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Stereochemistry–activity relationship of orally active tetralin S1P agonist prodrugs

Bin Ma [a,*], Kevin M. Guckian [a], Edward Yin-Shiang Lin [a], Wen-Cherng Lee [a], Daniel Scott [a], Gnanasambandam Kumaravel [a], Timothy L. Macdonald [b], Kevin R. Lynch [c], Cheryl Black [a], Sowmya Chollate [a], Kyungmin Hahm [a], Gregg Hetu [a], Ping Jin [a], Yi Luo [a], Ellen Rohde [a], Anthony Rossomando [a], Robert Scannevin [a], Joy Wang [a], Chunhua Yang [a]

[a] BiogenIdec Inc., 14 Cambridge Center, Cambridge, MA 02142, USA
[b] Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, VA 22904-4319, USA
[c] Department of Biochemistry and Molecular Genetics, and Department of Pharmacology, University of Virginia, McCormick Road, Charlottesville, VA 22904-4319, USA

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ABSTRACT

Modifying FTY720, an immunosuppressant modulator, led to a new series of well phosphorylated tetralin analogs as potent S1P1 receptor agonists. The stereochemistry effect of tetralin ring was probed, and (−)-(*R*)-2-amino-2-((*S*)-6-octyl-1,2,3,4-tetrahydronaphthalen-2-yl)propan-1-ol was identified as a good SphK2 substrate and potent S1P1 agonist with good oral bioavailability.

Multiple sclerosis (MS) is a chronic de-myelinating autoimmune disease that progressively worsens over time, affecting the nerves in the brain, spinal cord, and other parts of the central nervous system.[1] MS affects two to three times as many women as men with over 400,000 people in the United States having MS and as many as 2,500,000 people affected worldwide.

Among many oral MS therapeutics under development, FTY720 (**1**, fingolimod) is interesting as it is the first in a new class of disease-modifying treatments called sphingosine 1-phosphate receptor (S1P-R) modulators and has a novel mode of action.[2] FTY720 is a synthetic analog of myriocin, an antifungal antibiotic isolated from entomopathogenic fungus *Isaria sinclairii*.[3–5] Both myriocin and FTY720 are sphingosine analogs that modulate immune responses in animals studies. Initial results from the two-year Phase III FREEDOMS study show that oral FTY720 was superior to placebo in reducing both relapses and disability progression in patients with relapsing–remitting MS (RRMS), and some adverse effects including bradycardia, skin cancer, liver injury, infections, and increased blood pressure were observed during the clinic trials.[6–9]

FTY720 is a prodrug that is phosphorylated in vivo by sphingosine kinase 2 (SphK2) to monophosphate FTY720-P (**2**)[10] which is an agonist of 4 of the 5 S1P receptors (S1P1, 3, 4, 5) but not S1P2.[11,12] Interaction of FTY720-P with S1P1 causes lymphopenia by sequestering lymphocytes in secondary lymphoid organs. Depletion of lymphocytes from the periphery is thought to be the primary mechanism of action for FTY720.[13] S1P3 activation of FTY720-P is thought to be connected with the adverse effects, such as bradycardia and bronchoconstriction in rodents.[14,15]

Here we report our effort to further define the molecular pharmacology of the S1P receptor family and SphK2 enzyme. By restricting the two rotatable bonds between the phenyl ring and the aminodiol head portion of FTY720 (**1**) with an sp^3 hybridized backbone, a conformational restricted tetralin analog **3** (Fig. 1) was identified, which evokes a profound, long lasting lymphopenia.[16] However, compound **3** was a mixture of two stereoisomers, and a clear understanding of biological activity of each isomer was necessary. In addition, it is reported that FTY720 is phosphorylated stereo specifically by SphK2 to produce the (*S*)-phosphate **2**.[10] This interesting observation prompted us to design the des-OH analog **5**. This report presents the synthesis of the two isomers of **3**, all four isomers of **5**, and the effect of stereochemistry on their in vitro and in vivo activities.

* Corresponding author. Tel.: +1 617 914 4955; fax +1 617 679 3635.
E-mail address: bin.ma@biogenidec.com (B. Ma).

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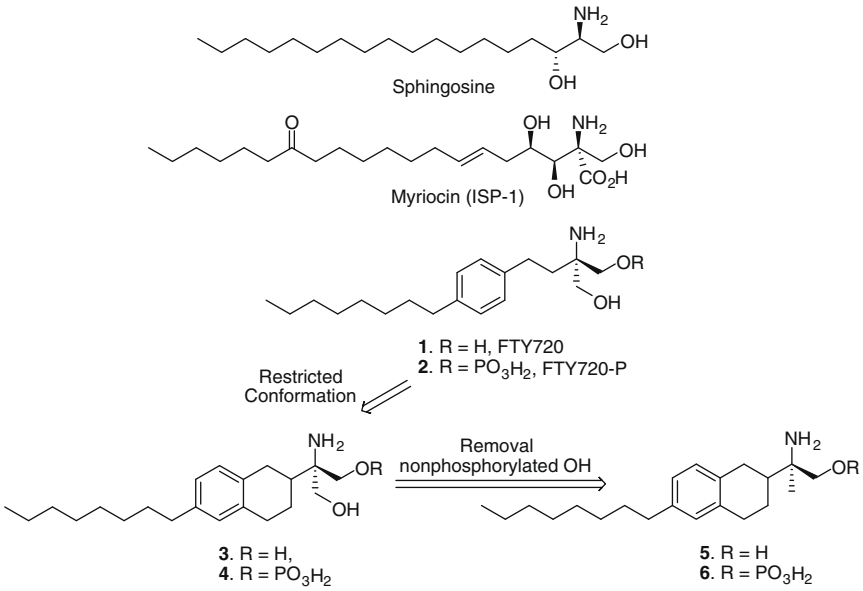


Figure 1. Further optimization strategy.

To obtain all isomers of **3** and **5**, a convergent route was designed to use a common intermediate **11** (Scheme 1). Starting from commercially available 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**7**), demethylation under HBr gave free phenol **8**. The phenol was converted to triflate **9** under mild condition. The C8 tail was installed by Suzuki coupling of **9** with *n*-octyl-BBN to yield **10**. Selective bromination of **10** with $CuBr_2$ in EtOAc/$CHCl_3$ yielded intermediate **11** smoothly.

The diol analog **3** was synthesized as follows (Scheme 2). Displacement of bromide **11** with sodium acetylamino diethylmalonate, followed by reduction gave diester **12**. Chiral separation of **12** with ChiralPAK AZ gave (*R*)-**13** and its enantiomer (*S*) -**13**. LAH reduction followed by hydrolysis yielded pure (+)-(2′*R*)-**3** and (−)-(2′*S*)-**3**. Crystallization of (2′*S*)-**3**·**HBr** in aqueous methanol yielded a single-crystal, and its X-ray diffraction established the structure unambiguously (Fig. 2).[17]

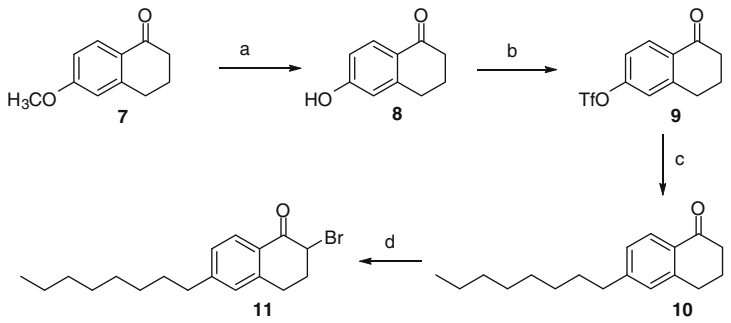
The methyl analog **5** was synthesized as illustrated in Scheme 3. Starting from bromide **11**, displacement of bromide with sodium methyl diethylmalonate gave ketone **14**. Reduction of the arylketone in the presence of the diester was achieved under $TiCl_4/Et_3SiH$/DCM condition[16] to yield **15** with moderate yield. Other conditions, including hydrogenation (H_2/Pd/C with AcOH/MeOH, HCl/EtOH or H_2SO_4/EtOAc), Zn reduction (with HCl or AcOH), and Et_3SiH reduction (with $BF_3{\cdot}Et_2O$ or TFA), failed to give acceptable yield of **15**, due to either lack of reactivity of the ketone or formation of lactone intermediates. Monohydrolysis of diester **15** under KOH/EtOH yielded acid **16**. A very mild Curtius reaction[18] was applied to acid **16** to yield free aminoester **17** directly in one pot.

Although **5** could be obtained by direct reduction of aminoester **17**, the 4 compounds mixture of **5** couldn't be separated in our hands, the acid **16** also proved to be problematic. To our delight, a two stages chiral separation can separate all four isomers of **17**. Separation with chiral AD-H gave (2*R*,2′*R*)-**17**, (2*R*,2′*S*)-**17** and a mixture of the other two isomers which was further separated with chiral AY to give (2*S*,2′*R*)-**17** and (2*S*,2′*S*)-**17**. (Scheme 4). LAH reduction of pure isomers of **17** yielded (+)-(2*R*,2′*R*)-**5**, (−)-(2*R*,2′*S*)-**5**, (+)-(2*S*,2′*R*)-**5** and (−)-(2*S*,2′*S*)-**5**, respectively.[20]

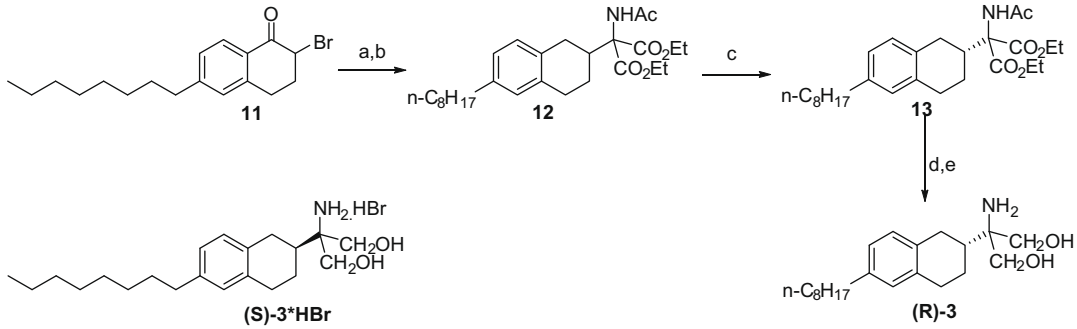
The phosphate of the diol analog **3** was synthesized as illustrated in Scheme 5. The amine (2′*R*)-**3** was protected with Cbz to afford diol **18**, which upon phosphorylation under $Ag_2O/[(BnO)_2PO]_2O$ gave the oxazoline **19**. Chiral separation of **19** with ChiralPAK AZ gave **20** and its diastereoisomer. Hydrogenation followed by hydrolysis yielded both isomers of (2′*R*)-**3**-**P**.

The phosphate **6** was synthesized as exemplified in Scheme 6. Boc protection of amine **5** followed by phosphorylation and hydrogenation gave Boc-protected phosphoronic acid **24**, and acid work-up gave phosphate **6**.

The diol **3** and methyl analog **5** show distinct activity when measuring phosphorylation in vitro on SphK2 (mouse and human) (Table 1). FTY720 is well phosphorylated into (*S*)-FTY720-P (**2**). In



Scheme 1. Synthetic scheme for preparation of **11**. Reagents and conditions: (a) 48% HBr, 120 °C, 7.5 h. 93%; (b) Tf_2O, DMAP, 2,6-lutidine, CH_2Cl_2, −30 °C to 0 °C, 2 h. 96%; (c) (i) 9-BBN, 1-octene, THF; (ii) **9**, KBr, $Pd(PPh_3)_4$, K_3PO_4, H_2O, THF, reflux, 3 h. 80%; (d) $CuBr_2$, EtOAc, $CHCl_3$, reflux, 2 h. 87%.



Scheme 2. Synthetic scheme for preparation of **3**. Reagents and conditions: (a) $AcNHCH(CO_2Et)_2$, NaH, DMF, 0 °C to rt, overnight, 78%; (b) $TiCl_4$, Et_3SiH, CH_2Cl_2, 0 °C to rt, overnight, 73%; (c) ChiralPAK AZ, hexane/*i*-PrOH, 92%, 99% ee; (d) LAH, THF, 0 °C to rt, 2 h, 59%; (e) LiOH, MeOH/THF/Water, reflux, 5 h, 59%.

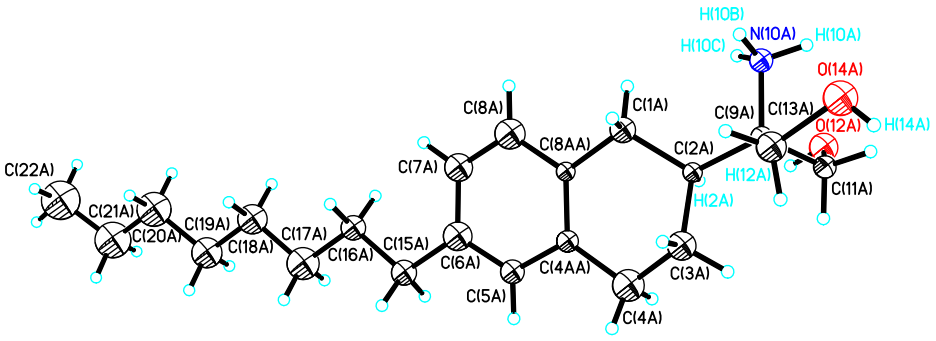
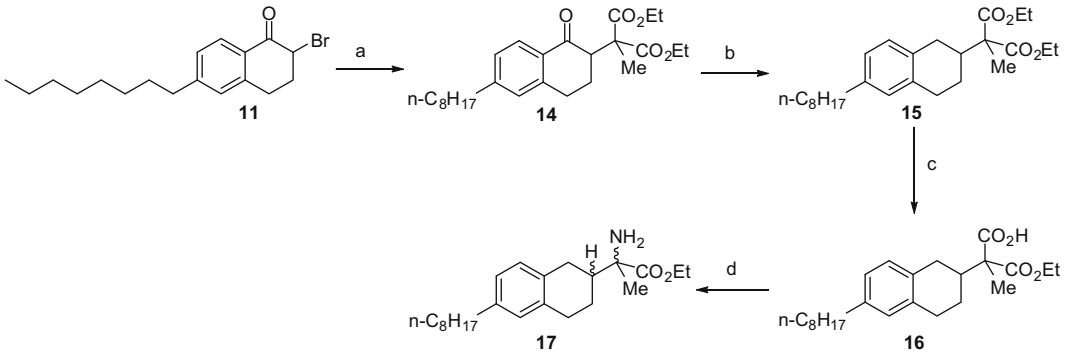


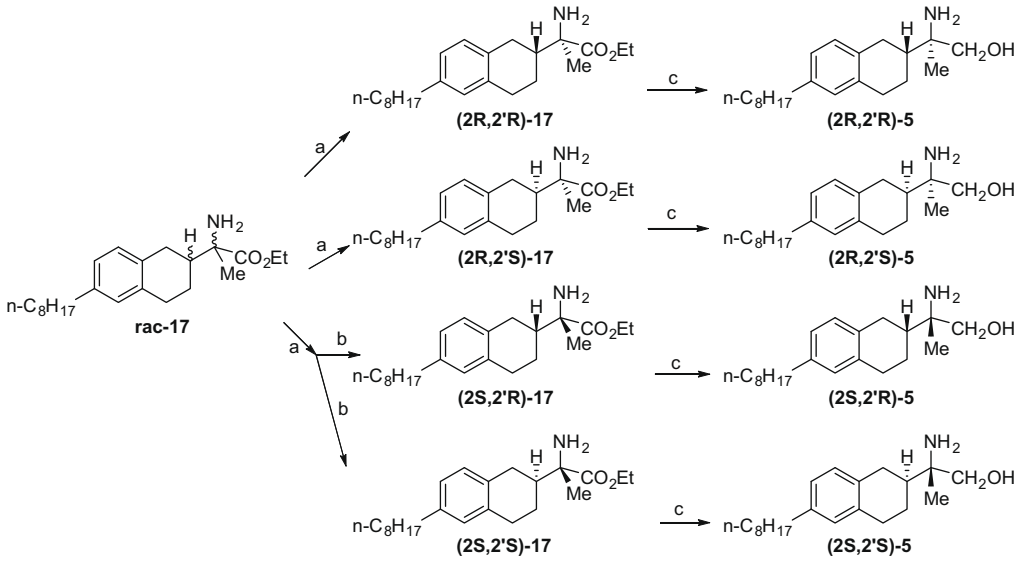
Figure 2. X-Ray crystal structure of (2′S)-**3**·**HBr** salt.



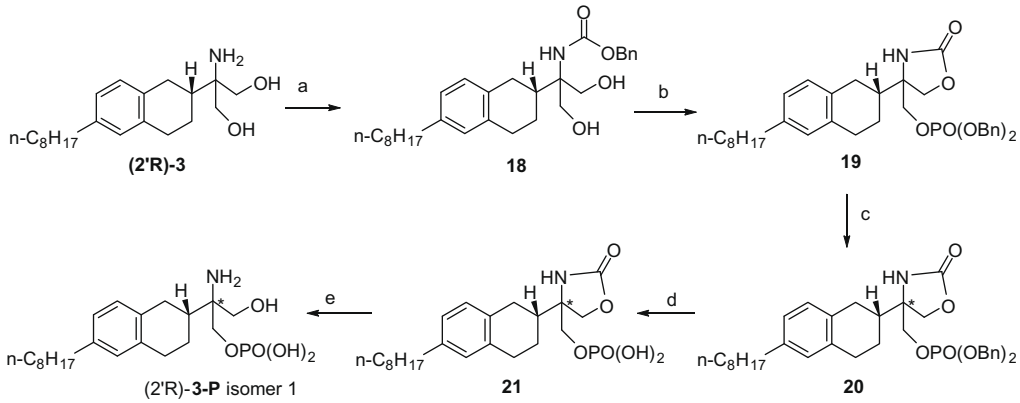
Scheme 3. Synthetic scheme for preparation of **17**. Reagents and conditions: (a) $MeCH(CO_2Et)_2$, NaH, DMF, 0 °C to rt, overnight. 83%; (b) $TiCl_4$, Et_3SiH, CH_2Cl_2, 0 °C to rt. 57%; (c) KOH, EtOH, 60 °C, overnight, 70%; (d) (i) DPPA, Et_3N, PhMe, reflux, 2 h; (ii) NaOTMS, THF, 0 °C to rt, overnight. 71%.

contrast, both diols (2′*R*)-**3** and (2′*S*)-**3** are poor SphK2 (human) substrates with <10% phosphorylation (9% and 3%, respectively). Phosphorylation of the methyl analogs, however, is much better with (2*R*,2′*S*)-**5** showing approximately equal phosphorylation (77% in human and 90% in mouse) to that seen with FTY720. It is interesting to note that (2*R*,2′R)-**5**, the exact methyl analog of better phosphorylated diol (2′*R*)-**3**, shows only moderate 38% phosphorylation by the human kinase. Both (2*S*,2′*R*)-**5** and (2*S*,2′*S*)-**5** are not substrates for SphK2, this implies that the R configuration of the aminoalcohol head portion is critical for in vivo phosphorylation to convert prodrug (2*R*,2′*S*)-**5** into its phosphate (2*R*,2′*S*)-**6**.

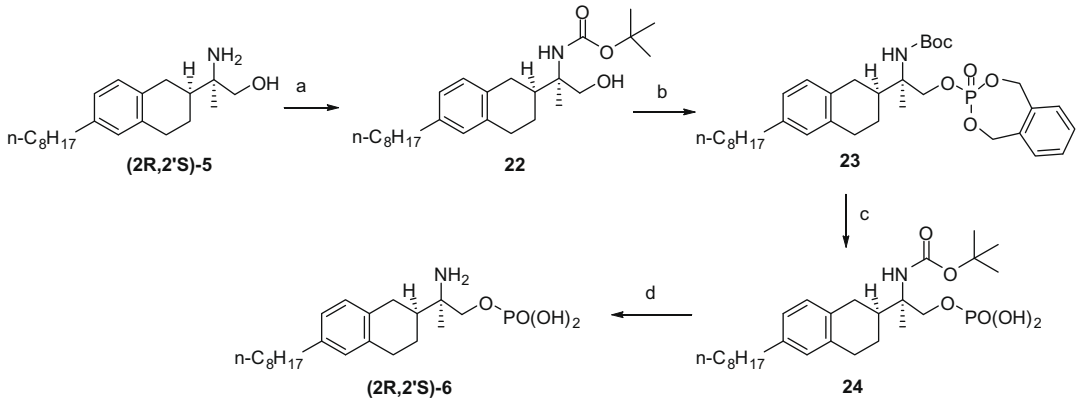
The phosphates were also studied in whole cell assay to determine their effect on S1P receptors. It's known that S1P1 couples to Gi solely and S1P3 couples to Gi and Gq, therefore, both Gi and Gq dependent cellular assays were used to determine agonist/antagonist activity of **3-P** and **6** at the human S1P1 or S1P3 receptors (Tables 2 and 3). In the Gi assay, (2′*R*)-**3-P** isomer **1** is similar to (*S*)-**FTY720-P**, and is sixfold less potent at S1P1 (EC_{50} = 0.077 nM) and twofold less potent at S1P3 (EC_{50} = 0.215 nM). Interestingly, its diastereoisomer (2′*R*)-**3-P** isomer **2** is quite active on S1P1 (EC_{50} = 0.344 nM), while (*R*)-**FTY720-P** is less active (EC_{50} = 23.25 nM). Both (*R*)-**FTY720-P** and (2′*R*)-**3-P** isomer **2** are not active on S1P3. It should be noted that only (*S*)-**FTY720-P** is made in vivo from FTY720. For the methyl analogs at S1P1, compound (2*R*,2′*S*)-**6** and (*S*)-**FTY720-P** have approximately equal EC_{50}s (0.018 nM vs 0.012 nM, respectively). (2*R*,2′*R*)-**6** is also similar to (*S*)-**FTY720-P** but less potent. Both (2*S*,2′*S*)-**6** and (2*S*, 2′*R*)-**6** were significantly less active at S1P1 and showed no activity at S1P3. The corresponding aminoalcohols of these two are not substrates for the kinase SphK2. This observation is consistent with FTY720 phosphates. It is interesting that those in vivo disfavored phosphates, (*R*)-**FTY720-P**, (2*S*,2′*S*)-**6** and (2*S*,2′*R*)-**6** show great S1P1/S1P3 selectivity. Clearly, stereochemistry can influence S1P1 and S1P3 activity significantly.



Scheme 4. Synthetic scheme for preparation of **5**. Reagents and conditions: (a) CHIRALPAK AD-H, ACN/MeOH, 93–98%, 97.6–98% ee; (b) CHIRALPAK AY, hexane/*i*-PrOH, 79–88%, 96.4–99% ee; (c) $LiAlH_4$, THF, reflux, 3 h, 41–85%.



Scheme 5. Synthetic scheme for preparation of (2′*R*)-**3**-**P**. Reagents and conditions: (a) Cbz-Cl, $KHCO_3$, EtOAc, H_2O, rt, 1.5 h, 92%; (b) $[(BnO)_2PO]_2O$, Ag_2O, hex_4NI, CH_2Cl_2, rt, 3d, 44%; (c) ChiralPAK AZ, ACN/MeOH, 42%, >99.9% de; (d) H_2, Pd-C, MeOH, rt, 2 h, 91%; (e) LiOH, EtOH/Water, reflux, overnight, 49%.



Scheme 6. Synthetic scheme for preparation of **6**. Reagents and conditions: (a) Boc_2O, $CHCl_3$, aq $NaHCO_3$, rt, overnight, 86%; (b) (i) *N*,*N*-diethyl-1,5-dihydrobenzo[e][1,3,2]dioxaphosphepin-3-amine, tetrazole, THF, rt, overnight; (ii) HOOH, rt, 1 h, 74%; (c) Pd-C, H_2, MeOH, rt, 1 h. 59%; (d) HOAc, HCl, rt, 6 h. 86%.

For the Gq dependent cellular assay, the trend was similar. (*S*)-**FTY720**-**P** and the (2*R*) methyl compounds (2*R*,2′*S*)-**6**, (2*R*,2′*R*)-**6** are very active, while their enantiomers (*R*)-**FTY720**-**P**, (2*S*,2′*S*)-**6** are not active. Similarly, the diol phosphate (2′*R*)-**3**-**P** isomer 1 (EC_{50} = 1.95 nM), is as active as (*S*)-**FTY720**-**P** (EC_{50} = 2.02 nM), and its diastereomer (2′*R*)-**3**-**P** isomer **2** (EC_{50} = 133 nM) is also active but less so. None of the compounds are active on S1P2 and all are active on S1P3, S1P4, and S1P5. Compared to

Table 1
Lymphopenia and phosphorylation of **3** and **5**[a]

Compounds	Mouse lymphopenia ED_{50}, mg/kg	Mouse PK phosphorylation %	Phosphorylation (mSphK2) %	Phosphorylation (hSphK2) %
FTY720	0.03	—	87	76
(2′*R*)-**3**	0.2	3	4	9
(2′S)-**3**	3.8	—	—	3
(2*R*,2′*S*)-**5**	0.1	63	90	77
(2*R*,2′*R*)-**5**	0.8	—	—	38
(2*S*,2′*R*)-**5**	>5	—	—	0
(2*S*,2′*S*)-**5**	>5	—	—	0

[a] Assay performed as described in the Ref. 19.

Table 2
hS1P1 and S1P3 receptors activation on calcium mobilization Gi assay[a]

EC_{50} (nM)	S1P1	S1P3
S1P	0.027	0.449
(*S*)-**FTY720-P**	0.012	0.134
(*R*)-**FTY720-P**	23.25	>5000
(2′*R*)-**3-P** isomer 1	0.077	0.215
(2′*R*)-**3-P** isomer 2	0.344	>5000
(2*R*,2′*S*)-**6**	0.018	0.286
(2*R*,2′*R*)-**6**	0.088	0.150
(2*S*,2′*R*)-**6**	19.72	>5000
(2*S*,2′*S*)-**6**	13.65	>5000

[a] Assay performed as described in the Ref. 19.

Table 3
hS1P1–S1P5 receptors activation on calcium mobilization Gq assay[a]

EC_{50} (nM)	S1P1	S1P2	S1P3	S1P4	S1P5
(*S*)-FTY720-P	2.02	>5000	27.84	22.16	0.36
(*R*)-**FTY720-P**	>5000	>5000	16.06	136.70	1988.00
(2′*R*)-**3-P** isomer 1	1.95	>5000	18.75	5.39	0.33
(2′*R*)-**3-P** isomer 2	133.00	>5000	25.72	41.45	32.96
(2*R*,2′*S*)-**6**	1.79	>5000	97.44	15.98	1.49
(2*R*,2′*R*)-**6**	5.62	—	38.17	—	—
(2*S*,2′*S*)-**6**	>5000	—	922.10	—	—

[a] Assay performed as described in the Ref. 19.

FTY720, moderate selectivity of S1P1 over S1P3 was observed for (2*R*,2′*S*)-**6**.

These compounds were investigated further in vivo by measuring their ability to induce mouse lymphopenia (Table 1). Both (2′*R*)-**3** and (2′*S*)-**3** induce lymphopenia, the superior activity of (2′*R*)-**3** (ED_{50} = 0.2 mg/kg) over (2′*S*)-**3** (ED_{50} = 3.8 mg/kg) implies (2′*R*) configuration is favored in the diol context. Interestingly, (2*S*,2′*R*)-**5** and (2*S*,2′*S*)-**5** are not active, while (2*R*, 2′*S*)-**5** is very active (ED_{50} = 0.1 mg/kg), and (2*R*,2′*R*)-**5** is less active (ED_{50} = 0.8 mg/kg). The favored (2′*S*) configuration in the methyl series is opposite to the diols, the reason for this is not well understood. Clearly, *R* configuration in the aminoalcohol head portion is necessary for the lymphopenia activity, which is consistent with the observation of FTY720 analogs AAL-R and AAL-S.[11]

Both (2′*R*)-**3** and (2*R*,2′*S*)-**5** was measured in mouse PK/PD studies at 10 × ED_{50} for both compounds. 2 mg/kg dose of (2′*R*)-**3** evokes 72 h sustained lymphopenia, with oral bioavailability of 55% and half life $t_{½}$ = 16 h. Only 3% conversion of (2′*R*)-**3** to its phosphate was observed in this study which is consistent with the low in vitro phosphorylation (4% in mouse in vitro assay, Table 1). The low conversion to phosphate for compound (2′*R*)-**3** and low ED_{50} (0.2 mg/kg) is unexpected, and we do not understand this disconnection. In contrast, 1 mg/kg dose of (2*R*,2′*S*)-**5** evokes one-week sustained lymphopenia, with oral bioavailability *F* = 55%, V_{max} = 16 L/Kg, Ci = 5.5 ml/min/kg, half life $t_{½}$ = 36 h, and 63% phosphorylation. Clearly, (2*R*,2′*S*)-**5** is very efficacious with very good oral bioavailability and good phosphorylation.

In summary, a potent, well phosphorylated, orally bioavailable tetralin analog of FTY720 was identified. Stereochemistry on the tetralin ring can significantly influence the phosphorylation and lymphopenia activity, as well as receptor activity. The S1P1 over S1P3 selectivity of this tetralin series was further improved and will be described at a later date.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.02.006.

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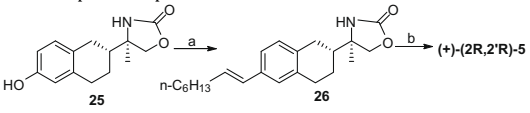
20. Absolute configuration of (+)-(2*R*,2′*R*)-**5** was established by a new synthesis listed in the following scheme from an intermediate (+)-(*R*)-4-((*R*)-6-hydroxy-1,2,3,4-tetrahydronaphthal-en-2-yl)-4-methyloxazolidin-2-one (**25**), whose structure was confirmed by X-ray crystal structure of a brominated derivative (unpublished results). The other isomers were assigned by careful comparison of spectroscopic data.



Conditions: (a) Tf_2O, py, CH_2Cl_2, rt; Pd(dppf)Cl_2, $tBuNH_2$, i-PrOH, H_2O, n-$C_6H_{13}CH{=}CHBF_3K$, 100 °C; (b). Pd/C, H_2, EtOH, rt; LiOH, EtOH, H_2O, reflux. **26**: ^1H NMR (400 MHz,$CDCl_3$) δ 7.12 (d, *J* = 7.8 Hz, 1H), 7.06 (s, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.32 (d, *J* = 15.8 Hz, 1H), 6.18 (dd, *J* = 6.7, 15.8 Hz, 1H), 4.34

(d, J = 8.6 Hz, 1H), 4.09 (d, J = 8.6 Hz, 1H), 2.96–2.71 (m, 3H), 2.62–2.51 (m, 1H), 2.19 (q, J = 6.8 Hz, 2H), 2.00–1.84 (m, 2H), 1.52–1.43 (m, 2H), 1.41 (s, 3H), 1.31 (br s., 7 H), 0.93–0.85 (m, 3H). ^{13}H NMR (100 MHz, $CDCl_3$) δ 158.8, 135.89, 135.87, 133.40, 130.7, 129.37, 129.28, 126.2, 123.6, 74.4, 60.0, 43.5, 33.0, 31.7, 30.0, 29.5, 29.4, 28.9, 24.1, 23.4, 22.6, 14.1. LC–MS: m/z = 342.20 ([M+1], 100%).