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Benzoyl methyl phosphate as an efficient reagent for the selective monobenzoylation of *N*-Bz-FTY720

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A novel and efficient method for the selective monobenzoylation of *N*-Bz-FTY720 with benzoyl methyl phosphate (BMP) promoted by $Zn(OAc)_2$ and Cs_2CO_3 was developed. Benzoyl methyl phosphate plays an important role as a biomimetic acylating agent for the monobenzoylation of 1,3-diols.

Introduction

Acyl adenylates are mixed carboxylic-phosphoric anhydrides that are potentially useful as biomimetic and efficient reagents for acylation reactions.[1,2] The mechanism of reactions with acyl phosphates has been reported by Jencks.[1] Kluger and co-workers reported that the direct monoacylation of diols by benzoyl phosphates in water was a good biomimetic model for the enzymatic aminoacylation of tRNA by aminoacyl adenylates.[2h] This is a promising progress for the potential use of benzoyl methyl phosphates **2** in organic synthesis. Furthermore, in biological systems, the syntheses of the compounds essential for life are accomplished efficiently and cleanly via enzymatic catalysis. Therefore, development of a synthetic pathway similar to a biosynthetic one is the attractive and much attention, yet most challenging, research goals for a synthetic chemist.[3]

We have been developing atom economical and environmentally benign reactions with green processes, such as unprotected syntheses, benzylic C-H activations, cascade reactions and chemoselective reactions in aqueous media.[4] Recently, we reported a novel and efficient method for the environmentally benign, catalyst- and auxiliary-free synthesis of 2-phenylbenzimidazoles in water.[4a] Benzoyl methyl phosphates play important roles as biomimetic acylating agents for the one-pot tandem approach without additional catalysts.

Herein, we report the development of a novel and efficient method for selective monobenzoylation of *N*-Bz-FTY720. Notably, benzoyl methyl phosphate **2** plays an important role as a biomimetic acylating agent. In general, selective protection of hydroxyl groups of polyols is very important in organic synthesis. Therefore, catalytic regioselective acylation of unprotected monosaccharides and natural products has been developed.[5] Muramatsu and co-workers reported an efficient method for selective monobenzoylation of 1,2- and 1,3-diols in water catalyzed by Me_2SnCl_2.[5a] Interestingly, a biomimetic approach was utilized for the reaction of acyl phosphate monoesters with diols in the presence of lanthanum salts in water, producing esters through chelation-directed selectivity by Kluger and co-workers.[2]

FTY720 (Fingolimod) is the first of a novel class of sphingosine 1-phosphate (S1P) receptor modulators (Figure 1),[6] and is rapidly monophosphorylated in vivo to form FTY720-phosphate, which is an agonist for four sphingosine-1-phosphate (S1P) receptors ($S1P_{1,3,4,5}$). Therefore, complementary agonists for each S1P receptor should be valuable tools to ascertain the mechanism of immunosuppressive action of FTY720, and provide further information to researchers. Indeed, Takeda and co-workers reported a method for selective and direct phosphorylation of various 1,3-diols using silver(I) oxide.[7] Furthermore, FTY720 has a propan-1,3-diol moiety, and protection of one of the hydroxyl groups is needed for the preparation of FTY720-phosphate. Kiuch and co-workers reported asymmetric synthesis of FTY720-phosphate using the lipase-catalyzed acylation as the key step.[8] While enzymatic acylation of *N*-protected FTY720 has been reported, to the best of our knowledge, the nonenzymatic monobenzoylation has not been described before.[9] Additionally, investigation for the reaction of FTY720 analogs using BMP **2** as a biomimetic acylating reagent will provide new insight into the phosphorylation mechanism of sphingosine kinase.

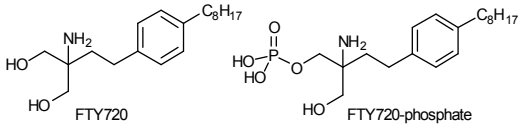
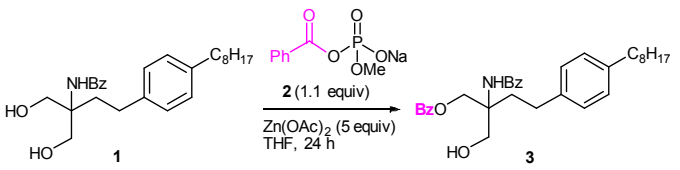


Figure 1. FTY720 and FTY720-phosphate.

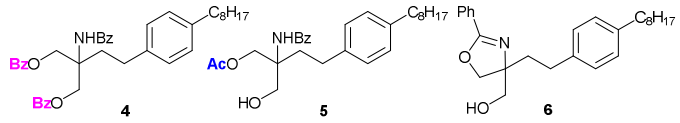
Results and discussion

First, we heated a mixture of *N*-Bz-FTY720 **1**, benzoyl methyl phosphate **2** (1.1 equiv) and $Zn(OAc)_2$ (5 equiv) in THF at 40 °C for 24 h. Desired monobenzoylated **3** was obtained in 34% yield along with dibenzoylated **4**, acetoxy **5** and recovery of SM **1** (entry 1, Table 1). When **1** was heated at 80 °C for 24 h, the reaction afforded desired **3** in only 25% yield along with **4** in 12% yield and **5** in 16% yield (entry 2). Unfortunately, water suppressed the reaction (entry 3).

Table 1. The reaction of *N*-Bz-FTY720 **1** with BMP **2**.[a]



Entry	Solv.	*T.* (°C)	Yield (%) mono **3**	di **4**	OAc **5**	SM **1**
1	THF	40	34	3	5	38
2	THF	80	25	12	16	0
3	THF-H_2O	40	No reaction			



[a] Reaction conditions: diol **1**, BMP **2** (5 equiv), $Zn(OAc)_2$ (1 equiv), THF (0.05 M), 40-80 °C, 24 h.

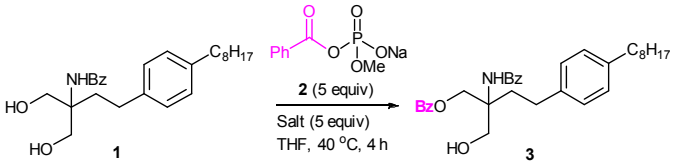
Thus, we investigated the effects of various salts as catalysts to improve the reactivity and selectivity of the monobenzoylation (Table 2). When a mixture of diol **1** and BMP **2** (5 equiv) was stirred in the presence of $Zn(OAc)_2$ (5 equiv) in THF at 40 °C for 4 h, desired **3** was obtained in 36% yield along with **4** and **5** (entry 1). ZnTAc24 was also an effective salt, giving desired **3** in 32% yield (entry 2).[10] In contrast, $ZnCl_2$ or $Zn(OTf)_2$ resulted in no reaction (entries 3 and 4). To compare $Zn(OAc)_2$ with other efficient salts, we tested the reaction using $CuCl_2$ or $Cu(OTf)_2$. Interestingly, the *N*-benzoyl group of **1** was activated by copper salts to give cyclized **6** (entry 5, 35%; entry 6, 48%). $Cu(OAc)_2$ was ineffective for monobenzylation (entry 7). The use of only 1 equiv. of $Zn(OAc)_2$ or BMP **2** resulted in slightly lower yields (entries 8 and 9). The reaction in the presence of a catalytic amount of $Zn(OAc)_2$ (0.2 equiv) afforded desired **3** in 15% yield (after 15 h) and in 26% yield (after 24 h), suggesting that the active Zn(II) species did not regenerate (entry 10). The reaction did not proceed in the absence of $Zn(OAc)_2$ (entry 11). Thus, diol **1** is less nucleophilic.

Next, we investigated the effect of solvents on the selective monobenzylation (Table 3). When using DMF, the reaction also proceeded to give desired **3** in 36% yield (entry 1). In contrast, CH_2Cl_2, hexane, or alcohols such as EtOH or ^{t}BuOH resulted in low yields (entries 2-5). Interestingly, when using pyridine, desired **3** was obtained in 14% yield along with byproduct **5** in 22% yield (entry 6).

A low concentration of SM **1** (0.005 M) did not afford byproducts **4** and **5** (entry 1, Table 4). In contrast, the byproduct increased at a higher concentration of SM **1** (entries 2-4).

Next, we investigated the effect of base on the selective monobenzylation (Table 5). The use of inorganic bases such as $NaHCO_3$, Na_2CO_3 and K_3PO_4, or an organic base, Et_3N, resulted in 38-48% yields (entries 1-4). Interestingly, Cs_2CO_3 enhanced the reaction to give desired **3** in 53% yield (entry 5). Furthermore, after 96 h, desired **3** was obtained in 60% yield (entry 6). The use of DMF enhanced the reaction to give desired **3** in 66% yield (entry 7). Notably, in the presence of a catalytic amount of $Zn(OAc)_2$ (0.2 equiv), the reaction proceeded smoothly to give desired **3** in 57% yield (entry 8).

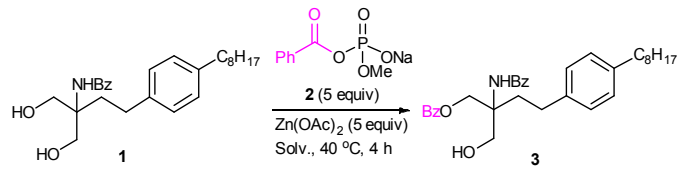
Table 2. Effect of salts.[a]



Entry	Salt (equiv)	BMP **2** (equiv)	Conv. (%)[b] mono **3**	di **4**	OAc **5**	**6**	SM **1**
1	$Zn(OAc)_2$ (5)	5	36	6	10	0	45
2	ZnTAc24 (5)	5	32	0	0	0	68
3	$ZnCl_2$ (5)	5	2	0	0	0	98
4	$Zn(OTf)_2$ (5)	5	No reaction				
5	$CuCl_2$ (5)	5	2	0	0	35	63
6	$Cu(OTf)_2$ (5)	5	16	0	0	48	27
7	$Cu(OAc)_2$ (5)	5	10	0	0	0	90
8	$Zn(OAc)_2$ (1)	5	28	1	0	0	71
9	$Zn(OAc)_2$ (5)	1	28	0	0	0	72
10	$Zn(OAc)_2$ (0.2)	5	15[c] (26)[d]	0	0	0	85
11[e]	none	1	No reaction				

[a] Reaction conditions: diol **1**, BMP **2** (1 or 5 equiv), salt (0.2-5 equiv), solvent (0.05 M), 40 °C, 4 h. [b] HPLC area%. [c] 15 h. [d] 24 h. [e] 8 h.

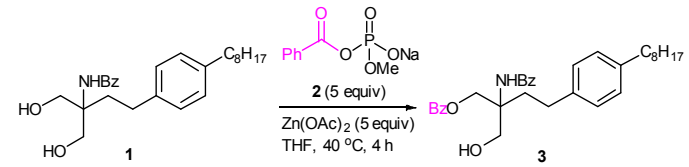
Table 3. Effect of solvents.[a]



Entry	Solv.	Conv. (%)[b] mono **3**	di **4**	OAc **5**	SM **1**
1	DMF	36	5	4	55
2	CH_2Cl_2	18	0	0	82
3	Hexane	No reaction			
4	EtOH	15	1	0	84
5	^{t}BuOH	27	0	2	71
6	Py	14	0	22	61

[a] Reaction conditions: diol **1**, BMP **2** (1 equiv), $Zn(OAc)_2$ (5 equiv), solvent (0.05 M), 40 °C, 4 h. [b] HPLC area%

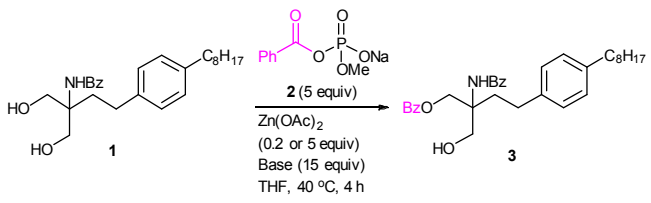
Table 4. Effect of concentration.



Entry	Conc. of SM **1** (M)	Conv. (%)[a] mono **3**	di **4**	OAc **5**	SM **1**
1	0.005	33	0	0	67
2	0.01	35	2	0	63
3	0.05	37	6	10	46
4	0.1	36	5	12	46

[a] HPLC area%.

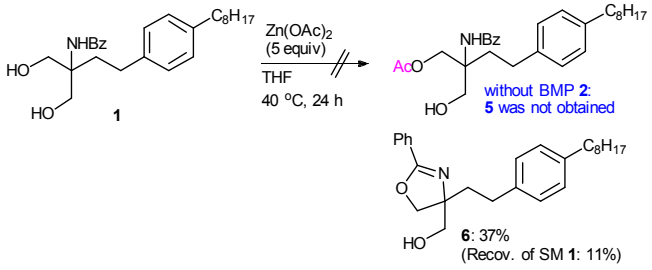
Table 5. Effect of base.[a]



Entry	Base	Solv.	*T.* / *t.* (°C / h)	Conv. (%) [b] mono **3**	di **4**	SM **1**
1	$NaHCO_3$	THF	40 / 4	38	0	62
2	Na_2CO_3	THF	40 / 4	40	0	60
3	K_3PO_4	THF	40 / 4	42	4	54
4	Et_3N	THF	40 / 4	48	6	46
5	Cs_2CO_3	THF	40 / 4	53	6	41
6	Cs_2CO_3	THF	40 / 96	60	11	25
7	Cs_2CO_3	DMF	40 / 2	66	14	20
8[c]	Cs_2CO_3	DMF	40 / 24	57	6	37

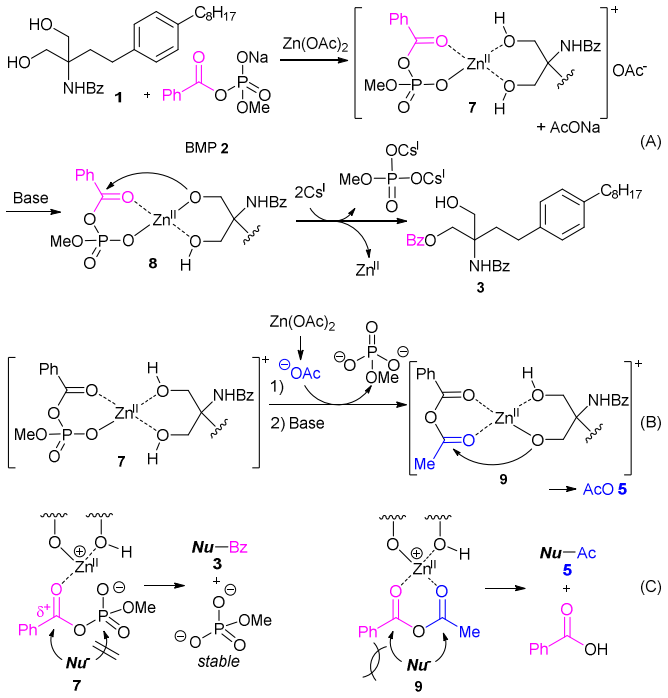
[a] Reaction conditions: diol **1**, BMP **2** (5 equiv), $Zn(OAc)_2$ (5 equiv), solvent (0.005 M), 40°C, 3 h. [b] HPLC area%. [c] Used 0.2 equiv of $Zn(OAc)_2$, 24 h.

To gain insight into the reaction mechanism, we carried out the reaction in the absence of BMP **2** (Scheme 1). BMP **2** played an important role in the production of acetylated **5**, since the reaction did not afford **5** in its absence.



Scheme 1. The reaction in the absence of BMP **2**.

On the basis of our results and literature reports, the following mechanism can be suggested. A mechanism for the selective monobenzoylation reaction of 1,3-diol to form a coordinated intermediate is shown in Scheme 2A and is based on Clarke's proposal. Clarke and Arnold reported that the mechanism of the lanthanide(III) salt catalyzed mono-acylation of diols proceeds via chelation of the diol and acid anhydride to the lanthanide salt, followed by an intramolecular acyl transfer.[11] Diol **1** is less nucleophilic, since in the absence of $Zn(OAc)_2$ the reaction of **1** with BMP **2** did not proceed (see Table 2, entry 10). First, diol **1** was reacted with BMP **2** in the presence of $Zn(OAc)_2$ to form intermediate **7** in which both a diol and BMP **2** coordinated to the Zn(II) salt. Next, in the presence of base, deprotonation of the hydroxyl group proceeded smoothly due to the increased acidity of **7**, followed by formation of alkoxide **8**. Indeed, the use of Cs_2CO_3 enhanced the reaction (see Table 5). Next, intramolecular nucleophilic attack from the alkoxide into the activated acyl group, which was a bisbidentate chelate of Zn(II), gave desired **3** along with regenerated Zn(II). Kluger and co-workers reported that Mg^{2+} scavenges the methyl phosphate byproduct to establish the La^{3+} catalyst.[2c] Indeed, in the presence of Cs_2CO_3 as a base, $Zn(OAc)_2$-catalyzed monobenzoylation occurred to give the desired **3** in 57% yield (entry 10 in Table 2 vs entry 8 in Table 5). Furthermore, as shown in Scheme 2B, BMP **2** reacts with acetoxy anion (AcO^-) to form anhydride **9**. Nucleophilic attack on the acetyl group affords byproduct **5**. When using pyridine as a solvent, desired **3** was obtained in 14% yield along with byproduct **5** in 22% yield (see entry 6 in Table 3). BMP **2** might react with pyridine to form a 1-benzoylpyridinium intermediate, which then reacts with AcO^- to form mixed anhydride **9**. Phosphorylation of diol **1** with BMP **2** did not occur in our catalytic system, suggesting that Zn(II) could activate the benzoyl group along with the ion pair of Zn(II) cation and phosphate anion to give desired **3** and stable $MeOPO_4^{2-}$ (Scheme 2C, left). Nucleophilic attack on the acetyl group of anhydride **9** is favored due to steric interactions between the phenyl ring of the benzoyl group and the hydroxyl group (Scheme 2C, right).



Scheme 2. Plausible mechanism.

Conclusions

In summary, we have for the first time achieved the $Zn(OAc)_2$-promoted monobenzoylation reaction of FTY720 with benzoyl methyl phosphate (BMP). Notably, benzoyl methyl phosphate plays an important role as an acylating reagent.[12] The development of this efficient biomimetic pathway promises to generate further innovative organic reactions. We are currently investigating the scope of various 1,2- and 1,3-diols, which are highly functionalized bioactive compounds, and new reactions using benzoyl methyl phosphates.

Experimental

Procedure for preparation of benzoyl methyl phosphates 2

A mixture of trimethylphosphate (11.5 mL, 0.1 mol) and NaI (15.5 g, 0.1 mol) in acetone (130 mL) was stirred at room temperature for 3 d, leading to crystallization of the product, sodium dimethyl phosphate (13.8 g, 94%).

Sodium dimethyl phosphate (1.0 g, 6.9 mmol) and *N*,*N*-dimethylaminopyridine (41 mg, 0.3 mmol) were suspended in dry tetrahydrofuran (15 mL), then benzoyl chloride (0.8 mL, 6.4 mmol) was added under argon. The mixture was stirred at

room temperature for 3 h. The reaction mixture was filtered to remove sodium chloride. Water (20 mL) was added to the filtrate, which was extracted with $CHCl_3$ (30 mL x 3). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give the benzoyl dimethyl phosphate as a colorless oil (1.3 g, 87%).

The mixture of benzoyl dimethyl phosphate (1.3 g, 5.5 mmol) and NaI (0.83 g, 5.5 mmol) in acetone (30 mL) was stirred at room temperature for 3 d, leading to crystallization of the product, the sodium salt of benzoyl methyl phosphate **2** (1.2 g, 93%).

Benzoyl methyl phosphate 2[2f]**:** white solid. dp 189-191 ℃; IR (KBr) (cm^{-1}) 2953, 1711, 1271; ^{1}H NMR (400 MHz, D_2O); δ 7.98 (d, *J*=9.6 Hz, 2H), 7.61 (t, *J*=8.3 Hz, 1H), 7.45 (t, *J*=7.7 Hz, 2H), 3.63 (d, *J*=11.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6); δ 151.2, 143.8, 135.0, 130.1, 129.8, 128.9, 126.4, 122.5, 121.7, 118.8, 111.3; MS (FAB); *m/z* 239 $[M+H]^+$.

Procedure for the preparation of *N*-(1-hydroxy-2-(hydroxymethyl)-4-(4-octylphenyl)butan-2-yl)benzamide 1

To a solution of (2-amino-2[2-(-4-octylphenyl)ethyl]propane-1,3-diol hydrochloride) (3.4 g, 10 mmol) and triethylamine (2.9 mL, 21 mmol) in CH_2Cl_2 (50 mL) and THF (10 mL) was added benzoyl chloride (1.27 mL, 11 mmol). The mixture was stirred at room temperature for 1 d. The reaction mixture was filtered to remove a precipitate. Water (20 mL) was added to the filtrate, which was extracted with $CHCl_3$ (50 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give **1** as a white solid (2.77 g, 68%).

***N*-(1-hydroxy-2-(hydroxymethyl)-4-(4-octylphenyl)butan-2-yl)benzamide 1:** white solid, mp 81-83 ℃; IR (KBr) (cm^{-1}) 3241, 1630; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.60 (dt, *J*=7.2 Hz, 1.5 Hz, 2H), 7.49 (tt, *J*=7.2 Hz, 1.5 Hz, 1H), 7.39 (tt, *J*=7.6 Hz, 7.6 Hz, 2H), 7.13 (d, *J*=8.2 Hz, 2H), 7.09 (d, *J*=8.2 Hz, 2H), 6.62 (brs, 1H), 4.00 (dd, *J*=11.8 Hz, 5.6 Hz, 2H), 3.88 (t, *J*=6.7 Hz, 2H), 3.72 (dd, *J*=11.3 Hz, 6.7 Hz, 2H), 2.72-2.68 (m, 2H), 2.55 (t, *J*=7.7 Hz, 2H), 2.12-2.08 (m, 2H), 1.60-1.53 (m, 2H), 1.32-1.22 (m, 10H), 0.87 (t, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 14.1, 22.7, 29.3, 29.4, 29.5, 31.5, 31.9, 34.8, 35.5, 61.7, 66.1, 126.9, 128.2, 128.6, 128.8, 131.8, 134.4, 138.5, 141.0, 168.5; MS (EI): *m/z* (%) 411 (M^+, 20), 105 (100); HRMS-EI: *m/z* (M^+) calcd for $C_{26}H_{37}NO_3$ 411.2773, found 411.2772.

Procedure for monobenzoylation of diol 1 with BMP 2.

A mixture of benzoyl methyl phosphate **2** (298 mg, 1.25 mmol) and **1** (102 mg, 0.25 mmol) in DMF (10 mL) was stirred at 40 ^{o}C for 24 h. After being poured into water, the mixture was extracted with EtOAc (20 mL x 3). The organic layer was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give **3** (65 mg, 50%) as colorless oil.

2-Benzamido-2-(hydroxymethyl)-4-(4-octylphenyl)butyl benzoate 3: colourless oil; IR (KBr) (cm^{-1}) 3382, 2926, 2854, 1722, 1649; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.06-8.03 (m, 2H), 8.69-8.67 (m, 2H), 7.60 (tt, *J*=7.2 Hz, 1.5 Hz, 1H), 7.53-7.40 (m, 5H), 7.13 (d, *J*=8.2 Hz, 2H), 7.07 (d, *J*=8.2 Hz, 2H), 6.71 (brs, 1H), 4.79 (d, *J*=11.3 Hz, 1H), 4.59 (d, *J*=11.3 Hz, 1H), 4.00-3.90 (m, 2H), 2.79 (ddd, *J*=13.3 Hz, 11.3 Hz, 5.6 Hz, 1H), 2.68 (ddd, *J*=13.3 Hz, 11.3 Hz, 5.6 Hz, 1H), 2.54 (t, *J*=7.7 Hz, 2H), 2.44 (ddd, *J*=14.3 Hz, 11.3 Hz, 5.6 Hz, 1H), 2.19 (ddd, *J*=14.3 Hz, 11.3 Hz, 5.6 Hz, 1H), 1.53 (m, 2H), 1.35-1.23 (m, 10H), 0.87 (t, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 14.1, 22.7, 29.3, 29.4, 29.5, 31.5, 31.9, 34.5, 35.5, 61.5, 65.6, 66.2, 126.9, 128.2, 128.6, 128.7, 129.4, 129.8, 131.8, 133.6, 134.4, 138.4, 140.9, 167.2, 168.3; MS (EI): *m/z* (%) 515 (M^+, 13), 159 (100); HRMS-EI: *m/z* (M^+) calcd for $C_{33}H_{41}NO_4$ 515.3036, found 515.3036.

2-Benzamido-2-(4-octylphenethyl)propane-1,3-diyl dibenzoate 4: collarless oil; IR (KBr) (cm^{-1}) 3412, 2925, 2854, 1722, 1651; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.02-7.99 (m, 4H), 7.74-7.67 (m, 2H), 7.57-7.49 (m, 3H), 7.46-7.38 (m, 6H) , 7.14 (d, *J*=8.2 Hz, 2H), 7.08 (d, *J*=8.2 Hz, 2H), 6.92 (brs, 1H), 4.90 (d, *J*=11.8 Hz, 2H), 4.82 (d, *J*=11.8 Hz, 2H), 2.81-2.76 (m, 2H), 2.56-2.52 (m, 4H), 1.54 (m, 2H), 1.35-1.23 (m, 10H), 0.87 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 14.1, 22.7, 29.3, 29.4, 29.5, 29.6, 31.5, 31.9, 34.3, 35.6, 59.6, 65.9, 126.9, 128.3, 128.5, 128.6, 128.7,129.5, 129.7, 131.6, 133.4, 134.6, 138.3, 140.9, 166.7, 167.3; MS (EI): *m/z* (%) 619 (M^+, 5), 159 (100); HRMS-EI: *m/z* (M^+) calcd for $C_{40}H_{45}NO_5$ 619.3298, found 619.3297.

2-Benzamido-2-(hydroxymethyl)-4-(4-octylphenyl)butyl acetate 5: collarless oil; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.66 (dt, *J*=7.2 Hz, 1.5 Hz, 2H), 7.51 (tt, *J*=7.2 Hz, 1.5 Hz, 1H), 7.46-7.40 (m, 2H), 7.14-7.06 (m, 4H), 6.59 (brs, 1H), 4.58-4.52 (m, 2H), 4.30 (d, *J*=11.8 Hz, 1H), 3.90 (dd, *J*= 12.4 Hz, 7.2 Hz, 1H), 3.85 (dd, *J*= 12.4 Hz, 6.1 Hz, 1H), 2.73 (ddd, *J*=13.3 Hz, 11.3 Hz, 5.6 Hz, 1H), 2.62 (ddd, *J*=13.3 Hz, 10.7 Hz, 5.6 Hz, 1H), 2.54 (t, *J*=7.7 Hz, 2H), 2.31 (ddd, *J*=14.3 Hz, 11.3 Hz, 5.6 Hz, 1H), 2.08 (ddd, *J*=14.3 Hz, 11.3 Hz, 5.6 Hz, 1H), 1.60-1.53 (m, 2H), 1.35-1.22 (m, 10H), 0.87 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 14.1, 20.9, 22.7, 29.3, 29.3, 29.4, 29.5, 31.5, 31.9, 34.5, 35.5, 61.2, 65.6, 65.9, 126.9, 128.2, 128.6, 128.7, 131.8, 134.3, 138.4, 140.9, 168.3, 171.6; MS (EI): *m/z* (%) 453 (M^+, 16), 159 (100); HRMS-EI: *m/z* (M^+) calcd for $C_{28}H_{39}NO_4$ 453.2879, found 453.2879.

{4-(4-Octylphenethyl)-2-phenyl-4,5-dihydrooxazol-4-yl}methanol 6: colorless oil; IR (KBr) (cm^{-1}) 2923, 2853, 1648; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.96 (dt, *J*=7.2 Hz, 1.5 Hz, 2H), 7.50 (tt, *J*=7.2 Hz, 1.5 Hz, 1H), 7.45-7.40 (m, 2H), 7.08 (brs, 4H), 4.42 (d, *J*= 8.2 Hz, 2H), 4.28 (d, *J*=8.7 Hz, 1H), 3.83 (dd, *J*= 11.3 Hz, 3.6 Hz, 1H), 3.55 (dd, *J*= 11.3 Hz, 8.7 Hz, 1H), 2.65-2.52 (m, 4H), 2.01 (ddd, *J*=14.3 Hz, 11.3 Hz, 5.6 Hz, 1H), 1.89-1.81 (m, 2H), 1.60-1.53 (m, 2H), 1.35-1.22 (m, 10H), 0.87 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 14.1, 22.7, 29.3, 29.4, 29.5, 31.6, 31.9, 35.5, 38.2, 67.7, 72.6, 75.0, 76.7, 77.0, 77.2, 77.3, 128.1, 128.4, 128.4, 128.5, 128.6, 131.6, 138.8, 140.6; MS (EI): *m/z* (%) 393 (M^+, 30), 177 (100); HRMS-EI: *m/z* (M^+) calcd for $C_{26}H_{35}NO_2$ 393.2668, found 393.2667.

Notes and references

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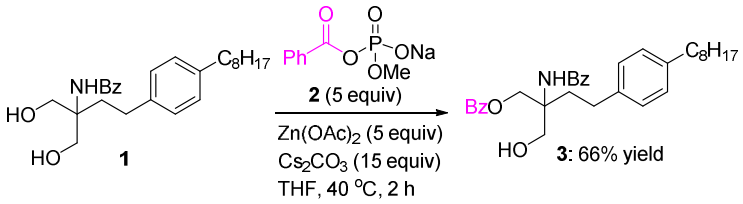

A novel and efficient method for the selective monobenzoylation of *N*-Bz-FTY720 with benzoyl methyl phosphate (BMP) promoted by $Zn(OAc)_2$ and Cs_2CO_3 was developed. Benzoyl methyl phosphate plays an important role as a biomimetic acylating agent for the monobenzoylation of 1,3-diols.