Supplementary Information

A Cyanide-catalyzed Imino-Stetter Reaction Enables the Concise Total Syntheses of Rucaparib

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1. General Information

All reactions were carried out in an oven-dried glassware under an argon atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using pre-coated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm). Flash column chromatography was performed using silica gel 60 (230 – 400 mesh). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. Methyl 5-fluoro-2-methyl-3-nitrobenzoate (2), methyl 3-amino-5-fluoro-2-iodobenzoate (3), 4-((N-tert-butoxycarbonyl)(N-methyl)aminomethyl)benzaldehyde (5) and methyl 5-fluoro-2-iodo-3-nitrobenzoate (22) were obtained from commercial suppliers. 4-Fluoro-6-methoxycarbonyl-2-nitrophenyl trifluoromethanesulfonate (SII) was prepared by the literature procedure. Other reagents were purchased from chemical suppliers and used without further purification. $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR, and $^{31}$P NMR spectra were recorded on 500 MHz, 125 MHz, 471, and 202 MHz spectrometers, respectively. Residual NMR solvents {CDCl$_3$ ($\delta_H$: 7.26 ppm, $\delta_C$: 77.16 ppm), DMSO-$d_6$ ($\delta_H$: 2.50 ppm, $\delta_C$: 39.52 ppm), CD$_3$OD ($\delta_H$: 3.31 ppm, $\delta_C$: 49.00 ppm)} were used as internal standards for $^1$H NMR and $^{13}$C NMR spectra, respectively. For $^{19}$F NMR and $^{31}$P NMR, no external standard was used. The proton spectra are reported as follows $\delta$ (position of proton, multiplicity, coupling constant $J$, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad). High resolution mass spectra (HRMS) were recorded on quadrupole time-of-flight mass spectrometer (QTOF-MS) using electrospray ionization (ESI) as an ionization method.
2. First-generation Synthesis of Rucaparib (1)

**Synthesis of (4-fluoro-2-methoxycarbonyl-6-nitrobenzyl)triphenylphosphonium bromide (8)**

Methyl 5-fluoro-2-methyl-3-nitrobenzoate (2, 11 g, 50 mmol), N-bromosuccinimide (NBS; 45 g, 250 mmol) and 1,1’-azobis(cyclohexanecarbonitrile) (ACHN; 6.1 g, 25 mmol) were dissolved in 1,2-dichloroethane (DCE; 500 mL). The reaction mixture was stirred at 90 °C with an oil bath and monitored by TLC for 2 h. After the complete consumption of 2, the reaction mixture was cooled to 20 °C and quenched with saturated Na₂S₂O₃ aqueous solution (500 mL). The crude mixture was extracted with dichloromethane (500 mL) three times. The organic layers were combined, dried over MgSO₄ and concentrated in vacuo to afford a crude product of benzyl bromide, which was directly used in the next step without further purification.

To a solution of the crude product of the benzyl bromide in chloroform (500 mL) was added triphenylphosphine (20 g, 75 mmol). The reaction mixture was stirred at 50 °C with an oil bath and monitored by TLC for 4 h. After the complete consumption of the benzyl bromide, the reaction mixture was concentrated in vacuo. The crude mixture was purified by column chromatography on silica using a mixture of dichloromethane and methanol (10:0 to 9:1) as the eluent to afford compound 8 (25 g, 45 mmol, 90% over 2 steps) as a dark yellow foamy solid.

**[1H NMR (500 MHz, CDCl₃) δ 7.79 - 7.72 (m, 10H), 7.68 (dd, J = 6.9, 2.7 Hz, 1H), 7.64 - 7.58 (m, 6H), 5.77 (br, 2H), 3.77 (s, 3H); **

**[13C {1H} NMR (125 MHz, CDCl₃) δ 164.7, 161.2 (d, J = 253.4 Hz), 151.5 (d, J = 7.3 Hz), 135.0 (d, J = 2.7 Hz), 134.1 (d, J = 10.0 Hz), 130.1 (d, J = 12.7 Hz), 123.0 (d, J = 25.4 Hz), 122.2, 118.7 (d, J = 88.2 Hz), 116.5 (d, J = 26.3 Hz), 54.1, 26.7 (d, J = 52.7 Hz); **

**[19F NMR (471 MHz, CDCl₃) δ -106.1; **

**[31P NMR (202 MHz, CDCl₃) δ 25.0; mp 184-185 °C; HRMS (ESI-TOF) m/z: [M]+ calcd for C₂₇H₂₂FNO₄P 474.1265; found 474.1268.**
Synthesis of (E)-ethyl 4-fluoro-2-methoxylcarbonyl-6-nitrocinnamate (9)

To a solution of phosphonium salt 8 (11 g, 20 mmol) in 1,2-dichloroethane (DCE; 200 mL) were added ethyl glyoxalate 7a (~50% in toluene, 12 mL, 60 mmol) and triethylamine (8.4 mL, 60 mmol). The reaction mixture was stirred at 60 °C with an oil bath and monitored by TLC for 2 h. After the complete consumption of 8, the reaction mixture was quenched with water (500 mL), and the resulting mixture was extracted with dichloromethane (200 mL) three times. The organic layers were combined, dried over MgSO₄ and concentrated in vacuo. The crude mixture was purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:2) as the eluent to afford compound 9 (4.3 g, 14.4 mmol, 72%) as brown oil.

¹H NMR (500 MHz, CDCl₃) δ 8.06 (d, J = 16.0 Hz, 1H), 7.84 (dd, J = 8.0, 2.7 Hz, 1H), 7.76 (dd, J = 7.2, 2.7 Hz, 1H), 5.83 (d, J = 16.2 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 165.2, 164.85 (J = 1.8 Hz), 161.2 (J = 255.2 Hz), 150.5, 139.2, 134.5 (J = 7.3 Hz), 128.0 (J = 3.6 Hz), 124.1, 121.5 (J = 22.7 Hz), 115.1 (J = 26.3 Hz), 61.1, 53.3, 14.3; ¹⁹F NMR (471 MHz, CDCl₃) δ -107.8; HRMS (ESI-TOF) m/z: [M+Na]+ calcd for C₁₃H₁₂FNNaO₆ 320.0546; found 320.0543.

Synthesis of (E)-ethyl 2-amino-4-fluoro-6-methoxylcarbonylcinnamate (4a)

To a solution of compound 9 (3.6 g, 12 mmol) in a mixture of ethanol and 35% aqueous HCl (6:1, 140 mL) was added iron powder (13.4 g, 240 mmol). The reaction mixture was stirred at 60 °C with an oil bath and monitored by TLC for 10 min. After the complete consumption of 9, the reaction mixture was cooled to room temperature, filtered through Celite to remove the insoluble residues, and the filtrate was concentrated in vacuo. To the crude mixture was added saturated NH₄Cl aqueous solution (150 mL) and the resulting mixture was extracted with ethyl acetate (150 mL) three times. The organic layers were combined, dried over MgSO₄ and concentrated in vacuo. The crude mixture was purified by column
chromatography on silica using a mixture of ethyl acetate and hexanes (1:2) as the eluent to afford compound 4a (2.8 g, 10.6 mmol, 88%) as a yellow solid.

$^{1}$H NMR (500 MHz, CDCl$_3$) δ 7.95 (d, $J = 16.5$ Hz, 1H), 7.00 (dd, $J = 8.9, 2.6$ Hz, 1H), 6.57 (dd, $J = 9.9, 2.6$ Hz, 1H), 6.18 (d, $J = 16.5$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 4.18 (br, 2H), 3.86 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H); $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) δ 166.8 (d, $J = 3.6$ Hz), 166.6, 162.7 (d, $J = 247.0$ Hz), 147.0 (d, $J = 10.9$ Hz), 141.5, 132.8 (d, $J = 9.1$ Hz), 122.7, 116.9 (d, $J = 2.7$ Hz), 107.3 (d, $J = 24.5$ Hz), 105.8 (d, $J = 24.5$ Hz), 60.7, 52.5, 14.3; $^{19}$F NMR (471 MHz, CDCl$_3$) δ -111.6; mp 105-106 °C; HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd for C$_{13}$H$_{14}$FNNaO$_4$ 290.0805; found 290.0802.

**Synthesis of ethyl 2-(4-(N-tert-butoxycarbonyl-N-methylamino)methyl)phenyl)-6-fluoro-4-methoxycarbonyl-indole-3-acetate (6a)**

To a solution of 2-aminocinnamate 4a (3.0 g, 10 mmol), aldehyde 5 (2.5 g, 10 mmol), and triethylamine (4.2 mL, 30 mmol) in dichloromethane (100 mL) was added a solution of titanium tetrachloride in dichloromethane (1.0 M, 7.0 mL, 7.0 mmol). The reaction mixture was stirred at 20 °C and monitored by TLC and $^{1}$H NMR analysis for 30 min. After the complete consumption of 4a and 5, the reaction mixture was quenched with water (100 mL) and extracted with dichloromethane (100 mL) three times. The organic layers were combined, dried over MgSO$_4$ and concentrated in vacuo to afford a crude mixture of aldimine, which was directly used in the next step without purification.

To a solution of the crude mixture of aldimine in N,N-dimethylformamide (DMF,100 mL) were added 4 Å molecular sieves (3.0 g) and sodium cyanide (98 mg, 2.0 mmol). The reaction mixture was stirred at 20 °C and monitored by TLC for 1 h. After complete consumption of aldimine, insoluble residues were removed by filtration and washed with ethyl acetate. The combined filtrate was concentrated in vacuo and purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:2) as the eluent to afford indole-3-acetate 6a (4.2 g, 8.4 mmol, 84% over 2 steps) as a yellow solid.
\[^1\text{H} \text{NMR} \ (500 \text{ MHz, CDCl}_3) \ \delta \ 8.36 \ (\text{br, 1H}), \ 7.52 \ - \ 7.45 \ (\text{m, 3H}), \ 7.33 \ (\text{d, } J = 7.9 \text{ Hz, 2H}), \ 7.24 \ (\text{dd, } J = 8.5, 2.4 \text{ Hz, 1H}), \ 4.48 \ (\text{br, 2H}), \ 4.15 \ (\text{q, } J = 7.2 \text{ Hz, 2H}), \ 4.01 \ (\text{s, 2H}), \ 3.92 \ (\text{s, 3H}), \ 2.87 \ (\text{br, 3H}), \ 1.50 \ (\text{br, 9H}), \ 1.24 \ (\text{t, } J = 7.1 \text{ Hz, 3H}); \ ^{13}\text{C}\{^1\text{H}\} \ \text{NMR} \ (125 \text{ MHz, CDCl}_3) \ \delta \ 173.4, \ 167.7, \ 158.2 \ (\text{d, } J = 238.9 \text{ Hz}), \ 156.2 \ (\text{d, } J = 60.8 \text{ Hz}), \ 139.6, \ 138.5 \ (\text{d, } J = 30.9 \text{ Hz}), \ 137.4 \ (\text{d, } J = 11.8 \text{ Hz}), \ 131.0, \ 129.1, \ 127.8, \ 124.6, \ 123.4, \ 111.7 \ (\text{d, } J = 24.5 \text{ Hz}), \ 105.9, \ 101.8 \ (\text{d, } J = 25.4 \text{ Hz}), \ 80.2, \ 60.7, \ 52.3, \ 52.2 \ (\text{d, } J = 76.3 \text{ Hz}), \ 34.4 \ (\text{d, } J = 33.6 \text{ Hz}), \ 32.8, \ 28.6, \ 14.3; \ ^{19}\text{F} \ \text{NMR} \ (471 \text{ MHz, CDCl}_3) \ \delta \ -121.8; \ \text{mp} \ 111-112 \ ^\circ\text{C}; \ \text{HRMS (ESI-TOF) } m/z: \ [\text{M+Na}]^+ \ \text{calcd for C}_{27}\text{H}_{31}\text{FN}_2\text{NaO}_6 \ 521.2064; \ \text{found} \ 521.2061.

**Synthesis of N-(4-methoxybenzyl)-2-(4-(N-tert-butoxycarbonyl-N-methylamino)methyl)phenyl)-6-fluoro-4-methoxycarbonyl-indole-3-acetamide (6b)**

To a solution of 4-methoxybenzylamine (PMBNH$_\text{2}$; 0.26 mL, 2.0 mmol) in dichloromethane (20 mL) was added a solution of trimethylaluminum in hexanes (2.0 M, 1.0 mL, 2.0 mmol) at 0 °C (ice/water), and the reaction mixture was stirred at the same temperature. After 30 min, indole-3-acetate 6a (1.0 g, 2.0 mmol) was added to the reaction mixture. The reaction mixture was stirred at 40 °C with an oil bath and monitored by TLC. After the 18 h, the reaction mixture was cooled to 0 °C (ice/water) and quenched with 1.0 N HCl aqueous solution (20 mL). The crude mixture was extracted with dichloromethane (20 mL) three times. The organic layers were combined, dried over MgSO$_\text{4}$ and concentrated in vacuo. The crude mixture was purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:1) as the eluent to afford compounds 6b (0.36 g, 0.62 mmol, 31%) and 14 (0.42 g, 0.60 mmol, 30%), respectively, along with unreacting starting 6a (0.25 g, 0.50 mmol, 25%).

**Compound 6b:**

A yellow solid; \[^1\text{H} \text{NMR} \ (500 \text{ MHz, DMSO-}d_6) \ \delta \ 11.80 \ (\text{s, 1H}), \ 8.04 \ (\text{t, } J = 5.9 \text{ Hz, 1H}), \ 7.51 \ (\text{d, } J = 7.5 \text{ Hz, 2H}), \ 7.37 \ (\text{m, 1H}), \ 7.34 \ (\text{d, } J = 7.8 \text{ Hz, 2H}), \ 7.28 \ (\text{m, 1H}), \ 7.16 \ (\text{d, } J = 8.2 \text{ Hz, 2H}), \ 6.85 \ (\text{d, } J = 7.5 \text{ Hz, 2H}), \ 6.34 \ (\text{m, 1H}), \ 2.85 \ (\text{s, 3H}), \ 1.32 \ (\text{s, 9H}), \ 1.21 \ (\text{s, 3H})\].
8.2 Hz, 2H), 4.44 (s, 2H), 4.17 (d, J = 5.8 Hz, 2H), 3.80 (s, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 2.81 (s, 3H), 1.46 - 1.40 (br, 9H); 13C{1H} NMR (125 MHz, DMSO-d$_6$) $\delta$ 171.0, 167.0 (d, J = 2.7 Hz), 158.1, 157.1 (d, J = 235.2 Hz), 139.5, 138.3, 137.3 (d, J = 11.8 Hz), 131.9, 130.8, 128.9, 128.5, 127.5, 124.7 (d, J = 8.2 Hz), 123.1, 113.5, 109.6 (d, J = 25.4 Hz), 106.0, 101.1 (d, J = 24.5 Hz), 78.9, 55.0, 52.1, 50.8, 41.7, 34.0, 32.9, 28.1; 19F NMR (471 MHz, DMSO-d$_6$) $\delta$ -122.4; mp 150-151 °C; HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for C$_{33}$H$_{36}$FN$_3$NaO$_6$ 612.2480; found 612.2482.

**Compound 14:**

A white solid; $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 11.63 (s, 1H), 8.84 (t, J = 5.8 Hz, 1H), 8.00 (t, J = 5.7 Hz, 1H), 7.55 (d, J = 7.3 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.23 (dd, J = 9.3, 2.1 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 6.96 (dd, J = 9.8, 2.1 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 4.44 (s, 2H), 4.31 (d, J = 5.6 Hz, 2H), 4.17 (d, J = 5.8 Hz, 2H), 3.78 (s, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 2.81 (s, 3H), 1.50 - 1.38 (br, 9H); 13C{1H} NMR (125 MHz, DMSO-d$_6$) $\delta$ 171.2, 167.9, 158.1 (J = 7.3 Hz), 157.5 (J = 236.2 Hz), 137.9, 136.8 (J = 11.8 Hz), 131.8, 131.4, 131.1, 130.9 (J = 8.2 Hz), 128.6, 128.5, 128.4, 127.4, 122.2, 113.7, 113.5, 107.3 (J = 24.5 Hz), 106.2, 98.6 (J = 24.5 Hz), 78.9, 55.0, 51.6, 50.9, 42.1, 41.8, 33.9, 32.4, 28.1; 19F NMR (471 MHz, DMSO-d$_6$) $\delta$ -122.3; mp 189-190 °C; HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for C$_{40}$H$_{43}$FN$_4$NaO$_6$ 717.3064; found 717.3060.

**General procedure for chemoselective reduction of amide 6b (Table 1)**

To a solution of indole-3-acetamide 6b (59 mg, 0.10 mmol) and nickel catalyst (0.010 mmol) in toluene (1.0 mL) was added phenylsilane (0.12 mL, 1.0 mmol) at 20 °C. The reaction mixture was stirred at 115 °C with an oil bath and monitored by TLC. After 18 h, the reaction mixture was cooled to 0 °C and quenched with 1.0 N NaOH aqueous solution (2.0 mL). The crude mixture was extracted with ethyl acetate (2.0 mL) three times. The organic layers were combined, dried over MgSO$_4$ and concentrated in vacuo to provide a mixture of compounds 6b, 15, and 17 with a variable ratio.
Compound 15:

A yellow solid; $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.55 (d, $J$ = 6.1 Hz, 2H), 7.45 - 7.39 (m, 3H), 7.33 (dd, $J$ = 8.7, 2.4 Hz, 1H), 7.21 (d, $J$ = 8.7 Hz, 2H), 6.90 (d, $J$ = 8.5 Hz, 2H), 4.52 (s, 2H), 3.90 (s, 3H), 3.89 (s, 2H), 3.79 (s, 3H), 3.38 - 3.33 (m, 2H), 2.99 - 2.94 (m, 2H), 2.88 (s, 3H), 1.50 (d, $J$ = 13.4 Hz, 9H); $^{13}$C{$^1$H} NMR (125 MHz, CD$_3$OD) $\delta$ 169.2 (d, $J$ = 2.7 Hz), 161.5, 159.4 (d, $J$ = 237.1 Hz), 157.7 (d, $J$ = 50.9 Hz), 140.1, 139.8, 139.3 (d, $J$ = 11.8 Hz), 132.8, 131.9, 130.4, 129.0 (d, $J$ = 20.0 Hz), 126.9 (d, $J$ = 21.8 Hz), 124.9 (d, $J$ = 9.1 Hz), 123.8, 115.2, 112.1 (d, $J$ = 26.3 Hz), 108.9, 102.9 (d, $J$ = 25.4 Hz), 81.3, 55.8, 53.3, 53.0, 52.5, 52.2, 34.6, 30.8, 28.7, 25.0; $^{19}$F NMR (471 MHz, CD$_3$OD) $\delta$ -124.0; mp 148-149 °C; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for C$_{33}$H$_{39}$FN$_3$O$_5$ 576.2874; found 576.2876.

Compound 17:

Orange oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.16 (s, 1H), 7.51 (d, $J$ = 7.9 Hz, 2H), 7.31 (d, $J$ = 8.4 Hz, 4H), 6.92 (dd, $J$ = 9.1, 2.1 Hz, 1H), 6.88 (d, $J$ = 8.5 Hz, 2H), 6.61 (dd, $J$ = 10.2, 2.0 Hz, 1H), 4.46 (br, 2H), 4.20 (s, 2H), 3.84 (s, 2H), 3.82 (s, 3H), 3.19 (m, 2H), 3.12 (m, 2H), 2.85 (br, 3H), 1.50 (br, 9H); $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) $\delta$ 159.9 (d, $J$ = 238.9 Hz), 158.9, 137.5, 136.3 (d, $J$ = 12.7 Hz), 134.3 (br), 132.2, 131.5, 130.3, 127.8, 124.3, 113.8, 113.1, 106.7 (d, $J$ = 23.6 Hz), 95.0 (d, $J$ = 26.3 Hz), 80.0, 61.6, 58.2, 55.4, 54.7, 34.2, 29.9, 28.6, 27.9; $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ -121.1; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for C$_{32}$H$_{37}$FN$_3$O$_3$ 530.2819; found 530.2818.

Reduction of Indole-3-acetamide 6b Using Borane

Table S1. Reduction of indole-3-acetamide (6b) using borane
| Entry | Borane (equiv)       | Results<sup>a</sup>               |
|------|---------------------|----------------------------------|
| 1    | BH<sub>3</sub>·THF (2.0) | 15 (33%), 6b (46%)               |
| 2    | BH<sub>3</sub>·SMe<sub>2</sub> (2.0) | 15 (27%), S1 (11%)               |
| 3    | BH<sub>3</sub>·NHMe<sub>2</sub> (2.0) | No reaction                     |
| 4    | BH<sub>3</sub>·THF (4.0) | 15 (29%), S1 (trace)             |

We investigated the chemoselective reduction of indole-3-acetamide 6b using BH<sub>3</sub> as a reducing reagent. It was found that the efficiency of the reduction of 6b with BH<sub>3</sub> showed the strong dependence on Lewis basic component on the boron atom in the borane complex. Borane·tetrahydrofuran (BH<sub>3</sub>·THF) complex provided the desired aminoester 15 albeit at a moderate yield along with unreacting starting compound 6b (46% recovered) (entry 1). On the other hand, borane·dimethylsulfide (BH<sub>3</sub>·SMe<sub>2</sub>) complex reduced both carbonyl groups leading to aminoester 15 and aminoalcohol S1 in 27% and 11% yields, respectively (entry 2). However, borane·dimethylamine (BH<sub>3</sub>·NHMe<sub>2</sub>) complex displayed no reactivity (entry 3). To increase the yield of the desired amine 15, we further attempted to carry out this reduction with a large amount of BH<sub>3</sub>·THF complex. When the reaction was performed with four equivalents of BH<sub>3</sub>·THF complex, unfortunately, the yield of the desired amine 15 was not improved and the ester moiety was reduced under these conditions leading to the formation of S1 albeit at low yield (entry 4). Thus, we decided to explore other reducing agents to prepare the desired amine 15.

**Compound S1:**

A colorless oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.55 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.03 (dd, J = 9.2, 2.4 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 6.87 (dd, J = 10.5, 2.4 Hz, 1H), 4.94 (s, 2H), 4.51 (s, 2H), 3.91 (s, 2H), 3.80 (s, 3H), 3.40 - 3.35 (m, 2H), 3.10 - 3.04 (m, 2H), 2.87 (s, 3H), 1.50 (d, J = 8.7 Hz, 9H); <sup>13</sup>C<sup>1</sup>H NMR (125 MHz, CDCl<sub>3</sub>) δ 161.6, 160.7 (d, J = 237.1 Hz),
139.2, 138.4 (d, J = 12.7 Hz), 138.1, 135.5 (d, J = 9.1 Hz), 133.3, 131.9, 129.8, 129.1, 129.0, 126.5, 123.7, 115.4, 109.8 (d, J = 24.5 Hz), 108.5, 97.8 (d, J = 25.4 Hz), 81.4, 63.7, 55.8, 52.2, 49.9, 34.6, 30.8, 28.7, 24.4; $^{19}$F NMR (471 MHz, CDCl$_3$) δ -124.1; HRMS (ESI-TOF) $m/z$: [M + H]$^+$ calcd for C$_{32}$H$_{37}$FN$_3$O$_3$ 548.2925; found 548.2928.

_Synthesis of N-(4-methoxybenzyl)-N-(tert-butoxycarbonyl)rucaparib (16)_

To a solution of indole-3-acetamide 6b (590 mg, 1.0 mmol) and NiCl$_2$(DPPP) (162 mg, 0.30 mmol) in toluene (10 mL) was added phenylsilane (1.2 mL, 10 mmol) at 20 °C. The reaction mixture was heated to 115 °C with an oil bath and stirred at the same temperature. Then, additional phenylsilane (1.2 mL, 10 mmol) was added to the reaction mixture two times in a two-hour interval, and the reaction mixture was allowed to stir at 115 °C for additional 14 h. After 6b was completely consumed, the reaction mixture was cooled to 0 °C and quenched with 1.0 N NaOH aqueous solution (20 mL). The crude mixture was extracted with ethyl acetate (20 mL) three times. The organic layers were combined, dried over MgSO$_4$ and concentrated _in vacuo_ to provide a crude mixture of compound 15, which was directly used in the next step without further purification.

To a solution of the crude mixture of 15 in THF (10 mL) was added a solution of lithium hexamethyldisilazane (LiHMDS) in THF (1.0 M, 3.0 mL, 3.0 mmol) at 20 °C. Then, the reaction mixture was allowed to stir at 70 °C with an oil bath and monitored by TLC for 12 h. After complete consumption of 15, the reaction mixture was quenched with water (10 mL). The crude mixture was extracted with ethyl acetate (10 mL) three times. The organic layers were combined, dried over MgSO$_4$ and concentrated _in vacuo_. The crude mixture was purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:2) as the eluent to afford compound 16 (451 mg, 0.83 mmol, 83% over 2 steps) as a yellow solid.
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.92 (s, 1 H), 7.79 (dd, \(J = 2.2, 10.9\) Hz, 1H), 7.50 - 7.39 (m, 2H), 7.32 (d, \(J = 8.5\) Hz, 2H), 7.28 (br, 2H), 7.19 (d, \(J = 7.9\) Hz, 1H), 6.88 (d, \(J = 8.5\) Hz, 2H), 4.94 - 4.72 (m, 2H), 4.44 (s, 2H), 3.81 (s, 3H), 3.62 (br, 2H), 2.95 (br, 2H), 2.83 (br, 3H), 1.49 (d, \(J = 12.5\) Hz, 9H);
\(^{13}\)C\{\(^1\)H\} NMR (125 MHz, CDCl\(_3\)) \(\delta\) 168.5 (d, \(J = 1.8\) Hz), 159.7 (d, \(J = 238.9\) Hz), 159.1, 156.2 (d, \(J = 55.4\) Hz), 137.8 (d, \(J = 17.3\) Hz), 136.6 (d, \(J = 11.8\) Hz), 135.1, 130.8, 129.73, 129.71, 128.0, 127.9, 126.5 (d, \(J = 8.2\) Hz), 123.7, 114.2, 112.4, 112.2 (d, \(J = 26.3\) Hz), 101.1 (d, \(J = 26.3\) Hz), 80.1, 55.4, 52.5, 51.8, 49.0, 34.3, 28.6, 28.0; \(^{19}\)F NMR (471 MHz, CDCl\(_3\)) \(\delta\) -120.1; mp 217-218 °C; HRMS (ESI-TOF) m/z: [M + Na]\(^+\) calced for C\(_{32}\)H\(_{34}\)FN\(_3\)NaO\(_4\) 566.2426; found: 566.2429.

**Synthesis of rucaparib (1)**

Compound 16 (270 mg, 0.50 mmol) was dissolved in a mixture of trifluoroacetic acid and anisole (10:1, 5.0 mL). The reaction mixture was stirred at 100 °C with an oil bath and monitored by TLC for 6 h. After complete consumption of 16, the reaction mixture was concentrated in vacuo. The crude mixture was purified by column chromatography on silica using a mixture of dichloromethane, methanol and triethylamine (90:10:1) as the eluent to afford rucaparib (1, 160 mg, 0.49 mmol, 98%) as a white solid. Spectroscopic data were in good agreement with the literature values.\(^{1-4}\)

\(^1\)H NMR (500 MHz, CD\(_3\)OD) \(\delta\) 7.57 (d, \(J = 8.2\) Hz, 2H), 7.51 (dd, \(J = 10.8, 2.3\) Hz, 1H), 7.46 (d, \(J = 8.2\) Hz, 2H), 7.30 (dd, \(J = 9.0, 2.4\) Hz, 1H), 3.75 (s, 2H), 3.53 (br, 2H), 3.15 - 3.10 (m, 2H), 2.40 (s, 3H);
\(^{13}\)C\{\(^1\)H\} NMR (125 MHz, CD\(_3\)OD) \(\delta\) 172.6, 160.6 (d, \(J = 235.2\) Hz), 140.2, 138.6 (d, \(J = 11.8\) Hz), 137.3 (d, \(J = 3.6\) Hz), 132.3, 130.0, 129.2, 125.8 (d, \(J = 9.1\) Hz), 125.0, 112.9, 111.2 (d, \(J = 26.3\) Hz), 102.2 (d, \(J = 26.3\) Hz), 56.0, 43.8, 35.6, 30.0; \(^{19}\)F NMR (471 MHz, CD\(_3\)OD) \(\delta\) -123.4; mp 133-134 °C; HRMS (ESI-TOF) m/z: [M + H]\(^+\) calcd for C\(_{19}\)H\(_{19}\)FN\(_3\)O 324.1507; found: 324.1510.
3. Modified First-generation Synthesis of Rucaparib (1)

Synthesis of N-(4-methoxybenzyl)-4-fluoro-2-methoxycarbonyl-6-nitrocinnamamide (18)

To a solution of 8 (28 g, 50 mmol) and glyoxalamide 7b (11 g, 55 mmol) in 1,2-dichloroethane (DCE; 500 mL) was added triethylamine (21 mL, 150 mmol). The reaction mixture was stirred at 60 °C with an oil bath and monitored by TLC for 4 h. After the complete consumption of 8, the reaction mixture was quenched with water (500 mL), and the resulting mixture was extracted with dichloromethane (500 mL) three times. The organic layers were combined, dried over MgSO₄ and concentrated in vacuo. The crude mixture was purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:2) as the eluent to afford compounds (Z)-18 (15.5 g, 40 mmol, 80%) and (E)-18 (970 mg, 2.5 mmol, 5%), respectively.

Compound (Z)-18:

A white solid; ¹H NMR (500 MHz, CDCl₃) δ 7.90 (dd, J = 8.2, 2.7 Hz, 1H), 7.84 (dd, J = 7.5, 2.7 Hz, 1H), 7.30 (dd, J = 11.7, 1.6 Hz, 1H), 7.11 - 7.07 (m, 2H), 6.84 - 6.80 (m, 2H), 5.92 (d, J = 11.7 Hz, 1H), 5.70 (br, 1H), 4.22 (br, 2H), 3.88 (s, 3H), 3.78 (s, 3H); ¹³C {¹H} NMR (125 MHz, CDCl₃) δ 164.7 (d, J = 2.7 Hz), 164.1, 160.7 (d, J = 251.6 Hz), 159.2, 150.3 (d, J = 8.2 Hz), 136.7, 133.0 (d, J = 7.3 Hz), 130.2 (d, J = 4.6 Hz), 129.9, 129.4, 122.7, 121.6 (d, J = 23.6 Hz), 115.2 (d, J = 26.3 Hz), 114.2, 55.4, 52.9, 43.0; ¹⁹F NMR (471 MHz, CDCl₃) δ -110.3; mp 134-135 °C; HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd for C₁₉H₁₇FN₂NaO₆ 411.0963; found 411.0964.

Compound (E)-18:

A white solid; ¹H NMR (500 MHz, CDCl₃) δ 7.95 (d, J = 15.9 Hz, 1H), 7.80 (dd, J = 8.0, 2.7 Hz, 1H), 7.70 (dd, J = 7.2, 2.7 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 5.81 (d, J = 15.9 Hz, 1H), 5.76 (br, 1H), 4.47 (d, J = 5.5 Hz, 2H), 3.90 (s, 3H), 3.80 (s, 3H); ¹³C {¹H} NMR (125 MHz, CDCl₃) δ 165.1, 163.9, 161.0 (d, J = 254.3 Hz), 159.3, 150.5, 135.3, 134.7 (d, J = 7.3 Hz), 129.9, 129.6,
128.1 (d, $J = 4.5$ Hz), 126.5, 121.3 (d, $J = 22.7$ Hz), 114.9 (d, $J = 26.3$ Hz), 114.3, 55.5, 53.4, 43.6; $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ -108.2; mp 191-192 °C; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for C$_{19}$H$_{17}$FN$_2$NaO$_6$ 411.0963; found 411.0962.

**Synthesis of (Z)-N-(tert-butoxycarbonyl)-N-(4-methoxybenzyl)-4-fluoro-2-methoxylcarbonyl-6-nitrocinnamamide ((Z)-19)**

To a solution of (Z)-18 (15.5 g, 40 mmol) in dichloromethane (400 mL) were added di-tert-butyl dicarbonate (Boc$_2$O, 26 g, 120 mmol), DMAP (1.5 g, 12 mmol) and triethylamine (17 mL, 120 mmol). The reaction mixture was stirred at 20 °C and monitored by TLC for 6 h. After the complete consumption of (Z)-18, the reaction mixture was quenched with water (400 mL) and the resulting mixture was extracted with dichloromethane (400 mL) three times. The organic layers were combined, dried over MgSO$_4$ and concentrated in vacuo. The crude mixture was purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:5) as the eluent to afford compound (Z)-19 (19 g, 39 mmol, 98%) as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.83 - 7.79 (m, 2H), 7.26 (dd, $J = 11.7$, 1.5 Hz, 1H), 7.03 - 6.99 (m, 2H), 6.81 (d, $J = 11.9$ Hz, 1H), 6.79 - 6.75 (m, 2H), 4.62 (br, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 1.43 (s, 9H); $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) $\delta$ 167.4, 165.0 (d, $J = 2.7$ Hz), 160.7 (d, $J = 251.6$ Hz), 158.8, 152.7, 150.3 (d, $J = 8.2$ Hz), 134.3, 134.2, 130.0, 129.7 (d, $J = 3.6$ Hz), 129.1, 125.6, 121.3 (d, $J = 22.7$ Hz), 114.9 (d, $J = 26.3$ Hz), 113.7, 83.9, 55.3, 53.0, 46.5, 28.0; $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ -110.1; mp 109-110 °C; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for C$_{24}$H$_{25}$FN$_2$NaO$_8$ 511.1487; found 511.1491.

**Synthesis of (E)-N-(tert-butoxycarbonyl)-N-(4-methoxybenzyl)-4-fluoro-2-methoxylcarbonyl-6-nitrocinnamamide ((E)-19)**
To a solution of (Z)-19 (9.8 g, 20 mmol) in 1,2-dichloroethane (DCE; 200 mL) were added N-bromosuccinimide (NBS; 7.1 g, 40 mmol) and 1,1’-azobis(cyclohexanecarbonitrile) (ACHN; 1.0 g, 4.0 mmol). The reaction mixture was stirred at 90 °C with an oil bath and monitored by TLC. After 30 min, saturated Na₂S₂O₃ aqueous solution (200 mL) was added to the reaction mixture to quench the remaining NBS. Then, the resulting mixture was extracted with dichloromethane (200 mL) three times. The organic layers were combined, dried over MgSO₄ and concentrated in vacuo. The crude mixture was purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:5) as the eluent to afford compound (E)-19 (6.4 g, 13 mmol, 65%) as a white solid and unreacting starting (Z)-19 (1.5 g, 3.0 mmol, 15%) was recovered.

1H NMR (500 MHz, CDCl₃) δ 8.06 (dd, $J = 15.7, 1.1$ Hz, 1H), 7.79 (dd, $J = 7.9, 2.7$ Hz, 1H), 7.76 (dd, $J = 7.3, 2.7$ Hz, 1H), 7.27 - 7.24 (m, 2H), 6.88 (d, $J = 15.7$ Hz, 1H), 6.86 - 6.82 (m, 2H), 4.85 (s, 2H), 3.89 (s, 3H), 3.79 (s, 3H), 1.39 (s, 9H); 13C{¹H} NMR (125 MHz, CDCl₃) δ 167.1, 165.2 (d, $J = 2.7$ Hz), 161.0 (d, $J = 254.3$ Hz), 159.0, 153.1, 150.3 (d, $J = 8.2$ Hz), 136.1, 135.1 (d, $J = 7.3$ Hz), 130.2, 129.5, 128.8 (d, $J = 4.5$ Hz), 127.0, 121.4 (d, $J = 22.7$ Hz), 114.9 (d, $J = 26.3$ Hz), 113.8, 83.8, 55.4, 53.3, 47.4, 28.0; 19F NMR (471 MHz, CDCl₃) δ -108.5; mp 111-112 °C; HRMS (ESI-TOF) m/z: [M + Na]⁺ calcd for C₂₄H₂₅FN₂NaO₈ 511.1487; found 511.1485.

**Synthesis of (E)-N-(4-methoxybenzyl)-2-amino-4-fluoro-6-methoxylcarbonylcinnamamide (4b)**

To a solution of (E)-19 (5.4 g, 11 mmol) in a mixture of ethanol, dichloromethane, and 35% aqueous HCl (6:3:1, 180 mL) was added iron powder (12 g, 220 mmol). The reaction mixture was stirred at 60 °C with an oil bath and monitored by TLC for 10 min. After the complete consumption of (E)-19, the reaction mixture was filtered through Celite to remove the insoluble residues and the filtrate was concentrated in vacuo. To the crude mixture was added saturated NH₄Cl aqueous solution (200 mL) and the resulting mixture was extracted with ethyl acetate (200 mL) three times. The organic layers were
combined, dried over MgSO₄ and concentrated in vacuo to afford the corresponding amine 20 along with Boc-deprotected compound 4b. Thus, the resulting mixture was directly subjected to the deprotection conditions without further purification.

To a solution of the crude mixture of compounds 4b and 20 in dichloromethane (110 mL) was added trifluoroacetic acid (TFA; 17 mL, 220 mmol). The reaction mixture was stirred at 20 °C and monitored by TLC for 2 h. After the complete consumption of 20, the reaction mixture was quenched with water (110 mL) and the resulting mixture was extracted with dichloromethane (110 mL) three times. The organic layers were combined, dried over MgSO₄ and concentrated in vacuo. The crude mixture was dissolved in ethyl acetate and recrystallized in hexanes to afford compound 4b (3.6 g, 10 mmol, 92% over 2 steps) as a white solid.

1H NMR (500 MHz, DMSO-d₆) δ 8.50 (t, J = 5.9 Hz, 1H), 7.49 (d, J = 16.0 Hz, 1H), 7.22 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.65 (dd, J = 11.2, 2.7 Hz, 1H), 6.62 (dd, J = 8.9, 2.6 Hz, 1H), 6.20 (d, J = 16.0 Hz, 1H), 5.73 (s, 2H), 4.30 (d, J = 6.0 Hz, 2H), 3.75 (s, 3H), 3.73 (s, 3H); 13C{1H} NMR (125 MHz, DMSO-d₆) δ 167.6 (d, J = 3.6 Hz), 164.7, 161.9 (d, J = 242.5 Hz), 158.3, 149.4 (d, J = 11.8 Hz), 133.9, 133.7 (d, J = 10 Hz), 131.3, 128.8, 125.8, 115.3 (d, J = 2.7 Hz), 113.7, 103.4 (d, J = 24.5 Hz), 103.3 (d, J = 24.5 Hz), 55.1, 52.3, 41.8; 19F NMR (471 MHz, DMSO-d₆) δ -113.1; mp 184-185 °C; HRMS (ESI-TOF): m/z: [M + Na]+ calcd for C₁₉H₁₉FNN₂NaO₄ 381.1221; found 381.1226.

Synthesis of N-(4-methoxybenzyl)-2-(4-(N-tert-butoxycarbonyl-N-methylaminomethyl)phenyl)-6-fluoro-4-methoxycarbonyl indole-3-acetamide (6b)

To a solution of 2-aminocinnamamide 4b (3.6 g, 10 mmol), aldehyde 5 (2.5 g, 10 mmol), and triethylamine (4.2 mL, 30 mmol) in dichloromethane (100 mL) was added a solution of titanium tetrachloride in dichloromethane (1.0 M, 7.0 mL, 7.0 mmol). The reaction mixture was stirred at 20 °C and monitored by TLC and 1H NMR analysis for 30 min. After the complete consumption of 4b and 5,
the reaction mixture was quenched with water (100 mL) and extracted with dichloromethane (100 mL) three times. The organic layers were combined, dried over MgSO$_4$ and concentrated in vacuo to afford a crude mixture of aldimine, which was directly used in the next step without purification.

To a solution of the crude mixture of the resulting aldimine in DMF (100 mL) were added 4 Å molecular sieves (3.0 g) and sodium cyanide (98 mg, 2.0 mmol). The reaction mixture was stirred at 20 °C and monitored by TLC for 1 h. After complete consumption of the aldimine, insoluble residues were removed by filtration and washed with ethyl acetate. The combined filtrate was concentrated in vacuo and purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:2) as the eluent to afford indole-3-acetamide 6b (4.7 g, 8.0 mmol, 80% over 2 steps) as a yellow solid.

Spectroscopic data of compound 6b were identical with ones obtained from the amide formation of 6a.
4. Second-generation Synthesis of Rucaparib (1)

Synthesis of (E)-2-amino-4-fluoro-6-methoxycarbonylcinnaminitrile (4c)

To a solution of ortho-aminaryl iodide 3 (2.95 g, 10 mmol), Pd(PtBu$_3$)$_2$ (255 mg, 0.50 mmol) and triethylamine (4.2 mL, 30 mmol) in toluene (100 mL) was added acrylonitrile (2.0 mL, 30 mmol). The reaction mixture was stirred at 80 °C with an oil bath and monitored by TLC for 4 h. After the complete consumption of 3, the reaction mixture was cooled to 20 °C. Insoluble solids were removed by filtration through Celite, and the filtrate was concentrated in vacuo. To the crude mixture was added saturated NH$_4$Cl aqueous solution (100 mL), and the resulting mixture was extracted with ethyl acetate (100 mL) three times. The organic layers were combined, dried over MgSO$_4$, and concentrated in vacuo. The crude mixture was dissolved in ethyl acetate and recrystallized in hexanes to afford compound 4c (2.0 g, 9.2 mmol, 92%) as a yellow solid.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.77 (d, $J = 17.1$ Hz, 1H), 7.05 (dd, $J = 8.8$, 2.5 Hz, 1H), 6.60 (dd, $J = 9.7$, 2.5 Hz, 1H), 5.74 (d, $J = 16.9$ Hz, 1H), 4.13 (br, 2H), 3.88 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) $\delta$ 166.4 (d, $J = 3.6$ Hz), 163.1 (d, $J = 247.9$ Hz), 148.1, 146.9 (d, $J = 10.9$ Hz), 132.5 (d, $J = 9.1$ Hz), 117.7, 116.1 (d, $J = 3.6$ Hz), 108.1 (d, $J = 24.5$ Hz), 106.4 (d, $J = 24.5$ Hz), 101.7, 52.8; $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ -110.0; mp 135-136 °C; HRMS (ESI-TOF) $m/z$: [M + H]$^+$ calcd for C$_{11}$H$_{10}$FN$_2$O$_2$ 221.0726; found 221.0728.

Synthesis of 2-(4-((N-tert-butoxycarbonyl)-(N-methyl)aminomethyl)phenyl)-6-fluoro-4-methoxycarbonyl-indole-3-acetonitrile (6c)

To a solution of 2-aminocinnaminitrile 4c (2.2 g, 10 mmol), aldehyde 5 (2.5 g, 10 mmol), and triethylamine (4.2 mL, 30 mmol) in dichloromethane (100 mL) was added a solution of titanium tetrachloride in dichloromethane (1.0 M, 7.0 mL, 7.0 mmol). The reaction mixture was stirred at 20 °C
and monitored by TLC and $^1$H NMR analysis for 30 min. After the complete consumption of 4c and 5, the reaction mixture was quenched with water (100 mL) and extracted with dichloromethane (100 mL) three times. The organic layers were combined, dried over MgSO$_4$, and concentrated in vacuo to afford a crude mixture of aldimine, which was directly used in the next step without further purification.

To a solution of the crude product of the resulting aldimine in DMF (100 mL) were added 4 Å molecular sieves (4.0 g) and sodium cyanide (98 mg, 2.0 mmol). The reaction mixture was stirred at 20 °C and monitored by TLC for 1 h. After complete consumption of aldimine, the insoluble solid was removed by filtration and washed with ethyl acetate. The combined filtrate was concentrated in vacuo and purified by column chromatography on silica using a mixture of ethyl acetate and hexanes (1:2) as the eluent to afford indole 6c (3.6 g, 8.0 mmol, 80% over 2 steps) as a white solid.

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.56 (d, $J = 7.9$ Hz, 2H), 7.47 (dd, $J = 10.2$, 2.4 Hz, 1H), 7.42 (d, $J = 8.1$ Hz, 2H), 7.34 (dd, $J = 8.7$, 2.4 Hz, 1H), 4.51 (s, 2H), 4.08 (s, 2H), 3.98 (s, 3H), 2.88 (br, 3H), 1.49 (d, $J = 15.9$ Hz, 9H); $^{13}$C($^1$H) NMR (125 MHz, CD$_3$OD) $\delta$ 168.7, 159.6 (d, $J = 237.1$ Hz), 157.7 (d, $J = 49.1$ Hz), 141.5 (d, $J = 3.6$ Hz), 140.3 (d, $J = 22.7$ Hz), 139.1 (d, $J = 11.8$ Hz), 131.6, 130.2, 129.0, 124.8 (d, $J = 9.1$ Hz), 123.3, 120.9, 112.5 (d, $J = 26.3$ Hz), 103.1 (d, $J = 25.4$ Hz), 102.4, 81.4, 52.9 (d, $J = 100.8$ Hz), 52.8, 34.7, 28.7, 17.0; $^{19}$F NMR (471 MHz, CD$_3$OD) $\delta$ -123.0; mp 146-147 °C; HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ calcd for C$_{25}$H$_{26}$FN$_3$NaO$_4$ 474.1805; found 474.1802.

First approach for second-generation synthesis of rucaparib (I) (Scheme 10(b))

To a solution of indole 6c (451 mg, 1.0 mmol) and nickel(II) chloride hexahydrate (NiCl$_2$·6H$_2$O; 238 mg, 1.0 mmol) in methanol (10 mL) was added sodium borohydride (265 mg, 7.0 mmol) at 0 °C (ice/water). The reaction mixture was stirred at 60 °C with an oil bath and monitored by TLC for 18 h. After the complete consumption of 6c, the reaction mixture was cooled to 20 °C and quenched with diethylenetriamine (1.1 mL, 10 mmol). The crude mixture was stirred at 20 °C for 30 min and
concentrated in vacuo. To the crude mixture was added saturated NaHCO₃ aqueous solution (10 mL) and the resulting mixture was extracted with ethyl acetate (10 mL) three times. The organic layers were combined, dried over MgSO₄, and concentrated in vacuo to afford a crude mixture of compound 26, which was directly used in the next step without further purification.

To a solution of the crude mixture of 26 in dichloromethane (10 mL) was added trifluoroacetic acid (TFA; 1.6 mL, 20 mmol). The reaction mixture was stirred at 20 °C and monitored by TLC for 1 h. After the complete consumption of 26, the reaction mixture was concentrated in vacuo. The crude mixture was purified by column chromatography on silica using a mixture of dichloromethane, methanol, and triethylamine (90:10:1) as the eluent to afford rucaparib (1, 239 mg, 0.74 mmol, 74% over 2 steps) as a white solid.

Spectroscopic data of rucaparib (1) were identical with ones obtained from the first-generation total synthesis of rucaparib.

Second approach for second-generation synthesis of rucaparib (1) (Scheme 10(c))

To a solution of indole 6c (451 mg, 1.0 mmol), Boc₂O (655 mg, 3.0 mmol) and nickel(II) chloride hexahydrate (NiCl₂·6H₂O; 238 mg, 1.0 mmol) in methanol (10 mL) was added sodium borohydride (265 mg, 7.0 mmol) at 0 °C (ice/water). The reaction mixture was stirred at 20 °C and monitored by TLC for 18 h. After the complete consumption of 6c, the reaction mixture was quenched with diethylenetriamine (1.1 mL, 10 mmol). The crude mixture was stirred for 30 min and concentrated in vacuo. To the crude mixture was added saturated NaHCO₃ aqueous solution (10 mL) and the resulting mixture was extracted with ethyl acetate (10 mL) three times. The organic layers were combined, dried over MgSO₄ and concentrated in vacuo to afford a crude mixture of compound 27, which was used in the next step without further purification.
To a solution of the crude mixture of 27 in dichloromethane (10 mL) was added TFA (1.6 mL, 20 mmol). The reaction mixture was stirred at 20 °C and monitored by TLC for 1 h. After the complete consumption of 27, the reaction mixture was concentrated in vacuo to afford a crude mixture of compound 28, which was directly used in the next step without further purification.

To a solution of the crude mixture of 28 in methanol (10 mL) was added triethylamine (0.14 mL, 1.0 mmol). The reaction mixture was stirred at 60 °C with an oil bath and monitored by TLC for 12 h. After the complete consumption of 28, the reaction mixture was concentrated in vacuo. The crude mixture was purified by column chromatography on silica using a mixture of dichloromethane, methanol and triethylamine (90:10:1) as the eluent to afford rucaparib (I, 260 mg, 0.80 mmol, 80% over 3 steps) as a white solid.

Spectroscopic data of rucaparib (I) were identical with ones obtained from the first-generation total synthesis of rucaparib.
5. References

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6. $^{1}H$, $^{13}C^{1}H$, $^{19}F$ and $^{31}P$ NMR Spectra

6-1. NMR Spectra of (4-Fluoro-2-methoxycarbonyl-6-nitrobenzyl)triphenylphosphonium Bromide (8)

a) $^{1}H$ NMR Spectrum (in CDCl$_3$, 500 MHz)
b) $^{13}C\textsuperscript{1}H$ NMR Spectrum (in CDCl$_3$, 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
d) $^{31}$P NMR Spectrum (in CDCl$_3$, 202 MHz)
6-2. NMR Spectra of (E)-Ethyl 4-Fluoro-2-methoxycarbonyl-6-nitrocinnamate (9)

a) $^1$H NMR Spectrum (in CDCl$_3$, 500 MHz)
b) $^{13}\text{C}^{1}\text{H}$ NMR Spectrum (in CDCl$_3$, 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
6-3. NMR Spectra of (E)-Ethyl 2-Amino-4-fluoro-6-methoxylcarbonylcinnamate (4a)

a) $^1$H NMR Spectrum (in CDCl$_3$, 500 MHz)
b) $^{13}\text{C}^{1}\text{H}$ NMR Spectrum (in CDCl$_3$, 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
6-4. NMR Spectra of Ethyl 2-(4-(N-tert-Butoxycarbonyl-N-methylaminomethyl)phenyl)-6-fluoro-4-methoxycarbonyl-indole-3-acetate (6a)

a) $^1$H NMR Spectrum (in CDCl$_3$, 500 MHz)
b) $^{13}$C\(^{1}H\) NMR Spectrum (in CDCl\(_3\), 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
6-5. NMR Spectra of \(N\)-(4-Methoxybenzyl)-2-(4-(\(N\)-\(\text{tert}\)-butoxycarbonyl-\(N\)-methylaminomethyl)phenyl)-6-fluoro-4-methoxycarbonyl-indole-3-acetamide (6b)

a) \(^1\)H NMR Spectrum (in DMSO-\(d_6\), 500 MHz)
b) $^{13}\text{C}^{1\text{H}}$ NMR Spectrum (in DMSO-$d_6$, 125 MHz)
c) $^{19}$F NMR Spectrum (in DMSO-$d_6$, 471 MHz)
6-6. NMR Spectra of \( N-(4\text{-Methoxybenzyl})-2-(4-(N\text{-tert-butoxycarbonyl-N-methylaminomethyl})\text{-phenyl})-6\text{-fluoro-4-(N-4-methoxybenzylamincarbonyl)-indole-3-acetamide} \) (14)

a) \( ^1\text{H NMR Spectrum (in DMSO-}d_6, \text{ 500 MHz)} \)
b) $^{13}$C$^{1}{H}$ NMR Spectrum (in DMSO-$d_6$, 125 MHz)
c) $^{19}$F NMR Spectrum (in DMSO-$d_6$, 471 MHz)
6-7. NMR Spectra of \( N-(4\text{-Methoxybenzyl})-2-(4-(N\text{-tert-butoxycarbonyl}-N\text{-methylaminomethyl})phenyl)-6\text{-fluoro}-4\text{-}(\text{methoxycarbonyl})tryptamine (15) \)

a) \( ^1\text{H} \) NMR Spectrum (in CD\(_3\)OD, 500 MHz)

![NMR Spectrum Image]
b) $^{13}\text{C}\{^1\text{H}\}$ NMR Spectrum (in CD$_3$OD, 125 MHz)
c) $^{19}$F NMR Spectrum (in CD$_3$OD, 471 MHz)
6-8. NMR Spectra of tert-Butyl (4-(8-Fluoro-2-(4-methoxybenzyl)-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indol-5-yl)benzyl)(methyl)carbamate (17)

a) $^1$H NMR Spectrum (in CDCl$_3$, 500 MHz)
b) $^{13}$C{$^1$H} NMR Spectrum (in CDCl$_3$, 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
6-9. NMR Spectra of $N$-(4-Methoxybenzyl)-2-(4-($N$-tert-butoxycarbonyl-$N$-methylaminomethyl)phenyl)-6-fluoro-4-(hydroxymethyl)tryptamine (S1)

a) $^1$H NMR Spectrum (in CD$_3$OD, 500 MHz)
b) $^{13}$C$^1$H NMR Spectrum (in CD$_3$OD, 125 MHz)
c) $^{19}$F NMR Spectrum (in CD$_3$OD, 471 MHz)
6-10. NMR Spectra of \( N-(4\text{-Methoxybenzyl})-N-(\text{tert-butoxycarbonyl})\text{rucaparib (16)} \)

a) \(^1\text{H NMR Spectrum (in CDCl}_3\text{, 500 MHz)}\)
b) $^{13}\text{C}^{1\text{H}}$ NMR Spectrum (in CDCl$_3$, 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
6-11. NMR Spectra of Rucaparib (1)

a) $^1$H NMR Spectrum (in CD$_3$OD, 500 MHz)
b) $^{13}\text{C}^{1}\text{H}$ NMR Spectrum (in CD$_3$OD, 125 MHz)
c) $^{19}$F NMR Spectrum (in CD$_3$OD, 471 MHz)
6-12. NMR Spectra of (Z)-N-(4-Methoxybenzyl)-4-fluoro-2-methoxycarbonyl-6-nitrocinnamamide ((Z)-18)

a) $^1$H NMR Spectrum (in CDCl$_3$, 500 MHz)
b) $^{13}$C$^1$H NMR Spectrum (in CDCl$_3$, 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
6-13. NMR Spectra of (E)-N-(4-Methoxybenzyl)-4-fluoro-2-methoxylcarbonyl-6-nitrocinnamamide ((E)-18)

a) $^1$H NMR Spectrum (in CDCl$_3$, 500 MHz)
b) $^{13}$C$^{1}$H NMR Spectrum (in CDCl$_3$, 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
6-14. NMR Spectra of (Z)-N-\((\text{tert-Butoxycarbonyl})-\)N-\((4\text{-methoxybenzyl})\)-4-fluoro-2-methoxycarbonyl-6-nitrocinnamamide ((Z)-19)

a) \(^1H\) NMR Spectrum (in CDCl\(_3\), 500 MHz)
b) $^{13}$C$^{1}$H NMR Spectrum (in CDCl$_3$, 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
6-15. NMR Spectra of \((E)-N-(\text{tert-Butoxycarbonyl})-N-(4\text{-methoxybenzyl})-4\text{-fluoro-2-methoxycarbonyl-6-nitrocinnamamide})\ ((E)-19)

a) \(^1H\) NMR Spectrum (in CDCl\textsubscript{3}, 500 MHz)
b) $^{13}$C$^1$H NMR Spectrum (in CDCl$_3$, 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
6-16. NMR Spectra of (E)-N-(4-Methoxybenzyl)-2-amino-4-fluoro-6-methoxycarbonylcinnamamide (4b)

a) $^1$H NMR Spectrum (in DMSO-$d_6$, 500 MHz)
b) $^{13}$C{$^1$H} NMR Spectrum (in DMSO-$d_6$, 125 MHz)
c) $^{19}$F NMR Spectrum (in DMSO-$d_6$, 471 MHz)
6-17. NMR Spectra of (E)-2-Amino-4-fluoro-6-methoxycarbonylcinnamonicnitrile (4c)

a) $^1$H NMR Spectrum (in CDCl$_3$, 500 MHz)
b) $^{13}\text{C}^{1}\text{H}$ NMR Spectrum (in CDCl$_3$, 125 MHz)
c) $^{19}$F NMR Spectrum (in CDCl$_3$, 471 MHz)
6-18. NMR Spectra of 2-(4-((N-tert-Butoxycarbonyl)-(N-methyl)aminomethyl)phenyl)-6-fluoro-4-methoxycarbonyl-indole-3-acetonitrile (6c)

a) $^1$H NMR Spectrum (in CD$_3$OD, 500 MHz)
b) $^{13}$C$^{1}{H}$ NMR Spectrum (in CD$_3$OD, 125 MHz)
c) $^{19}$F NMR Spectrum (in CD$_3$OD, 471 MHz)