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# Synthesis of potent BCRP inhibitor—Ko143

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**Abstract**

Two routes for the synthesis of potent BCRP inhibitor—Ko143 are reported. The key intermediate, 6-methoxytryptophan derivative, was synthesized by an improved procedure, ytterbium triflate-promoted coupling between 6-methoxyindole and optically active 1-benzyl-2-methyl-(*S*)-1,2-aziridinecarboxylate in the second protocol.


*Keywords:* BCRP inhibitor; Ko143; Ytterbium triflate; Aziridinecarboxylate

Breast cancer resistance protein (BCRP) is a 655-aa member of the ATP-binding cassette membrane transporters.[1–3] BCRP is a half transporter functioning as a dimer and confers multidrug resistance to topotecan, mitoxantrone, doxorubin, and related compounds by ATP-dependent drug extrusion.[2–5] Ko143 is a novel fumitremorgin C analogue and a more specific inhibitor of BCRP than other known inhibitors of BCRP such as fumitremorgin C and GF120918.[6–8] More importantly, Ko143 is nontoxic at effective in vitro and in vivo concentrations, which makes it one of the most promising compounds for the development of clinical modulators of BCRP-mediated efflux.[9]

The solid phase synthesis of Ko134, a demethoxy analogue, was published by Koomen's group.[10,11] To prepare larger quantities of Ko143 for in vivo studies, we opted to develop solution phase synthesis of Ko143, instead of utilizing Koomen's protocol (Scheme 1). To synthesize the key intermediate product **6**, 6-methoxytryptophan methyl ester, commercially available (*S*)-methyl 3-(1*H*-indol-3-yl)-2-(methoxycarbonyl)propanoate **1** was used as the starting material. Treatment of **1** with 85% phosphoric acid provided the cyclic isomer **2** that was converted to the *N*-acetyl derivative **3** by acetic anhydride.[12] Lead tetraacetate oxidation of the *N*-acetyl cyclic isomer **3** followed by methylation gave the 6-methoxy derivative **4**. The ring opening of **4** with 10% $H_2SO_4$–MeOH yielded the 6-methoxytryptophan derivative **5**.[13] Pictet–Spengler condensation of **5** with excess isovaleraldehyde followed by coupling of the resulting secondary amine with *N*-Fmoc-5-*tert*-butyl L-glutamic acid ester provided **8**.[10] Fmoc-deprotection and subsequent cyclization/cleavage of **8** gave the target compound **9**, Ko143 in an overall yield of 0.4%.[10]

Incorporation of methoxy group required five steps. We decided therefore to develop a shorter route. First, we thought that the Horner–Emmons olefination of commercially available 6-methoxyindole-3-carboxaldehyde **10** followed by enantiomerically selective hydrogenation of the resulting alkene **11** could provide 6-methoxytryptophan derivative **12**.[14,15] Unfortunately, the hydrogenation yielded no desired product even at 80 psi for 24 h (Scheme 2).

Second, we tried regioselective alkylation of readily available 6-methoxyindole with methyl (*S*)-2-((*tert*-butoxycarbonyl) amino)-3-bromopropiate mediated by zinc triflate.[16] Once again, no desired product was found from

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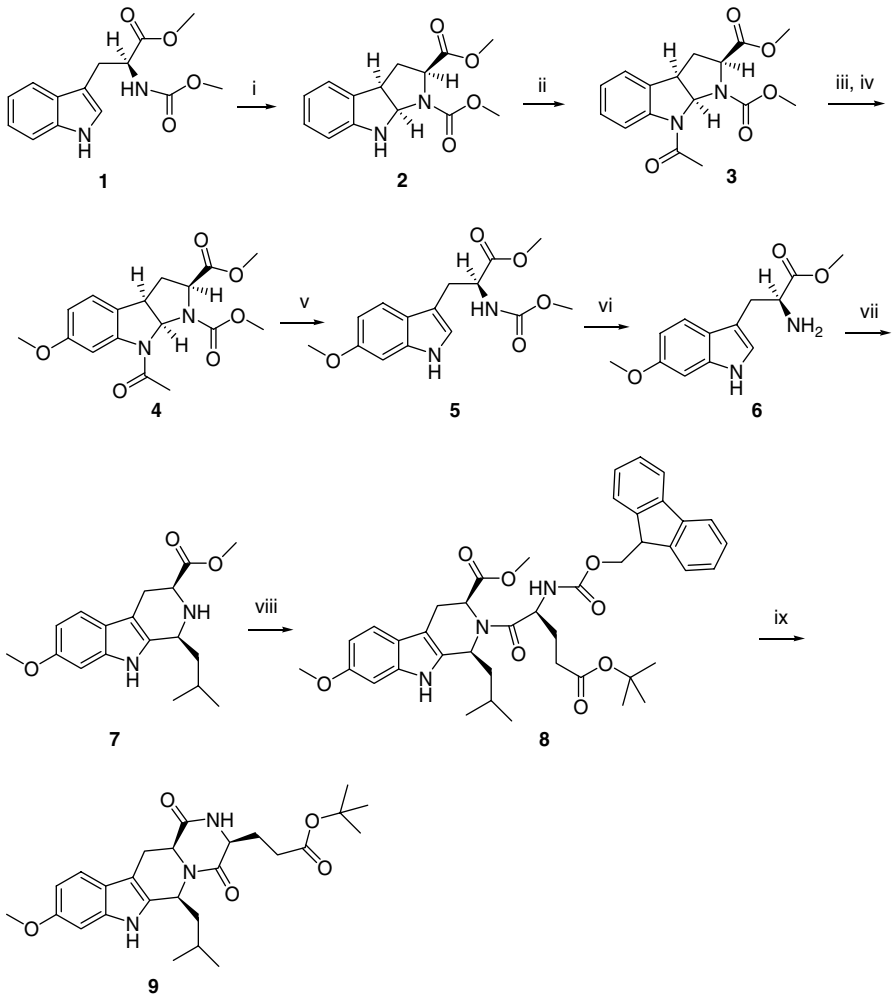
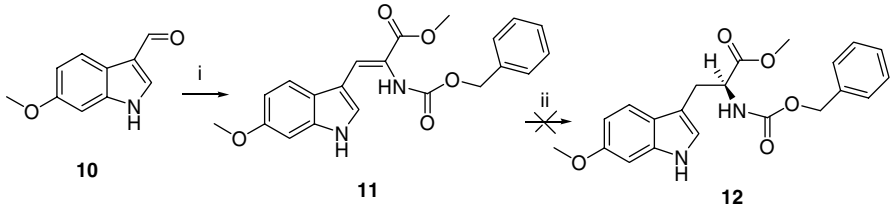
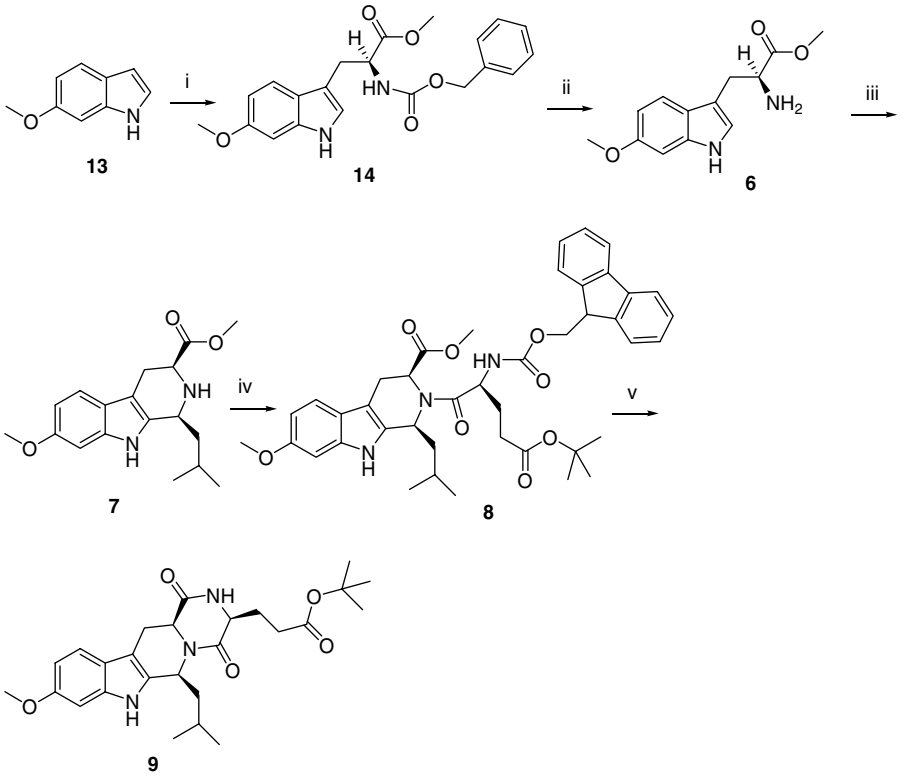



Scheme 1. Reagents and conditions: (i) $H_3PO_4$, rt, 3 h, 85%; (ii) $Ac_2O$, pyridine, rt, 20 h, 60%; (iii) $Pb(OAc)_4$, TFA, 0 °C, 3 h; (iv) MeI, $K_2CO_3$, acetone, rt, 24 h, 22% (iii and iv); (v) 10% $H_2SO_4$, MeOH, rt, 3 h; (vi) $Me_3SiI$, $CHCl_3$, reflux, 2 h, 34% (v and vi); (vii) isovaleraldehyde, TFA, $CH_2Cl_2$, rt, 1.5 h, 34%; (viii) *N*-Fmoc-5-*tert*-butyl L-glutamic acid ester, diisopropylethylamine, 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate, *N*-methylpyrrolidinone, rt, 5 days, 54%; (ix) piperidine, THF, rt, 18 h, 54%.




Scheme 2. Reagents and conditions: (i) $(MeO)_2P(O)CH(NHCbz)COOMe$, DBU, $CH_2Cl_2$, rt, 5 h, 92%; (ii) $H_2$, MeOH, (*S*,*S*)(COD) Et-DUPHOS Rh(I) OTf, 80 psi, 24 h.

the reaction. Sato and Kozikowski[17] prepared 5-methoxytryptophan derivative from 5-methoxyindole and (*2S*)-2-aziridinecarboxylate mediated by zinc triflate. We tried to use this method to synthesize 6-methoxytryptophan derivative and obtained the product in a very low yield. Isobe et al.[18] reported that ytterbium triflate was a superior Lewis acid for regioselective ring opening of aziridine carboxylate with 2-methylindole. Following this report, we prepared 6-methoxytryptophan derivative **14** by reacting 6-methoxyindole **13** with 1-benzyl-2-methyl-(*S*)-1,2-aziridinedicarboxylate and ytterbium triflate (Scheme 3). The key intermediate product, 6-methoxytryptophan methyl ester **6** was prepared by deprotection of **14**. The last three steps followed the same procedures as in Scheme 1 to get the target compound **9**, Ko143 in an overall yield 5%. The Pictet–Spengler reaction of this route was carried out under conditions of kinetic control to improve the stereoselectivity. The cis:trans ratio was changed favorably from 45:55 at




Scheme 3. Reagents and conditions: (i) 1-benzyl-2-methyl-(*S*)-1,2-aziridinedicarboxylate, ytterbium triflate, $CH_2Cl_2$, rt, 24 h, 52%; (ii) $H_2$ balloon, MeOH, 10% Pd/C, 3 h; (iii) isovaleraldehyde, TFA, $CH_2Cl_2$, 0 °C, 1.5 h, 40% (ii and iii); (iv) *N*-Fmoc-5-*tert*-butyl L-glutamic acid ester, diisopropylethylamine, 2-chloro-1,3-dimethylimmidazolinium hexafluorophosphate, *N*-methylpyrrolidinone, rt, 5 days, 38%; (v) piperidine, THF, rt, 18 h, 60%.

rt to 63:37 at 0 °C.[19,20] These results are comparable to that reported by Bailey et al. Compared to Scheme 1, Scheme 2 is shorter and provided the target compound in higher overall yield.[21,22]

In conclusion, we have developed two routes to synthesize BCRP inhibitor, Ko143. The first route includes nine steps in an overall yield of 0.4%. The second route includes only five steps in an overall yield of 5%. The key step of the second route involves ytterbium triflate-promoted coupling between 6-methoxyindole and optically active 1-benzyl-2-methyl-(*S*)-1,2-aziridinedicarboxylate. Currently, in vivo investigations of our experimented drugs with Ko143 are being explored to adequately characterize the drug-transporter interactions.

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21. *Compound* **14**: *General procedure*: 1-Benzyl-2-methyl-(*S*)-1,2-aziridinedicarboxylate and 6-methoxyindole (2 equiv) were dissolved in methylene chloride (3.8 mL/mmol). Ytterbium(III) triflate (1 equiv) was added by portion and the reaction allowed stirring for 24 h. The reaction mixture was washed with water. The organic layer was then dried over magnesium sulfate and rotary-evaporated to dryness. Residue was purified by flash column chromatography on silica gel using a gradient of hexanes and ethyl acetate. Product containing fractions was combined and dried in vacuum to yield **1** as yellow oil (30–60%).
22. All new compounds were characterized on the basis of $^{1}H$, $^{13}C$ NMR and HRMS data. Analytical data for selected compounds are given below:
Compound **14**: $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.81 (s, 1H), 7.21 (s, 5H), 7.13 (d, $J = 3.5$, 1H), 6.70 (dd, $J = 2.3$, $J = 8.2$, 2H), 6.62 (dd, $J = 1.8$ $J = 8.2$, 1H), 5.16 (s, 1H), 4.97 (t, 2H), 4.56 (m, 1H), 3.69 (s, 3H), 3.55 (s, 3H), 3.14 (s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 173.02, 157.27, 156.34, 137.64, 136.89, 129.14, 128.80, 122.58, 122.20, 119.88, 110.38, 95.27, 67.64, 61.15, 56.25, 55.12, 53.02, 28.62, 14.90; HRMS *m*/*z*: calcd 383.1601 (M+1), found 383.1585.
Compound **7**: mp = 157 °C; $^{1}H$ NMR (300 MHz, DMSO): $\delta$ 10.59 (s, 1H), 7.21 (d, $J = 8.8$, 1H), 6.75 (d, $J = 1.8$, 1H), 6.56 (dd, $J = 1.8$, $J = 8.2$, 1H), 4.08 (d, $J = 7.6$, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 2.87 (dd, $J = 2.3$, $J = 14.7$, 1H), 2.59 (t, 1H), 1.72–2.02 (m, 3H), 1.46 (t-like, 1H), 0.95 (d, $J = 6.5$, 3H), 0.89 (d, $J = 6.5$, 3H); $^{13}C$ NMR (100 MHz, DMSO): $\delta$ 173.49, 155.07, 136.65, 135.77, 121.22, 117.79, 107.86, 105.72, 94.62, 56.09, 55.12, 51.62, 50.35, 43.12, 25.74, 23.98, 23.66, 21.50; HRMS *m*/*z*: calcd 317.1860 (M+1), found 317.1849 (M+1).
Compound **9**: mp = 147 °C; $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.87 (s, 1H), 7.42 (d, $J = 8.2$ Hz, 1H), 6.89 (d, $J = 1.8$, 1H), 6.83 (dd, $J = 2.3$, $J = 8.8$, 1H), 6.79 (s, 1H), 5.46 (dd, $J = 4.1$, $J = 9.4$, 1H), 3.99–4.07 (m, 2H), 3.85 (s, 3H), 3.52 (dd, $J = 4.7$, $J = 15.9$, 1H), 3.03 (dd, $J = 11.7$, $J = 15.3$, 1H), 2.50 (t, 2H), 2.31–2.44 (m, 1H), 2.14–2.28 (m, 1H), 1.69–1.82 (m, 1H), 1.51–1.66 (m, 2H), 1.46 (s, 9H), 1.05 (d, $J = 6.5$, 3H), 0.83 (d, $J = 6.5$, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 173.97, 170.28, 168.97, 157.15, 137.16, 133.52, 121.26, 119.42, 110.36, 107.41, 95.77, 82.13, 56.54, 56.40, 54.92, 51.77, 46.57, 32.07, 28.73, 25.64, 25.51, 24.48, 22.47, 22.30; HRMS *m*/*z*: calcd 470.2649 (M+1), found 470.2629 (M+1) $[\alpha]_D$ −98.9 ($c = 0.010$, methanol).