Enantioselective Desymmetrization of FTY720

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A method for enantioselective desymmetrization of *N*-Ac and *N*-Boc-FTY720 by nonenzymatic asymmetric acylation was developed. Effective enantioselective monobenzylation using benzoyl chloride in the presence of the tetraphenylbisoxazoline (L2)–CuCl₂ complex gave the desired products **3a and **3b** in 52–62% yield with 64% ee.**

Key words desymmetrization; FTY720; CuCl₂; asymmetric synthesis; tetraphenylbisoxazoline

FTY720 (Fingolimod) is a first-in-class orally bioavailable compound that has shown efficacy in advanced clinical trials for the treatment of multiple sclerosis (MS), and has already been approved in the U.S., Russia, Switzerland, Australia and the EU as a first-line treatment for relapsing forms of MS. FTY720 is the first of a novel class of sphingosine-1-phosphate (S1P) receptor modulators^{1–3)} (Fig. 1), and is rapidly monophosphorylated *in vivo* to form FTY720-phosphate, which is an agonist for four sphingosine-1-phosphate (S1P) receptors (S1P_{1,3,4,5}). Notably, although FTY720 was designed by deleting the asymmetric centers of its lead compound, FTY720-phosphate has an asymmetric carbon.^{4–8)} Therefore, a practical asymmetric synthesis of both enantiomers of the immunosuppressive FTY720-phosphate is essential for pharmacological evaluation. Recently, efficient enzymatic asymmetric acylation of *N*-protected FTY720 has been reported. Kiuchi *et al.* reported the asymmetric synthesis of FTY720-phosphate using lipase-catalyzed acylation as a key step.³⁾ In contrast, to the best of our knowledge, nonenzymatic enantioselective acylation of FTY720 derivatives has not been described before.

Enantioselective desymmetrization of symmetric molecules has been investigated for constructing versatile chiral building blocks, and is an economical way to generate chirality. Re-

cently, much attention has been focused on the nonenzymatic asymmetric acylation of prochiral and *meso* diols. While catalytic asymmetric desymmetrization methods for *meso* 1,2-diols have been reported,^{9–11)} prochiral 1,3-diols are extremely rare.^{12–17)}

Herein, we report the first example of nonenzymatic enantioselective monobenzylation of *N*-Ac and *N*-Boc-FTY720. Asymmetric synthesis using benzoyl chloride in the presence of tetraphenylbisoxazoline (L2)–CuCl₂ complex gave the desired product **3**. We have been developing this method for the selective monobenzylation of FTY720 analogs. Investigation of the acylation of FTY720 analogs will provide new insights into the phosphorylation mechanism of sphingosine kinase. Most recently, we reported the selective monobenzylation of *N*-Bz-FTY720 using benzoyl methyl phosphate as an efficient reagent.¹⁸⁾

Results and Discussion

First, we stirred a mixture of *N*-Ac-FTY720 **1a**, benzoyl chloride **2a** (1.1 eq), CuCl₂ (1 eq) and diphenylbisoxazoline (L1) in tetrahydrofuran (THF) at room temperature for 2 h. The desired monobenzyolated **3a** was obtained in 44% yield with 49% ee (entry 1). The reaction of *N*-Boc-FTY720 **1b** with benzoyl chloride **2a** resulted in almost the same enantioselectivity (entry 2, 51% ee). With regard to the acylating agents, the use of Ac₂O instead of benzoyl chloride **2a** resulted in 38% yield with only 30% ee (entry 3). Furthermore, when using CH₂Cl₂, the reaction resulted in a lower ee value (entry 4, 12% ee; entry 5, 8% ee). AcCl was ineffective (entry 6, 0% ee). With regard to the box ligands, the best result was obtained when tetraphenylbisoxazoline (L2) was used instead of

Fig. 1. FTY720 and FTY720-Phosphate

Chart 1. Desymmetrization of Serinol **4**¹⁵⁾

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Table 1. Effect of Catalysts and Solvents on the Desymmetrization of **1** with Acylating Agents **2**^{a)}

Entry	Ligand	P ¹	Solvent	Reagent 2	P ²	Product	Yield (%) ^{b)}	ee (%)
1	L1	Ac (1a)	THF	BzCl (2a)	Bz	3a	44	49
2	L1	Boc (1b)	THF	BzCl (2a)	Bz	3b	24	51
3	L1	Ac (1a)	THF	Ac ₂ O (2b)	Ac	3c	38	30
4	L1	Ac (1a)	CH ₂ Cl ₂	Ac ₂ O (2b)	Ac	3c	50	12
5	L1	Boc (1b)	CH ₂ Cl ₂	Ac ₂ O (2b)	Ac	3d	48	8
6	L1	Ac (1a)	THF	AcCl (2c)	Ac	3c	21	0
7 ^{c)}	L2	Ac (1a)	THF	BzCl (2a)	Bz	3a	62	64
8 ^{c)}	L2	Boc (1b)	THF	BzCl (2a)	Bz	3b	52	64

a) Reaction conditions: 1) CuCl₂ (20 mol%), **L1** or **L2** (20 mol%), solvents (10 mL), rt, 1 h. 2) **1** (0.5 mmol), **2** (1.1 eq), Et₃N (1.1 eq), solvents (10 mL), rt, 2 h. b) Yield of isolated product. c) 24 h.

Fig. 2. Proposed Transition State Models

L1 (entries 7 and 8, 64% ee).

Kang and colleagues reported the enantioselective formation of *tert*-alkylamines with benzoyl chloride by desymmetrization of 2-substituted serinols using Box–CuCl₂ complexes.¹⁵⁾ The best desymmetrization was achieved with the benzamide diol using the **L3**–CuCl₂ catalyst (94% yield with 92% ee), while the reaction of *N*-Boc serinol with **L1**–CuCl₂ catalyst resulted in moderate stereoselection (only 6% yield with 49% ee) (Chart 1). However, to achieve a practically efficient protocol, *N*-Ac or *N*-Boc groups must be cleaved under mild conditions, while harsh conditions are required for *N*-benzoyl deprotection.^{2,3,19–26)} Therefore, the use of protecting groups such as acetyl or Boc groups needs further development for enantioselective desymmetrization of *N*-protected FTY720. Additionally, the yield of acylation was increased by introduction of the *n*-octyl group on the benzene ring (entry 2 in Table 1 vs. Chart 1). Therefore, the hydrophobic properties of diols **1** might be important in this catalytic system (**1b**: *c* log *P* value of 6.9; **4a**: *c* log *P* value of 2.7).

On the basis of our results and literature reports by Kang and colleagues,¹⁵⁾ an attempt was made to formulate a transi-

tion state model to explain the stereochemical outcome of the enantioselective reaction (Fig. 2). First, the Cu(II) was ligated with both *N*-protected FTY720 **1** as a tridentate ligand and Box ligand to form a pyramidal-shaped complex, and benzoyl chloride coordinated to Cu(II) from the bottom face to form intermediate **A** or **B**. The desymmetrization of the 1,3-diol through complex **B** is disfavored since **B** is in a higher energy state due to steric interactions between the phenyl ring of benzoyl chloride and the phenyl ring in the oxazoline ring. Indeed, using Ac₂O or AcCl, which are less bulky molecules, was ineffective (see entries 3–6 in Table 1).

Conclusion

In summary, we have developed the first method for enantioselective desymmetrization of *N*-Ac and *N*-Boc-FTY720 **1** by nonenzymatic asymmetric acylation. Effective desymmetrization was achieved using benzoyl chloride (**2a**) and triethylamine in the presence of tetraphenylbisoxazoline (**L2**)–CuCl₂ complex in THF at room temperature to give the desired **3a, b** in 52–62% yield with 64% ee. Additionally, protecting groups such as acetyl or Boc groups could be used in the enantioselective desymmetrization.

Experimental

2-Acetamido-2-(hydroxymethyl)-4-(4-octylphenyl)butyl Benzoate 3a (Entry 7) To a solution of tetraphenylbisoxazoline (**L2**) (24 mg, 0.05 mmol) in THF (2.5 mL) was added CuCl₂ (6.7 mg, 0.05 mmol) and stirred at room temperature for 1 h. To the mixture was added THF (5.0 mL), *N*-(1-hydroxy-2-(hydroxymethyl)-4-(4-octylphenyl)butan-2-yl)acetamide (87 mg, 0.25 mmol), Et₃N (0.37 mL, 0.26 mmol), benzoyl chloride (0.23 mL, 0.26 mmol) were added. After being stirred at room temperature for 24 h, the mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane–EtOAc) to give **3a** (70 mg, 62%) as a colorless oil.

IR (KBr) (cm^{−1}) 3296, 1719, 1650; ¹H-NMR (400 MHz, CDCl₃) δ: 0.87 (t, *J*=6.9 Hz, 3H), 1.20–1.35 (m, 10H), 1.57 (quin., *J*=7.3 Hz, 2H), 1.95 (s, 3H), 2.04 (ddd, *J*=14.2, 11.5, 6.0 Hz, 1H), 2.27 (ddd, *J*=14.2, 11.0, 5.5 Hz, 1H), 2.55 (t,

$J=7.8$ Hz, 2H), 2.61 (ddd, $J=13.5$, 11.2, 5.5 Hz, 1H), 2.71 (ddd, $J=13.5$, 11.2, 5.5 Hz, 1H), 3.80 (d, $J=12.1$ Hz, 1H), 3.84 (d, $J=12.1$ Hz, 1H), 4.48 (d, $J=11.5$ Hz, 1H), 4.62 (d, $J=11.5$ Hz, 1H), 5.89 (s, 1H), 7.08 (d, $J=8.5$ Hz, 2H), 7.11 (d, $J=8.5$ Hz, 2H), 7.47 (dd, $J=8.0$, 1.6 Hz, 2H), 7.60 (tt, $J=7.3$, 1.4 Hz, 1H), 8.03 (dd, $J=7.3$, 1.4 Hz, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ : 14.1, 22.7, 24.1, 29.3, 29.5, 31.6, 31.9, 34.6, 35.5, 61.1, 65.4, 65.7, 128.2, 128.4, 128.6, 129.4, 129.7, 133.6, 138.4, 140.9, 166.9, 171.4; MS-electron ionization (EI): m/z (%) 453 (M^+ , 16), 97 (100); high resolution (HR)-MS-EI: m/z (M^+) Calcd for $\text{C}_{28}\text{H}_{39}\text{NO}_4$ 453.2879, Found 453.2880. The enantiomeric ratios of **3a** was determined using HPLC through Daicel CHIRALPAK IC column (*n*-Hex/IPA=80/20, 0.5 mL/min, UV 254 nm), $t_{\text{R}}=15.0$ min and 23.7 min, 64% ee. $[\alpha]_{\text{D}}^{26} -5.7$ ($c=1.12$, CHCl_3).

2-(tert-Butoxycarbonylamino)-2-(hydroxymethyl)-4-(4-octylphenyl)butyl Benzoate 3b (Entry 8) To a solution of tetraphenylbisoazoline (**L2**) (24 mg, 0.05 mmol) in THF (2.5 mL) was added CuCl_2 (6.7 mg, 0.05 mmol) and stirred at room temperature for 1 h. To the mixture was added THF (5.0 mL), *tert*-butyl(1-hydroxy-2-(hydroxymethyl)-4-(4-octylphenyl)butan-2-yl)carbamate (102 mg, 0.25 mmol), Et_3N (0.37 mL, 0.26 mmol), benzoyl chloride (0.23 mL, 0.26 mmol) were added. After being stirred at room temperature for 24 h, the mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane–EtOAc) to give **3b** (67 mg, 52%) as a colorless oil.

IR (KBr) (cm^{-1}) 3279, 1719, 1682; ^1H -NMR (400 MHz, CDCl_3) δ : 0.87 (t, $J=7.1$ Hz, 3H), 1.20–1.35 (m, 10H), 1.57 (quin., $J=7.3$ Hz, 2H), 1.98 (ddd, $J=13.7$, 12.1, 5.3 Hz, 1H), 2.20 (ddd, $J=14.0$, 12.1, 5.0 Hz, 1H), 2.55 (t, $J=8.0$ Hz, 2H), 2.58 (ddd, $J=13.1$, 13.1, 5.0 Hz, 1H), 2.69 (ddd, $J=13.1$, 13.1, 5.0 Hz, 1H), 3.78 (t, $J=5.5$ Hz, 2H), 3.97 (brs, 1H), 4.46 (d, $J=11.5$ Hz, 1H), 4.58 (d, $J=11.5$ Hz, 1H), 4.94 (brs, 1H), 7.07 (d, $J=8.5$ Hz, 2H), 7.10 (d, $J=8.5$ Hz, 2H), 7.46 (t, $J=8.0$ Hz, 2H), 7.59 (tt, $J=6.2$, 1.4 Hz, 1H), 8.03 (dd, $J=8.5$, 1.4 Hz, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ : 14.1, 22.7, 28.3, 29.3, 29.4, 29.5, 31.6, 31.9, 35.5, 59.0, 65.2, 65.5, 80.2, 128.2, 128.5, 129.5, 129.8, 133.4, 138.7, 140.7, 155.7, 166.8; MS-EI: m/z (%) 511 (M^+ , 2.5), 105 (100); HR-MS-EI: m/z (M^+) Calcd for $\text{C}_{31}\text{H}_{45}\text{NO}_5$ 511.3298, Found 511.3297. The enantiomeric ratios of **3b** was determined using HPLC through Daicel CHIRALPAK IC column (*n*-Hex/IPA=80/20, 0.5 mL/min, UV 254 nm), $t_{\text{R}}=39.0$ min and 41.6 min, 64% ee. $[\alpha]_{\text{D}}^{26} -5.0$ ($c=1.58$, CHCl_3).

(R)-2-Acetamido-2-(hydroxymethyl)-4-(4-octylphenyl)-butyl Acetate 3c³ (Entry 3) White solid; mp 75–78°C; IR (KBr) (cm^{-1}) 3303, 1737, 1631; ^1H -NMR (400 MHz, CDCl_3) δ : 0.88 (t, $J=6.6$ Hz, 3H), 1.20–1.40 (m, 10H), 1.57 (quin., $J=7.1$ Hz, 2H), 1.85–2.00 (m, 1H), 1.94 (s, 3H), 2.06–2.20 (m, 1H), 2.11 (s, 3H), 2.55 (t, $J=7.6$ Hz, 2H), 2.50–2.60 (m, 1H), 2.65 (ddd, $J=13.5$, 11.2, 5.5 Hz, 1H), 3.72 (d, $J=12.1$ Hz, 1H), 3.77 (d, $J=12.1$ Hz, 1H), 4.19 (d, $J=11.5$ Hz, 1H), 4.37 (d, $J=11.5$ Hz, 1H), 4.62 (brs, 1H), 5.83 (brs, 1H), 7.09 (s, 4H); ^{13}C -NMR (100 MHz, CDCl_3) δ : 14.1, 20.9, 22.7, 24.0, 29.2, 29.3, 29.5, 31.6, 31.9, 34.5, 35.5, 60.7, 65.3, 65.4, 128.2, 128.6, 138.4, 140.8, 171.3, 171.4; MS-EI: m/z (%) 391 (M^+ , 16), 97 (100); HR-MS-EI: m/z (M^+) Calcd for $\text{C}_{23}\text{H}_{37}\text{NO}_4$ 391.2723, Found 391.2715. The enantiomeric ratios of **3c** was determined

using HPLC through Daicel CHIRALPAK IC column (CH_2Cl_2 only, 1.0 mL/min, UV 254 nm), $t_{\text{R}}=39.0$ min and 41.9 min, 30% ee. $[\alpha]_{\text{D}}^{26} -2.0$ ($c=1.78$, CHCl_3).

2-(tert-Butoxycarbonylamino)-2-(hydroxymethyl)-4-(4-octylphenyl)butyl Acetate 3d (Entry 6) Colorless oil; IR (KBr) (cm^{-1}) 3393, 1746, 1719, 1700; ^1H -NMR (400 MHz, CDCl_3) δ : 0.88 (t, $J=6.6$ Hz, 3H), 1.20–1.40 (m, 10H), 1.45 (s, 9H), 1.58 (quin., $J=7.6$ Hz, 2H), 1.88 (ddd, $J=14.0$, 12.1, 5.3 Hz, 1H), 2.07 (ddd, $J=14.0$, 12.1, 5.0 Hz, 1H), 2.10 (s, 3H), 2.48–2.58 (m, 1H), 2.36 (t, $J=7.6$ Hz, 2H), 2.63 (ddd, $J=13.5$, 11.2, 5.5 Hz, 1H), 3.68 (dd, $J=11.9$, 6.2 Hz, 1H), 3.74 (dd, $J=11.9$, 6.2 Hz, 1H), 3.93 (s, 1H), 4.16 (d, $J=11.2$ Hz, 1H), 4.34 (d, $J=11.2$ Hz, 1H), 4.87 (brs, 1H), 7.09 (s, 4H); ^{13}C -NMR (100 MHz, CDCl_3) δ : 14.1, 20.9, 22.7, 28.3, 29.1, 29.3, 29.4, 31.6, 31.9, 34.9, 35.5, 58.6, 65.3, 80.2, 128.2, 128.5, 138.7, 140.7, 155.7, 171.2; MS-EI: m/z (%) 449 (M^+ , 4.8), 318 (100); HR-MS-EI: m/z (M^+) Calcd for $\text{C}_{26}\text{H}_{43}\text{NO}_5$ 449.3141, Found 449.3143. The enantiomeric ratios of **3d** was determined using HPLC through Daicel CHIRALPAK IC column (CH_2Cl_2 only, 1.0 mL/min, UV 254 nm), $t_{\text{R}}=9.1$ min and 26.7 min, 8% ee. $[\alpha]_{\text{D}}^{26} -0.2$ ($c=3.76$, CHCl_3).

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