41 (s, 3H), 1.26 (s, 3H); FT-IR (Neat) 3419, 2923, 2852, 1806 1716, 1609, 1463, 1312, 1264, 1205, 1154, 1019, 1039, 749 cm^{-1}; HRMS (ESI-TOF) calcd for $[C_{34}H_{34}O_8+H]^+$ 571.2332, found 571.2334.

Determination of the absolute configuration of C14 position in S2

Determination of the absolute configuration of the allylic alcohol at C14 position was performed by circular dichroism spectroscopy. Positive Cotton effect (+50.6) was observed as shown below, thus the absolute configuration of the allylic alcohol at C14 position was determined to be R.





Result of MTT assay for Paclitaxel (1) (left), and 2b (right) against KB-3-1 and KB-G2 cells