Synthesis of a Key Intermediate for the Preparation of FTY720 Analogs

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A concise synthesis of a useful intermediate **10 for the preparation of fingolimod (FTY720) analogs was achieved by utilizing a chemoselective Sonogashira reaction of trihalobenzene **12** with alkyne **13**. The reaction proceeded with high selectivity to give alkyne **11** containing the dihalobenzene moiety in good yield. Compound **11** was converted into intermediate **10** by hydrogenation without reduction of the halogen atoms.**

Key words fingolimod; KRP-203; palladium; chemoselectivity; cross-coupling

Pd-catalyzed cross-coupling reactions, such as the Suzuki, Heck, and Sonogashira reactions, are useful for construction of aralkyl skeletons. These reactions are commonly used in the field of drug discovery because a variety of compounds can often be provided in a short-step synthesis using commercially available reagents in combination with properly designed reaction partners (alkenes, alkynes, and boronic acids).^{1,2)}

Fingolimod^{3–6)} (FTY720, Fig. 1) is the first of a novel class of sphingosine 1-phosphate (SIP) receptor modulators and has been approved in the U.S., Russia, Switzerland, Australia and the EU to date as a first-line treatment for relapsing forms of multiple sclerosis (MS). The FTY720 analog KRP-203⁷⁾ (**2**) showed a potent immunomodulating effect comparable to **1**. Compound **2** is distinguished by having a chlorine atom on the phenyl ring close to the 2-aminopropane-1,3-diol group. Moreover, we have reported that the introduction of a chlorine atom at the same position in related analogs improved the *in vivo* activity (compounds **3**, **4**).⁸⁾ Thus, it is important to produce an intermediate having a benzene ring with an *o*-chlorine substituent in order to provide the next generation of SIP receptor modulators.

Compounds **2**, **3**, and **4** were synthesized from common intermediate **10**.^{8–10)} However, twelve steps were required to obtain **10** using our previous synthetic route, as shown in Chart 1 (overall yield 22%).¹¹⁾ The starting 4-bromo-2-chlorobenzoic acid (**5**) was converted to homologous compound **6** in 5 steps. Condensation of diethyl malonate analog **8** with **7**, which was obtained from **6** in 3 steps, led to a side reaction forming the corresponding styrene derivative by competitive elimination resulting in the formation of **9** in low yield.

In this paper, we present a short-step synthesis of intermediate **10** using a chemoselective Pd-catalyzed cross-coupling reaction. The retrosynthetic strategy for the preparation of **10** is shown in Chart 2. Using this sequence, **10** can be obtained from **11** by hydrogenation followed by protecting group exchange. Alkyne **11** can be prepared by a chemoselective Sonogashira reaction of trihalobenzene **12** having different halogen atoms and alkyne **13** having all the required carbon fragments. This route eliminated the elongation steps required to form the aralkyl fragment and avoided the side reaction that generated the styrene derivative.

A Sonogashira reaction of 1-iodo-4-octylbenzene with alkyne **13** for the synthesis of **1** and chemoselective Sonogashira

reactions of trihalobenzene **12** with cyclopropylacetylene or 1-hexyne have already been reported.^{12,13)} On the basis of these reports, we initiated the synthesis of **10** as shown in Chart 3.

A chemoselective Sonogashira reaction between **12** and **13** was examined. The optimization results for this key step are summarized in Table 1. In the synthesis of analogs of **10**,¹⁴⁾ we successfully adopted a Sonogashira coupling reaction where 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) was used in the presence of dichlorobis(triphenylphosphine)-palladium at 80°C. First, we tried the reaction at 50°C because we were apprehensive that high temperature (80°C) might lead to a decrease in selectivity between halogen atoms; however, the reaction did not proceed at all (run 1). Raising temperature from 50 to 80°C failed to give the desired compound **11**, only producing compound **14** (run 2). Since these results showed that the desired product **11** reacted with **13** more quickly than with **12**, we changed the ligand from X-phos to triphenylphosphine in expectation of reducing the formation of **14** (runs 3, 4). The combination of Pd(PPh₃)₄ and CuI employed for the synthesis of **1**¹²⁾ gave the desired product (**11**, 53%) along with the starting material (**12**, 25%) without producing by-product **14** (run 3). Moreover, by using Bytschkov's reaction conditions using a secondary amine (*i*-PrNH)¹³⁾ the reaction proceeded promptly and chemo-selectively to give the desired product **11** in 94% yield (run 4).

Target compound **10** was obtained from **11** in a straightforward manner as shown in Chart 4. Fortunately, hydrogenation of the internal alkyne of **11** over PtO₂ in a H₂ atmosphere gave saturated compound **15** without reduction of the halogen atoms. Product **15** was a mixture of desired compound **15a** and *tert*-butoxycarbonyl (*t*-Boc) deprotected **15b**. Treatment of the mixture with concentrated HCl in EtOH gave **16** (HCl salt

Fig. 1. Structures of FTY720 and FTY720 Analogs

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Chart 1. Previous Synthetic Route of Compound 10

Chart 2. Retrosynthesis of Compound 10

Chart 3

Table 1. Sonogashira Reaction of Trihalobenzene 12

Run	Temp. (°C)	11 (%)	14 (%)	Rec. 12 (%)
1 ^{a)}	50		No reaction	
2 ^{a)}	80		14	58
3 ^{b)}	80	53		25
4 ^{c)}	80	94		

a) Pd(CH₃CN)₂, X-Phos, Cs₂CO₃, MeCN, 3 h. *b)* Pd(PPh₃)₄, CuI, DMF–Et₃N, 3 h. *c)* PdCl₂(PPh₃)₂, CuI, PPh₃, (*i*-Pr)₂NH, 3 h.

of **15b**) as a solid, which was acetylated to give **10** in good yield.

In conclusion, a concise synthesis of the useful intermediate, compound **10**, has been developed (4 steps, 66% overall yield). The key step was a chemoselective Sonogashira reaction of a trihalobenzene with an alkyne. This route shortened the preparation of **10** from that previously used and provided easier access to some interesting analogs (e.g., **2–4**) for biochemical and pharmacological studies.

Experimental

Silica gel column chromatography was performed on a Moritex Purif- α 2 system using Purif-Pack 30- μ m or 60- μ m silica gel columns and the reported solvents as eluents under gradient conditions. ¹H-NMR spectra were recorded on a Bruker AVANCE 400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane (TMS) as an internal standard. Mass spectra were measured in an apparatus comprising a Waters Acquity UPLC system (CH₃CN+0.05% trifluoroacetic acid (TFA)/H₂O+0.05% TFA)

Reagents and conditions: (a) PtO_2 , H_2 , EtOH, rt; (b) concentrated HCl, EtOH, 50°C , 72% (from **12**); (c) Ac_2O , Py, rt, 92%.

Chart 4. Synthesis of Compound **10** from Alkyne **11**

and a Micromass ZQ (electrospray ionization (ESI)) spectrometer. Melting points were obtained on a Büchi 535 melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin Elmer 2400 II CHN Analyzer.

tert-Butyl 2,2-Dimethyl-5-[(4-bromo-2-chlorophenyl)ethynyl]-1,3-dioxan-5-ylcarbamate (11**)** To a mixture of **12** (317 mg, 1.0 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (4 mg, 2 mol%), PPh_3 (10.5 mg, 4 mol%), and CuI (7.6 mg, 4 mol%) in $(i\text{-Pr})_2\text{NH}$ (3.3 mL) was added alkyne **13** (281 mg, 1.1 mmol). The mixture was stirred at 80°C for 3 h, and EtOAc (10 mL) was then added. After removal of the precipitate by filtration, the filtrate was diluted with water and extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane–EtOAc) to give **11** (430 mg, 94%) as a pale brown solid.

mp $90\text{--}92^\circ\text{C}$ MS (ESI) m/z : 344 $[\text{M} - \text{Boc} + \text{H}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.45 (3H, s), 1.48 (9H, s), 1.51 (3H, s), 4.06 (2H, d, $J=11.2$ Hz), 4.12 (2H, d, $J=11.2$ Hz), 5.22 (1H, brs), 7.33 (2H, m), 7.56 (1H, s). *Anal.* Calcd for $\text{C}_{19}\text{H}_{23}\text{BrClNO}_4$: C, 51.31; H, 5.21; N, 3.15. Found: C, 51.38; H, 5.14; N, 3.10.

2-Amino-2-(2-[4-bromo-2-chlorophenyl]ethyl)-1,3-propanediol Hydrochloride (16**)** To a mixture of **12** (10 g, 31.5 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (442 mg, 2 mol%), PPh_3 (331 mg, 4 mol%), and CuI (240 mg, 4 mol%) in $(i\text{-Pr})_2\text{NH}$ (105 mL) was added alkyne **13** (8.85 g, 1.1 mmol). The mixture was stirred at 80°C for 4 h, and EtOAc (50 mL) was then added. After removal of the precipitate by filtration, the filtrate was concentrated *in vacuo*, diluted with water (150 mL), and extracted with EtOAc (150 mL, 3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane–EtOAc) to give **11**. A mixture of **11** in EtOH (140 mL) was stirred under a hydrogen atmosphere in the presence of PtO_2 (700 mg) for 24 h at room temperature. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*. To a solution of the residue in EtOH (50 mL) was added concentrated HCl (10 mL). The mixture was stirred at 50°C for 6 h. After the solution was concentrated *in vacuo*, the residue was collected by filtration to give **16** (7.84 g, 72%) as a white solid.

mp $186\text{--}188^\circ\text{C}$ MS (ESI) m/z : 308 $[\text{M} + \text{H}]^+$. $^1\text{H-NMR}$

(400 MHz, $\text{DMSO}-d_6$) δ : 1.77 (2H, dt, $J=8.7$, 4.6 Hz), 2.73 (2H, dt, $J=8.7$, 4.6 Hz), 3.55 (4H, d, $J=5.1$ Hz), 5.44 (2H, t, $J=5.1$ Hz), 7.35 (1H, d, $J=8.2$ Hz), 7.52 (1H, dd, $J=8.2$, 2.0 Hz), 7.69 (1H, d, $J=2.0$ Hz), 7.96 (3H, brs). *Anal.* Calcd for $\text{C}_{11}\text{H}_{15}\text{BrClNO}_2 \cdot \text{HCl}$: C, 38.29; H, 4.67; N, 4.06; Cl, 20.55; Br, 23.16. Found: C, 38.29; H, 4.67; N, 4.05; Cl, 20.57; Br, 23.09.

2-Acetamido-2-[2-(4-bromo-2-chlorophenyl)ethyl]-propane-1,3-diol Diacetate (10**)** Compound **16** (7.12 g, 20 mmol) was dissolved in pyridine (40 mL). Acetic anhydride (20 mL) was added to the solution at 0°C . After stirring at room temperature for 2.5 h, water (150 mL) was added to the reaction mixture at 0°C . The mixture was extracted with EtOAc (150 mL, 3×50 mL), and the combined organic layers were washed successively with water, 0.5 N HCl, saturated NaHCO_3 , and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was precipitated from EtOH–water (1 : 2) to give a solid. Recrystallization from hexane–EtOAc (40 : 1) gave **10** (8.23 g, 92%) as a white solid.

mp $97\text{--}99^\circ\text{C}$ MS (ESI) m/z : 434 $[\text{M} + \text{H}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 2.00 (3H, s), 2.10 (6H, s), 2.14 (2H, dt, $J=8.7$, 4.6 Hz), 2.69 (2H, dt, $J=8.7$, 4.6 Hz), 4.36 (4H, s), 5.73 (1H, brs), 7.10 (1H, d, $J=8.2$ Hz), 7.32 (1H, dd, $J=8.2$, 2.0 Hz), 7.50 (1H, d, $J=2.0$ Hz). *Anal.* Calcd for $\text{C}_{17}\text{H}_{21}\text{BrClNO}_5$: C, 46.97; H, 4.87; N, 3.22; Cl, 8.16; Br, 18.38. Found: C, 47.22; H, 4.84; N, 3.25; Cl, 8.08; Br, 18.20.

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