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ORIGINAL PAPER

# A convenient synthesis of the immunosuppressive agent FTY720

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**Abstract** This paper describes a practical synthetic approach to preparation of an immunosuppressant, FTY720. The key steps involve an iron-catalyzed cross-coupling reaction and a Wittig reaction. The advantages of this synthesis include readily available starting materials, inexpensive reagents, simple operations and good yields.

**Keywords** FTY720 · Immunosuppressant · Synthesis · Iron-catalyzed · Wittig reaction

## Introduction

FTY720 (**1**), a synthetic analogue of sphingosine ISP-1 (myriocin) currently in phase III clinical trials [1, 2], has had favorable immunosuppressive properties in numerous investigations (Scheme 1).

It contains a hydrophilic head group (2-aminopropane-1,3-diol) and a lipophilic hydrocarbon chain. Thus, synthesis of FTY720 involves, mainly, the construction of the two moieties. So far, a variety of methods of preparation of FTY720 have been reported [3–9]. The hydrophilic head group (2-aminopropane-1,3-diol) of FTY720 has commonly been prepared from diethyl acetamidomalonate [3–5], nitrodiol [6], benzylamine [7] or tris(hydroxymethyl)aminomethane (TRIS) [8, 9]. The hydrocarbon chain has traditionally been constructed via Friedel–Crafts acylation and subsequent Wolff–Kishner reduction [3]. Recently, Fürstner et al. [10, 11] developed a convenient synthesis of alkylbenzene derivatives by iron-catalyzed cross-coupling. Subsequently, this methodology was applied to formal synthesis of FTY720 [4], but suffered from the need for expensive reagents. Although each of these reported methods has its own merits, each has such disadvantages as long steps, low yield, expensive reagents/starting materials, or inconvenient operations. Thus, it is necessary to integrate the merits of the known methods to develop a more convenient synthesis of FTY720.

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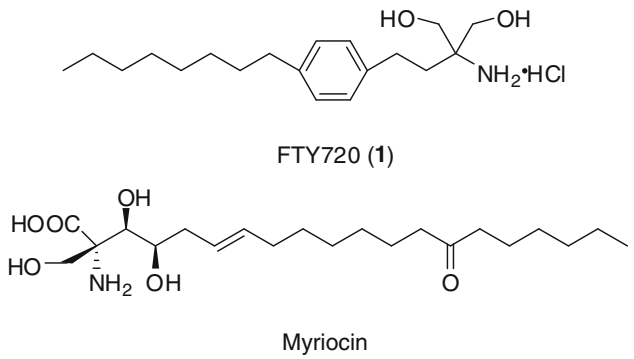
## Results and discussion

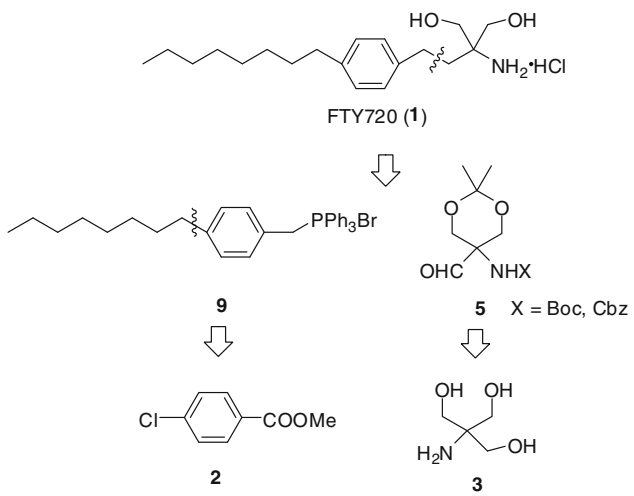
Retrosynthetic analysis shown in Scheme 2 indicates that FTY720 could be constructed from tris(hydroxymethyl)aminomethane (**3**) and methyl 4-chlorobenzoate (**2**) via an iron-catalyzed cross-coupling reaction and a Wittig reaction. The advantages of this synthesis include inexpensive starting materials, short reaction steps, simple work-up, and good yields.

The synthetic route to FTY720 is shown in Scheme 3. First, the hydrophilic head group and the lipophilic hydrocarbon chain were synthesized separately. Coupling of methyl 4-chlorobenzoate (**2**) with octylmagnesium bromide in the presence of catalytic amounts of $Fe(acac)_3$ proceeded smoothly to give compound **6** in 93% yield. Reduction of compound **6** with $KBH_4$/LiCl gave alcohol **7**, which was treated with $PBr_3$ to afford bromide **8** in good yield. Reaction of **8** with $PPh_3$ provided the Wittig salt **9** in excellent yield.

The aldehyde moieties **5a** and **5b** can be obtained from tris(hydroxymethyl)aminomethane (TRIS, **3**) as the starting substrate. N-Boc-protected aldehyde **5a** was prepared in two steps by the reported method [12]. N-Cbz-protected aldehyde **5b** was synthesized form the corresponding alcohol **4a** which could be accessed by a known procedure [13] by using a Swern oxidation reaction.




**Scheme 1**




**Scheme 2**

Then, heating of Wittig salt **9** with aldehydes **5a** and **5b** in the presence of $K_2CO_3$ furnished the desired alkenes **10a** (83% yield) and **10b** (78% yield), respectively, in an *E*/*Z* mixture. Compound **10a** can be converted to FTY720 by use of a reported method [8]. Simple hydrogenation removed the Cbz group and reduced the double bond of compound **10b** in one step to give compound **11**. Removal of the acetonide groups afforded FTY720 in a yield of 81%.

In conclusion, a convenient strategy for synthesis of FTY720 (**1**) was developed from readily available starting materials in seven steps with 48% overall yield. This approach provides an easy strategy for preparation of FTY720 and its analogues.

## Experimental

$^1$H NMR spectra were recorded on a Bruker DRX-500 (500 MHz). $^{13}$C NMR spectra were obtained on a JNM-EX400 (100 MHz). Mass spectra were determined on a Finnigan MAT-95 mass spectrometer. All reagents were used directly as obtained commercially, unless otherwise noted.

*5-(Cbz-amino)-2,2-dimethyl-1,3-dioxane-5-carbaldehyde* (**5**, $C_{15}H_{19}NO_5$)

To a cooled (−60 °C) solution of 5 cm$^3$ DMSO in 20 cm$^3$ $CH_2Cl_2$ was added a solution of 4.5 cm$^3$ $(COCl)_2$ in 20 cm$^3$ $CH_2Cl_2$, and the mixture was stirred for 15 min. A solution of 7.0 g **4** (24 mmol) in 20 cm$^3$ $CH_2Cl_2$ was then added dropwise, and stirring was continued for 30 min. Then 30 cm$^3$ triethylamine was added slowly. After stirring for 15 min, the mixture was left to reach room temperature and quenched with 15 cm$^3$ aqueous HCl (1 M). The organic layer was washed with brine, dried with $Na_2SO_4$ and concentrated under vacuum to give crude **5**. Crystallization from petroleum ether–ethyl acetate 8:1 gave pure **5** as a light yellow solid (5.2 g, 77% yield). M.p.: 80–82 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 1.46$ (s, 3H), 1.48 (s, 3H), 4.01–4.09 (m, 4H), 5.13 (s, 2H), 5.78 (s, 1H), 7.34–7.38 (m, 5H), 9.69 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 27.0$, 39.5, 60.2, 62.5, 67.4, 98.8, 128.2, 128.4, 128.6, 135.7, 155.9, 199.1 ppm; MS (EI): $m/z = 293$.

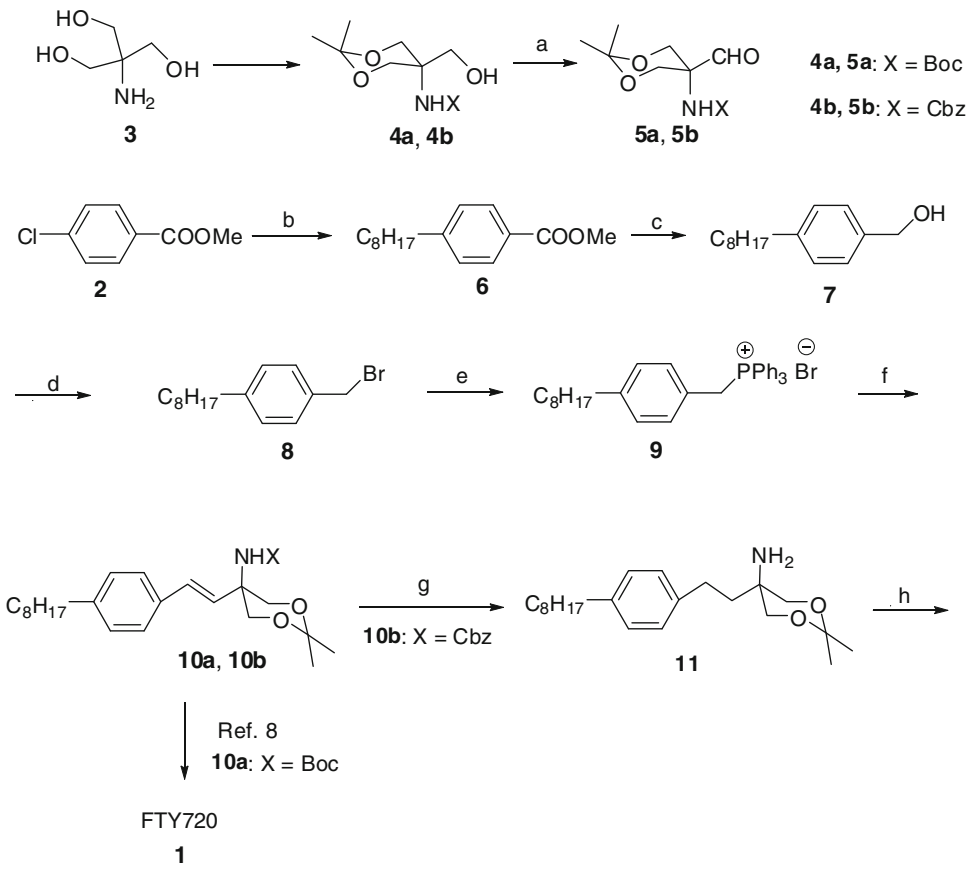
*4-Octylbenzoic acid methyl ester* (**6**)

A mixture of 17.0 g **2** (0.1 mol) and 1.8 g $Fe(acac)_3$ (5 mmol) in 35 cm$^3$ NMP and 250 cm$^3$ anhydrous THF was cooled to −5 °C. To the mixture was added a solution of 150 cm$^3$ octylmagnesium bromide (1 M in anhydrous THF), over a period of 30 min, under nitrogen atmosphere. After the solution had been stirred for 15 min, the reaction was quenched with 20 cm$^3$ aqueous HCl (1 M). THF was evaporated under vacuum and the mixture was then extracted with ethyl acetate (3 × 30 cm$^3$). The organic extract was washed with brine, dried over $Na_2SO_4$ and evaporated to give crude **6** as a yellow oil (23.1 g, 93%), which could be used in the next step without purification. A small sample of **6** was purified by column chromatography on silica gel eluted with petroleum ether ($R_f = 0.4$) and characterized. $^1$H NMR and $^{13}$C NMR spectra were identical with those reported in the literature [14].

*4-Octylbenzyl alcohol* (**7**)

A mixture of 24.8 g **6** (0.1 mol), 6.5 g $KBH_4$ (0.12 mol), and 5.0 g LiCl (0.12 mol) in 100 cm$^3$ THF was heated under reflux for 8 h, then cooled to room temperature and quenched with 80 cm$^3$ saturated $NH_4Cl$ solution. After stirring for 2 h, THF was evaporated and the mixture was extracted with ethyl acetate (3 × 30 cm$^3$). The organic phase was washed with brine, dried with $Na_2SO_4$ and concentrated to give crude **7** as a colorless viscous oil (19.8 g, 90% yield). A small sample of **7** was purified by column chromatography on silica gel eluted with

**Scheme 3**




Reagents and conditions: (a) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, 77%; (b) $C_8H_{17}MgBr$ (in THF), $Fe(acac)_3$, THF-NMP, 93%; (c) $KBH_4$, LiCl, THF, reflux, 90%; (d) $PBr_3$, $CH_2Cl_2$, 96%; (e) $PPh_3$, toluene, 97%; (f) compound **5a** or **5b**, $K_2CO_3$, THF-DMF (3:1), reflux, (g) $H_2$, Pd/C (10 wt%), MeOH, r.t., 76% ( two steps); (h) aq. HCl (1 M), MeOH, 50 °C, 81%.

petroleum ether–ethyl acetate 20:1 ($R_f = 0.3$) and characterized. $^1$H NMR and $^{13}$C NMR spectra were identical with those reported in the literature [15].

*1-Bromomethyl-4-octylbenzene* (**8**)

To a solution of 30.8 g compound **7** (0.14 mol) in 65 cm$^3$ $CH_2Cl_2$ at −10 °C was added 5.3 cm$^3$ $PBr_3$ (0.056 mol) dropwise over a period of 20 min. The mixture was then stirred for 4 h at room temperature and poured into 80 cm$^3$ ice water. The solution was extracted with $CH_2Cl_2$ (3 × 20 cm$^3$), washed with brine, dried over $Na_2SO_4$ and concentrated to give crude **8** as a faint yellow viscous oil (38 g, 96%). A small sample of **8** was purified by column chromatography on silica gel with petroleum ether ($R_f = 0.8$) and characterized. $^1$H NMR and $^{13}$C NMR spectra were identical with those reported in the literature [16].

*4-Octylbenzyl triphenylphosphonium bromide* (**9**, $C_{33}H_{38}BrP$)

A mixture of 19.0 g **8** (67 mmol) and 17.5 g $PPh_3$ (67 mmol) in 100 cm$^3$ toluene was heated under reflux under a nitrogen atmosphere for 6 h. The reaction mixture was then cooled. The precipitated white solid was collected, washed with 30 cm$^3$ toluene and dried to give pure **9** as white solid (35.4 g, 97%). M.p.: 162–163 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7$ Hz, 3H), 1.26–1.31 (m, 10H), 1.50–1.54 (m, 2H), 2.50 (t, $J = 7$ Hz, 2H), 5.33 (d, $J = 14$ Hz, 2H), 6.93 (d, $J = 8$ Hz, 2H), 6.98 (d, $J = 6$ Hz, 2H), 7.61–7.64 (m, 6H), 7.70–7.77 (m, 9H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 22.6, 29.1, 29.2, 29.3, 30.3, 31.2, 31.8, 35.4, 128.8, 130.0, 130.1, 131.2, 131.3, 134.2, 134.3, 134.9 ppm.

*2,2-Dimethyl-5-[2-(4-octylphenyl)ethyl]-1,3-dioxan-5-amine* (**11**, $C_{22}H_{39}NO_2$)

A suspension of 1.5 g aldehyde **5b** (5.6 mmol), 3.1 g Wittig salt **9** (5.6 mmol), and 2.0 g $K_2CO_3$ (14 mmol) in a mixture of 30 cm$^3$ THF and 10 cm$^3$ DMF was heated under reflux for 20 h. After completion of the reaction, THF was evaporated and the reaction mixture was quenched with water and then extracted with ethyl acetate (3 × 10 cm$^3$). The combined organic layers were washed with brine, dried with $Na_2SO_4$, and concentrated to give a

residue, which was purified by silica gel flash chromatography with ether–ethyl acetate 8:1 ($R_f = 0.4$) to give alkene **10b** in *E*/*Z* mixture. To a solution of the mixture in 20 $cm^3$ methanol was added 0.2 g 10% Pd/C. The reaction mixture was hydrogenated for 3 h at room temperature. The mixture was then filtered. The filtrate was concentrated to give compound **11** as a colorless oil (1.4 g, 76% from **9**). $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 7$ Hz, 3H), 1.24–1.28 (m, 10H), 1.40 (s, 3H), 1.42 (s, 3H), 1.55–1.62 (m, 4H), 2.41 (s, 2H), 2.54 (t, $J = 8$ Hz, 2H), 2.60–2.63 (m, 2H), 3.47 (d, $J = 11$ Hz, 2H), 3.77 (d, $J = 12$ Hz, 2H), 7.01–7.14 (m, 4H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 22.6, 27.3, 28.2, 29.2, 29.3, 29.4, 29.6, 31.5, 31.8, 35.5, 37.5, 48.7, 65.9, 69.9, 98.2, 128.0, 128.4, 138.9, 140.5 ppm; HRMS-FAB: *m/z* calcd. for $C_{22}H_{39}NO_2$ $[M]^+$ 347.2824, found 347.2825.

*2-Amino-2-[2-(4-octylphenyl)ethyl]-1,3-propandiol, hydrochloride* (FTY720, **1**)

A solution of 0.7 g **11** (2.1 mmol) in 2 $cm^3$ methanol and 2.5 $cm^3$ aqueous HCl (1 M) was heated at 50 °C for 3 h. The solvent was then evaporated to dryness to give crude compound **1**, which was crystallized from $CH_2Cl_2$–MeOH (15:1) to give pure FTY720 (0.5 g, 81%). M.p.: 103–105 °C ([8] 105 °C).

Free base of **1**: M.p.: 122–124 °C ([8] 121–124 °C).

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## References

1. Praditpornsilpa K, Avihigsanon Y (2004) Transplant Proc 36:1228
2. Huwiler A, Pfeilschifter J (2008) Biochem Pharmacol 75:1893
3. Kinchi M, Adachi K, Kohara T, Minoguchi M, Hanano T, Aoki Y, Mishina T, Arita M, Nakao N, Ohtsuki M, Hoshino Y, Teshima K, Chiba K, Sasaki S, Fujita T (2000) J Med Chem 43:2946
4. Seidu G, Laurich D, Fürstner A (2004) J Org Chem 69:3950
5. Adachi K, Kohara T, Nakao N, Arita M, Chiba K, Mishina T, Sasaki S, Fujita T (1995) Bioorg Med Chem Lett 5:853
6. Kalita B, Barua NC, Bezbarua MS, Bez G (2001) Synlett 1411
7. Sugiyama S, Arai S, Kiriyama M, Ishii K (2005) Chem Pharm Bull 53:100
8. Kim S, Lee H, Lee M, Lee T (2006) Synthesis 753
9. Balasubramaniam S, Annamalai S, Aidhen IS (2007) Synlett 2841
10. Fürstner A, Leitner A, Mendez M, Krause H (2002) J Am Chem Soc 124:13856
11. Fürstner A, Leitner A (2002) Angew Chem Int Ed 41:609
12. Ooi H, Ishibashi N, Iwabuchi Y, Ishihara J, Hatakeyama S (2004) J Org Chem 69:7765
13. Wathier M, Polidori A, Ruiz K, Fabiano AS, Pucci B (2001) New J Chem 25:1588
14. Foss FW Jr, Mathews TP, Kharel Y, Kennedy PC, Snyder AH, Davis MD, Lynch KR, Macdonald TL (2009) Bioorg Med Chem 17:6123
15. Everson DA, Shrestha S, Weix DJ (2010) J Am Chem Soc 132:920
16. Gill GS, Grobelny DW (2010) S1p Receptors Modulators and their use thereof. Patent WO2010043000, Apr 22, 2010