Discovery of G protein biased EP2 receptor agonists.

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Supporting Information

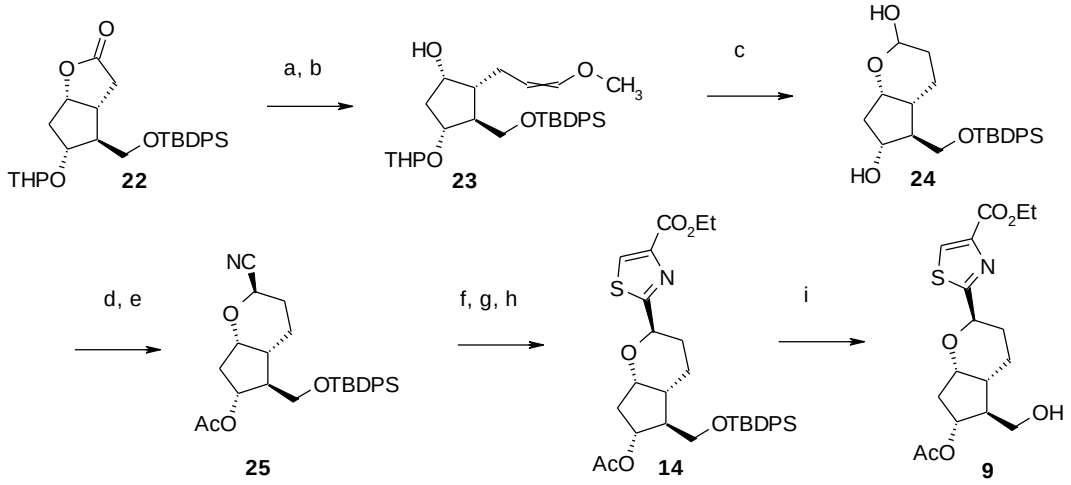
37 pages

Contents:

Synthesis of common intermediate 9

Synthesis of common intermediate **9** is outlined in Scheme S1. The protected Corey lactone **22** was reduced to a lactol by DIBAL and Wittig olefination of which afforded the vinyl ether **23**. The vinyl ether **23** was transformed to lactol **24** under acidic hydrolysis conditions. The lactol **24** was treated with acetic anhydride, and the resulting diacetate was transformed to **25** by introducing a cyano group in the presence of Lewis acid catalyst as a diastereomeric mixture (β/α ratio = 5/1). Thioamidation, condensation with bromopyruvate and cyclization by treatment with TFAA generated thiazole **14**. Deprotection of the silyl group with TBAF afforded the common intermediate **9**.

Scheme S1



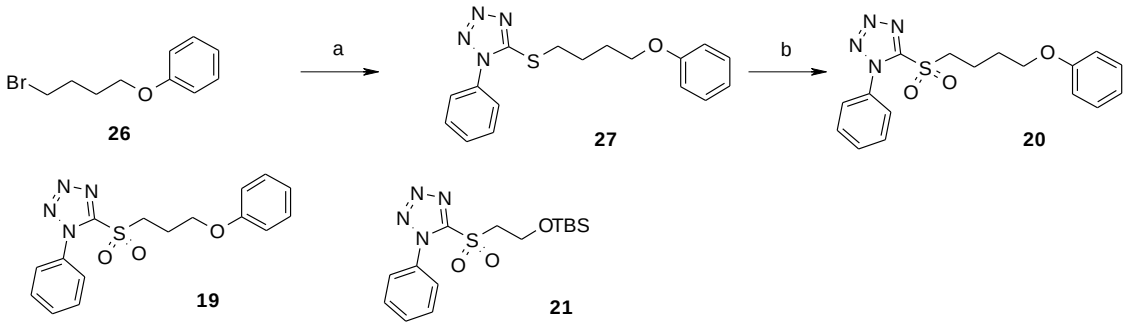
Reagents and conditions: (a) DIBAL, toluene, −78°C, (b) (methoxymethyl)(triphenyl)-phosphonium chloride, KO*t*Bu, THF, −78°C, 88% (2 steps), (c) AcOH, THF, H_2O, 55°C, 63%, (d) Ac_2O, Py, rt, (e) TMSCN, $SnCl_4$, MeCN, 0°C, 97% (2 steps), (f) $(NH_4)_2S$, Py, 10°C, 55%, (g) ethyl bromopyruvate, $KHCO_3$, DME, −25°C, (h) TFAA, Py, −25°C, 97%, (i) TBAF, AcOH, THF, rt, 84%.

Abbreviations; DIBAL, diisobutylaluminium hydride; TFAA, trifluoroacetic anhydride; TBAF, tetra-*n*-butylammonium fluoride; THP, 2-tetrahydropyranyl; TBDPS, *t*-butyldiphenylsilyl.

Syntheses of Julia-Kocienski reagents 19-21

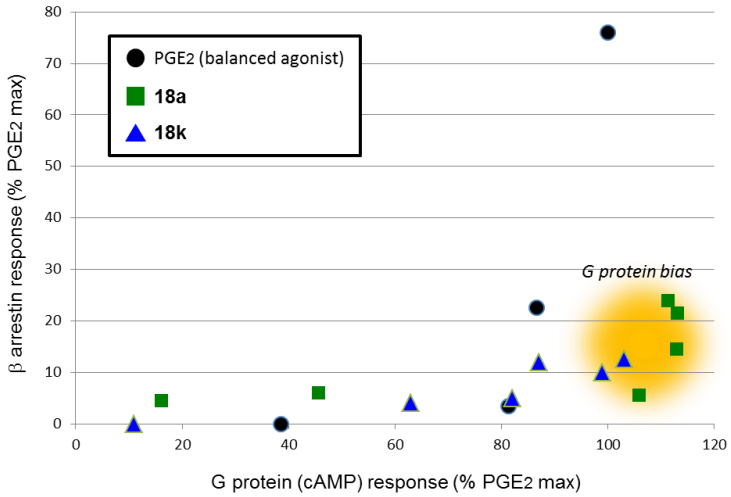
Julia-Kocienski reagent **20** was synthesized as outlined in Scheme S2. Commercially available halide **26** was treated with potassium carbonate and 1-phenyl-1*H*-tetrazole-5-thiol, and oxidation of a sulfide **27** afforded compound **20**. Compound **19** and **21** were synthesized in a similar manner using the corresponding halides.

Scheme S2



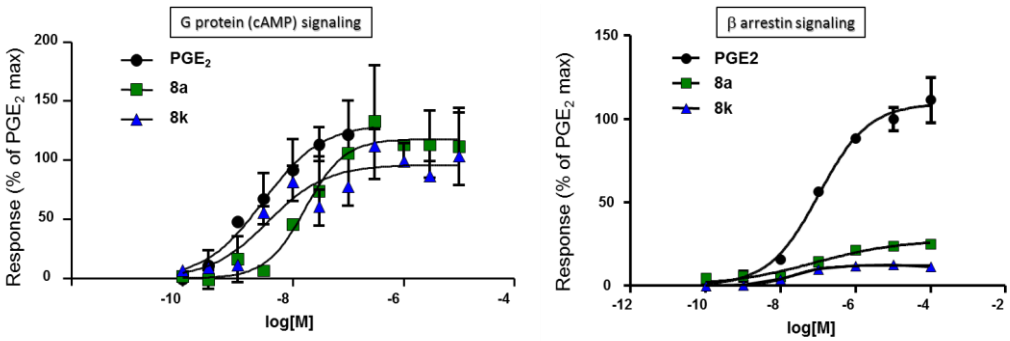
Reagents and conditions: (a) 1-phenyl-1*H*-tetrazole-5-thiol, K_2CO_3, acetone, 60 °C, 94% (b) 30%H_2O_2aq., Na_2WO_4 $2H_2O$, $PhPO(OH)_2$, $(C_8H_{17})_3NMe$ HCl, rt, 71%

Figure S1. Equimolar comparison of G protein and b arrestin responses of PGE_2, 18a and 18k



The equimolar curves of **18a** and **18k** (G protein biased agonists) shifted to right side relative to PGE_2 (balanced agonists), that is, **18a** and **18k** show markedly less β arrestin activity with equivalent G protein activity relative to PGE_2.

Figure S2. Concentration-response curves of PGE_2, 18a and 18k



General Experimental.

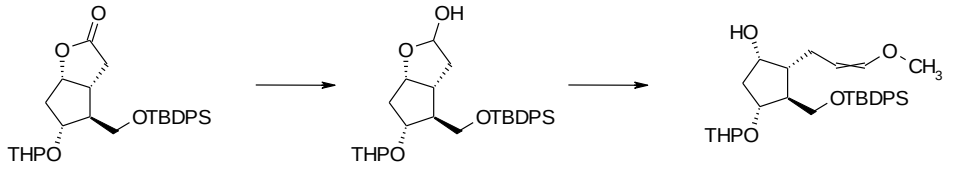
Analytical samples were homogeneous as confirmed by TLC, and spectroscopic results were consistent with the assigned structures. NMR spectra were recorded as designated on either a Varian Mercury 300 spectrometer or INOVA-500 spectrometer using deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent. Fast atom bombardment (FABMS, HRMS) and electron ionization (EI) were performed on a JEOL JMS-DX303HF spectrometer. Purity analysis was carried out by the following LC/MS system. LC/MS: Waters ACQUITY UPLC system fitted by with Waters Micromass ZQ-2000 spectrometer. Column; YMC Triart C18 (2.0 mm × 30 mm). Eluting over 1.5 min with 5−95% acetonitrile(0.1% TFA) in water (0.1%TFA), flow rate of 1.0 mL/min, column temperature of 30 °C, detection with UV (PDA) and ELSD. Column chromatography was performed with silica gel [Merck Silica Gel 60 (0.063−0.200 μm), Wako gel C-200, Fuji Silysia PSQ-100B or Fuji Silysia FL60D]. Thin layer chromatography was performed with silica gel (Merck TLC or HPTLC plates, Silica Gel 60 F254). Medium-pressure preparative liquid chromatography was performed with a medium-pressure preparative liquid chromatograph W-prep 2XY (manufactured by Yamazen Corporation; column: main column size S-5L, inject column size SS-2L).

The following abbreviations for solvents and reagents are used: DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; EtOH, ethanol; EtOAc, ethyl acetate; MeOH methanol; THF, tetrahydrofuran; CH_2Cl_2, dichloromethane; *tert*-BuOMe, *tert*-butyl methyl ether; iPr_2O, diisopropyl ether; CH_3CN, acetonitrile; Et_3N, triethylamine; TFA, trifluoroacetic acid; IPA, isopropyl alcohol;

Experimental Procedure

Scheme S1

(1*S*,2*R*,3*S*,4*R*)-2-(3-methoxy-2-propen-1-yl)-3-({[(2-methyl-2-propanyl)(diphenyl)silyl]oxy}methyl)-4-(tetrahydro-2*H*-pyran-2-yloxy)cyclopentanol (23)



22 **22-2** **23**

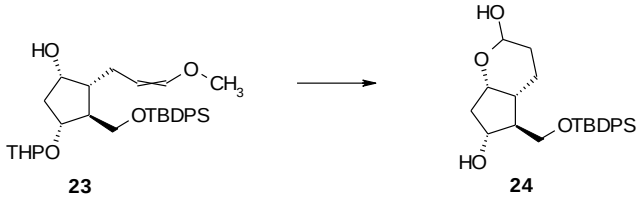
To a solution of **22** (422 g, 853 mmol) in toluene (1.50 L) at –78 °C was added diisobutylaluminium hydride (1.00 M in toluene, 995 mL, 995 mmol). After stirred at –78 °C for 1 h, potassium sodium tartrate tetrahydrate (434 g, 1.54 mol) in H_2O (650 mL) was added. The reaction mixture was stirred at room temperature for 20 h and extracted with *tert*-BuOMe. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Concentration gave **22-2** (462 g, crude), which was directly used in the next reaction.

To a suspension of potassium *tert*-butoxide (253 g, 2.26 mol) in THF (2.30 L) was slowly added (methoxymethyl)triphenylphosphonium chloride (775 g, 2.26 mol). After the mixture was stirred at 0 °C for 30 min, **22-2** (456 g, crude) in THF (600 mL) was added. After stirred at 0 °C for 30 min, the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration gave crude mixture (1100 g), which was purified by recrystallization from IPA (400 mL) and hexane (400 mL) to remove triphenylphosphine oxide. After filtration of the phosphine oxide, the filtrate was concentrated, and flash column chromatography (Fuji silicia PSQ-100B, hexane/EtOAc 1:0-10:1-5:1-2:1) gave **23** (391 g) in 88% yield over 2 steps.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.60 (m, 4H), 7.46-7.35 (m, 6H), 6.33 (m, 0.7H), 5.90 (m, 0.3H), 4.73 (m, 0.7H), 4.70-4.62 (m, 1H), 4.41 (m, 0.3H), 4.36-4.24 (m, 1H), 4.17-4.00 (m, 1H), 3.92-3.66 (m, 3H), 3.58 (s, 0.45H), 3.57 (s, 0.45H), 3.55-3.44 (m,

1H), 3.43 (s, 1.05 H), 3.42 (s, 1.05 H), 2.39-2.20 (m, 2H), 2.03 (m, 1H), 2.07-1.67 (m, 4H), 1.57-1.47 (m, 5H), 1.054 (s, 4.5H), 1.045 (s, 4.5H) (Peak of O*H* was not observed.).

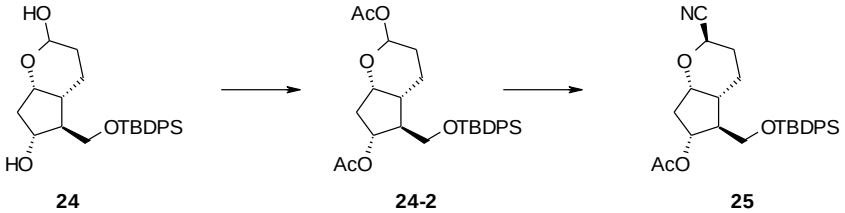
(4a*R*,5*S*,6*R*,7a*S*)-5-({[(2-methyl-2-propanyl)(diphenyl)silyl]oxy}methyl)octahydrocyclopenta[*b*]pyran-2,6-diol (24)



To a solution of **23** (410 g, 781 mmol) in THF (1.50 L) and H_2O (600 mL) was added acetic acid (1.20 L). After stirred at 55 °C for 3 h, the reaction mixture was extracted with toluene. The organic layer was washed with H_2O, 1.0 M hydrochloric acid and brine, dried over Na_2SO_4, and concentrated. The crude product (372 g) was purified by flash column chromatography (Fuji silicia PSQ-100B, hexane/EtOAc 1:0-4:1-2:1-1:3) to give **24** (211 g) in 63% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.62 (m, 4H), 7.43-7.35 (m, 6H), 5.27 (m, 0.4H), 4.90 (m, 0.6H), 4.65 (m, 0.6H), 4.40 (m, 0.4H), 4.19-4.09 (m, 1H), 4.02 (m, 0.4H), 3.79 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.65-3.60 (m, 1H), 3.54 (m, 0.6H), 2.92 (d, *J* = 6.0 Hz, 0.6H), 2.81 (d, *J* = 9.6 Hz, 0.4H), 2.74 (d, *J* = 9.6 Hz, 0.6H), 2.66 (d, *J* = 6.0 Hz, 0.4H), 2.15-2.00 (m, 3H), 1.87-1.72 (m, 3H), 1.63-1.46 (m, 1H), 1.05 (s, 9H).

(2*R*,4a*R*,5*S*,6*R*,7a*S*)-2-cyano-5-({[(2-methyl-2-propanyl)(diphenyl)silyl]oxy}methyl)octahydrocyclopenta[*b*]pyran-6-yl acetate (25)



To a solution of **24** (211 g, 494 mmol) in pyridine (900 mL) at 0 °C was added acetic anhydride (182 g, 1.78 mol). After stirred at room temperature for 14 h, the reaction mixture was diluted with toluene (500 mL) and H_2O (1.8 L) and extracted with toluene. The organic layer was washed with H_2O, 1.0 M hydrochloric acid, saturated aqueous $NaHCO_3$ and brine, successively, and dried over Na_2SO_4. Concentration gave **24-2** (268 g crude), which was directly used in the next reaction.

To a solution of **24-2** (268 g, crude) and trimethylsilyl cyanide (91.9 g, 889 mmol) in CH_3CN (1.40 L) at 0 °C was added $SnCl_4$ (1.0 M in CH_2Cl_2, 494 mL, 494 mmol). After stirred at 0 °C for 40 min, the reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ and ice. The mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4. Concentration gave **25** (230 g) in 97% yield over 2 steps.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.60 (m, 4H), 7.45-7.35 (m, 6H), 5.17 (m, 1H), 4.80 (m, 1H), 4.26 (m, 1H), 3.81 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.63 (dd, *J* = 10.8, 4.2 Hz, 1H), 2.37 (m, 1H), 2.32 (m, 1H), 2.10-1.90 (m, 4H), 2.04 (s, 3H), 1.74-1.63 (m, 2H), 1.04 (s, 9H).

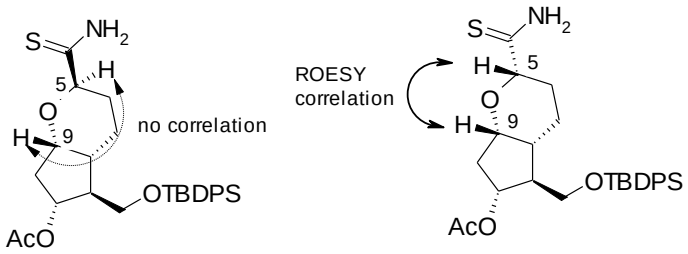
(2*R*,4a*R*,5*S*,6*R*,7a*S*)-2-carbamothioyl-5-({[(2-methyl-2-propanyl)(diphenyl)silyl]oxy}methyl)octahydrocyclopenta[*b*]pyran-6-yl acetate (25-2)

25 **25-2**

To a solution of **25** (230 g, 482 mmol) in pyridine (1.20 L) at 0 °C was added $S(NH_4)_2$ (20% in aqueous solution, 163 g, 478 mmol). After the mixture was stirred under 10 °C for 22 h, $S(NH_4)_2$ (20% in aqueous solution, 82 g, 240 mmol) was added, and the mixture stirred at 10 °C for 2 h. Ice (300 g) and H_2O (2.0 L) were added, and the

mixture was extracted with toluene. The organic layer was washed with H_2O and brine. Concentration and flash column chromatography (Fuji silicia PSQ-100B, hexane/EtOAc 9:1-5:1-4:1-3:1-2:1) gave **25-2** (86.5 g) in 34% yield and diastereomeric mixture (107 g). **25-2** (71.5 g) and its diastereomeric mixture (167 g) were synthesized in the same procedure using **25** (249 g, 523 mmol). Further purification of diastereomeric mixtures (107 g and 167 g) by flash column chromatography (Fuji silicia PSQ-100B, hexane/EtOAc 9:1-5:1-4:1-3:1-2:1) gave **25-2** (124 g), total **25-2** (282g) in 55% yield.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 1H), 7.65-7.60 (m, 4H), 7.52 (m, 1H), 7.45-7.35 (m, 6H), 5.06 (m, 1H), 4.42 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.22 (m, 1H), 3.73 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.63 (dd, *J* = 10.2, 4.2 Hz, 1H), 2.38 (m, 1H), 2.26 (m, 1H), 2.09-2.01 (m, 2H), 2.03 (s, 3H), 1.96-1.84 (m, 4H), 1.05 (s, 9H).

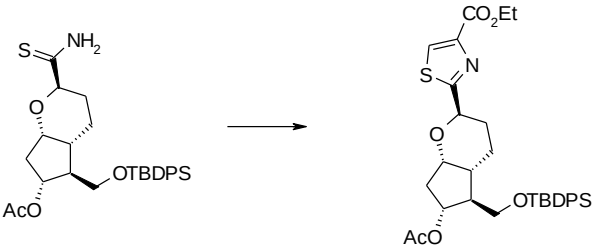
The stereochemistry of C5 position was determined by 2D NMR (ROESY).



25-2 The diastereomer of **25-2**

The diastereomer of **25-2** showed ROESY correlation between H5 and H9.

Ethyl 2-[(2*R*,4a*R*,5*S*,6*R*,7a*S*)-6-acetoxy-5-({[(2-methyl-2-propanyl)(diphenyl)silyl]-oxy}methyl)octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylate (14)



25-2 **14**

To a solution of **25-2** (129 g, 252 mmol) in 1,2-dimethoxyethane (1.10 L) at –25 °C was added $KHCO_3$ (202 g, 2.02 mol). Ethyl bromopyruvate (164 g, 756 mmol, purity 90%) was added at –25 °C, and the mixture was stirred for 4 h. Then, pyridine (160 g, 2.02 mol) and trifluoroacetic anhydride (212 g, 1.01 mol) were added at –25 °C for 35 min. After stirred at –25 °C for 30 min, the mixture was quenched with H_2O and extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Concentration and flash column chromatography (Fuji silicia BW-820MH, hexane/EtOAc 1:0-10:1-6:1-4:1-3:1) gave **14** (150 g) in 97% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.65-7.60 (m, 4H), 7.45-7.31 (m, 6H), 5.14 (t, *J* = 5.7 Hz, 1H), 5.12 (m, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.23 (m, 1H), 3.77 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.65 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.37 (m, 1H), 2.25 (m, 1H), 2.13 (m, 2H), 2.04 (s, 3H), 1.96-1.82 (m, 3H), 1.62-1.50 (m, 1H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 9H).

Ethyl 2-[(2*R*,4a*R*,5*S*,6*R*,7a*S*)-6-acetoxy-5-(hydroxymethyl)octahydrocyclopenta[*b*]-pyran-2-yl]-1,3-thiazole-4-carboxylate (9)

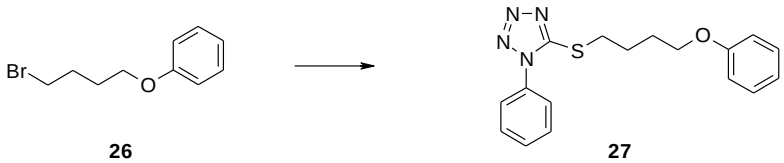
14 **9**

To a solution of **14** (150 g, 247 mmol) in THF (370 mL) and acetic acid (38.5 g, 642 mmol) at room temperature was added tetra-*n*-butylammonium fluoride (1.00 M in THF, 642 mL, 642 mmol). After stirred at 44 °C for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Concentration and flash column chromatography (Fuji silicia BW-820MH, hexane / EtOAc 1:1-1:2) gave alcohol **9** (77.3 g) in 84% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 5.18 (t, *J* = 5.4 Hz, 1H), 5.02 (dt, *J* = 8.7, 4.8 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.23 (m, 1H), 3.70 (m, 1H), 3.61 (m, 1H), 2.70 (m, 1H), 2.35-2.14 (m, 3H), 2.12 (s, 3H), 2.06-1.98 (m, 2H), 1.79-1.61 (m, 3H), 1.40 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.33, 20.79, 21.37, 24.84, 37.14, 38.75, 50.63, 61.40, 62.63, 72.65, 73.49, 76.38, 128.07, 147.10, 161.42, 172.09, 173.52. MS (FAB, Pos.) *m/z* 370 $(M + H)^+$. HRMS (FAB, Pos.) $C_{17}H_{24}NO_6S$ $(M + H)^+$ calc. mass 370.1324, found 370.1331.

Scheme S2

5-[(4-phenoxybutyl)thio]-1-phenyl-1*H*-tetrazole (27)



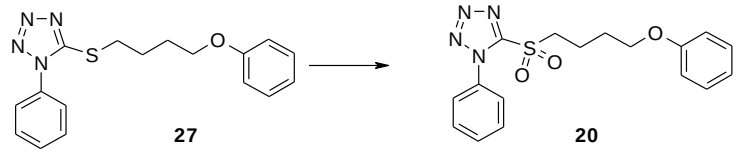
26 **27**

To a solution of **26** (3.00 g, 13.1 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (2.46 g, 13.8 mmol) in acetone (15.0 mL) at room temperature was added K_2CO_3 (1.90 g, 13.8 mmol). After stirred at 60 °C for 16 h, the reaction mixture was quenched with 1.0 M hydrochloric acid and extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography L,

hexane/EtOAc 9:1-2:1) gave **27** (4.01 g) in 94% yield.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60-7.53 (m, 5H), 7.28 (d, J = 7.2 Hz, 2H), 6.94 (t, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 2H), 4.00 (t, J = 6.0 Hz, 2H), 3.49 (t, J = 7.2 Hz, 2H), 2.05 (m, 2H), 1.95 (m, 2H).

5-[(4-phenoxybutyl)sulfonyl]-1-phenyl-1*H*-tetrazole (20)

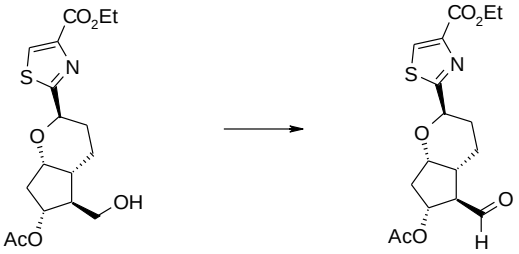


To a solution of **27** (2.00 g, 6.13 mmol) in CH_2Cl_2 (15.0 mL) at 0 °C was added 3-chloroperoxybenzoic acid (3.21 g, 12.1 mmol). After the mixture was stirred at room temperature for 2 h, 3-chloroperoxybenzoic acid (1.66 g, 6.76 mmol, purity 70%) was added. After stirred at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous Na_2SO_3 and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (Yamazen W-prep 2XY flash column chromatography L, hexane/EtOAc 9:1-2:1) gave **20** (1.55 g) in 71% yield.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.71-7.68 (m, 2H), 7.64-7.58 (m, 3H), 7.29 (d, J = 6.9 Hz, 2H), 6.96 (t, J = 6.9 Hz, 1H), 6.87 (d, J = 6.9 Hz, 2H), 4.03 (t, J = 5.7 Hz, 2H), 3.87 (t, J = 6.0 Hz, 2H), 2.20 (m, 2H), 2.03 (m, 2H).

Scheme 1A

Ethyl 2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-acetoxy-5-formyloctahydrocyclopenta[*b*]pyran -2-yl]-1,3-thiazole-4-carboxylate (9-2)

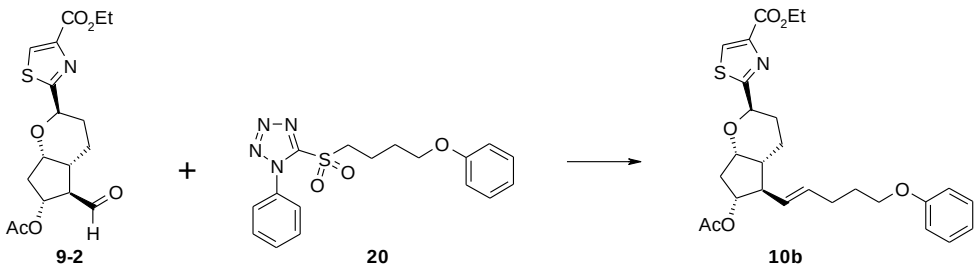


9 **9-2**

To a solution of **9** (3.00 g, 8.12 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added Dess-Martin periodinane (4.00 g, 9.43 mmol). After stirred at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography, hexane/EtOAc 1:1-0:1) gave **9-2** (2.30 g) in 77% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (d, *J* = 2.4 Hz, 1H), 8.17 (s, 1H), 5.29 (m, 1H), 5.18 (t, *J* = 5.1 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.20 (m, 1H), 3.02 (m, 1H), 2.37 (m, 1H), 2.25 (m, 2H), 2.17 (m, 1H), 2.10 (s, 3H), 2.10-2.00 (m, 2H), 1.72 (m, 1H), 1.40 (t, *J* = 7.2 Hz, 3H).

Ethyl 2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-acetoxy-5-[(1*E*)-5-phenoxy-1-penten-1-yl] -octahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylate (10b)



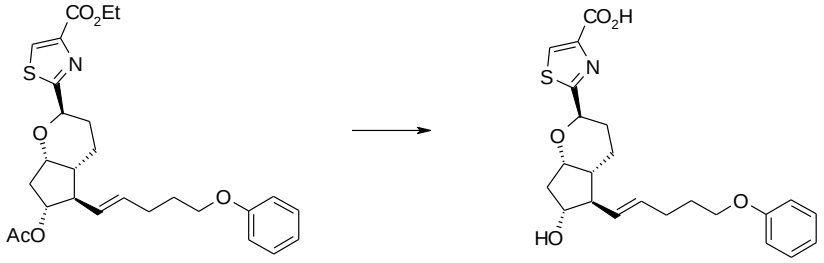
9-2 **20** **10b**

To a solution of **20** (143 mg, 0.389 mmol) in 1,2-dimethoxyethane (2.0 mL) at –60 °C

was added potassium bis(trimethylsilyl)amide (0.50 M in toluene, 0.80 mL, 0.40 mmol). After the mixture was stirred at –60 °C for 10 min, **9-2** (73.4 mg, 0.20 mmol) in 1,2-dimethoxyethane (1.0 mL) was added. After stirred at 0 °C for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography M, hexane/EtOAc 9:1-3:1-7:3) gave **10b** (66.0 mg) in 34% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.31-7.24 (m, 2H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 2H), 5.58 (dt, *J* = 15.6, 6.3 Hz, 1H), 5.31 (dd, *J* = 15.6, 8.4 Hz, 1H), 5.17 (t, *J* = 5.1 Hz, 1H), 4.84 (m, 1H), 4.41 (q, *J* = 6.9 Hz, 1H), 4.13 (m, 1H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.79 (m, 1H), 2.49 (m, 4H), 2.21 (m, 4H), 2.05 (s, 3H), 1.86 (m, 3H), 1.71 (m, 1H), 1.40 (t, *J* = 6.9 Hz, 3H).

2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-[(1*E*)-5-phenoxy-1-penten-1-yl]octahydrocyclopenta[b]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (11a)

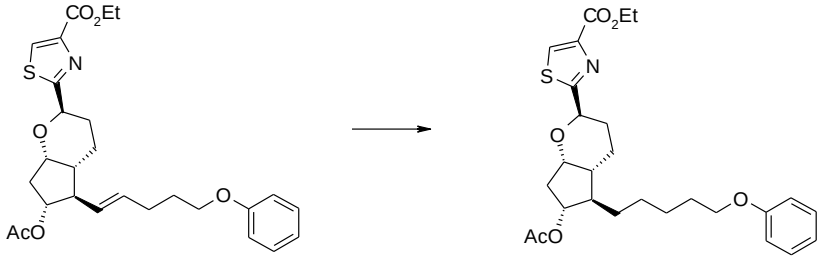


10b **11a**

To a solution of **10b** (30 mg, 0.060 mmol) in 1,2-dimethoxyethane (0.50 mL) and ethanol (0.50 mL) at room temperature was added 1.0 M sodium hydroxide (0.50 mL, 0.50 mmol). After stirred at room temperature for 3 h, the reaction mixture was extracted with *tert*-BuOMe. The aqueous layer was acidified by 1.0 M hydrochloric acid and extracted with EtOAc. The EtOAc layer was washed with brine and dried over $MgSO_4$. Concentration gave **11a** (23.2 mg) in 90% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.27 (t, *J* = 7.5 Hz, 2H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 2H), 5.62 (dt, *J* = 15.0, 5.4 Hz, 1H), 5.30 (dd, *J* = 15.0, 8.4 Hz, 1H), 5.17 (t, *J* = 4.5 Hz, 1H), 4.13-4.08 (m, 1H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.92-3.86 (m, 1H), 2.61-2.51 (m, 1H), 2.32-2.19 (m, 5H), 1.92-1.85 (m, 3H), 1.83-1.76 (m, 1H), 1.59-1.53 (m, 2H), (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.94 min (97.3%). MS (FAB, Pos.) *m/z* 430 $(M + H)^+$. HRMS (FAB, Pos.) $C_{23}H_{28}NO_5S$ $(M + H)^+$ calc. mass 430.1688, found 430.1691.

Ethyl 2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-acetoxy-5-(5-phenoxypentyl)octahydrocyclopenta -[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylate (10c)

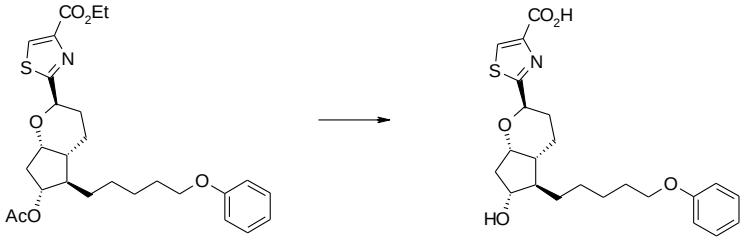


10b **10c**

To a solution of **10b** (32.0 mg, 0.064 mmol) and sodium acetate (105 mg, 1.28 mmol) in EtOH (0.50 mL) and H_2O (1.00 mL) at room temperature was added *p*-toluenesulfonyl hydrazide (119 mg, 0.64 mmol). After the mixture was stirred at 80 °C for 14.5 h, H_2O was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration and preparative thin layer chromatography gave **10c** (17.7 mg) in 55% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.27 (t, *J* = 7.2 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 2H), 5.13 (t, *J* = 6.0 Hz, 1H), 4.80 (m, 1H), 4.40 (q, *J* = 6.9 Hz, 2H), 4.21 (m, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 2.39 (m, 1H), 2.23 (m, 1H), 2.15-1.90 (m, 4H), 2.06 (s, 3H), 1.87-1.74 (m, 4H), 1.75-1.69 (m, 2H), 1.58-1.38 (m, 4H), 1.40 (t, *J* = 6.9 Hz, 3H).

2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-(5-phenoxypentyl)octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylic acid (11b)



To a solution of **10c** (17.5 mg, 0.035 mmol) in 1,2-dimethoxyethane (0.50 mL) and EtOH (0.50 mL) at room temperature was added 1.0 M sodium hydroxide (0.50 mL, 0.50 mmol). After stirred at room temperature for 2 h, the reaction mixture was extracted with *tert*-BuOMe. The aqueous layer was acidified by 1.0 M hydrochloric acid and extracted with EtOAc. The EtOAc layer was washed with brine and dried over $MgSO_4$. Concentration and column chromatography (Wakogel, chloroform/MeOH 1:0-95:5) gave **11b** (8.4 mg) in 56% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.26 (m, 2H), 6.92 (m, 1H), 6.88 (d, J = 7.8 Hz, 2H), 5.17 (t, J = 5.1 Hz, 1H), 4.15 (m, 1H), 3.96 (t, J = 6.3 Hz, 2H), 3.91 (m, 1H), 2.28-2.21 (m, 2H), 2.06-1.91 (m, 4H), 1.81 (m, 2H), 1.67 (m, 1H), 1.55-1.31 (m, 7H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.99 min (>98%). MS (FAB, Neg.) *m/z* 430 $(M - H)^-$. HRMS (FAB, Neg.) $C_{23}H_{28}NO_5S$ $(M - H)^-$ calc. mass 430.1688, found 430.1691.

8 was synthesized in a similar manner by using Julia Kocienski reagent **19**.

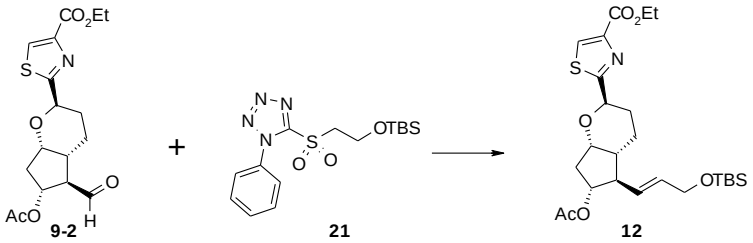
2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-[(1*E*)-4-phenoxy-1-buten-1-yl]octahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (8)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.27 (d, J = 7.2 Hz, 2H), 6.93 (t, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 2H), 5.66 (dt, J = 15.0, 6.9 Hz, 1H), 5.41 (dd, J = 15.0, 8.7 Hz, 1H), 5.18 (t, J = 4.8 Hz, 1H), 4.13 (m, 1H), 4.00 (t, J = 6.9 Hz, 2H), 3.99 (m, 1H),

2.64-2.49 (m, 3H), 2.34-2.18 (m, 3H), 1.94 (m, 1H), 1.81 (m, 1H), 1.61 (m, 2H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.89 min (>98%). MS (FAB, Pos.) *m/z* 416 $(M + H)^+$. HRMS (FAB, Pos.) $C_{22}H_{26}NO_5S$ $(M + H)^+$ calc. mass 416.1532, found 416.1531.

Scheme 1B

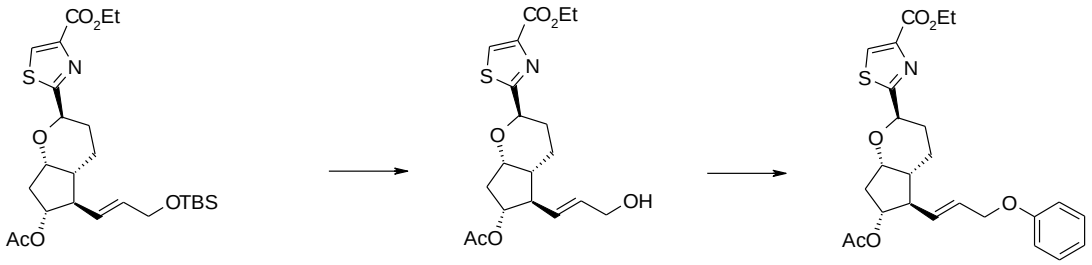
Ethyl 2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-acetoxy-5-[(1*E*)-3-{[dimethyl(2-methyl-2-propanyl)-silyl]oxy}-1-propen-1-yl]octahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylate (12)



To a solution of **21** (501 mg, 1.36 mmol) and **9-2** (252 mg, 0.689 mmol) in 1,2-dimethoxyethane (6.8 mL) at –60 °C was added potassium bis(trimethylsilyl)amide (0.50 M in toluene, 2.04 ml, 1.02 mmol) slowly. After stirred at –60 °C to –30 °C for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography L, hexane/EtOAc 97:3-85:15-4:1) gave **12** (128 mg) in 18%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 5.69 (dt, *J* = 15.3, 4.8 Hz, 1H), 5.51 (dd, *J* = 15.3, 8.7 Hz, 1H), 5.18 (t, *J* = 5.1 Hz, 1H), 4.86 (m, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.17 (m, 2H), 2.86 (m, 1H), 2.52 (m, 1H), 2.24 (m, 2H), 2.06 (s, 3H), 1.93 (m, 1H), 1.70 (m, 1H), 1.64-1.57 (m, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

Ethyl 2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-acetoxy-5-[(1*E*)-3-phenoxy-1-propen-1-yl] -octahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylate (13)

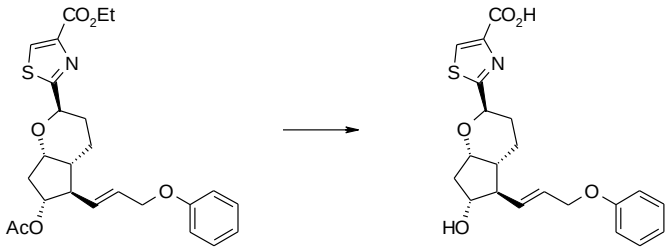


To a solution of **12** (125 mg, 0.245 mmol) in THF (1.5 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 0.38 mL, 0.38 mmol). After stirred at room temperature for 2.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography M, hexane/EtOAc 1:1-3:7) gave **12-2**, which was directly used in the next reaction.

To a solution of **12-2**, phenol (31.1 mg, 0.330 mmol) and triphenyl phosphine (86.6 mg, 0.430 mmol) in THF (1.0 mL) at room temperature was added diethyl azodicarboxylate (2.2 M in toluene, 150 μL, 0.430 mmol). After stirred at room temperature for 1 h, the reaction mixture was concentrated. A medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography M, hexane/EtOAc 9:1-3:1-7:3) gave **13** (97.3 mg) in 84% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.27-7.24 (m, 2H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 2H), 5.81 (dt, *J* = 15.0, 5.4 Hz, 1H), 5.68 (dd, *J* = 15.0, 8.1 Hz, 1H), 5.18 (t, *J* = 5.1 Hz, 1H), 4.89 (m, 1H), 4.51 (d, *J* = 4.5 Hz, 2H), 4.40 (q, *J* = 6.9 Hz, 2H), 4.16 (m, 1H), 2.90 (m, 1H), 2.51 (m, 1H), 2.24 (m, 2H), 2.06 (s, 3H), 1.94 (m, 1H), 1.72 (m, 1H), 1.66-1.54 (m, 2H), 1.40 (t, *J* = 6.9 Hz, 3H).

2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-[(1*E*)-3-phenoxy-1-propen-1-yl]octahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (11c)

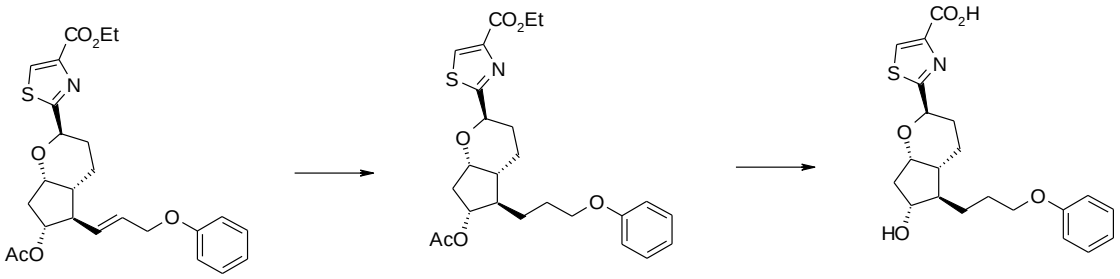


13 **11c**

To a solution of **13** (95.0 mg, 0.201 mmol) in 1,2-dimethoxyethane (1.50 mL) and EtOH (1.50 mL) at room temperature was added 1.0 M sodium hydroxide (1.50 mL, 1.50 mmol). After stirred at room temperature for 2 h, the reaction mixture was extracted with *tert*-BuOMe. The aqueous layer was acidified by 1.0 M hydrochloric acid and extracted with EtOAc. The EtOAc layer was washed with brine and dried over $MgSO_4$. Concentration gave **11c** (56.6 mg) in 70% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.29 (m, 2H), 6.93 (m, 3H), 5.87 (dt, *J* = 15.3, 5.7 Hz, 1H), 5.70 (dd, *J* = 15.3, 8.4 Hz, 1H), 5.19 (t, *J* = 4.8 Hz, 1H), 4.54 (d, *J* = 4.5 Hz, 2H), 4.13 (m, 1H), 4.00 (m, 1H), 2.69 (m, 1H), 2.31 (m, 1H), 2.26 (m, 2H), 1.95 (m, 1H), 1.85 (m, 1H), 1.69-1.58 (m, 2H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.85 min (>98%). MS (EI, Pos.) *m/z* 401 $(M)^+$. HRMS (EI, Pos.) $C_{21}H_{23}NO_5S$ $(M)^+$ calc. mass 401.1297, found 401.1292.

2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-(3-phenoxypropyl)octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylic acid (11d)



13 **13-2** **11d**

To a solution of **13** (75.0 mg, 0.159 mmol) and AcONa (262 mg, 3.20 mmol) in EtOH

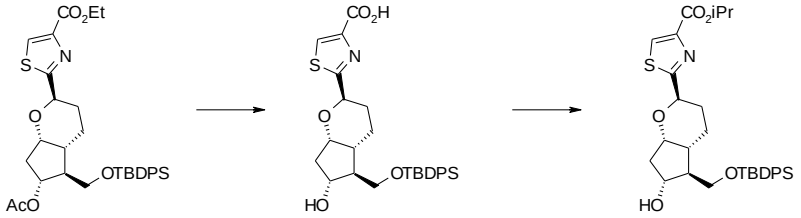
(1.0 mL) and H_2O (2.0 mL) at room temperature was added *p*-toluenesulphonyl hydrazide (298 mg, 1.60 mmol). After the reaction mixture was stirred at 80 °C for 3 days, H_2O was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography M, hexane/EtOAc 92:8-3:1-65:35) gave **13-2** (53.7 mg) in 71% yield.

To a solution of **13-2** (51.0 mg, 0.108 mmol) in 1,2-dimethoxyethane (1.00 mL) and EtOH (1.00 mL) at room temperature was added 1.0 M sodium hydroxide (1.00 mL, 1.00 mmol). After stirred at room temperature for 2 h, the reaction mixture was extracted with *tert*-BuOMe. The aqueous layer was acidified by 1.0 M hydrochloric acid and extracted with EtOAc. The EtOAc layer was washed with brine and dried over $MgSO_4$. Concentration gave **11d** (40.4 mg) in 93% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.27 (t, J = 7.5 Hz, 2H), 6.93 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 7.5 Hz, 2H), 5.17 (t, J =4.8 Hz, 1H), 4.16 (m, 1H), 4.00 (t, J = 6.3 Hz, 2H), 3.95 (m, 1H), 2.32-2.15 (m, 2H), 2.07-1.90 (m, 6H), 1.76-1.43 (m, 4H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.89 min (>98%). 1.5 min. MS (FAB, Neg.) *m/z* 402 $(M - H)^-$. HRMS (FAB, Neg.) $C_{21}H_{24}NO_5S$ $(M - H)^-$ calc. mass 402.1375, found 402.1372.

Scheme 1C

Isopropyl 2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-({[(2-methyl-2-propanyl)(diphenyl)-silyl]oxy}methyl)octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylate (14-3)



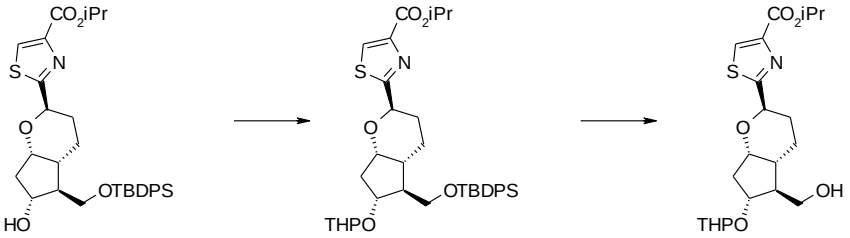
14 **14-2** **14-3**

To a solution of **14** (44.2 g, 72.8 mmol) in MeOH (900 mL) at room temperature was added 1.0M sodium hydroxide (180 mL, 180 mmol). After stirred at room temperature for 2 h, the reaction mixture was evaporated. The residue was dissolved in THF (400 mL), 1 M hydrochloric acid (210 mL) and EtOAc (400 mL). The mixture was extracted with EtOAc and the organic layer was washed with brine and dried over Na_2SO_4. Concentration gave **14-2** (40.5 g, crude), which was directly used in the next reaction.

To a solution of **14-2** (40.5 g, crude) and isopropyl iodide (24.7 g, 145 mmol) in DMF (190 mL) at room temperature was added K_2CO_3 (20.1 g, 145 mmol). After the reaction mixture was stirred at 50 °C for 14 h, H_2O (200 mL) was added and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (Fuji silicia BW-820MH, hexane/EtOAc 4:1-3:1-2:1) gave **14-3** (23.1 g) in 54% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.66-7.61 (m, 4H), 7.43-7.34 (m, 6H), 5.26 (sep, *J* = 6.3 Hz, 1H), 5.16 (t, *J* = 5.4 Hz, 1H), 4.20-4.12 (m, 2H), 3.78 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.61 (dd, *J* = 9.9, 6.3 Hz, 1H), 2.63 (d, *J* = 7.5 Hz, 1H), 2.24-2.06 (m, 4H), 1.95 (m, 1H), 1.90 (m, 1H), 1.79-1.74 (m, 1H), 1.55-1.48 (m, 1H), 1.37 (d, *J* = 6.3 Hz, 6H), 1.04 (s, 9H).

Isopropyl 2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-5-(hydroxymethyl)-6-(tetrahydro-2*H*-pyran-2-yloxy)octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylate (15)



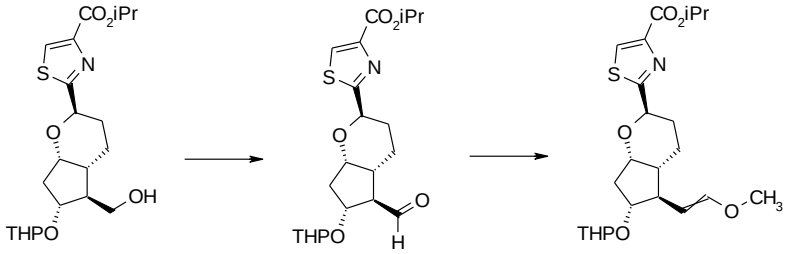
14-3 **14-4** **15**

To a solution of **14-3** (54.8 g, 94.5 mmol) and pyridinium *para*-toluenesulfonate (2.30 g, 9.15 mmol) in CH_2Cl_2 (220 mL) at room temperature was added 3,4-dihydro-2*H*-pyran (15.9 g, 189 mmol). After stirred at room temperature for 14 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Concentration gave **14-4** (64.0 g, crude), which was directly used in the next reaction.

To a solution of **14-4** (64.0 g, crude) in THF (160 mL) at room temperature was added tetra-*n*-butylammonium fluoride (1.00 M in THF, 240 mL, 240 mmol). After stirred at room temperature for 2.5 h, the reaction mixture was evaporated. The residue was dissolved in H_2O (200 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (Fuji silicia BW-820MH, hexane/EtOAc 1:1-1:2) gave **15** (38.8 g) in 96% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 5.27 (sep, *J* = 6.3 Hz, 1H), 5.14 (t, *J* = 6.3 Hz, 1H), 4.76 (m, 0.5H), 4.62 (m, 0.5H), 4.24-4.02 (m, 2H), 3.96-3.86 (m, 2H), 3.77 (dd, *J* = 10.8, 4.5 Hz, 0.5H), 3.71 (dd, *J* = 10.8, 5.7 Hz, 0.5H), 3.62-3.48 (m, 2H), 2.38-2.23 (m, 3H), 2.19-1.92 (m, 4H), 1.92-1.48 (m, 7H), 1.37 (d, *J* = 6.3 Hz, 6H).

Isopropyl 2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-5-(2-methoxyvinyl)-6-(tetrahydro-2*H*-pyran-2-yloxy)octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylate (15-3)



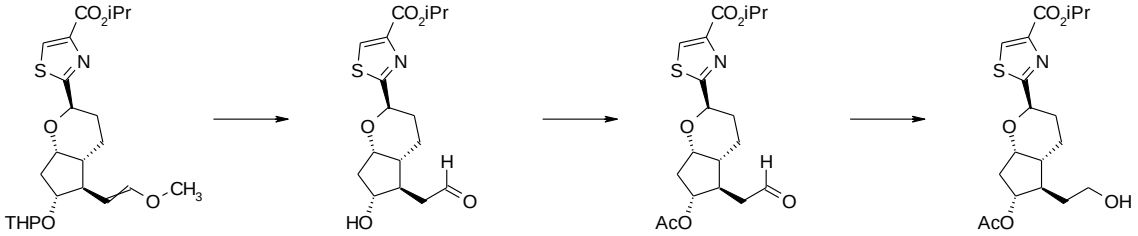
15 **15-2** **15-3**

To a solution of **15** (200 mg, 0.470 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C was added Dess-Martin periodinane (259 mg, 0.611 mmol). After stirred at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. Concentration gave **15-2**, which was directly used in next reaction.

To a suspension of 85%-potassium *tert*-butoxide (79.1 mg, 0.705 mol) in THF (4.70 mL) at 0 °C was slowly added (methoxymethyl)triphenylphosphonium chloride (242 mg, 0.705 mol). After the mixture was stirred at 0 °C for 30 min, **15-2** in THF (1.4 mL) was added and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography L, hexane/EtOAc 9:1-7:3) gave **15-3** (137 mg) in 64% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 6.40-6.36 (m, 0.8H), 6.03-5.96 (m, 0.2H), 5.26 (sep, J = 6.3 Hz, 1H), 5.14 (t, J = 5.4 Hz, 1H), 4.71 (m, 1H), 4.58 (m, 1H), 4.16 (m, 1H), 3.95-3.78 (m, 2H), 3.53 (brs, 3H), 3.48 (m, 1H), 2.58 (m, 1H), 2.37 (m, 1H), 2.18 (m, 2H), 1.94-1.81 (m, 3H), 1.74-1.45 (m, 7H), 1.37 (d, J = 6.3 Hz, 6H).

Isopropyl 2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-acetoxy-5-(2-hydroxyethyl)octahydro -cyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylate (17)



15-3 **16** **16-2** **17**

To a solution of **15-3** (120 mg, 0.266 mmol) in acetone (4.95 mL) and H_2O (50 μL) at room temperature was added *p*-toluene sulfonic acid monohydrate (15.1 mg, 0.0795 mmol). After stirred at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography L, hexane/EtOAc 3:2-1:3-0:100) gave **16** (73.0 mg) in 78% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (t, *J* = 1.2 Hz, 1H), 8.12 (s, 1H), 5.26 (sep, *J* = 6.3 Hz, 1H), 5.18 (t, *J* = 5.1 Hz, 1H), 4.14 (m, 1H), 3.89 (m, 1H), 3.08 (d, *J* = 5.1 Hz, 1H), 2.75 (m, 1H), 2.54 (m, 1H), 2.45 (m, 1H), 2.29-2.16 (m, 3H), 2.04 (m, 1H), 1.93 (m, 1H), 1.57 (m, 1H), 1.37 (d, *J* = 6.3 Hz, 6H) (Peak of O*H* was not observed.).

To a solution of **16** (70.0 mg, 0.198 mmol) in pyridine (1.50 mL) at 0 °C was added acetic anhydride (37.4 μL, 0.396 mmol). After stirred at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography L, hexane/EtOAc 3:1-1:1) gave **16-2** (64.0 mg) in 82% yield.

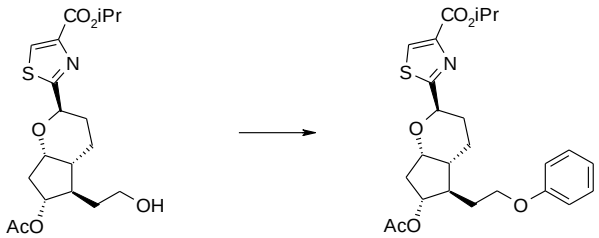
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.2 Hz, 1H), 8.12 (s, 1H), 5.27 (sep, *J* = 6.0 Hz, 1H), 5.17 (t, *J* = 5.1 Hz, 1H), 4.84 (m, 1H), 4.19 (m, 1H), 2.68-2.56 (m, 2H), 2.45

(m, 1H), 2.26 (m, 1H), 2.18-1.97 (m, 3H), 2.07 (s, 3H), 1.86 (m, 1H), 1.70-1.53 (m, 2H), 1.37 (d, *J* = 6.0 Hz, 6H).

To a solution of **16-2** (62.0 mg, 0.157 mmol) in THF (1.50 mL) at 0 °C was added $NaBH_4$ (7.1 mg, 0.188 mmol). After stirred at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography L, hexane/EtOAc 3:2-3:7) gave **17** (38.1 mg) in 61% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 5.26 (sep, *J* = 6.3 Hz, 1H), 5.14 (t, *J* = 5.7 Hz, 1H), 4.86 (m, 1H), 4.24 (m, 1H), 3.73 (m, 2H), 2.42 (m, 1H), 2.23 (m, 2H), 2.14-2.01 (m, 2H), 2.09 (s, 3H), 1.97 (m, 1H), 1.86 (m, 1H), 1.75 (m, 1H), 1.63-1.55 (m, 2H), 1.37 (d, *J* = 6.3 Hz, 6H) (Peak of O*H* was not observed.).

Isopropyl 2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-acetoxy-5-(2-phenoxyethyl)octahydro -cyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylate (17-2)



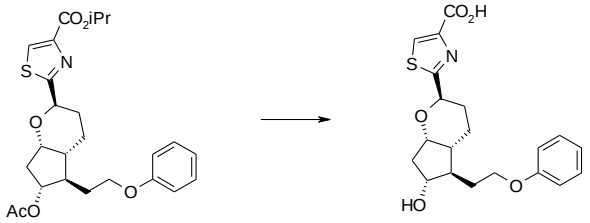
17 **17-2**

To a solution of **17** (35.1 mg, 0.0883 mmol), phenol (11.3 mg, 0.120 mmol) and 1,1'-azobis(*N*,*N*-dimethylformamide) (31.7 mg, 0.182 mmol) in THF (0.90 mL) at room temperature was added tributylphosphine (45.4 μL, 0.184 mmol). After stirred at room temperature for 16 h, the mixture was concentrated. A medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography M, hexane/EtOAc 9:1-2:3) gave **17-2** (26.4 mg) in 63% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.30-7.24 (m, 2H), 6.93 (t, *J* = 7.5 Hz,

1H), 6.87 (d, *J* = 7.5 Hz, 2H), 5.27 (sep, *J* = 6.6 Hz, 1H), 5.16 (t, *J* = 5.4 Hz, 1H), 4.93 (m, 1H), 4.20 (m, 1H), 4.06-3.97 (m, 2H), 2.50-2.36 (m, 2H), 2.26 (m, 1H), 2.17 (m, 1H), 2.05 (s, 3H), 2.05-1.92 (m, 2H), 1.83 (m, 1H), 1.75 (m, 1H), 1.72-1.64 (m, 2H, 1.37 (d, *J* = 6.6 Hz, 6H).

2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-(2-phenoxyethyl)octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylic acid (11e)

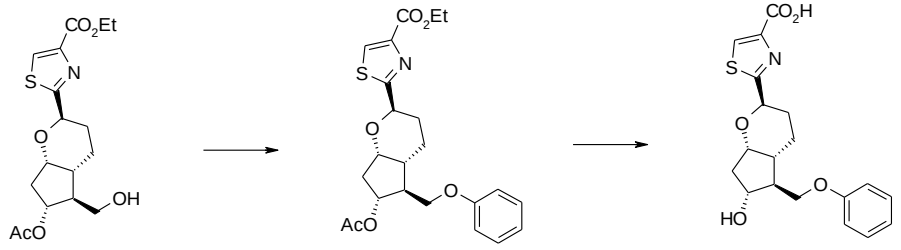


To a solution of **17-2** (25.0 mg, 0.0528 mmol) in MeOH (1.0 mL) at room temperature was added 2.0 M sodium hydroxide (0.14 mL, 0.28 mmol). After stirred at room temperature for 1.5 h, the reaction mixture was extracted with *tert*-BuOMe. The aqueous layer was acidified by 1.0 M hydrochloric acid and extracted with EtOAc. The EtOAc layer was washed with brine and dried over $MgSO_4$. Concentration gave **11e** (17.5 mg) in 85% yield.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.27 (dd, *J* = 8.7, 7.2 Hz, 2H), 6.90 (m, 3H), 5.06 (t, *J* = 6.6 Hz, 1H), 4.81 (d, *J* = 5.4 Hz, 1H), 4.07 (m, 3H), 3.66 (m, 1H), 2.14 (m, 2H), 1.81 (m, 5H), 1.64 (m, 1H), 1.56 (m, 2H) (Peak of CO_2H was not observed.). LCMS (ELSD) *RT* = 0.85 min (>98%). MS (FAB, Neg.) *m/z* 388 $(M - H)^-$. HRMS (FAB, Neg.) $C_{20}H_{22}NO_5S$ $(M - H)^-$ calc. mass 388.1219, found 388.1215.

Scheme 1D

2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-(phenoxymethyl)octahydrocyclopenta[*b*]pyran -2-yl]-1,3-thiazole-4-carboxylic acid (18a)



9 **9-3** **18a**

To a solution of **9** (50.0 mg, 0.135 mmol), phenol (38.2 mg, 0.406 mmol) and 1,1'-azobis(*N*,*N*-dimethylformamide) (70.0 mg, 0.406 mmol) in THF (1.0 mL) at room temperature was added tributylphosphine (82.5 mg, 0.404 mmol). After the mixture was stirred at 50 °C for 2 h, concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography M, hexane/EtOAc 9:1-2:3) gave **9-3** (55.6 mg) in 92% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.29 (d, *J* = 7.2 Hz, 2H), 6.94 (t, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 2H), 5.18 (t, *J* = 5.4 Hz, 1H), 5.10 (m, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.40 (m, 1H), 4.13-4.01 (m, 2H), 2.57-2.48 (m, 1H), 2.43 (m, 1H), 2.32-2.23 (m, 1H), 2.18-2.11 (m, 1H), 2.09 (s, 3H), 2.08-1.97 (m, 2H), 1.93 (m, 1H), 1.75 (m, 1H), 1.40 (t, *J* = 7.2 Hz, 3H).

To a solution of **9-3** (44.6 mg, 0.100 mmol) in MeOH (1.0 mL) at room temperature was added 2.0 M sodium hydroxide (0.50 mL, 1.0 mmol). After stirred at room temperature for 16 h, the reaction mixture was quenched with 1.0 M hydrochloric acid and extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Concentration gave **18a** (36.2 mg) in 96 % yield

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.30 (t, *J* = 7.2 Hz, 2H), 6.96 (t, *J* = 7.2 Hz, 2H) 6.89 (d, *J* = 7.2 Hz, 2H), 5.22 (t, *J* = 4.8 Hz, 1H), 4.23 (m, 2H), 4.08 (m, 1H), 3.96 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.46 (m, 1H), 2.29 (m, 2H), 2.16 (m, 1H), 2.11-1.95 (m, 2H), 1.90 (m, 1H), 1.74 (m, 1H) (Peaks of O*H* and CO_2H were not observed.). ^{13}C NMR

(75 MHz, $CDCl_3$) δ 20.52, 23.65, 40.01, 40.91, 50.81, 68.91, 72.83, 74.92, 75.91, 114.45(2C), 121.00, 129.50(2C), 129.55, 146.08, 158.81, 163.24, 173.64. LCMS (ELSD) *RT* = 0.82 min (>98%). MS (FAB, Neg.) *m/z* 374 $(M - H)^-$. HRMS (FAB, Neg.) $C_{19}H_{20}NO_5S$ $(M - H)^-$ calc. mass 374.1062, found 374.1070.

All compounds in Table 3 were synthesized in the same procedure.

2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-5-[(2-chlorophenoxy)methyl]-6-hydroxyoctahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (18b)

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.40 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.29 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 7.40 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.92 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 5.04 (t, *J* = 6.0 Hz, 1H), 4.18 (m, 2H), 4.02 (m, 1H), 3.92 (m, 1H), 2.23-2.08 (m, 3H), 1.95-1.65 (m, 5H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.87 min (>98%). MS (FAB, Neg.) *m/z* 408 $(M - H)^-$. HRMS (FAB, Neg.) $C_{19}H_{19}{}^{35}ClNO_5S$ $(M - H)^-$ calc. mass 408.0672, found 408.0682.

2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-{[2-(trifluoromethyl)phenoxy]methyl}octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylic acid (18c)

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 5.08 (t, *J* = 5.4 Hz, 1H), 4.21 (dd, *J* = 9.9, 3.0 Hz, 1H), 4.11 (m, 2H), 3.88 (m, 1H), 2.15 (m, 3H), 1.86 (m, 3H), 1.70 (m, 2H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.90 min (>98%). MS (FAB, Neg.) *m/z* 442 $(M - H)^-$. HRMS (FAB, Neg.) $C_{20}H_{19}F_3NO_5S$ $(M - H)^-$ calc. mass 442.0936, found 442.0932

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2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-5-[(2-fluorophenoxy)methyl]-6-hydroxyoctahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (18d)

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.17 (m, 3H), 6.94 (m, 1H), 5.07 (t, *J* =

5.4 Hz, 1H), 4.21-4.10 (m, 2H), 4.04 (m, 1H), 3.90 (m, 1H), 2.27-2.04 (m, 3H), 1.96-1.65 (m, 5H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.83 min (>98%). MS (FAB, Neg.) *m/z* 392 $(M - H)^-$. HRMS (FAB, Neg.) $C_{19}H_{19}FNO_5S$ $(M - H)^-$ calc. mass 392.0968, found 392.0964

2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-[(3-methylphenoxy)methyl]octahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (18e)

^1H NMR (300 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.74-6.70 (m, 3H), 5.08 (t, *J* = 6.3 Hz, 1H), 4.88 (d, *J* = 5.1 Hz, 1H), 4.15-4.03 (m, 2H), 3.95-3.82 (m, 2H), 2.26 (s, 3H), 2.23-2.08 (m, 3H), 1.90-1.65 (m, 5H) (Peak of CO_2H was not observed.). LCMS (ELSD) *RT* = 0.88 min (>98%). MS (FAB, Neg.) *m/z* 388 $(M - H)^-$. HRMS (FAB, Neg.) $C_{20}H_{22}NO_5S$ $(M - H)^-$ calc. mass 388.1219, found 388.1212

2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-5-[(3-chlorophenoxy)methyl]-6-hydroxyoctahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (18f)

^1H NMR (300 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.28 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.01 (m, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 5.08 (t, *J* = 6.0 Hz, 1H), 4.89 (d, *J* = 5.4 Hz, 1H), 4.10 (m, 2H), 4.01 (m, 1H), 3.86 (m, 1H), 2.25-2.04 (m, 3H), 1.93-1.60 (m, 5H) (Peak of CO_2H was not observed.). LCMS (ELSD) *RT* = 0.90 min (>98%). MS (FAB, Neg.) *m/z* 408 $(M - H)^-$. HRMS (FAB, Neg.) $C_{19}H_{19}{}^{35}ClNO_5S$ $(M - H)^-$ calc. mass 408.0672, found 408.0663

2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-{[3-(trifluoromethoxy)phenoxy]methyl}octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylic acid (18g)

^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.27 (m, 1H), 6.81 (m, 2H), 6.74 (m, 1H), 5.22 (t, *J* = 4.8 Hz, 1H), 4.21 (m, 2H), 4.07 (m, 1H), 3.96 (m, 1H), 2.47 (m, 1H), 2.27 (m, 2H), 2.22-2.12 (m, 1H), 2.11-2.00 (m, 2H), 1.87 (m, 1H), 1.77 (m, 1H) (Peaks of

O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.95 min (>98%). MS (FAB, Neg.) *m/z* 458 $(M - H)^-$. HRMS (FAB, Neg.) $C_{20}H_{19}F_3NO_6S$ $(M - H)^-$ calc. mass 458.0885, found 458.0883

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2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-{[3-(trifluoromethyl)phenoxy]methyl}octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylic acid (18h)

^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.38 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.22 (m, 1H), 7.07 (m, 2H), 5.22 (t, *J* = 5.1 Hz, 1H), 4.23 (m, 2H), 4.10 (m, 1H), 3.99 (m, 1H), 2.49 (m, 1H), 2.32 (m, 2H), 2.19 (m, 1H), 2.05 (m, 2H), 1.91 (m, 1H), 1.79 (m, 1H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.92 min (>98%). MS (FAB, Neg.) *m/z* 442 $(M - H)^-$. HRMS (FAB, Neg.) $C_{20}H_{19}F_3NO_5S$ $(M - H)^-$ calc. mass 442.0936, found 442.0930

2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-5-[(3-fluorophenoxy)methyl]-6-hydroxyoctahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (18i)

^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.19 (m, 1H), 6.68-6.57 (m, 3H), 5.22 (t, *J* = 4.8 Hz, 1H), 4.22 (m, 2H), 4.04 (m, 1H), 3.94 (m, 1H), 2.45 (m, 1H), 2.27 (m, 2H), 2.20-1.98 (m, 3H), 1.87 (m, 1H), 1.75 (m, 1H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.85 min (>98%). MS (FAB, Neg.) *m/z* 392 $(M - H)^-$. HRMS (FAB, Neg.) $C_{19}H_{19}FNO_5S$ $(M - H)^-$ calc. mass 392.0968, found 392.0959

2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-[(4-methylphenoxy)methyl]octahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (18j)

^1H NMR (300 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 8.1 Hz, 2H), 5.08 (t, *J* = 5.7 Hz, 1H), 4.87 (d, *J* = 5.4 Hz, 1H), 4.11 (m, 1H), 4.03 (m, 1H), 3.88 (m, 2H), 2.21 (s, 3H), 2.15 (m, 1H), 2.07 (m, 2H), 1.91-1.64 (m, 5H) (Peak of CO_2H was not observed.). LCMS (ELSD) *RT* = 0.88 min (>98%). MS (FAB, Neg.)

m/z 388 (M - H)$^-$. HRMS (FAB, Neg.) $C_{20}H_{22}NO_5S$ (M - H)$^-$ calc. mass 388.1219, found 388.1215

2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-5-[(4-chlorophenoxy)methyl]-6-hydroxyoctahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (18k)

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 5.08 (t, *J* = 6.0 Hz, 1H), 4.91 (m, 1H), 4.09 (m, 2H), 3.96 (m, 1H), 3.85 (m, 1H), 2.27-2.07 (m, 3H), 1.90-1.63 (m, 5H) (Peak of CO_2H was not observed.). LCMS (ELSD) *RT* = 0.90 min (>98%). MS (FAB, Neg.) *m/z* 408 (M - H)$^-$. HRMS (FAB, Neg.) $C_{19}H_{19}{}^{35}ClNO_5S$ (M - H)- calc. mass 408.0672, found 408.0677

2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-{[4-(trifluoromethoxy)phenoxy]methyl}octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylic acid (18l)

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 5.08 (t, *J* = 6.3 Hz, 1H), 4.90 (m, 1H), 4.10 (m, 2H), 3.99 (m, 1H), 3.87 (m, 1H), 2.19 (m, 1H), 2.10 (m, 2H), 1.90-1.64 (m, 5H) (Peak of CO_2H was not observed.). LCMS (ELSD) *RT* = 0.94 min (>98%). MS (FAB, Neg.) *m/z* 458 (M - H)$^-$. HRMS (FAB, Neg.) $C_{20}H_{19}F_3NO_6S$ (M - H)$^-$ calc. mass 458.0885, found 458.0883

2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-{[4-(trifluoromethyl)phenoxy]methyl}octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylic acid (18m)

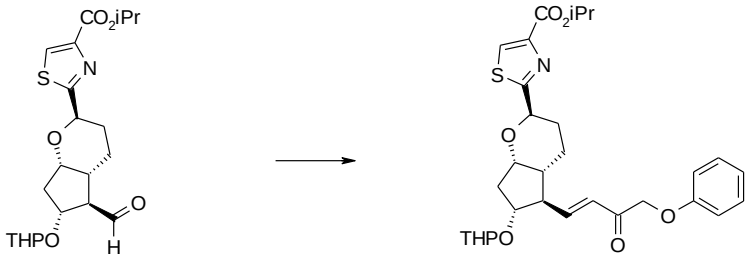
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 9.0 Hz, 2H), 5.09 (t, *J* = 6.3 Hz, 1H), 4.92 (m, 1H), 4.14 (m, 2H), 4.09 (m, 1H), 3.87 (m, 1H), 2.21 (m, 1H), 2.12 (m, 2H), 1.92-1.61 (m, 5H) (Peak of CO_2H was not observed.). LCMS (ELSD) *RT* = 0.93 min (>98%). MS (FAB, Neg.) *m/z* 442 (M - H)$^-$. HRMS (FAB, Neg.) $C_{20}H_{19}F_3NO_5S$ (M - H)$^-$ calc. mass 442.0936, found 442.0932

2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-5-[(4-fluorophenoxy)methyl]-6-hydroxyoctahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (18n)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 6.96 (m, 2H), 6.83 (m, 2H), 5.21 (t, *J* = 4.8 Hz, 1H), 4.22 (m, 2H), 4.04 (m, 1H), 3.91 (m, 1H), 2.43 (m, 1H), 2.29 (m, 2H), 2.18 (m, 1H), 2.04 (m, 2H), 1.90 (m, 1H), 1.76 (m, 1H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.83 min (>98%). MS (FAB, Neg.) *m/z* 392 (M - H)$^-$. HRMS (FAB, Neg.) $C_{19}H_{19}FNO_5S$ (M - H)$^-$ calc. mass 392.0968, found 392.0962

Synthesis of 7

Isopropyl 2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-5-[(1*E*)-3-oxo-4-phenoxy-1-buten-1-yl]-6-(tetrahydro-2*H*-pyran-2-yloxy)octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4-carboxylate (15-4)



15-2 **15-4**

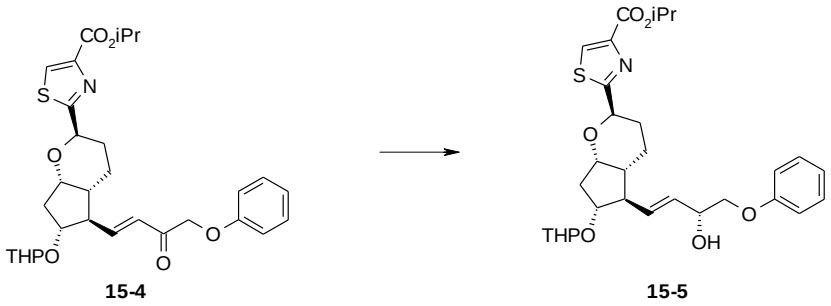
To a solution of **15-2** (450 mg, 1.06mmol), dimethyl (2-oxo-3-phenoxypropyl)

-phosphonate (549 mg, 2.13 mmol) and triethylamine (0.296 mL, 2.13 mmol) in THF (5.0 mL) at room temperature was added LiCl (91 mg, 2.14 mmol). After stirred at room temperature for 16 h, the reaction mixture was quenched with 1.0 M hydrochloric acid and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography L SI50, hexane/EtOAc 3:1-1:1) gave **15-4** (309 mg) in 52% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (brs, 1H), 7.33-7.25 (m, 2H), 7.05-6.98 (m, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.57 (dd, *J* = 15.0, 7.5 Hz, 1H), 5.27 (sep, *J* = 6.3 Hz, 1H),

5.16 (m, 1H), 4.72 (s, 1H), 4.70 (s, 1H), 4.62 (m, 0.5H), 4.51 (m, 0.5H), 4.21-3.96 (m, 2H), 3.84 (m, 0.5H), 3.71 (m, 0.5H), 3.42 (m, 1H), 2.94 (m, 1H), 2.41 (m, 1H), 2.22-2.17 (m, 2H), 1.92 (m, 1H), 1.84-1.69(m, 3H), 1.63-1.45 (m, 6H), 1.37 (d, *J* = 6.3 Hz, 6H).

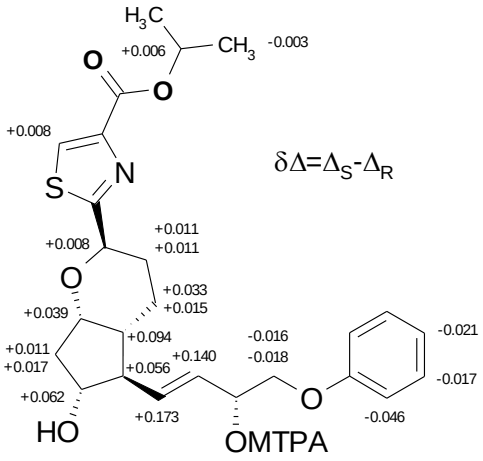
Isopropyl 2-[(2*R*,4a*R*,5*R*,6*R*,7a*S*)-5-[(1*E*,3*R*)-3-hydroxy-4-phenoxy-1-buten-1-yl] -6-(tetrahydro-2*H*-pyran-2-yloxy)octahydrocyclopenta[*b*]pyran-2-yl]-1,3-thiazole-4 -carboxylate (15-5)



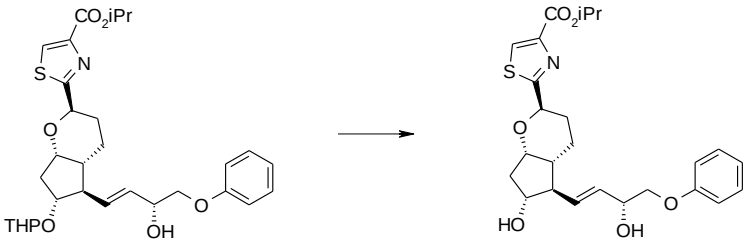
To a solution of **15-4** (289 mg, 0.520 mmol) and (3aR)-1-methyl-3,3-diphenyl -tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaborole (1.0 M THF solution, 0.182 mL, 0.182 mmol) in THF (4.0 mL) at 0 °C was added borane-dimethyl sulfide complex (35.6 mg, 0.468 mmol). After stirred at 0 °C for 1 h, the reaction mixture was quenched with MeOH and H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography L SI50, hexane/EtOAc 3:1-1:1) gave **15-5** (267 mg) in 92% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (brs, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 2H), 5.85-5.65 (m, 2H), 5.27 (sep, *J* = 6.0 Hz, 1H), 5.16 (t, *J* = 5.4 Hz, 1H), 4.70 (m, 1H), 4.54 (m, 1H), 4.17 (m, 1H), 4.02 (m, 2H), 3.87 (m, 2H), 3.46 (m, 1H), 2.78 (m, 1H), 2.40 (m, 2H), 2.29-2.10 (m, 2H), 1.97-1.76 (m, 3H), 1.72-1.43 (m, 6H), 1.33 (d, *J* = 6.0 Hz, 6H) (Peak of O*H* was not observed.).

The stereochemistry of C15 position was determined by modified Mosher's method.



Isopropyl 2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-[(1*E*,3*R*)-3-hydroxy-4-phenoxy-1-buten-1-yl]octahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylate (15-6)

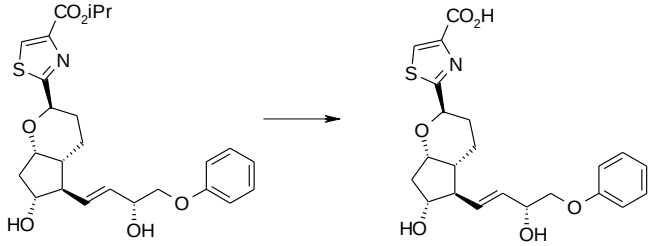


15-5 **15-6**

To a solution of **15-5** (130 mg, 0.233 mmol) in MeOH (4.0 mL) at room temperature was added *p*-toluene sulfonic acid monohydrate (4.4 mg, 0.023 mmol). After stirred at room temperature for 5 h, the reaction mixture was quenched with Et_3N. Concentration and a medium-pressure preparative liquid chromatography (Yamazen W-prep 2XY flash column chromatography L SI50, hexane/EtOAc 3:1-1:1) gave **15-6** (89.0 mg) in 81% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 2H), 5.73 (m, 2H), 5.27 (sep, *J* = 6.0 Hz, 1H), 5.19 (t, *J* = 5.1 Hz, 1H), 4.55 (m, 1H), 4.16 (m, 1H), 4.01 (dd, *J* = 15.3, 3.3 Hz, 1H), 3.97 (m, 1H), 3.89 (dd, *J* = 15.3, 7.8 Hz, 1H), 2.66 (m, 1H), 2.46 (m , 1H), 2.33-2.24 (m, 3H), 1.98 (m, 1H), 1.85 (m, 1H), 1.64 (m, 1H), 1.38 (d, *J* = 6.0 Hz, 6H) (Peaks of O*H* were not observed.).

2-{(2*R*,4a*R*,5*R*,6*R*,7a*S*)-6-hydroxy-5-[(1*E*,3*R*)-3-hydroxy-4-phenoxy-1-buten-1-yl]octahydrocyclopenta[*b*]pyran-2-yl}-1,3-thiazole-4-carboxylic acid (7)



15-6 **7**

To a solution of **15-6** (64.0 mg, 0.135 mmol) in MeOH (2.0 mL) at room temperature was added 2.0 M sodium hydroxide (1.0 mL, 2.0 mmol). After stirred at room temperature for 2 h, the reaction mixture was quenched with 1.0 M hydrochloric acid and extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Concentration gave **7** (56.2 m) in 96 % yield: colorless viscous oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.28 (m, 2H), 6.99 (t, *J* = 6.6 Hz, 1H), 6.92 (d, *J* = 6.6 Hz, 2H), 5.74 (m, 2H), 5.19 (t, *J* = 5.1 Hz, 1H), 4.56 (m, 1H), 4.14 (m, 1H), 4.01 (m, 2H), 3.91 (m, 1H), 2.68 (m, 1H), 2.33 (m, 1H), 2.25 (m, 2H), 1.96 (m, 1H), 1.85 (m, 1H), 1.69-1.56 (m, 2H) (Peaks of O*H* and CO_2H were not observed.). LCMS (ELSD) *RT* = 0.75 min (>98%). MS (FAB, Neg.) *m/z* 430 $(M - H)^-$. HRMS (FAB, Neg.) $C_{22}H_{24}NO_6S$ $(M - H)^-$ calc. mass 430.1324, found 430.1321.

Biology

In vitro assay

EP2, EP4 and IP cAMP assay

Chinese hamster ovary (CHO) cells (1.25×10^5 cells/well) expressing human EP2 or human EP4 or human IP receptor were harvested and suspended in a 96-well 1/2 area plate. cAMP concentrations were measured using a cAMP HTRF HiRange kit (Cisbio Bioassays)* after treatment of compounds. The reaction rate (%) of the compounds relative to the cAMP concentration obtained with PGE_2 treatment at 1μM was calculated. Furthermore, a non-linear regression analysis was performed using the Sigmoid Emax Model to estimate EC_{50} values.

*http://www.cisbio.com/usa/drug-discovery/membrane-based-assays-camp-hirange-assay-kit (accessed Nov 24, 2015)

EP2 β arrestin recruitment assay

PathHunter β-arrestin HEK-293 PTGER2 cell lines (DiscoveRx) were seeded at a density of 5000 cells/well into a 384-well plate and cultured at 37 °C in the presence of 5 % CO_2 for 24 hours. β-arrestin recruitment were measured using a PathHunter Detection Kit (DiscoveRx)* after treatment of compounds. The reaction rate (%) of the compounds relative to the β-arrestin recruitment obtained with PGE_2 treatment at 10μM was calculated. Furthermore, a non-linear regression analysis was performed using the Sigmoid Emax Model to estimate EC_{50} values.

* https://www.discoverx.com/product-data-sheets-3-tab/93-0214c1 (accessed Nov 24, 2015)

EP1, EP3 and FP Ca assay

Chem-1 cells expressing human FP receptor or Chinese hamster ovary (CHO) cells expressing human EP1 or human EP3 were seeded at a density of 1×10^4 cells per well into 96-well plates and cultured at 37℃ in the presence of 5% CO_2 for 2 days. Load

buffer (HBSS containing Calcium 5, 10 mM HEPES, 20μM indomethacin, and 2.5 mM probenecid) was added in each well and incubated in the dark at room temperature for 1 hour. After addition of the compounds, intracellular Ca^{2+} concentration was measured using a fluorescence drug screening system (FDSS-7000 : Hamamatsu Photonics, Tokyo, Japan)*. The reaction rate (%) of the compounds relative to intracellular Ca^{2+} concentration obtained with maximum increases of PGE_2 treatment was calculated. Futhermore, a non-linear analysis was performed using the Sigmoid Emax Model to estimate EC_{50} values.

* http://www.hamamatsu.com/jp/ja/FDSS7000EX.html (accessed Nov 24, 2015)