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Chiral Vinylphosphonate and Phosphonate Analogues of the Immunosuppressive Agent FTY720

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Abstract

(*S*)-**4**, (*S*)-**5**: X = NH₂, Y = CH₂OH Both have anti-apoptotic activity; (*S*)-**5** is not a S1P₁ agonist

(*R*)-**4**, (*R*)-**5**: X = CH₂OH, Y = NH₂ Both lack anti-apoptotic activity but are S1P₁ agonists

The first enantioselective synthesis of chiral isosteric phosphonate analogues of FTY720 is described. One of these analogues, FTY720-(*E*)-vinylphosphonate (*S*)-**5**, but not its *R* enantiomer, elicited a potent anti-apoptotic effect in intestinal epithelial cells, suggesting that it exerts its action via the enantioselective activation of a receptor. (*S*)-**5** failed to activate the sphingosine 1-phosphate type 1 (S1P₁) receptor.

FTY720 (2-amino-[2-(4-*n*-octylphenyl)ethyl]-1,3-propanediol, FingolimodTM, **1**, Chart 1) is a synthetic analogue of the chiral sphingolipid myriocin (**2**).¹ As an analogue of sphingosine, FTY720 is phosphorylated *in vivo* by sphingosine kinases, affording (*S*)-FTY720-phosphate (**3**), which activates four of the five known sphingosine 1-phosphate (S1P, **2a**) G protein-coupled receptors.²

Internalization and subsequent polyubiquitination of the S1P receptors leads to their proteasomal degradation and renders the cells unresponsive to S1P; therefore, lymphocytes are not capable of recirculation to peripheral inflammatory tissues.³ Thus, FTY720 has therapeutic potential, and in fact is the first S1P receptor modulator that has entered the stage of a phase-III clinical study.⁴

Several syntheses of **1**⁵ and of phosphate **3** have been accomplished.⁶ In contrast to phosphates such as **3**, phosphonate analogues are resistant to the action of lipid phosphate phosphatases and may offer improved cellular stability. A racemic mixture of the nonhydrolyzable phosphonate analogue of FTY720 (**4**) was reported in which the C-O-P bond is replaced with

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Supporting Information Available: Experimental details for the synthesis of compounds **6–8**, **10**, **11**, **12**, **16**, and **4**, and NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org/>

a C-C-P bond;^{2b} *rac*-**4** was found to be a high-affinity agonist of the S1P-type 1 receptor (S1P₁), with a similar potency as (*S*)-**3**.⁷ We report here the first asymmetric syntheses of the chiral phosphonate analogues of FTY720, (*R*)-**4** and (*S*)-**4**. Oxazoline intermediate (*S*)-**14** (Scheme 1), prepared by a modification of our previous route,^{6c} was further elaborated to give the corresponding (*E*)-vinylphosphonate analogue (*S*)-**5**. We have included a preliminary pharmacological characterization of the effects of these analogues on the non-transformed rat intestinal epithelial cell line IEC-6. This study revealed that (*S*)-**5**, but not its (*R*) enantiomer, exerts a potent anti-apoptotic effect in a camptothecin (CPT)-induced apoptosis model.⁸ Unlike phosphate (*S*)-**3**, (*S*)-**5** did not activate the S1P₁ receptor of the Endothelial Differentiation Gene (EDG) family of G protein-coupled receptors, making it a novel enantioselective probe activating a cytoprotective mechanism against apoptosis induced by DNA damage.

Wittig reaction of 4-bromobenzaldehyde with the ylide of *n*-heptyltriphenylphosphonium bromide gave arylalkene **6** as an *E,Z* (1:3) mixture (Scheme 1). Sonogashira coupling between **6** and 4-(phenylmethoxy)-1-butyne delivered enyne **7** as a 1:3 *E:Z* mixture in 92% yield. Alcohol **8** was obtained on reduction of the unsaturated bonds and hydrogenolysis of the *O*-benzyl group in the presence of Pearlman's catalyst. After Swern oxidation of **8** provided aldehyde **9**, use of a Mannich reagent, Eschenmoser's salt,⁹ afforded α -methylene aldehyde **10**. Reduction of **10** with NaBH₄ in the presence of CeCl₃ (to suppress conjugate reduction) gave allyl alcohol **11**.¹⁰ CeCl₃, which is a mild Lewis acid, is not required, since CsCl also provided **11** as the only product. Asymmetric Sharpless epoxidation¹¹ of **11** with cumene hydroperoxide (CHP) in the presence of L-(+)-DIPT, Ti(OPr-*i*)₄, and molecular sieves gave epoxide (*S*)-**12**.¹² The synthesis of (*S*)-**12** was accomplished in 7 steps from *p*-bromobenzaldehyde and in 46% overall yield. Reaction of alcohol (*S*)-**12** with trichloroacetonitrile in the presence of DBU gave 2,3-epoxy-1-trichloroacetimidate (*R*)-**13**. The tetrasubstituted carbon in oxazoline **14** was set up bearing the desired nitrogen substituent by opening of epoxide (*R*)-**13** with catalytic Et₂AlCl,¹³ affording (*S*)-**14** in 74% yield for the two steps.

Swern oxidation of oxazoline (*S*)-**14** gave oxazoline aldehyde **15** (Scheme 2), which on Horner-Wadsworth-Emmons reaction with tetramethyl methylenediphosphonate afforded ester (*S*)-**16** in 87% yield and with an *E/Z* ratio of ~10:1. Simultaneous demethylation and release of the hydroxy and amino groups by treatment with trimethylsilyl bromide (TMSBr) provided (*S*)-**5**, but the yield was low. Therefore, the hydroxy and amino groups were first released by treatment with 1 M HCl. After the amine hydrochloride was neutralized (saturated aq Na₂CO₃), amino alcohol **17** was converted to (*S*)-**5** with TMSBr followed by 95% methanol; 84% yield for the two steps. Reduction of (*S*)-**5** using Pearlman's catalyst gave (*S*)-**4**.

Asymmetric epoxidation of **11** with D-(-)-DIPT gave epoxide (*R*)-**12**, which was converted via (*R*)-**14** to (*R*)-**5** in six steps (Scheme 2). Catalytic hydrogenation of (*R*)-**5** afforded (*R*)-**4** (Scheme 3).

S1P promotes the survival of many cell types.¹⁴ Both **2a** and (*S*)-**3** protect oligodendrocyte progenitor cells from apoptotic cell death in response to growth factor withdrawal, and (*S*)-**3** was also shown to be cytoprotective in response to pro-apoptotic cytokines and microglial activation.¹⁵ The ability of **2a**, (*S*)-**3**, and phosphonate analogues **4** and **5** to protect IEC-6 cells from apoptotic cell death in response to the topoisomerase inhibitor CPT was assessed by DNA fragmentation. Pretreatment with **2a**, (*S*)-**3**, (*R*)-**4**, or (*R*)-**5** did not result in a significant reduction in DNA fragmentation in response to a 4-h treatment with 20 μ M CPT. However, we found that the cytoprotective effect was enantioselective, since pretreatment with 1 μ M of (*S*)-**4** or (*S*)-**5** showed a significant reduction (21 and 50%, respectively) in DNA fragmentation in response to CPT.

In a preliminary study of the activity of the FTY720-phosphonate analogues on S1P receptors, we performed Ca^{2+} mobilization assays with HTC4 cells that were stably transfected with S1P₁. As shown in Figure 1, the S1P₁ transfectants were activated by (S)-**3** to 76% of the maximal S1P-induced activation, and displayed a similar potency as S1P (13 ± 2 nM for S1P vs 9 ± 1 nM for (S)-**3**). (R)-**5** and (R)-**4** both showed a modest activity against S1P₁ with E_{max} values that ranged from 73 to 93% of the maximal S1P-induced responses, and EC_{50} values that were increased by ~2- to 3-fold. (S)-**4** activated S1P₁ to 36% of the maximal S1P-induced response, and the EC_{50} value was increased by ~5-fold to 75 ± 21 nM. Since (S)-**5** did not elicit a Ca^{2+} response from cells transfected with the S1P₁ receptor, we conclude that the potent cytoprotective effect of (S)-**5** is not mediated by S1P₁.

In conclusion, we have described the synthesis of the enantiomers of FTY720 phosphonate analogues **4** and **5**. (S)-**4** and (S)-**5**, but not **2a** or (S)-**3**, all at 1 μM , protected IEC-6 cells from apoptosis. The extent of CPT-induced DNA fragmentation was reduced by 50% and 21% in the presence of 1 μM of (S)-**5** and (S)-**4**, respectively. The potent cytoprotective activity of (S)-**5** is not mediated by S1P₁. Experiments are underway to characterize the cellular effects of these analogues.

Experimental Section

(2S)-2-(2'-(Trichloromethyl)-4',5'-dihydrooxazol-5-yl)-4-(4''-octylphenyl)-butan-1-ol [(S)-(+)-**14**]

To a solution of 435 mg (1.5 mmol) of epoxy alcohol (S)-**12** in 25 mL of CH_2Cl_2 at 0 °C were added Cl_3CCN (0.17 mL, 1.65 mmol) and DBU (0.023 mL, 0.15 mmol). After being stirred at 0 °C for 1.5 h, the reaction mixture was diluted with Et_2O (20 mL) and water (20 mL). The organic layer was separated, washed with brine (20 mL), dried (MgSO_4), and concentrated. The residue was purified by chromatography (hexane/ EtOAc 20:1) to give 565 mg (87%) of (R)-**13**; R_f 0.58 (EtOAc /hexane 1:3). To an ice-cold solution of 565 mg (1.31 mmol) of (R)-**13** in 20 mL of CH_2Cl_2 was added Et_2AlCl (0.75 mL, 0.75 mmol, a 1.0 M solution in hexane). After the mixture was stirred at 0 °C for 20 min and then at rt for 3 h, the reaction was quenched with saturated aq NaHCO_3 solution (20 mL). The organic layer was washed with brine (20 mL), dried (MgSO_4), and concentrated. The residue was purified by chromatography (hexane/ EtOAc 3:1) to give 480 mg (85%) of (S)-**14** as a white solid; mp 56.7–57.5 °C; R_f 0.29 (EtOAc /hexane 1:3); $[\alpha]_{25\text{D}} +24.9$ (c 1.60, CHCl_3); ^1H NMR (CDCl_3) δ 0.88 (t, 3H, $J = 6.8$ Hz), 1.26–1.38 (m, 10H), 1.58 (m, 2H), 1.84 (m, 1H), 2.01 (m, 1H), 2.57 (m, 4H), 3.30 (s, 1H), 3.55 (dd, 1H, $J = 11.6, 8.4$ Hz), 3.85 (dd, 1H, $J = 11.6, 4.8$ Hz), 4.45 (d, 1H, $J = 8.4$ Hz), 4.65 (d, 1H, $J = 8.4$ Hz), 7.08 (s, 4H); ^{13}C NMR (CDCl_3) 14.2, 22.7, 29.3, 29.4, 29.5, 29.8, 31.6, 32.0, 35.6, 37.6, 66.8, 76.0, 86.5, 128.2, 128.9, 138.2, 140.8, 163.2. HRMS (MNa^+) m/z calcd for $\text{C}_{21}\text{H}_{30}\text{Cl}_3\text{NO}_2\text{Na}$ 456.1234, found 456.1241. **Data for (R)-**14****: $[\alpha]_{25\text{D}} -25.0$ (c 2.75, CHCl_3); ^1H NMR (CDCl_3) δ 0.88 (t, 3H, $J = 6.8$ Hz), 1.26–1.38 (m, 10H), 1.58 (m, 2H), 1.85 (m, 1H), 2.01 (m, 1H), 2.14 (s, 1H), 2.60 (m, 4H), 3.54 (d, 1H, $J = 11.6$ Hz), 3.83 (d, 1H, $J = 11.6$ Hz), 4.45 (d, 1H, $J = 8.4$ Hz), 4.63 (d, 1H, $J = 8.4$ Hz), 7.09 (s, 4H); ^{13}C NMR (CDCl_3) δ 14.1, 22.7, 29.0, 29.3, 29.5, 29.7, 31.6, 31.9, 35.5, 37.5, 67.0, 75.9, 86.4, 128.1, 128.6, 138.1, 140.9, 163.3.

(3S)-3-(Amino)-3-(hydroxymethyl)-5-(4'-octylphenyl)-pent-(1E)-enyl-phosphonic acid [(S)-(+)-**5**]

To a solution of 269 mg (0.50 mmol) of (S)-**16** in 10 mL of THF at rt was added 3 mL of 1 M HCl. After the reaction mixture was stirred overnight, the solvent was evaporated and the residue was extracted with a mixture of CHCl_3 and saturated Na_2CO_3 aq solution. The organic phase was dried (MgSO_4) and concentrated. The residue was purified by chromatography ($\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ 135:25:4) to give 185 mg (90%) of (S)-**17** as a pale yellow oil after

filtration through a Teflon syringe filter; R_f 0.37 (CHCl₃/MeOH/NH₄OH 135:25:4); $[\alpha]^{25}_D$ +18.8 (c 1.52, CHCl₃); ¹H NMR (CDCl₃) δ 0.88 (t, 3H, J = 6.4 Hz), 1.26–1.29 (m, 10H), 1.58 (m, 2H), 1.48–1.86 (m, 5H), 2.49–2.58 (m, 4H), 3.50 (dd, J = 21.2, 10.6 Hz), 3.73 (s, 3H), 3.75 (s, 3H), 5.93 (dd, 1H, J = 20.0, 17.6 Hz), 6.85 (dd, 1H, J = 22.8, 17.6 Hz), 7.05–7.10 (m, 4H); ¹³C NMR (CDCl₃) δ 14.1, 22.7, 29.3, 29.36, 29.44, 29.5, 31.6, 31.9, 35.5, 39.4, 52.4 (d, J = 6.0 Hz), 59.4 (d, J = 19.1 Hz), 69.2, 115.0 (d, J = 188.1 Hz), 128.1, 128.3, 128.6, 138.6, 140.8, 157.9 (d, J = 6.0 Hz); ³¹P NMR (CDCl₃) δ 21.8. **Data for (R)-17**: $[\alpha]^{25}_D$ -17.1 (c 1.51, CHCl₃); ¹H NMR (CDCl₃) δ 0.88 (t, 3H, J = 6.4 Hz), 1.26–1.29 (m, 10H), 1.58 (m, 2H), 1.79–1.82 (m, 5H), 2.53–2.57 (m, 4H), 3.50 (dd, J = 21.2, 10.6 Hz), 3.73 (s, 3H), 3.75 (s, 3H), 5.93 (dd, 1H, J = 20.0, 17.6 Hz), 6.85 (dd, 1H, J = 22.8, 17.6 Hz), 7.07–7.10 (m, 4H); ¹³C NMR (CDCl₃) δ 14.1, 22.7, 29.3, 29.4, 29.42, 29.5, 29.7, 31.6, 31.9, 35.5, 39.4, 52.4 (d, J = 2.0 Hz), 52.5 (d, J = 2.0 Hz), 59.4 (d, J = 19.1 Hz), 69.1, 115.0 (d, J = 188.1 Hz), 128.1, 128.4, 128.5, 138.7, 140.7, 157.9 (d, J = 6.0 Hz); ³¹P NMR (CDCl₃) δ 21.8. To a solution of (S)-17 in 10 mL of dry CH₂Cl₂ at rt was added 0.66 mL (5.0 mmol) of TMSBr. After the reaction mixture was stirred for 4 h, the solvent was removed, and the residue was dried and dissolved in 2 mL of 95% MeOH with stirring for 1 h. Removal of the solvent afforded 224 mg (93%) of (S)-5 as a white solid: mp 159.2–161.1 °C; R_f 0.14 (CHCl₃/MeOH/H₂O/AcOH 65:25:4:1); $[\alpha]^{25}_D$ +12.2 (c 1.04, CHCl₃/MeOH 9:1); ¹H NMR (CDCl₃/CD₃OD 9:1) δ 0.87 (t, 3H, J = 6.8 Hz), 1.26 (br s, 10H), 1.51 (s, 2H), 1.95–2.10 (m, 2H), 2.47 (t, 2H, J = 7.6 Hz), 2.55–2.68 (m, 2H), 3.83 (br s, 2H), 4.08 (br s, 4H), 6.30 (m, 1H), 6.60 (m, 1H), 6.99 (d, 2H, J = 8.0 Hz), 7.07 (d, 2H, J = 8.0 Hz); ¹³C NMR (CDCl₃/CD₃OD 9:1) δ 14.1, 22.9, 29.1, 29.5, 29.6, 31.8, 32.3, 35.8, 36.5, 62.2 (d, J = 20.1 Hz), 64.4, 123.3, 125.2, 128.3, 128.9, 137.6, 141.4, 144.2; ³¹P NMR (CDCl₃/CD₃OD 9:1) δ 13.1. HRMS (MNa⁺) m/z calcd for C₂₀H₃₄NO₄PNa 406.2118, found 406.2106. **Data for (R)-5**: $[\alpha]^{25}_D$ -13.0 (c 1.05, CHCl₃/MeOH 9:1); ¹H NMR (CDCl₃/CD₃OD 9:1) δ 0.88 (t, 3H, J = 6.8 Hz), 1.26–1.27 (m, 10H), 1.52–1.55 (m, 2H), 2.01–2.11 (m, 2H), 2.52 (t, 2H, J = 7.6 Hz), 2.55–2.68 (m, 2H), 3.26 (br s, 4H), 3.82 (br s, 2H), 6.30 (m, 1H), 6.59 (dd, 1H, J = 23.2, 18.0 Hz), 7.03 (d, 2H, J = 8.0 Hz), 7.08 (d, 2H, J = 8.0 Hz), 8.34 (br s, 1H); ¹³C NMR (CDCl₃/CD₃OD 9:1) δ 14.2, 22.9, 29.0, 29.5, 29.6, 29.7, 29.9, 31.8, 32.3, 35.8, 36.5, 62.2 (d, J = 20.1 Hz), 64.4, 123.4, 125.2, 128.3, 128.9, 137.6, 141.4, 144.2; ³¹P NMR (CDCl₃/CD₃OD 9:1) δ 13.1.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Ca²⁺ mobilization dose-response relationships for S1P (2a), (S)-3, and FTY720 analogues 4 and 5 in HTC4 cells expressing the S1P₁ receptor.

Scheme 1.
Synthesis of (S)-**14** from 4-bromobenzaldehyde

Scheme 2.
 Synthesis of (S)-4 from (S)-14

Scheme 3. Outline of the synthesis of **(R)-5** and **(R)-4**

Chart 1.

Structures of FTY720 (1); myriocin (2); S1P (2a); and FTY720 phosphate, phosphonate, and (*E*)-vinylphosphonate analogues 3–5.