Efficient Synthesis of the Immunomodulating Compound KRP-203

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Abstract: A practical and concise synthesis of KRP-203 (**1**) was achieved by utilizing a palladium coupling reaction mediated by XantPhos and $Pd_2(dba)_3$ as the key step. The coupling reaction of aryl bromide **5** with 3-hydroxythiophenol (**6**) proceeded chemoselectively to give phenol **7** in spite of the presence of a chlorine substituent on **5** and a hydroxyl group on **6**. Phenol **7** was converted into KRP-203 by benzylation and removal of the protecting groups in high yield.

Key words: palladium, cross-coupling, synthesis, KRP-203, FTY720

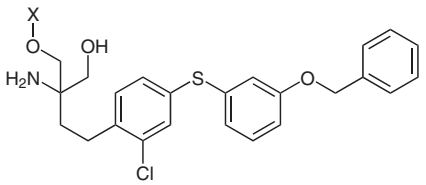
Diaryl sulfides are common functionalities found in biologically active compounds.[1] The traditional methods for the construction of diaryl sulfides like Ullmann condensation often need harsh conditions.[2] Recently, mild and highly selective methods for the formation of diaryl sulfides using metal-catalyzed (Cu, Pd) coupling reactions were reported.[3] These methods could shorten the synthetic schemes using traditional substitution reaction for compounds possessing a diaryl sulfide moiety.

KRP-203 (**1**, Figure 1) is a novel immunomodulating compound with a diaryl sulfide moiety.[4] The hydrophilic part of **1**, 2-aminopropane-1,3-diol, is the same as that of FTY720 (**2**).[5] Compound **2** is a synthetic immunomodulating agent with a sphingosine-like structure, and was efficacious against multiple sclerosis and kidney transplant rejection in clinical studies.[6] For the immunomodulating mechanism of action is presumed that **2** is converted into the monophosphate ester of **2**, FTY720-P (**3**), in vivo, and then **3** interacts with sphingosine 1-phosphate (S1P) receptor type-1 ($S1P_1$), among five known S1P receptors ($S1P_{1-5}$), as an agonist.[7] In the clinical trials of **2**, transient bradycardia was reported as a frequent adverse event.[6] It is considered that the effect of **2** on heart rate is also related to the agonism at S1P receptors, especially $S1P_3$ in rodents.[8] Interestingly, while **1** showed potent immunomodulating effect comparable to **2**, the effect on heart rate of **1** was weak in guinea pigs.[4] Furthermore, the potential of the monophosphate ester of **1**, KRP-203-P (**4**), causing bradycardia in rats was ten-fold weaker than that of **3**.[9] These data show that **1** is a unique and useful compound to investigate the physiological role of S1P receptors. We present here a new concise synthetic approach to **1** using a Pd-catalyzed cross-coupling reaction.

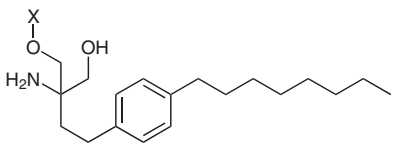
In the previous preparations of **1**, the construction of the diaryl sulfide moiety was accomplished by a traditional substitution reaction using 2-chloro-4-fluorobenzaldehyde as the starting material.[10] For the efficient proceeding of the substitution reaction, the aryl fluoride activated by the carbonyl group was required. However, the one-carbon elongation steps after the construction of the diaryl sulfide moiety were the main reason for the long synthetic schemes.

Our strategy for synthesis of **1** was to prepare the diaryl sulfide moiety by a Pd-catalyzed cross-coupling reaction of aryl bromide **5**, which was easily accessible by an established synthetic procedure[11] from diethyl 2-[*N*-(*tert*-butoxycarbonyl)amino]malonate and 4-bromo-2-chlorobenzoic acid, with commercially available thiol **6**. The synthesis of **1** is shown in Scheme 1.

The first step was the formation of the diaryl sulfide. We adopted the condition using $Pd_2(dba)_3$ in combination with 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos) as the phosphine ligand reported by Itoh.[12] Although nonactivated aryl chlorides showed poor reactivity under the condition, aryl–sulfur bonds were efficiently



X = H (HCl salt): KRP-203 (**1**)
X = P(O)(OH)$_2$: KRP-203-P (**4**)



X = H (HCl salt): FTY720 (**2**)
X = P(O)(OH)$_2$: FTY720-P (**3**)

Figure 1

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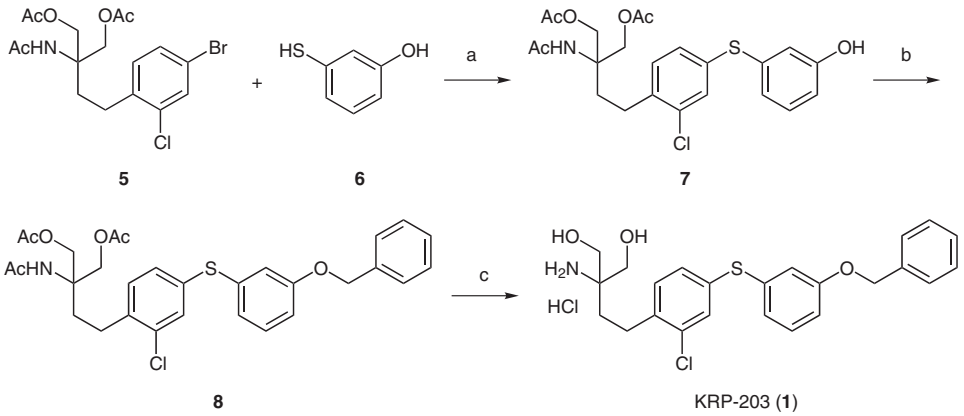

Scheme 1 *Reagents and conditions*: (a) $Pd_2(dba)_3$ (2.5 mol%), XantPhos (5 mol%), DIPEA (2.0 equiv), 1,4-dioxane, 120 °C; (b) BnBr (1.3 equiv), K_2CO_3 (3 equiv), DMF, r.t.; (c) 1. $LiOH·H_2O$ (5 equiv), MeOH–H_2O–THF, 80 °C, 2. 2 M HCl/EtOH, EtOH.

formed from aryl bromides and thiols. This selectivity to bromide over chloride was favorable to our synthetic strategy using bromo- and chloro-substituted aryl compound **5** as the starting compound.

Under this condition we were able to obtain the desired product **7** in 86% yield. The carbon–sulfur bond formation proceeded chemoselectively in spite of the presence of a phenolic hydroxyl group.[12] In addition, the reaction of **5** with the thiol group of **6** occurred at the bromine atom exclusively. Triacetyl KRP-203 (**8**) was obtained by benzylation of the phenol group of **7** by a standard method using benzyl bromide and potassium carbonate. Removal of the acetyl groups was accomplished by treatment with LiOH in an aqueous medium to give free base of **1**. Finally, the free base of **1** was converted into its HCl salt **1** by treatment with 2 M HCl in EtOH. The three steps yield from **7** was 91%, and the spectroscopic data well supported the structure and high purity of compound **1** obtained by this scheme.

In conclusion, we have developed a practical and concise synthetic method for KRP-203 (**1**). The key step was the chemoselective coupling reaction of thiol **6** with aryl bromide **5**. This route shortened the previously reported synthetic schemes of **1**, and makes it easier to utilize **1** for pharmacological and biochemical studies.

Silica gel column chromatography was performed using Fuji Silysia PSQ100B. ^{1}H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm relative to TMS as an internal standard. IR spectra were recorded on a PerkinElmer FT-IR Spectrum One spectrometer. Mass spectra were measured in a combination with a Waters Acquity UPLC system (0.05% TFA in MeCN/0.05% TFA in H_2O) and a Micromass ZQ (ESI) spectrometer. Melting points were obtained on a Büchi 535 melting point apparatus and are uncorrected. Elemental analyses were performed on a Yonako CHN coder MT-5 analyzer.

_N_-{1,1-Bis(acetoxymethyl)-3-[2-chloro-4-(3-hydoxyphenylthio)phenyl]propyl}acetamide (7)

A mixture of **5** (10.0 g, 23.0 mmol), 3-hydroxythiophenol (2.8 mL, 27.6 mmol), tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (600 mg, 0.58 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (665 mg, 1.2 mmol) and *N*,*N*-diisopropylethylamine (8.0 mL, 46.0 mmol) in 1,4-dioxane (46 mL) was stirred at 120 °C for 9 h. After pouring into aq 1 M HCl (100 mL), the mixture was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (2 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc) to give **7** (9.48 g, 86%) as a white solid; mp 142–143 °C.

IR (ATR): 3468, 3271, 3072, 1740, 1714, 1641 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.84 (s, 3 H), 1.92–1.97 (m, 2 H), 2.02 (s, 6 H), 2.62–2.66 (m, 2 H), 4.20 (d, *J* = 11.0 Hz, 2 H), 4.29 (d, *J* = 11.0 Hz, 2 H), 6.71–6.78 (m, 3 H), 7.18–7.33 (m, 4 H), 7.69 (s, 1 H), 9.70 (br s, 1 H).

MS (ESI): *m*/*z* = 480 [M + H].

Anal. Calcd for $C_{23}H_{26}ClNO_6S$: C, 57.55; H, 5.46; N, 2.92. Found: C, 57.46; H, 5.44; N, 2.86.

_N_-{3-[4-(3-Benzyloxyphenylthio)-2-chlorophenyl]-1,1-bis(acetoxymethyl)propyl}acetamide (8)

To a solution of **7** (9.48g, 19.8 mmol) in DMF (65 mL) were added K_2CO_3 (8.20 g, 59.3 mmol) and benzyl bromide (3.0 mL, 25.2 mmol). The mixture was stirred at r.t. overnight. After pouring into H_2O (150 mL), the mixture was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with H_2O (3 × 150 mL) and brine (2 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc) to give **8** (10.9 g, 97%) as a white solid; mp 81–82 °C.

IR (ATR): 3269, 3097, 1744, 1732, 1650 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.84 (s, 3 H), 1.93–1.97 (m, 2 H), 2.02 (s, 6 H), 2.62–2.66 (m, 2 H), 4.20 (d, *J* = 11.0 Hz, 2 H), 4.29 (d, *J* = 11.0 Hz, 2 H), 5.09 (s, 2 H), 6.89–7.00 (m, 3 H), 7.24 (dd, *J* = 8.0 Hz, 1.6 Hz, 1 H), 7.30–7.42 (m, 8 H), 7.69 (s, 1 H).

MS (ESI): *m*/*z* = 570 [M + H].

Anal. Calcd for $C_{30}H_{32}ClNO_6S$: C, 63.20; H, 5.66; N, 2.46. Found: C, 63.16; H, 5.61; N, 2.42.

2-Amino-2-{2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl}propan-1,3-diol Hydrochloride (KRP-203, 1)

To a solution of **8** (10.9 g, 19.1 mmol) in MeOH (90 mL), THF (30 mL), and H_2O (90 mL) was added $LiOH·H_2O$ (4.14 g, 100 mmol). After stirring at 80 °C for 2 h, the organic solvents were removed in vacuo. The solid obtained was collected by filtration to give the free base of **1**. The solid was dissolved in 2 M HCl in EtOH (30 mL) and

EtOH (50 mL). After stirring, the precipitate formed was collected by filtration to give **1** (8.6 g, 94%); white solid; mp 199–200 °C (dec.).

IR (ATR): 3238, 3034, 2943 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.76–1.80 (m, 2 H), 2.71–2.76 (m, 2 H), 3.55 (d, *J* = 4.8 Hz, 4 H), 5.10 (s, 2 H), 5.42 (t, *J* = 4.8 Hz, 2 H), 6.90–7.01 (m, 3 H), 7.25 (dd, *J* = 7.9, 1.2 Hz, 1 H), 7.30–7.42 (m, 8 H), 7.91 (br s, 3 H).

MS (ESI): *m*/*z* = 444 [M + H].

Anal. Calcd for $C_{24}H_{27}Cl_2NO_3S$: C, 60.00; H, 5.66; N, 2.92. Found: C, 59.83; H, 5.59; N, 2.90.

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