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Enantioselective synthesis of the phosphate esters of the immunosuppressive lipid FTY720

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Abstract—The enantiomers of FTY720-phosphate (**3**) were synthesized via 2-methylene-4-(4-octylphenyl)butan-1-ol (**7**), 2,3-epoxy alcohol **8**, and Δ^2-oxazoline **10**. These compounds have potential use in the treatment of autoimmune diseases and prevention of kidney transplant rejection.

The sphingolipid FTY720 (2-amino-[2-(4-*n*-octylphenyl)ethyl]-1,3-propanediol, **1**; Fig. 1) modulates the recirculation of lymphocytes between the blood and lymphoid tissues, and is currently in clinical studies to evaluate its effects on prevention of kidney transplant rejection in humans.[1] FTY720 is also efficacious against autoimmune diseases, including multiple sclerosis,[2a] rheumatoid arthritis,[2b] and type 1 diabetes.[2c] FTY720 is phosphorylated in vivo by endogenous sphingosine kinases[3] to afford (*S*)-**3**, which is a structural analogue of the lysophospholipid sphingosine 1-phosphate (S1P, **2**).[1b,4] Compound **2** interacts with G-protein coupled receptors that are involved in emigration of thymocytes and lymphocytes.[5] (*S*)-**3** binds tightly to $S1P_1$ (one of the five known G protein-coupled receptors for S1P) in thymocytes and lymphocytes, rendering the cells unresponsive to **2** and blocking lymphocyte egress from lymph nodes.[1b,6] Additional beneficial features of **1** are that sphingolipid biosynthesis is not inhibited and that host immune defense responses to most infections are not decreased by administration of **1**.[1]

To further elucidate the mechanisms of action of FTY720, the availability of (*S*)-**3** is required. In fact, a practical route to both enantiomers is desired, since (*R*)-**3** may serve as an agonist or antagonist ligand of some of the G-protein coupled receptors, such as $S1P_1$, for **2**. Previous preparations of the enantiomers of **3** were accomplished by a lipase-catalyzed asymmetric acylation of the prochiral hydroxymethyl groups,[7] by

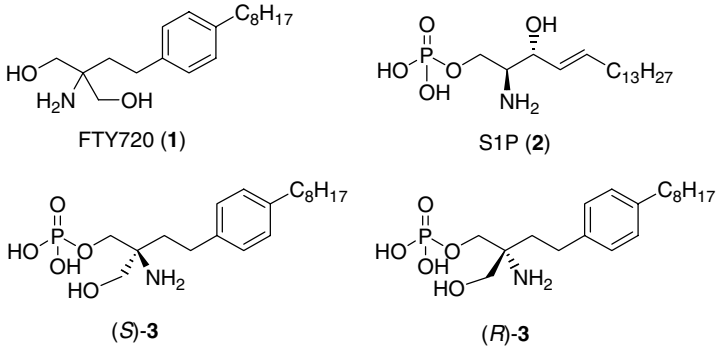

Figure 1. Structures of FTY720 (**1**), S1P (**2**), and FTY720 phosphate analogues **3**.

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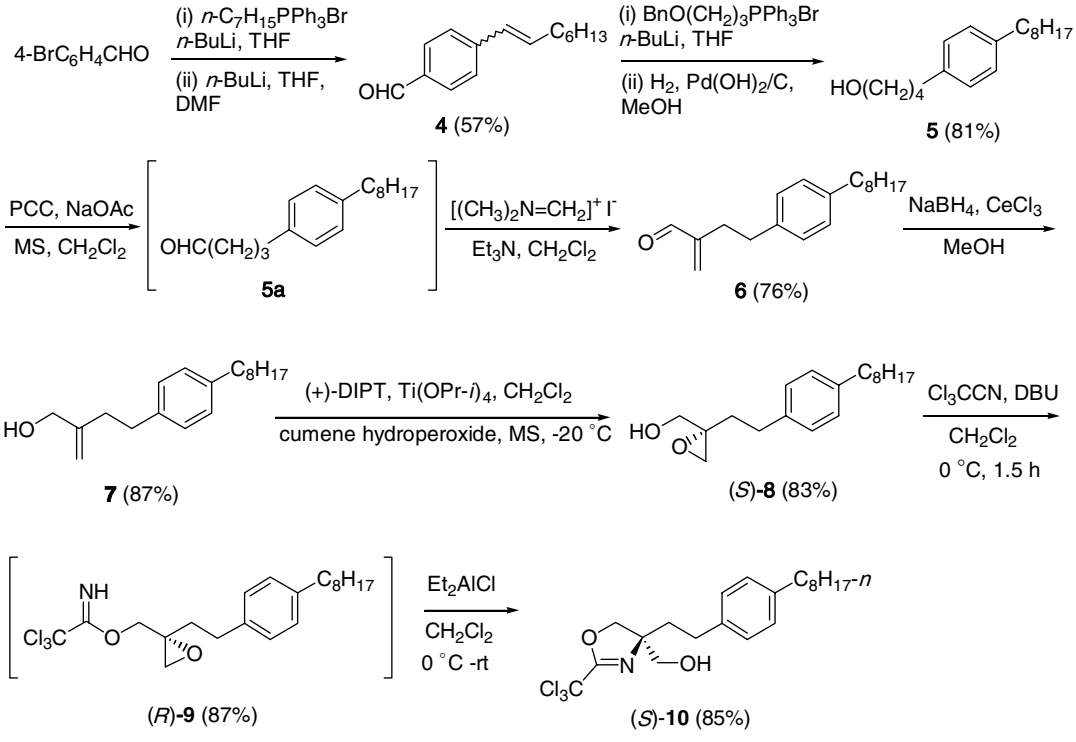
chiral HPLC separation of fully protected derivatives,[4,8] and by a lengthy synthesis starting with a L-serine-derived oxazolidine.[8] Syntheses of analogues of **3** have also been reported,[9] some of which start with the precious compound **1**.

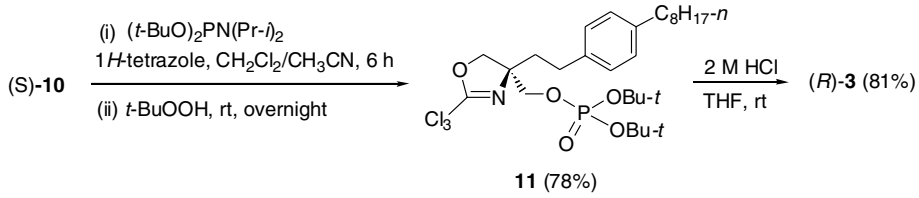
Thus, in view of the drawbacks and limitations noted above, we sought to develop an enantioselective method to prepare the enantiomers of **3**. We report here the application of asymmetric Sharpless epoxidation[10] for the preparation of 2,3-epoxy alcohol (*R*)- and (*S*)-**8**, which was converted to 2,3-epoxy-1-trichloroacetimidate **9**. After a Lewis-acid mediated cyclization furnished 2-trichloromethyloxazoline **10**, the oxazoline group was used to mask the C(1)-hydroxy and C(2)-amino groups of one of the prochiral hydroxymethyl groups of **1**, allowing the installation of the phosphate group into the unprotected hydroxymethyl group, affording (*R*)- and (*S*)-**3** in good overall yields.

As illustrated in Scheme 1, Wittig reaction of 4-bromobenzaldehyde with the ylide of *n*-heptyltriphenylphosphonium bromide, followed by lithium–halogen exchange and reaction with DMF, afforded aldehyde **4**. Another Wittig reaction with (3-(benzyloxy)propyl)triphenylphosphonium bromide, which was obtained from 1,3-propanediol in three steps,[11] followed by reduction of the double bonds and hydrogenolysis of the *O*-benzyl group in the presence of $Pd(OH)_2/C$ (Pearlman's catalyst),[12] furnished alcohol **5**. PCC oxidation of alcohol **5** provided aldehyde **5a**, which was converted to α-methylene aldehyde **6** in good yield by Mannich reaction with Eschenmoser's salt[13] in the presence of Et_3N. Reduction of aldehyde **6** with $NaBH_4$ in the presence of $CeCl_3$ (to suppress conjugate reduction) gave allylic alcohol **7**.[14] Asymmetric Sharpless epoxidation of allylic alcohol **7** with (+)-diisopropyl tartrate (DIPT, 0.5 equiv), $Ti(OPr\text{-}i)_4$ (0.5 equiv), and cumene hydroperoxide provided epoxy alcohol (*S*)-**8**, and reaction with trichloroacetonitrile in the presence of catalytic DBU gave trichloroacetimidate **9**. Treatment with 0.6 equiv of Et_2AlCl in methylene chloride resulted in intramolecular cyclization at the quaternary stereocenter with inversion to afford oxazoline (*S*)-**10** in 74% overall yield.[15] The overall yield of **10** for the seven steps from aldehyde **4** was 33%.

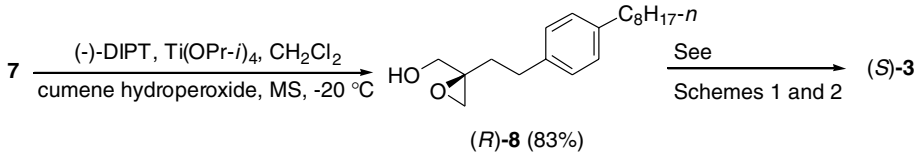
The unmasked hydroxyl group of chiral oxazoline **10** was converted to phosphate ester **11** with di-*tert*-butyl diisopropylphosphoramidite in the presence of 1*H*-tetra-



Scheme 1. Synthesis of Δ^2-oxazoline (*S*)-**10**.



Scheme 2. Conversion of (*S*)-**10** to FTY720 and (*R*)-**3**.



Scheme 3. Synthesis of (*S*)-**3**.

zole,[16] followed by oxidation of the phosphite triester with *tert*-butyl hydroperoxide (Scheme 2).[17] Finally, a one-pot reaction to hydrolyze the *tert*-butyl ester groups and release the hydroxy and amino groups provided (*R*)-**3** in 63% overall yield from **10**.[18]

The target compound (*S*)-**3** was prepared by Sharpless epoxidation of allylic alcohol **7** with (−)-DIPT, affording 2,3-epoxy alcohol (*R*)-**8** (Scheme 3). The methodology outlined above was used to convert (*R*)-**8** to (*S*)-**3** via (*R*)-**10**.[19]

In summary, a convenient method for the preparation of both enantiomers of **3** from *p*-bromobenzaldehyde has been described. Δ^2-Oxazoline **10** was obtained by intramolecular cyclization at the quaternary stereocenter of **9**, enabling the construction of (*R*)-**3** from (*S*)-**10** and (*S*)-**3** from (*R*)-**10**.

Acknowledgements

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17. Data for **11**: R_f 0.15 (EtOAc/hexane 1:3); $[\alpha]_D^{25}$ −10.8 (*c* 3.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.22–1.36 (m, 10H), 1.54–1.64 (m, 20H), 1.86–2.04 (m, 2H), 2.57 (m, 2H), 2.64 (m, 2H), 4.06 (m, 2H), 4.42 (d, 1H, $J = 8.8$ Hz), 4.72 (d, 1H, $J = 8.8$ Hz), 7.11 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 28.9, 29.3, 29.5, 29.9, 31.6, 31.9, 35.5, 37.8, 61.2, 73.9, 74.7, 82.8, 100.0, 128.2, 128.6, 138.2, 140.8, 162.5; ^{31}P NMR ($CDCl_3$) δ −9.80.
18. Data for (*R*)-**3** and (*S*)-**3**: R_f 0.30 ($CHCl_3$/MeOH/H_2O/AcOH 65:25:4:1); ^1H NMR (CD_3OD) δ 0.88 (t, 3H, $J = 6.8$ Hz), 1.22–1.36 (m, 10H), 1.54–1.64 (m, 2H), 1.86–2.04 (m, 2H), 2.52 (m, 2H), 2.68 (m, 2H), 3.60 (m, 2H), 3.90 (m, 2H), 7.07 (m, 4H); ^{31}P NMR (CD_3OD) δ 0.28; MS (ESI, MH^+) *m*/*z* calcd for $C_{19}H_{35}NO_5P$ 388.2, found 388.2.
19. (*S*)-**10**: $[\alpha]_D^{25}$ +24.9 (*c* 1.60, $CHCl_3$); (*R*)-**10**: $[\alpha]_D^{25}$ −25.0 (*c* 2.75, $CHCl_3$).