A Convenient Synthesis of Immunosuppressive Agent FTY720 Using the Petasis Reaction

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A convenient synthesis of immunosuppressive agent FTY720 (1) using the Petasis reaction was developed. 4-Octylbenzaldehyde (9) was converted into 1-ethenyl-4-octylbenzene (11) by two-step synthesis. Hydroboration of 11 using catecholborane and hydrolysis gave (*E*)-2-(4-octylphenyl)vinylboronic acid (4). The Petasis reaction of 4, dihydroxyacetone (3), and benzylamine following catalytic hydrogenation afforded FTY720 (1).

Key words FTY720; immunosuppressive agent; Petasis reaction; boronic acid

A potent immunosuppressant ISP-I (myriocin, themozymocidin) was isolated from the culture broth of *Isaria sinclairii* (ATCC24400), and this compound was structurally simplified to give FTY720 (**1**),[1—4] which also possesses considerable immunosuppressive activity and is now being examined in clinical studies.[5,6] FTY720 (**1**) is gaining wide interest in the transplantation field owing to its efficacy against autoimmune diseases, and graft and transplant rejection without the deterrent side effects, such as generalized immunosuppression, typically seen with the widely utilized drug cyclosporine.[5] FTY720 (**1**), which is an analog of sphingosine, is phosphorylated by sphingopsine kinase to give FTY720-P like sphingosine-1-phosphate (S1P),[5,6] and FTY720-P is a potent agonist at S1P receptors.[5,6] The biological effects of FTY720 on lymphocyte trafficking and the growing evidence that these effects are mediated by the interaction of FTY720-P with S1P receptors place S1P-mediated migration under the spotlight of therapeutics.[5]

Due to the potent biological activity and simple structure of FTY720 (**1**), the development of efficient routes to it has been the subject of synthetic interest. Some synthetic routes to **1** have been reported in 6.4% to 24% overall yield, including the alkylation of diethyl 2-acetamidomalonate with 2-(4-octylphenyl)ethyl iodide[1,4,7] or 2-bromo-1-(4-octylphenyl)-1-ethanone[8] in the presence of bases and the bis-formylation of 1-nitro-2-(4-octylphenyl)ethane by treatment with an aqueous formaldehyde solution in the presence of Amberlyst A-21 resin.[9]

On the other hand, Petasis reported a Mannich-type coupling reaction of vinyl- and arylboronic acids, amines and α-hydroxyalkyl carbonyl compounds to afford aminoalcohols.[10—12] It was envisaged that this methodology would allow an efficient synthesis of FTY720 (**1**) *via* the synthetic elaboration of the 2-amino-1,3-propanediol **2** derived from the Petasis reaction of (*E*)-2-(4-octylphenyl)ethenylboronic acid (**4**), dihydroxyacetone (**3**) and benzylamine (Chart 1).

For the primal study, we examined the reactivity of dihydroxyacetone (**3**) and hydroxyacetone (**5**) for the Petasis reaction using (*E*)-2-phenylvinylboronic acid (**6**) and benzylamine in ethanol at room temperature (Chart 2). This reaction system gave (*E*)-2-benzylamino-2-styrylpropane-1,3-diol (**7**) in 40%. A similar reaction using hydroxyacetone (**5**) did not proceed, and we could not obtain aminoalcohol **8**. The Petasis reaction has been applied for α-hydroxyalkanals, glyoxylic acid, and pyruvic acid as carbonyl components.[10—12] We also showed here that dihydroxyacetone (**3**)[10] was also a good carbonyl component for the Petasis reaction to afford 2-substituted 1,3-propanediol derivatives.

On the basis of the result using **6** (Chart 2) we synthesized FTY720 (**1**) *via* the Petasis reaction using (*E*)-2-(4-octylphenyl)vinylboronic acid (**4**) (Chart 3). Following the literature protocol,[13,14] 4-octylbenzaldehyde (**9**) was treated with triphenylphosphine and carbon tetrabromide in dichloromethane to give 1,1-dibromostyrene **10**. The reaction of *n*-butyl lithium with **10** in THF gave 1-ethenyl-4-octylbenzene (**11**).[13] The hydroboration[15,16] of **11** using cathecolborane in THF following hydrolysis[15] gave 2-(4-octylphenyl)-vinylboronic acid (**4**). The Petasis reaction using dihydroxyacetone (**3**), benzylamine and boronic acid **4** gave the desired 2-amino-1,3-propanediol **2**, and the subsequent catalytic hydrogenolysis of **2** gave FTY720 (**1**).

In conclusion, we realized that dihydroxyacetone (**3**) was a good carbonyl component for the Petasis reaction. Two hydroxyl groups of dihydroxyacetone (**3**) appear to play an important role in the Petasis reaction. FTY720 (**1**) was synthesized by a five-step synthesis from 4-octylbenzaldehyde (**9**) in 28% overall yield. The key step was the Petasis reac-

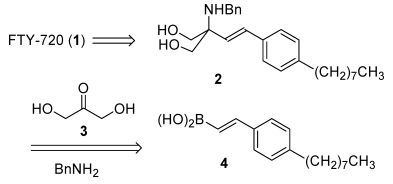

Chart 1

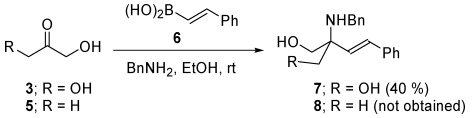

Chart 2

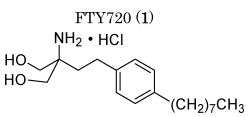

Fig. 1. FTY720 (**1**)

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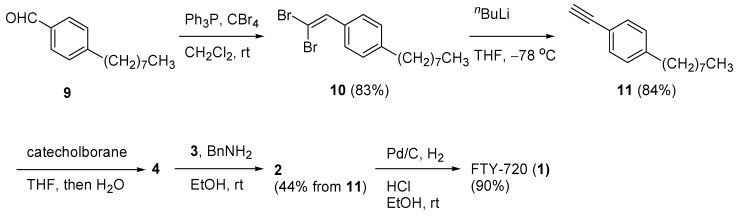

Chart 3

tion using dihydroxyacetone (**3**), benzylamine and 2-(*p*-octylphenyl)vinylboronic acid (**4**).

Experimental

General All commercially available starting materials were used without further purification. 4-Octylbenzaldehyde was purchased from Acros. Melting points were measured with Yanaco MP-3 apparatus and are uncorrected. IR spectra were recorded on a Hitachi 215 spectrophotometer. NMR spectra were obtained with JEOL JNM-GSX400 (^{1}H-NMR: 400 MHz and ^{13}C-NMR: 100 MHz) and JEOL JMS-DX302 (^{1}H-NMR: 300 MHz) spectrometers using tetramethylsilane as an internal standard. MS and high-resolution MS (HR-MS) were taken on a JEOL JMS-DX302 spectrometer. Column chromatography was performed with Merck silica gel 60 (230—400 mesh). Analytical TLC was performed on plates pre-coated with 0.25 mm layer of silica gel 60 F_{254} (Merck).

(*E*)-2-Benzylamino-2-styrylpropane-1,3-diol (7) A mixture of (*E*)-2-phenylvinylboronic acid (**6**, 100 mg, 0.68 mmol), dihydroxyacetone (**3**, dimer, 61.5 mg, 0.68 mmol as the monomer) and benzylamine (72.9 mg, 0.68 mmol) in ethanol (7.0 ml) was stirred for 24 h at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was diluted with saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. The extracts were combined, dried with magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/ethyl acetate, 7 : 3) to give **7** (77.9 mg, 40%). This product was recrystallized from *tert*-butyl methyl ether to afford colorless solid, which was used for the spectral analysis. Colorless solid, mp 118—119 °C (^{t}BuOMe). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.25—7.40 (10H, m, Ar), 6.55 (1H, d, J=16.6 Hz, PhC<u>H</u>=CH), 6.14 (1H, d, J=16.6 Hz, PhCH=C<u>H</u>), 3.76 (4H, s, $CH_2O\times2$), 3.74 (2H, s, Ph<u>C</u>H$_2$). ^{13}C-NMR ($CDCl_3$) δ: 140.3 (C), 136.3 (C), 131.4 (CH), 129.2 (CH), 128.5 (CH×2), 128.4 (CH×2), 128.1 (CH×2), 127.8 (CH), 127.0 (CH), 126.2 (CH×2), 65.7 ($HOCH_2\times2$), 61.5 (NC), 46.6 (Ph<u>C</u>H$_2$). IR (KBr) cm^{-1}: 3470, 3300, 3520, 1450, 1065, 975, 750, 705. FAB-MS (glycerol), *m/z*: 284 (M+1). *Anal.* Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.21; H, 7.58; N, 4.75.

1-(2,2-Dibromovinyl)-4-octylbenzene (10) Triphenylphosphine (2.41 g, 9.19 mmol) was added to a stirring solution of carbon tetrabromide (1.53 g, 4.61 mmol) in dichloromethane (11.5 ml) under argon at 0 °C. After 15 min, 4-octylbenzaldehyde (1.00 g, 4.58 mmol) was added rapidly. The mixture was stirred for 1 h at 0 °C, and the reaction mixture was slowly poured into stirring hexane (180 ml). The supernatant liquid was decanted, and the solvent was removed by using rotary evaporator. The triphenylphosphine oxide was removed by filtration and washed with additional hexane. The solvent was removed from the filtrate, and the residue was chromatographed on silica gel (hexane/ethyl acetate, 95 : 5) to give **10** (1.42 g, 83%). Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.45 (2H, d, J=8.8 Hz, Ar), 7.44 (1H, s, CH=C), 7.17 (2H, d, J=8.1 Hz, Ar), 2.58 (2H, t, J=7.8 Hz, ArC<u>H</u>$_2$), 1.60 (2H, m, ArCH$_2$C<u>H</u>$_2$), 1.27 (10H, m, $CH_2\times5$), 0.88 (3H, t J=6.6 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 143.5 (C), 136.6 (<u>C</u>H=C), 132.5 (C), 128.3 (CH×2), 128.2 (CH×2), 35.9 (CH_2), 32.0 (CH_2), 31.3 (CH_2), 29.6 (CH_2), 29.43 (CH_2), 29.36 (CH_2), 22.8 (CH_2), 14.3 (CH_3). IR (film) cm^{-1}: 2930, 1620, 1470. EI-MS *m/z*: 372.0086 (Calcd for $C_{16}H_{22}Br_2$: 372.0089) MS *m/z*: 376 (M+4, 48%), 374 (M+2, 100%), 372 (M$^+$, 50%).

1-Ethynyl-4-octylbenzene (11) *n*-Butyl lithium (1.58 mol/l in hexane, 1.54 ml, 2.42 mmol) was added dropwise to a solution of 1-(2,2-dibromovinyl)-4-octylbenzene (**10**, 412 mg, 1.10 mmol) in THF (5.5 ml) at −78 °C. The resulting mixture was stirred for 1 h at −78 °C and then for 2 h at room temperature. A mixture of saturated aqueous ammonium chloride/water (4 : 1) was added to the reaction mixture, and the mixture was stirred for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with dichloromethane and washed with water. The aqueous layer was extracted with dichloromethane. The extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane) to afford **11** (198 mg, 84%). Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39 (2H, d, J=8.1 Hz, Ar), 7.12 (2H, d, J=8.1 Hz, Ar), 3.02 (1H, s, HC≡C), 2.59 (2H, t-like m, ArC<u>H</u>$_2$), 1.59 (2H, m, ArCH$_2$C<u>H</u>$_2$), 1.29 (10H, m, $CH_2\times5$), 0.88 (3H, t-like m, Me). ^{13}C-NMR ($CDCl_3$) δ: 143.8 (C), 131.9 (CH×2), 128.3 (CH×2), 119.1 (C), 83.9 (<u>C</u>≡C), 76.4 (C≡<u>C</u>), 36.0 (CH_2), 32.0 (CH_2), 31.3 (CH_2), 29.6 (CH_2), 29.4 ($CH_2\times2$), 22.8 (CH_2), 14.2 (Me). IR (film) cm^{-1}: 2930, 2860, 1515, 1465, 845, 830. EI-MS *m/z*: 214.1718 (Calcd for $C_{16}H_{22}$: 214.1723) MS *m/z*: 214 (M$^+$, 68%), 115 (100). *Anal.* Calcd for $C_{16}H_{22}$: C, 89.66; H, 10.35. Found: C, 89.33; H, 10.54.

(*E*)-2-Benzylamino-2-[2-(4-octylphenyl)ethenyl]propane-1,3-diol (2) Cathecolborane (1 mol/l in THF, 4.33 ml, 4.33 mmol) was added one-shot to a solution of 1-ethynyl-4-octylbenzene (**11**, 195 mg, 0.90 mmol) at room temperature under argon. The mixture was stirred for 4 h at 80 °C. After being cooled to room temperature the reaction mixture was diluted with dichloromethane, and the aqueous layer was extracted three times with dichloromethane. The extracts were combined, dried with magnesium, filtered and concentrated *in vacuo* to give a crude (*E*)-2-(4-octylphenyl)vinylboronic acid (**4**). Characteristic signals of ^{1}H-NMR spectrum (300 MHz, $CDCl_3$) δ: 7.75 (1H, d, J=18.5 Hz, CH=C), 6.42 (1H, d, J=18.5 Hz, C=CH).

A mixture of the crude **4**, dihydroxyacetone (**3**, dimmer, 90.1 mg, 0.50 mmol) and benzylamine (98.5 mg, 0.91 mmol) in ethanol (9.1 ml) was stirred for 1.5 d at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was diluted with saturated aqueous sodium bicarbonate and extracted three times with chloroform. The extracts were combined, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (chloroform/methanol, 97 : 3) to give a mixture of **2** and cathecol. The mixture was purifed with partition with diethyl ether/5% aqueous sodium hydroxide to give **2** (157 mg, 44%). Brown powder, mp 75—78 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.19—7.33 (7H, m, Ar), 7.13 (2H, d, J=7.8 Hz, Ar), 6.50 (1H, d, J=16.8 Hz, C=C<u>H</u>), 6.07 (1H, d, J=16.6 Hz, <u>H</u>C=C), 3.71 (6H, d-like m, J=10.5 Hz, $HOCH_2\times2$ and NCH_2Ph), 2.58 (2H, t, J=7.7 Hz, CH_2Ar), 1.57—1.59 (2H, m, CH_2), 1.26—1.29 (10H, m, $CH_2\times5$), 0.88 (3H, t, J=6.6 Hz, Me). ^{13}C-NMR ($CDCl_3$) δ: 142.8 (C, Ar), 140.3 (C, Ar), 133.7 (C, Ar), 131.3 (CH, Ar), 128.6 (CH×2, Ar), 128.4 (CH×2, Ar), 128.1 (CH×2, Ar), 128.0 (CH, Ar), 127.0 (CH, Ar), 126.1 (CH×2, Ar), 65.8 (CH_2), 61.3 (HNC), 46.6 (CH_2), 35.8 (CH_2), 32.0 (CH_2), 31.5 (CH_2), 29.6 (CH_2), 29.38 (CH_2), 29.36 ($CH_2\times2$), 22.8 (CH_2), 14.2 (Me). IR ($CHCl_3$) cm^{-1}: 2925, 2850, 1650, 1635, 1200. FAB-MS (glycerol) *m/z*: 396.2906 (Calcd for $C_{26}H_{38}NO_2$: 396.2902) MS *m/z*: 396 (M+1)$^+$.

2-Benzylamino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol Hydrochloride (FTY720), (1) A mixture of **2** (115 mg, 0.291 mmol) and 10% palladium carbon (115 mg) in ethanol (10 ml) with 10% aqueous hydrochloric acid (0.12 ml) was stirred for 12 h at room temperature in atmosphere of hydrogen. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford FTY720 (**1**) (90 mg, 90%). Yellow powder, mp 105—108 °C (decompose). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.91 (3H, br s), 7.10 (4H, s, Ar), 5.38 (2H, br s), 3.52 (4H, d, J=4.2 Hz, $CH_2O\times2$), 2.50—2.60 (4H, m, $CH_2\times2$), 1.75—1.81 (2H, m, CH_2), 1.53 (2H, br s, CH_2), 1.24 (10H, m, $CH_2\times5$), 0.85 (3H, t, J=6.3 Hz, Me); (400 MHz, CD_3OD) δ: 7.14 (2H, d, J=8.0 Hz, Ar), 7.08 (2H, d, J=8.0 Hz, Ar), 4.86 (4H, s, $CH_2O\times2$), 2.61—2.65 (2H, m, ArCH$_2$), 2.55 (2H, t, J=7.6 Hz, CCH$_2$), 1.92—1.97 (2H, br s, CH_2), 1.57 (2H, br s, CH_2), 1.28—1.30 (10H, m, $CH_2\times5$), 0.89 (3H, t, J=6.8 Hz, Me). ^{13}C-NMR (DMSO-d_6) δ: 139.4 (C, Ar), 138.5 (C, Ar), 127.9 (CH×2, Ar), 127.7 (CH×2, Ar), 60.9 ($CH_2O\times2$), 60.1 (NC), 34.7 (CH_2), 33.2 (CH_2), 31.2 (CH_2), 31.0 (CH_2), 28.8 (CH_2), 28.6 ($CH_2\times2$), 27.9 (CH_2), 22.0 (CH_2), 13.9 (Me); (CD_3OD) δ: 141.6 (C, Ar), 139.3 (C, Ar), 129.3 (CH×2, Ar), 128.9 (CH×2, Ar), 62.5

(CH_2O, ×2), 62.0 (C), 36.5 (CH_2), 34.7 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 23.7 (CH_2), 14.5 (Me). FAB-MS (glycerol) *m*/*z*: 308.2604 (Calcd for $C_{19}H_{35}ClNO_2$–HCl: 308.2591) MS *m*/*z*: 308 $(M+1-HCl)^+$.

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References

1) Kiuchi 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., *J. Med. Chem.*, **43**, 2946—2961 (2000).
2) Fujita T., Matsumoto N., Uchida S., Kohno T., Shimizu T., Hirose R., Yanada K., Kurio W., Watabe K., *Bioorg. Med. Chem. Lett.*, **10**, 337—339 (2000).
3) Kiuchi M., Adachi K., Kohara T., Teshima K., Masubuchi Y., Mishina T., Fujita T., *Bioorg. Med. Chem. Lett.*, **8**, 101—106 (1998).
4) Adachi K., Kohara T., Nakao N., Arita M., Chiba K., Mishina T., Sasaki S., Fujita T., *Bioorg. Med. Chem. Lett.*, **5**, 853—856 (1995).
5) Taha T. A., Argraves K. M., Obeid L. M., *Biochim. Biophys. Acta*, **1682**, 48—55 (2004).
6) Praditpornsilpa K., Avihingsanon Y., *Transplant. Proc.*, **36**, 1228—1231 (2004).
7) Seidel G., Laurich D., Fürstner A., *J. Org. Chem.*, **69**, 3950—3952 (2004).
8) Durand P., Peralba P., Sierra F., Renaut P., *Synthesis*, **2000**, 505—506 (2000).
9) Kalita B., Barua N. C., Bezbarua M., Bez G., *Synlett*, **2001**, 1411—1414 (2001).
10) Petasis N. A., "Method for the Synthesis of Amines and Amino Acids with Organoboran Derivatives." PCT/US97/11161, June 27, 1997.
11) Petasis N. A., Zavialov I. A., *J. Am. Chem. Soc.*, **120**, 11798—11799 (1998).
12) Petasis N. A., Zavialov I. A., *J. Am. Chem. Soc.*, **119**, 445—446 (1997).
13) Barton J. B., Groh B. L., *J. Org. Chem.*, **50**, 158—166 (1985).
14) Desai N. B., McKelvie N., *J. Am. Chem. Soc.*, **84**, 1745—1747 (1962).
15) Brown H. C., Gupta S. K., *J. Am. Chem. Soc.*, **97**, 5249—5255 (1975).
16) Brown H. C., Gupta S. K., *J. Am. Chem. Soc.*, **94**, 4370—4371 (1972).