通过 Michael 加成引发分子间的环丙烷化反应高效合成螺环嘧啶核苷

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摘要 报道了一种简单高效的螺环核苷合成方法,以 α -嘧啶取代的丙烯酸酯和 α -氯代环烷酮为原料, KO^tBu 为碱,通过 Michael 加成引发的环丙烷化反应,高效合成一系列 2'-螺环修饰的三元碳环嘧啶核苷。该反应底物适用范围较宽,非对映选择性较高(>20 : 1 *dr*),收率可高达 85%。

关键词 螺环核苷; 环丙烷化反应; α -氯代环烷酮

Efficient Synthesis of Spirocyclic Nucleosides via Michael Addition-Initiated Intermolecular Cyclopropanation Reaction

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Abstract An efficient route to synthesize 2'-spiro[2-oxocyclopentyl]cyclopropyl nucleoside analogues via KO^tBu promoted Michael addition-initiated cyclopropanation reactions of α -thymine acrylates with α -chloro-cycloalkanones has been developed. A wide range of C(2')-spirocyclic modified nucleoside analogues were obtained with excellent diastereoselectivities (>20 : 1) and good yields (up to 85%).

Keywords spirocyclic nucleoside; cyclopropanation reaction; α -chloro-cycloalkanone

1 Introduction

Structurally modified nucleosides attract synthetic and biological interest because selective compounds are vulnerable to treat diseases where the normal state differs from the diseased state regarding the enzymes involved in the processing of nucleic acid.^[1] The relevant enzymes possess strict conformational requirements of the furanose ring with respect to the geometry.^[2] This prompted several research groups to prepare modified nucleosides that feature restrictions in conformational flexibility in order to obtain not only new but also improved antiviral drugs.^[3] Thus, many spirocyclic nucleoside analogues with re-

stricted conformation have been designed and synthesized.^[4-8] For example, spirocyclic nucleoside **I** (Figure 1) is a novel potent and selective inhibitor of the HCV NS5B RNA-dependent RNA polymerase (RdRP), which is a clinically validated target for HCV treatment,^[4-6] whereas nucleosides **II** ~ **IV** display strong anti-HIV activities.^[7] Moreover, spirocyclic nucleoside **V** had also demonstrated strong inhibitory effect against human coronavirus.^[8]

Traditional routes to construct spirocyclic nucleoside have been based on either a linear approach or a convergent synthesis that requires multiple steps from an equivalent starting material.^[9] Hence, development of efficient methods to synthesize various spirocyclic nucleoside is

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Figure 1 Examples of biologically active spirocyclic nucleoside analogs

highly desirable. Recently, we developed a highly enantioselective synthesis of chiral cyclopropyl nucleosides via catalytic asymmetric intermolecular cyclopropanation reaction of α -purine acrylates with α -bromo-carboxylic esters.^[10b] Inspired by this work, α -chloro-cyclopentone was selected to react with α -thymine acrylate in the presence of base. Interestingly, Michael addition first occurred in the presence of base to generate intermediate A, which subsequently underwent the nucleophilic substitution (S_N2) to produce C(2')-spiro[2-oxocyclopentyl]cyclopropyl nucleoside. The excellent diastereoselectivity ($dr > 20 : 1$) was obtained due to the intramolecular S_N2 reaction process (Scheme 1). Continuing from our previous works on nucleosides,^[10] herein we report the intermolecular cyclopropanation reaction for the synthesis of a broad range of C(2')-spirocyclic modified cyclopropyl nucleosides, which could provide an easy access to various spirocyclic nucleosides with excellent diastereoselectivities and good yields.

Scheme 1 Our strategy to construct C(2')-spirocyclic modified cyclopropyl nucleoside analogs

2 Results and discussion

We conducted our studies with α -thymine acrylate **1a** and 2-chloro-cyclopentone **2a** as model substrates to optimize the reaction condition (Table 1). Initially, various bases were tested in CH₃CN at room temperature (r.t.) (Table 1, Entries 1~6). Only trace amount of products were obtained when Na₂CO₃ and Et₃N were used as bases, respectively (Table 1, Entries 1, 2). Interestingly, the desired products were obtained with 39%~56% yields when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), K₂CO₃ and Cs₂CO₃ were used as bases (Table 1, Entries 3~5). To our delight, the reaction proceeded well with KO^tBu as base and 60% yield was achieved (Table 1, Entry 6). Thus, the KO^tBu was selected as the best base to further screen solvents including CH₂Cl₂, MeOH, tetrahydrofuran (THF), toluene and dioxane. However, the obtained results were not further improved (Table 1, Entries 7~11). Therefore, CH₃CN was used in subsequent studies. Up increasing temperature from room temperature to 35 °C, the yield decreased (37% yield, Table 1, Entry 12). However, when the reaction was performed below room temperature, the optimal reaction temperature was -20 °C which afforded the desired product with up to 84% yield (Table 1, En-

Table 1 Screening of reaction conditions^{a,b}

Entry	Base	Solvent	Temp.	Yield ^c /%
1	Na ₂ CO ₃	CH ₃ CN	r.t.	Trace
2	Et ₃ N	CH ₃ CN	r.t.	Trace
3	DBU	CH ₃ CN	r.t.	39
4	K ₂ CO ₃	CH ₃ CN	r.t.	44
5	Cs ₂ CO ₃	CH ₃ CN	r.t.	56
6	KO ^t Bu	CH ₃ CN	r.t.	60
7	KO ^t Bu	CH ₂ Cl ₂	r.t.	8
8	KO ^t Bu	MeOH	r.t.	51
9	KO ^t Bu	THF	r.t.	17
10	KO ^t Bu	Toluene	r.t.	Trace
11	KO ^t Bu	Dioxane	r.t.	12
12	KO ^t Bu	CH ₃ CN	35	37
13	KO ^t Bu	CH ₃ CN	15	62
14	KO ^t Bu	CH ₃ CN	0	66
15	KO ^t Bu	CH ₃ CN	-10	73
16	KO ^t Bu	CH ₃ CN	-20	84
17	KO ^t Bu	CH ₃ CN	-30	79
18 ^d	KO ^t Bu	CH ₃ CN	-20	58
19 ^e	KO ^t Bu	CH ₃ CN	-20	84
20 ^f	KO ^t Bu	CH ₃ CN	-20	82
21 ^g	KO ^t Bu	CH ₃ CN	-20	83

^a Unless otherwise noted, the reaction was performed with **1a** (0.1 mmol), **2a** (1.5 equiv.), base (1.5 equiv.) in solvent (1.0 mL) at air for 5 h. ^b $dr > 20 : 1$. ^c Isolated yields. ^d KO^tBu (1.2 equiv.). ^e KO^tBu (2.0 equiv.). ^f 1 h. ^g 0.5 h.

tries 13~17). In addition, the effect of the base was also examined and the highest yield was obtained with 1.5 equiv. of KO^tBu (Table 1, Entries 18, 19). Surprisingly, the yield did not obviously decrease when the reaction time was shortened to 0.5 h (83% yield, Table 1, Entry 21). Based on the above results, the optimal reaction conditions were KO^tBu (1.5 equiv.) as base in CH₃CN (1.0 mL) at -20 °C for 0.5 h.

With the optimized reaction conditions in hand, the scope of the reaction was investigated and the results are presented in Table 2. In general, the reactions proceeded well and a series of C(2')-spirocyclic modified cyclopropyl nucleosides were obtained with up to 85% yield. The configuration of C(2')-spirocyclic modified cyclopropyl nucleosides was confirmed based on the X-ray analysis of **3fa**. Several α -thymine substituted acrylates bearing different ester groups, such as CO₂Me, CO₂Et and CO₂^tBu groups were used and desired products were obtained with excellent yields (**3aa**~**3ca**, 83%~85% yields). When CO₂Bn was used as ester group (**1d**), the cyclopropanation reaction proceeded smoothly and 65% yield was achieved (**3da**). Unfortunately, the yield marginally decreased when CO₂Ph was used as ester group (**3ea**, 24% yield). Subsequently, α -thymine substituted acrylates **1f**~**1i** bearing

F, Cl, Br and I at C(5) of thymine skeleton were also examined and the desired products were produced in good yields (**3fa**~**3ia**, 63%~68% yields). Unfortunately, introducing CF₃ at C(5) of thymine skeleton (**1j**) caused the yield to decrease to 31%. Acrylates **1k**~**1l** bearing H or Et at C(5) of thymine skeleton were also evaluated and the desired products were produced with good yields (**3ka**~**3la**, 81%~84% yields). Acrylate **1m** bearing MeO at C(5) of the thymine skeleton was investigated, and a satisfactory yield was obtained (**3ma**, 70% yield). Interestingly, varying the protecting groups at N(3) on thymine skeleton had no noticeable effect on the yields (**3na**~**3pa**, 70%~79% yields). When cytosine was used as nucleoside base, excellent yield was achieved (**3qa**, 84% yield). In addition, different 2-chloro-cycloalkanones were also probed. Good yield was obtained when 2-chloro-cyclohexanone **2b** was used and reaction time was prolonged to 12 h (**3ab**, 66% yield). Similarly, when 2-chloro-cycloheptanone **2c** was used as substrate, the reaction proceeded well with 72% yield.

To further evaluate the potential application of this reaction for synthesizing diverse C(2')-spirocyclic modified cyclopropyl nucleosides, the reaction was carried out on

Table 2 Scope of α -thymine acrylates and α -chloro-cycloalkanones^{a,b,c}

^a Unless otherwise noted, the reaction was performed with **1a**~**1q** (0.1 mmol), **2a**~**2c** (1.5 equiv.), KO^tBu (1.5 equiv.) in CH₃CN (1.0 mL) at -20 °C for 0.5 h. ^b Isolated yields. ^c >20 : 1 dr. ^d Configuration of spirocyclic cyclopropyl nucleosides **3fa** determined by single crystal X-ray analysis. ^e Reaction time: 12 h.

5.4 mmol scale. In the presence of 1.5 equiv. of KO^tBu, 5.4 mmol of α -thymine substituted acrylate **1a** reacted smoothly with 2-chloro-cyclopentone **2a**, affording 1.54 g (72% yield) of the desired adduct **3aa** (Scheme 2, a). Subsequently, further transformations were performed by using **3aa** as substrate (Scheme 2, b). When NaBH₄ was used as the reducing agent, only carbonyl group was reduced to hydroxy group, yielding hydroxyl-substituted spirocyclic nucleoside **4aa** with excellent diastereoselectivity (>20 : 1) and 60% yield. Lastly, Bz protecting group at N(3) position of **4aa** could be removed, giving the corresponding product **5aa** in 87% yield.

(a) Scale-up synthesis of **3aa**

(b) Further transformations of product **3aa**

Scheme 2 Scale-up synthesis of **3aa** and its further transformations

3 Conclusions

In summary, an efficient synthetic route to produce C(2')-spirocyclic modified cyclopropyl nucleosides analogues via Michael addition-initiated intermolecular cyclopropanation reaction was developed. Using KO^tBu as base, a series of C(2')-spirocyclic nucleoside analogues were obtained with excellent diastereoselectivities (>20 : 1) and good yields (up to 85%). Moreover, through further transformations, other hydroxyl-substituted spirocyclic nucleosides were obtained.

4 Experimental section

4.1 Instrument and reagent

¹H NMR spectra were recorded on Bruker Avance III HD 600 or Avance 400 MHz spectrometer. ¹³C NMR data were collected on commercial instruments (100 or 150

MHz) with complete proton decoupling. HRMS were obtained on a Bruker microToF II Mass Spectrometer (ESI Source). Single crystal X-ray crystallography data were obtained on a Supernova Atlas S2 CCD detector. IR absorption spectra were recorded on a PerkinElmer Spectrum 400F spectrometer. Melting point (m.p.) data were obtained on an X-5 micro melting point apparatus. All reagents were reagent grade quality and purchased from commercial sources unless otherwise indicated.

4.2 General procedure for cyclopropanation reaction

To a mixture of α -thymine substituted acrylate **1a**~**1q** (0.1 mmol) and KO^tBu (16.8 mg, 0.15 mmol) in CH₃CN (0.5 mL), the solution of α -chloro-cycloalkanones **2a**~**2c** (0.15 mmol) in CH₃CN (0.5 mL) was added. Then the mixture was stirred at $-20\text{ }^\circ\text{C}$ until the starting materials were consumed as indicated by thin layer chromatography (TLC) analysis. The reaction mixture was filtered, concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (*V* : *V* = 2 : 1) as the eluant to afford product.

Methyl 1-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (**3aa**): White solid, 32.9 mg, 83% yield. m.p. 227.2~232.5 $^\circ\text{C}$; >20 : 1 *dr*; ¹H NMR (CDCl₃, 400 MHz) δ : 7.90~7.88 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 3.2 Hz, 1H), 3.77 (s, 3H), 2.53~2.40 (m, 1H), 2.36~2.27 (m, 1H), 2.27~2.17 (m, 2H), 2.16~2.03 (m, 2H), 2.01~1.95 (m, 4H), 1.89 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 212.1, 167.7, 139.4, 135.0, 131.5, 130.7, 129.1, 111.5, 77.3, 53.6, 50.4, 42.6, 38.9, 28.5, 26.2, 20.2, 12.7; IR (KBr) ν : 1726, 1698, 1650, 1423, 1300, 1230, 776, 680, 754 cm⁻¹; HRMS (ESI-TOF) calcd for C₂₁H₂₀N₂NaO₆ (*M* + Na)⁺ 419.1214, found 419.1206.

Ethyl 1-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (**3ba**): Colorless oil, 34.9 mg, 85% yield. >20 : 1 *dr*; ¹H NMR (CDCl₃, 400 MHz) δ : 7.97~7.83 (m, 2H), 7.61 (t, *J* = 6.8 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 1.2 Hz, 1H), 4.26~4.19 (m, 2H), 2.52~2.41 (m, 1H), 2.39~2.28 (m, 1H), 2.27~2.16 (m, 2H), 2.17~2.03 (m, 2H), 2.01~1.93 (m, 4H), 1.92~1.82 (m, 1H), 1.28~1.24 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ : 212.1, 167.1, 162.8, 139.5, 134.9, 131.5, 130.7, 129.1, 111.3, 77.3, 62.8, 50.5, 42.5, 38.9, 28.6, 26.0, 20.2, 14.2, 12.7; IR (KBr) ν : 1725, 1702, 1656, 1425, 1296, 1232, 777, 763, 685 cm⁻¹; HRMS (ESI-TOF) calcd for C₂₂H₂₂N₂NaO₆ (*M* + Na)⁺ 433.1370, found 433.1370.

tert-Butyl 1-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (**3ca**): Colorless oil, 36.4 mg, 83% yield. >20 : 1 *dr*; ¹H NMR (methanol-*d*₄, 400 MHz) δ : 7.89~7.85 (m, 2H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 1.2 Hz, 1H), 7.56~7.52 (m, 2H), 2.45~2.42 (m, 1H), 2.25~2.20 (m, 3H), 2.07~2.06 (m, 2H), 1.97~1.87 (m, 6H), 1.45 (s, 9H); ¹³C NMR (methanol-*d*₄, 100 MHz) δ : 214.1, 169.7, 167.1, 142.9,

136.3, 132.7, 131.4, 130.3, 111.5, 84.8, 52.4, 43.8, 39.8, 29.9, 28.2, 26.9, 21.1, 12.2; IR (KBr) ν : 1724, 1703, 1651, 1423, 1297, 1246, 780, 764, 686 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{NaO}_6$ ($\text{M} + \text{Na}$)⁺ 461.1683, found 461.1688.

Benzyl 1-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (3da): Colorless oil, 30.7 mg, 65% yield. $>20 : 1$ *dr*; ¹H NMR (CDCl_3 , 600 MHz) δ : 7.79 (d, $J=6.0$ Hz, 2H), 7.52 (t, $J=7.2$ Hz, 1H), 7.35 (d, $J=7.2$ Hz, 2H), 7.30~7.18 (m, 6H), 7.00 (s, 1H), 5.13 (q, $J=8.0$ Hz, 2H), 2.35~2.31 (m, 2H), 2.17~2.09 (m, 2H), 2.04~2.02 (m, 2H), 1.90~1.86 (m, 4H), 1.81~1.77 (m, 1H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 212.0, 167.1, 162.8, 139.4, 134.9, 131.4, 130.6, 129.1, 128.8, 128.6, 127.7, 111.4, 68.2, 50.5, 42.7, 38.9, 28.5, 26.1, 20.2, 12.7; IR (KBr) ν : 1728, 1703, 1651, 1422, 1257, 1230, 798, 763, 685 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{27}\text{H}_{24}\text{N}_2\text{NaO}_6$ ($\text{M} + \text{Na}$)⁺ 495.1527, found 495.1519.

Phenyl 1-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (3ea): Colorless oil, 11.0 mg, 24% yield. $>20 : 1$ *dr*; ¹H NMR (CDCl_3 , 400 MHz) δ : 7.89 (d, $J=7.2$ Hz, 2H), 7.59 (t, $J=7.2$ Hz, 1H), 7.43~7.35 (m, 4H), 7.28~7.24 (m, 1H), 7.20 (s, 1H), 7.06~7.03 (m, 2H), 2.58~2.55 (m, 1H), 2.50~2.35 (m, 1H), 2.31~2.10 (m, 5H), 2.01 (s, 3H), 1.99~1.85 (m, 1H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 211.7, 166.0, 150.2, 139.1, 134.9, 131.3, 130.6, 129.6, 129.0, 126.5, 121.3, 111.6, 50.2, 43.0, 38.8, 28.5, 26.4, 20.1, 12.7; IR (KBr) ν : 1746, 1702, 1655, 1422, 1208, 1230, 778, 762, 685 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{26}\text{H}_{22}\text{N}_2\text{NaO}_6$ ($\text{M} + \text{Na}$)⁺ 481.1307, found 481.1366.

Methyl 1-(3-benzoyl-5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (3fa): White solid, 26.2 mg, 68% yield. m.p. 209.2~214.4 °C; $>20 : 1$ *dr*; ¹H NMR (CDCl_3 , 400 MHz) δ : 7.89~7.87 (m, 2H), 7.64 (t, $J=7.6$ Hz, 1H), 7.51~7.47 (m, 3H), 3.78 (s, 3H), 2.46~2.40 (m, 1H), 2.30~2.20 (m, 3H), 2.13~2.08 (m, 2H), 1.97 (d, $J=5.2$ Hz, 1H), 1.92~1.87 (m, 1H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 212.1, 167.1, 167.1, 149.7, 140.5, 135.4, 130.9, 130.7, 129.2, 109.4, 53.8, 50.7, 42.6, 38.9, 28.5, 26.4, 20.1; IR (KBr) ν : 1728, 1707, 1668, 1413, 1296, 1235, 967, 752, 679 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{20}\text{H}_{17}\text{FN}_2\text{NaO}_6$ ($\text{M} + \text{Na}$)⁺ 423.0963, found 423.0960.

Methyl 1-(3-benzoyl-5-chloro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (3ga): White solid, 27.0 mg, 65% yield. m.p. 202.5~207.3 °C; $>20 : 1$ *dr*; ¹H NMR (CDCl_3 , 400 MHz) δ : 7.89~7.87 (m, 2H), 7.64 (t, $J=7.6$ Hz, 1H), 7.52~7.47 (m, 3H), 3.79 (s, 3H), 2.48~2.41 (m, 1H), 2.30~2.20 (m, 3H), 2.14~2.09 (m, 2H), 1.98 (d, $J=5.2$ Hz, 1H), 1.92~1.85 (m, 1H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 212.1, 149.7, 140.5, 135.4, 130.9, 130.8, 129.2, 109.5, 77.3, 53.8, 50.7, 42.6, 38.9, 28.5, 26.4, 20.2; IR (KBr) ν : 1728, 1710, 1668, 1412, 1238, 1212, 816, 778, 684 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{20}\text{H}_{17}\text{ClN}_2\text{NaO}_6$ ($\text{M} + \text{Na}$)⁺ 439.0667, found 439.0665.

Methyl 1-(3-benzoyl-5-bromo-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (3ha): White solid, 29.0 mg, 63% yield. m.p. 194.0~199.4 °C; $>20 : 1$ *dr*; ¹H NMR (CDCl_3 , 400 MHz) δ : 7.88 (d, $J=7.2$ Hz, 2H), 7.65~7.59 (m, 2H), 7.49 (t, $J=8.0$ Hz, 2H), 3.79 (s, 3H), 2.45~2.40 (m, 1H), 2.30~2.20 (m, 3H), 2.11~2.08 (m, 2H), 1.98 (d, $J=5.2$ Hz, 1H), 1.92~1.87 (m, 1H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 212.1, 167.1, 167.1, 143.0, 135.3, 130.9, 130.7, 129.2, 97.2, 53.8, 50.7, 42.5, 38.9, 28.5, 26.4, 20.1; IR (KBr) ν : 1737, 1710, 1673, 1409, 1295, 1238, 962, 687, 649 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{20}\text{H}_{17}\text{BrN}_2\text{NaO}_6$ ($\text{M} + \text{Na}$)⁺ 483.0162, found 483.0167.

Methyl 1-(3-benzoyl-5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (3ia): Grey oil, 34.0 mg, 67% yield. $>20 : 1$ *dr*; ¹H NMR (CDCl_3 , 400 MHz) δ : 7.87 (d, $J=7.6$ Hz, 2H), 7.68~7.61 (m, 2H), 7.49 (t, $J=7.6$ Hz, 2H), 3.78 (s, 3H), 2.45~2.42 (m, 1H), 2.30~2.20 (m, 3H), 2.13~2.08 (m, 2H), 1.98~1.97 (m, 1H), 1.92~1.86 (m, 1H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 212.0, 167.2, 167.1, 150.3, 148.0, 135.3, 130.8, 130.7, 129.2, 68.7, 53.8, 50.5, 42.5, 38.9, 28.5, 26.5, 20.1; IR (KBr) ν : 1732, 1705, 1665, 1397, 1293, 1236, 757, 685, 648 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{20}\text{H}_{17}\text{IN}_2\text{NaO}_6$ ($\text{M} + \text{Na}$)⁺ 531.0024, found 531.0016.

Methyl 1-(3-benzoyl-2,4-dioxo-5-(trifluoromethyl)-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (3ja): Colorless oil, 14.0 mg, 31% yield. $>20 : 1$ *dr*; ¹H NMR (CDCl_3 , 400 MHz) δ : 7.88 (d, $J=7.2$ Hz, 2H), 7.71~7.64 (m, 2H), 7.51 (t, $J=7.6$ Hz, 2H), 3.81 (s, 3H), 2.57~2.41 (m, 1H), 2.37~2.21 (m, 3H), 2.16~2.10 (m, 2H), 1.99~1.89 (m, 2H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 135.5, 130.7, 129.3, 77.4, 76.8, 53.9, 42.4, 38.9, 28.5, 26.5, 20.2; IR (KBr) ν : 1755, 1720, 1680, 1430, 1296, 1237, 778, 647, 637 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{21}\text{H}_{17}\text{F}_3\text{N}_2\text{NaO}_6$ ($\text{M} + \text{Na}$)⁺ 473.0931, found 473.0923.

Methyl 1-(3-benzoyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (3ka): White solid, 32.1 mg, 84% yield. m.p. 187.4~192.1 °C; $>20 : 1$ *dr*; ¹H NMR (CDCl_3 , 400 MHz) δ : 7.90~7.88 (m, 2H), 7.62 (t, $J=7.6$ Hz, 1H), 7.49 (t, $J=7.6$ Hz, 2H), 7.26~7.23 (m, 1H), 5.84 (d, $J=8.4$ Hz, 1H), 3.77 (s, 3H), 2.46~2.43 (m, 1H), 2.28~2.19 (m, 3H), 2.12~2.08 (m, 2H), 1.95 (d, $J=5.2$ Hz, 1H), 1.89~1.86 (m, 1H); ¹³C NMR (100 MHz, CDCl_3) δ : 212.0, 167.4, 161.9, 143.7, 135.1, 131.3, 130.6, 129.1, 102.9, 53.6, 50.5, 42.4, 38.9, 28.5, 26.3, 20.1; IR (KBr) ν : 1727, 1704, 1665, 1431, 1230, 1220, 801, 756, 680 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_6$ ($\text{M} + \text{H}$)⁺ 383.1238, found 383.1232.

Methyl 1-(3-benzoyl-5-ethyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (3la): Colorless oil, 33.2 mg, 81% yield. $>20 : 1$ *dr*; ¹H NMR (CDCl_3 , 400 MHz) δ : 7.88 (d, $J=7.6$ Hz, 2H), 7.61 (d, $J=7.2$ Hz, 1H), 7.47 (d, $J=7.6$ Hz, 2H), 6.98 (s, 1H), 3.77 (s, 3H), 2.47~2.37 (m, 3H), 2.35~2.18 (m, 3H), 2.14~2.08 (m, 2H), 1.96 (d, $J=5.2$ Hz, 1H), 1.90~1.85

(m, 1H), 1.17 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 212.1, 168.6, 167.7, 138.5, 135.0, 131.5, 130.6, 129.1, 117.1, 53.6, 50.5, 42.6, 38.9, 28.5, 26.2, 20.3, 20.1, 12.5; IR (KBr) ν : 1744, 1732, 1692, 1429, 1237, 1214, 954, 769, 687 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{NaO}_6$ ($\text{M} + \text{Na}$) $^+$ 433.1370, found 433.1365.

Methyl 1-(3-benzoyl-5-methoxy-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (**3ma**): Colorless oil, 28.8 mg, 70% yield. $>20 : 1$ dr; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.88 (d, $J=6.8$ Hz, 2H), 7.62 (t, $J=7.6$ Hz, 1H), 7.48 (t, $J=8.0$ Hz, 2H), 6.76 (s, 1H), 3.78~3.77 (m, 6H), 2.45~2.41 (m, 1H), 2.28~2.18 (m, 3H), 2.10~2.06 (m, 2H), 1.96 (d, $J=5.2$ Hz, 1H), 1.89 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 212.0, 167.6, 149.3, 136.6, 135.1, 131.2, 130.7, 129.1, 123.5, 57.9, 53.6, 50.8, 43.0, 38.9, 28.5, 26.2, 20.1; IR (KBr) ν : 1727, 1704, 1660, 1433, 1292, 1241, 763, 685, 644 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{NaO}_6$ ($\text{M} + \text{Na}$) $^+$ 435.1163, found 435.1161.

tert-Butyl 3-(1-(methoxycarbonyl)-4-oxospiro[2.4]heptan-1-yl)-5-methyl-2,6-dioxo-3,6-dihydropyrimidine-1(2H)-carboxylate (**3na**): White solid, 30.9 mg, 79% yield. m.p. 180.0~185.4 $^{\circ}\text{C}$; $>20 : 1$ dr; ^1H NMR (CDCl_3 , 600 MHz) δ : 6.94~6.92 (m, 1H), 3.74 (s, 3H), 2.65~2.44 (m, 2H), 2.33~2.18 (m, 3H), 2.03 (d, $J=4.8$ Hz, 1H), 1.93~1.92 (m, 3H), 1.89 (d, $J=5.4$ Hz, 1H), 1.68 (s, 1H), 1.56 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 211.2, 167.8, 147.7, 139.0, 111.1, 86.5, 53.6, 50.6, 42.4, 38.8, 28.6, 27.5, 26.3, 20.2, 12.7; IR (KBr) ν : 1775, 1739, 1714, 1652, 1302, 1250 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{NaO}_7$ ($\text{M} + \text{Na}$) $^+$ 415.1476, found 415.1471.

Methyl 1-(3-(4-chlorobenzoyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (**3oa**): White solid, 30.1 mg, 70% yield. m.p. 196.0~200.2 $^{\circ}\text{C}$; $>20 : 1$ dr; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.82 (d, $J=8.8$ Hz, 2H), 7.45 (d, $J=8.8$ Hz, 2H), 7.06 (s, 1H), 3.77 (s, 3H), 2.50~2.40 (m, 1H), 2.32~2.19 (m, 3H), 2.13~2.08 (m, 2H), 1.96~1.87 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 212.3, 167.6, 150.6, 141.7, 139.5, 132.0, 130.0, 129.5, 111.5, 53.6, 50.4, 42.6, 39.0, 28.6, 26.3, 20.2, 12.7; IR (KBr) ν : 1746, 1699, 1644, 1422, 1228, 1217, 854, 805, 768 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{21}\text{H}_{19}\text{ClN}_2\text{NaO}_6$ ($\text{M} + \text{Na}$) $^+$ 453.0824, found 453.0825.

Methyl 1-(3-(4-methoxybenzoyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-oxospiro[2.4]heptane-1-carboxylate (**3pa**): White solid, 31.9 mg, 75% yield. m.p. 205.1~210.3 $^{\circ}\text{C}$; $>20 : 1$ dr; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.84 (d, $J=8.4$ Hz, 2H), 7.05 (s, 1H), 6.93 (d, $J=8.4$ Hz, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 2.46~2.43 (m, 1H), 2.24~1.80 (m, 10H); ^{13}C NMR (CDCl_3 , 150 MHz) δ : 212.5, 167.7, 165.1, 139.3, 133.3, 124.2, 114.4, 111.4, 55.7, 53.6, 50.4, 42.6, 38.9, 28.5, 26.2, 20.2, 12.7; IR (KBr) ν : 1728, 1699, 1651, 1421, 1247, 1166, 783, 602 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{NaO}_7$ ($\text{M} + \text{Na}$) $^+$ 449.1319, found 449.1315.

Methyl 1-(ditert-butyl-(1-allyl-2-oxo-1,2-dihydropyrimi-

din-4-yl)-4-oxospiro[2.4]heptane-1-carboxylate (**3qa**): Colorless oil, 40.0 mg, 84% yield. $>20 : 1$ dr; ^1H NMR (600 MHz, CDCl_3) δ : 7.47 (d, $J=7.2$ Hz, 1H), 7.06 (d, $J=7.2$ Hz, 1H), 3.68 (s, 3H), 2.67~2.59 (m, 2H), 2.28~2.20 (m, 3H), 2.02 (d, $J=4.8$ Hz, 1H), 1.93 (d, $J=5.4$ Hz, 1H), 1.89~1.87 (m, 1H), 1.53 (s, 18H); ^{13}C NMR (100 MHz, CDCl_3) δ : 211.2, 167.9, 162.6, 149.5, 147.5, 96.8, 84.9, 53.4, 51.9, 41.9, 38.9, 28.6, 27.7, 26.6, 20.4; IR (KBr) ν : 1777, 1738, 1665, 1457, 1323, 1247, 788 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{NaO}_8$ ($\text{M} + \text{Na}$) $^+$ 500.2003, found 500.1998.

Methyl 1-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-oxospiro[2.5]octane-1-carboxylate (**3ab**): white solid, 27.0 mg, 66% yield. m.p. 210.9~216.0 $^{\circ}\text{C}$; $>20 : 1$ dr; ^1H NMR (400 MHz, CDCl_3) δ : 7.86 (d, $J=7.2$ Hz, 2H), 7.62~7.60 (m, 1H), 7.49 (t, $J=8.0$ Hz, 2H), 7.03 (s, 1H), 3.78 (s, 3H), 2.45~2.44 (m, 2H), 2.31~2.29 (m, 2H), 1.96 (d, $J=1.3$ Hz, 4H), 1.98~1.88 (m, 6H), 1.78 (d, $J=5.2$ Hz, 1H), 1.73~1.63 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ : 205.5, 168.4, 167.5, 139.6, 135.1, 131.5, 130.6, 129.2, 111.3, 53.7, 51.2, 42.9, 39.3, 27.4, 25.1, 23.5, 21.7, 12.7; IR (KBr) ν : 1774, 1696, 1648, 1420, 1310, 1260, 970, 762, 684 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{NaO}_6$ ($\text{M} + \text{Na}$) $^+$ 433.1370, found 433.1364.

Methyl 1-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-oxospiro[2.6]nonane-1-carboxylate (**3ac**): white solid, 30.5 mg, 72% yield. m.p. 213.0~218.4 $^{\circ}\text{C}$; $>20 : 1$ dr; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.87 (d, $J=8.0$ Hz, 2H), 7.62 (t, $J=7.2$ Hz, 1H), 7.48 (t, $J=8.0$ Hz, 2H), 7.04 (s, 1H), 3.76 (s, 3H), 2.82 (t, $J=12.0$ Hz, 1H), 2.34~2.29 (m, 1H), 2.21~2.15 (m, 3H), 2.00~1.73 (m, 8H), 1.38~1.25 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 207.6, 168.4, 167.6, 150.5, 139.7, 135.0, 131.5, 130.6, 129.1, 111.4, 53.7, 51.3, 46.1, 44.0, 30.6, 27.5, 27.1, 26.4, 25.6, 12.6; IR (KBr) ν : 1744, 1702, 1655, 1423, 1226, 1170, 762, 728, 683 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{NaO}_6$ ($\text{M} + \text{Na}$) $^+$ 447.1527, found 447.1532.

Methyl 1-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-hydroxyspiro[2.4]heptane-1-carboxylate (**4aa**): white solid, 23.8 mg, 60% yield. m.p. 175.5~180.1 $^{\circ}\text{C}$; $>20 : 1$ dr; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.97~7.95 (m, 2H), 7.66~7.63 (m, 1H), 7.50 (t, $J=8.0$ Hz, 2H), 7.13 (s, 1H), 3.74 (s, 3H), 3.54 (d, $J=3.2$ Hz, 1H), 2.30 (s, 1H), 2.13~2.02 (m, 1H), 1.99~1.94 (m, 3H), 1.90~1.70 (m, 6H), 1.34 (d, $J=5.2$ Hz, 1H); ^{13}C NMR (CDCl_3 , 150 MHz) δ : 169.2, 167.8, 153.5, 139.8, 135.3, 131.2, 130.5, 129.3, 112.8, 77.4, 53.3, 49.8, 47.0, 32.9, 27.9, 26.6, 20.9, 12.6; IR (KBr) ν : 3414, 1741, 1647, 1423, 1300, 1258, 800, 775, 681 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{NaO}_6$ ($\text{M} + \text{Na}$) $^+$ 421.1370, found 421.1366.

Methyl 4-hydroxy-1-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)spiro[2.4]heptane-1-carboxylate (**5aa**): white solid, 25.5 mg, 87% yield. m.p. 233.0~238.4 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ : 9.36 (s, 1H), 7.00 (s, 1H), 4.23 (s, 1H), 3.71 (s, 3H), 3.52 (d, $J=3.2$ Hz, 1H), 2.38 (s,

1H), 2.11 (s, 1H), 1.95~1.72 (m, 8H), 1.69 (d, $J=5.3$ Hz, 1H), 1.27 (d, $J=5.2$ Hz, 1H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 169.4, 163.4, 154.3, 140.1, 112.7, 77.2, 53.3, 49.3, 47.0, 32.8, 27.9, 26.9, 20.9, 12.5; IR (KBr) ν : 3416, 1721, 1681, 1288, 1233 cm^{-1} ; HRMS (ESI-TOF) calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{NaO}_5$ ($\text{M}+\text{Na}$) $^+$ 317.1108, found 317.1107.

Supporting Information The synthesis method of the starting materials, compound characterization data and X-ray data for compounds **3fa**. The Supporting Information is available free of charge via the Internet at <http://sioc-journal.cn>.

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