Chinese Journal of Chemistry, **2004**, *22*, 1359—1365 **Article**

An Efficient Synthesis of Highly Optically Active 4-Substituted-2(5*H*)-furanones from Chiral 3-Bromo-2(5*H*)-furanone

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Highly optically active 4-substituted-2(5*H*)-furanones **6a—6j** were obtained in good yields with *de*⩾98% by the tandem Michael addition/elimination reaction of chiral 3-bromo-2(5*H*)-furanone (**4a**), which was conveniently prepared starting from 2-furaldehyde under mild conditions. The products were identified on the basis of their satisfactory elemental analysis and spectroscopic data of IR, UV, ^{1}H NMR, ^{13}C NMR and mass spectra. The stereochemistry and absolute configuration of this type of compounds were established by the X-ray crystallographic study. The reaction provided a short and efficient synthesis of the interesting highly optically active 4-substituted-2(5*H*)-furanones containing an active pyrimidine and a purine base group.

Keywords optically active 4-substituted-2(5*H*)-furanone, tandem asymmetric Michael addition/elimination reaction, pyrimidine or purine base group, X-ray crystallography

Butenolide derivatives are a group of important compounds containing unique carbon skeleton of 2(5H)-furanone which is widely present in many natural products.[1-3] They exhibit a variety of biological properties and have been considered as potential anti-tumor agents, fungicides, bactericides, insecticides, antibiotics, antiinflammatories, allergy inhibitors, antipsoriasis agents, cyclooxygenase inhibitors, phospholipase A_2 inhibitors, some microbial degradable products and so on.[4-8] Thus, much attention has been paid to the new asymmetric methods for synthesis of these interesting compounds.[9-12]

The well-known chiral 5-(*R*)-menthyloxy-2(5*H*)-furanone behaves as a Micheal acceptor towards carbon, oxygen, sulphur and nitrogen nucleophiles to afford chiral 4-(*R*)-menthyloxy-3-substituted butyrolactone via a simple Micheal addition.[13,14] The 5-(*R*)-menthyloxy-3,4-dihalo(chloro, bromo)-2(5*H*)-furanone reacts with corresponding nucleophiles to give chiral 5-(*R*)-menthyloxy-4-substituted-3-halo-2(5*H*)-furanone compounds via a tandem asymmetric Michael addition/elimination reaction.[15,16] Recently, we successfully synthesized the novel chiral synthon, 5-(*R*)-(—)-menthyloxy-3-bromo-2(5*H*)-furanone (**4a**) in good yield with *de* ⩾ 98% through a valuable synthetic route and applied the tandem double Michael addition/internal substitution of chiron **4a** to various nucleophiles to obtain the novel functionalized spiro-cyclopropanes containing multiple stereogenic centers.[17-19] The reaction of the heterocyclic amines **5a—5c** with chiral synthon **4a** in a molar ratio of 1∶2 underwent the expected reaction to form the spiro-cyclopropane products containing heterocyclic amino groups in 25%—30% yields. The stereochemistry and absolute configuration of the chiral spiro-cyclopropanes were characterized by spectroscopic data as well as X-ray crystallography.[19] The regioselective and stereoselective transformation of the auxiliary group in the obtained spiro-cyclopropane derivatives were also investigated.[20-22]

Results and discussion

On the basis of previous work, we have accomplished the tandem Michael addition/elimination reaction of chiral synthon **4a** with different nucleophiles, such as the heterocyclic amines (**5a—5c**), 2-naphthol (**5d**), 8-hydroxy-quinoline (**5e**), 2-amino-4-methylthiazole (**5f**), in the presence of potassium carbonate and *n*-tetrabutylammonium bromide (TBAB) as a phase transfer catalyst under mild conditions to give the novel chiral butenolides **6a—6f**. However, the reaction of this chiron **4a** with a new type of nucleophilic reagents such as imidazole (**5g**), 4,6-dimethyl-2-mercaptopyrimidine (**5h**), adenine (**5i**) and 8-azaguanine (**5j**) afforded the chiral products **6g—6j** containing an important organic base group, under the changed conditions, *i.e.* the presence of triethylamine as a base and DMF or DMSO as a solvent. Table 1 shows the results of the obtained optically active butenolides **6a—6j** by tandem Michael

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Table 1 Synthesis of optically active 4-substituted-2(5*H*)-furanones **6** from chiron **4** and nucleophiles **5** by the tandem Michael addition/elimination reaction

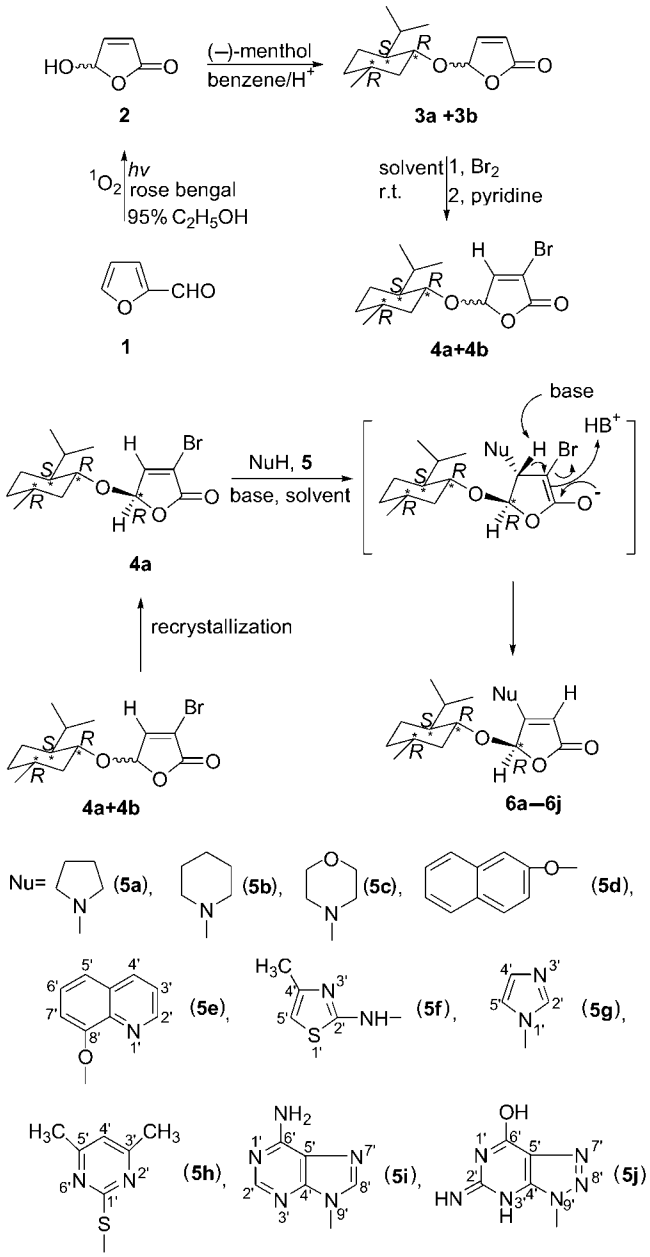
Entry	Nucleophile **5**	Amount (mmol) **5**∶**4**	Condition Solvent/Base/Time (day)	Yield of **6** [a]/%
1	**5a**	3∶1	CH_3CN/K_2CO_3/TBAB/3	85 (**6a**)
2	**5b**	3∶1	CH_3CN/K_2CO_3/TBAB/2	78 (**6b**)
3	**5c**	3∶1	CH_3CN/K_2CO_3/TBAB/4	90 (**6c**)
4	**5d**	1∶1	CH_3CN/K_2CO_3/TBAB/1	63 (**6d**)
5	**5e**	1∶1	CH_3CN/K_2CO_3/TBAB/1	58 (**6e**)
6	**5f**	1∶1	CH_3CN/K_2CO_3/TBAB/6	43 (**6f**)
7	**5g**	1∶1	DMF/Et_3N/6	72 (**6g**)
8	**5h**	1∶1	DMF/Et_3N/6	41 (**6h**)
9	**5i**	1∶1	DMSO/Et_3N/4	50 (**6i**)
10	**5j**	1∶1	DMSO/Et_3N/4	68 (**6j**)

[a] Yield of isolated products.

addition/elimination reaction of synthon **4a** with nucleophiles. The heterocyclic amines and chiral synthon **4a** were presented in a molar ratio of **5a**—**5c**∶**4a**=3∶1 to form the chiral compounds **6a**—**6c** (Entries 1—3) in 73%—90% yields with *de*⩾98% as shown in Scheme 1. It is probably that the excess heterocyclic amine as a base that caused the Michael addition/elimination reaction for the chiral 3-bromo-2(5*H*)-furanone.[16,17] Moreover, if chiral synthon **4a** and nucleophiles **5d**—**5f** were used in a molar ratio of 1∶1, the tandem reaction underwent easily to afford the chiral products **6d**—**6f** in 43%—63% yields (Entries 4—6). It could be noted that a bulkier or more basic nature of the nucleophilic molecules facilitated the tandem Michael addition/elimination reaction to offer the expected products **6d**—**6f**. Imidazole **5g** and 4,6-dimethyl-2-mercaptopyrimidine **5h** reacted with chiron **4a** via the reaction to afford the 4-functionalized substituted-2(5*H*)-furanones **6g**—**6h** in 41%—63% yields (Entries 7, 8). Due to the special bioactive properties of purine bases we have also synthesized the interesting butenolide derivatives **6i**—**6j** in 50%—68% yields (Entries 9, 10). Few reports on the Michael addition reaction of purine and its analogues as Michael donators were shown in literature.[23] We have improved the experimental process that the purine bases **5i**—**5j** were dissolved in DMSO at 40 ℃ followed by the addition of triethylamine and chiron **4a** at room temperature.

The synthesis of optically active 5-*l*-menthyloxy-3-bromo-2-(5*H*)-furanone **4a** was conveniently achieved starting from 5-hydroxy-2(5*H*)-furanone **2**. The photooxidation of 2-furaldehyde **1** is probably the most suitable for the preparation of **2**.[13,14,16,17] We have performed the photosynthetic procedure using 95% C_2H_5OH as a solvent at room temperature to provide 5-hydroxy-2(5*H*)-furanone **2** in good yield.[13] Epimeric mixture of 5-menthyloxy-2(5*H*)-furanone **3** was readily available through the asymmetric acetalization of the resulting 5-hydroxy-2(5*H*)-furanone **2** with (−)-menthol under reflux in benzene in the presence of a catalytic amount of concentrated sulfuric acid.[13,16] The prepara-

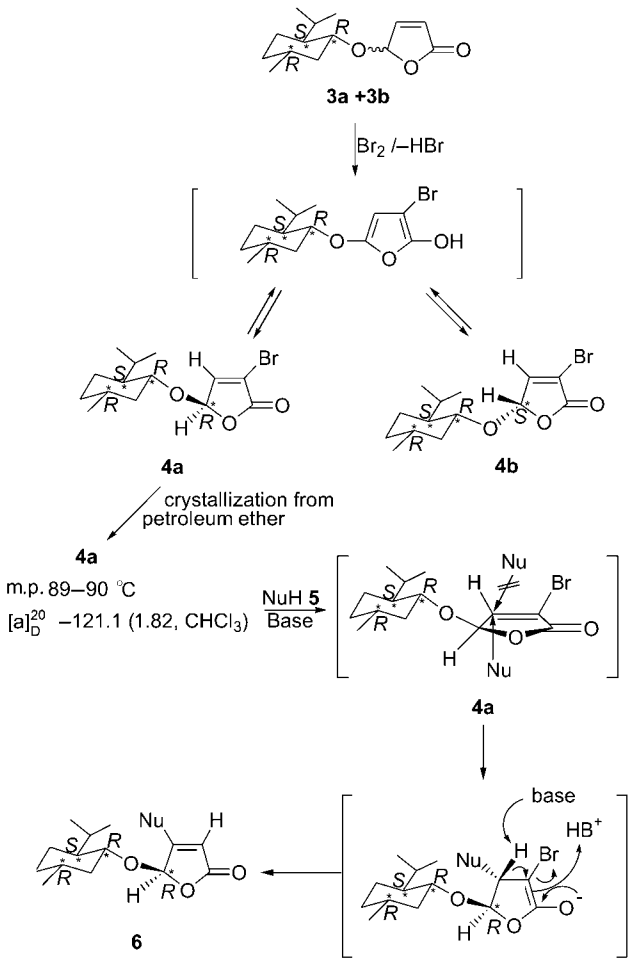
Scheme 1



tion of optically active **4a** was based on the crystallization of epimeric mixture of 5-menthyloxy-3-bromo-2(5*H*)-furanone **4a**+**4b** which was obtained from the bromination of epimeric mixture of **3** followed by the elimination of hydrogen bromide. Structure of **4a** was assigned to be the major diastereoisomer based on the NMR technique and X-ray differential studies of **6g** and **6h**. The diastereoisomeric ratio (**4a** : **4b**=60 : 40) was readily determined from the ^{1}H NMR spectrum of the product **4** by integration of the signals of the acetal hydrogen atoms of **4a**+**4b** (Scheme 2). 5-(*R*)-Menthyloxy-3-bromo-2-(5*H*)-furanones (**4a**+**4b**) have the ^{1}H NMR characterization shifts δ_{4a}: 5.97 (s, 0.6H, C_5-H) and δ_{4b}: 5.87 (s, 0.4H, C_5-H). After twice crystallization of the mixture **4a**+**4b** at −20 ℃ from petroleum ether (b.p. 30—60 ℃), the optically active **4a** was obtained as a light yellow crystalline chiron in diastereomeric excess of *de*≥98% as deduced from the ^{1}H NMR analysis. After the recrystallization process accompanied by a remarkable second order asymmetric transformation[24] of **4a** and **4b** in solution, a 60 : 40 ratio of diastereoisomers (**4a** : **4b**) was obtained again. The "crystallization induced epimerization" probably took place via enolization[25] of **4b** (and **4a**) to the unstable 5-(*l*-menthyloxy)-3-bromo-2-hydroxyfuran intermediate and is essentially driven by the continuous removal of the major crystalline isomer **4a** from the solution (Scheme 2). The ^{1}H NMR and ^{13}C NMR data showed a very high purity for compounds **6a**—**6j**. The absolute configurations of the product were established by X-ray crystallography.

The method presented an efficient synthetic route to highly optically active 4-substituted-2(5*H*)-furanones **6a**—**6j** in good yields with *de*≥98% (referred to the chirality of γ-position of the 4-substitued butenolide molecule) via tandem Michael addition/elimination reaction of chiral synthon **4a** with the corresponding nitrogen or oxygen nucleophiles **5a**—**5j**.

Scheme 2



Description of crystal structure of 6g

The ORTEP drawing and the crystal packing of molecule **6g** are shown in Figures 1 and 2, respectively. The crystal **6g** belongs to monoclinic system with $P2_1$ space group. The crystal lattice parameters are a=0.57824(12) nm, b=0.82816(17) nm, c=1.7988(4) nm, β=91.33(3)°, V=0.8612(3) nm^3, Z=2, D_c=1.174 g/cm^3, μ=0.081 mm^{-1}, F(000)=328. The deflection factor [$I>2\sigma(I)$] is R=0.0983, wR=0.02463 and the maximum residual peak in the D-value Fourier scheme is 0.390×10^2 e•nm^{-3}. (1*R*,2*S*,5*R*)-(−)-Menthyloxy group is an internal standard in the whole molecule.

Accordingly, the absolute configuration of molecule **6g** was established. The selected bond lengths (nm) and the main bond angles (°) of compound **6g** are shown in Tables 2 and 3.

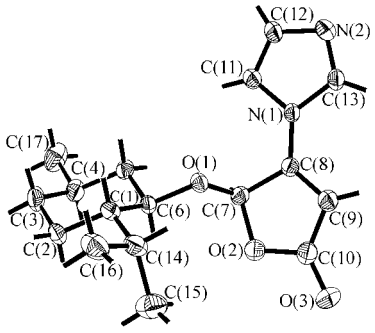


Figure 1 ORTEP drawing of molecule **6g**.

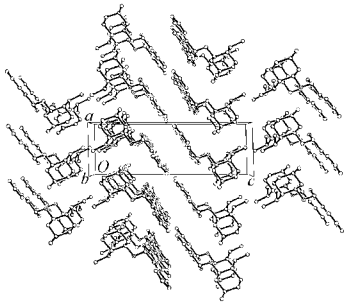


Figure 2 Crystal packing of molecule **6g**.

Description of crystal structure of 6h

The ORTEP drawing and the crystal packing of molecule **6h** are shown in Figures 3 and 4, respectively.

Table 2 Main bond lengths (nm) of compound **6g**

O(1)—C(7)	0.1372(9)	N(2)—C(13)	0.1300(12)	C(4)—C(17)	0.1524(16)
O(1)—C(6)	0.1464(8)	N(2)—C(12)	0.1361(11)	C(5)—C(6)	0.1521(13)
O(2)—C(10)	0.1379(10)	C(1)—C(2)	0.1514(12)	C(7)—C(8)	0.1494(10)
O(2)—C(7)	0.1437(10)	C(1)—C(6)	0.1524(11)	C(8)—C(9)	0.1309(11)
O(3)—C(10)	0.1223(12)	C(1)—C(14)	0.1548(14)	C(9)—C(10)	0.1418(13)
N(1)—C(8)	0.1376(9)	C(2)—C(3)	0.1517(16)	C(11)—C(12)	0.1313(11)
N(1)—C(13)	0.1388(10)	C(3)—C(4)	0.1528(15)	C(14)—C(15)	0.1519(16)
N(1)—C(11)	0.1393(11)	C(4)—C(5)	0.1516(11)	C(14)—C(16)	0.1547(13)

Table 3 Main bond angles (°) of compound **6g**

C(7)-O(1)-C(6)	113.9(5)	O(1)-C(6)-C(1)	107.7(6)	N(1)-C(8)-C(7)	120.4(7)
C(10)-O(2)-C(7)	108.1(7)	O(1)-C(7)-O(2)	111.8(6)	C(8)-C(9)-C(10)	108.6(8)
C(8)-N(1)-C(13)	127.3(6)	O(1)-C(7)-C(8)	112.1(7)	O(3)-C(10)-O(2)	118.5(9)
C(8)-N(1)-C(11)	103.6(6)	O(2)-C(7)-C(8)	103.2(6)	O(3)-C(10)-C(9)	131.9(9)
C(5)-C(6)-C(1)	111.4(6)	N(1)-C(8)-C(9)	129.4(7)	O(2)-C(10)-C(9)	109.5(8)
O(1)-C(6)-C(5)	110.6(6)	C(9)-C(7)-C(7)	110.1(7)	N(2)-C(13)-N(1)	113.7(7)

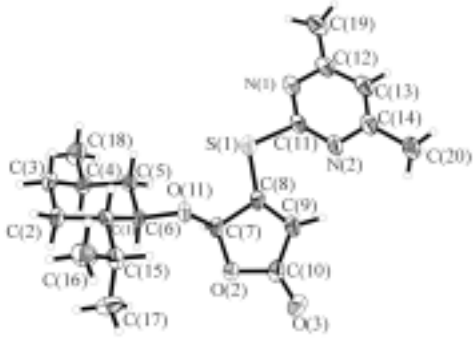


Figure 3 ORTEP drawing of molecule **6h**.

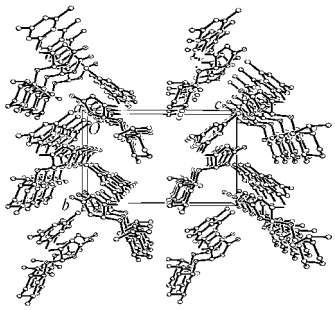


Figure 4 Crystal packing of molecule **6h**.

The crystal **6h** belongs to monoclinic system and $P2_1$ space group. The crystal lattice parameters are a=0.86271(17) nm, b=1.0014(2) nm, c=1.2189(2) nm, β=97.00(3)°, V=1.0453(4) nm^3, Z=2, D_c=1.196 g/cm^3, μ=0.175 mm^{-1}, F(000)=404. The deflection factor [$I>2\sigma(I)$] is R=0.0433, wR=0.0795 and the maximum residual peak in the D-value Fourier scheme is 0.152×10^2 e•nm^{-3}. Similarly, the absolute configuration of acetal carbon C-5 of the molecule **6h** was proven to be *R*. The selected bond lengths (nm) and the main bond angles (°) of compound **6h** are shown in Tables 4 and 5.

Experimental

Instruments and materials

A Yanaco/mp-50b melting point apparatus (uncorrected), a Shimazu UV-760 ultraviolet absorption detector, a 170-5x-Fourier infrared spectrometer, a Bruker DMX-300 or 500 MHz nuclear magnetic resonance spectrometer (TMS as internal standard), a Micro-Mass Zabspec spectrometer, a Perkin-Elmer 241-C polarimeter and a Perkin-Elmer 240-C elemental analyzer were used. All reagents were of reagent grade and purified when necessary. 5-(*R*)-(—)-Menthyloxy-3-bromo-2(5*H*)-furanone **4** was prepared by the method reported.[9] Yield 48%; m.p. 89—90 ℃ (pale yellow crystals from petroleum ether 30—60 ℃), $[\alpha]_D^{20}$ —121.1 (*c* 1.82, $CHCl_3$).

General procedure for preparation of chiral 4-substituted-2(5*H*)-furanones 6a—6f

Nucleophilic reagent (**5a—5f** 1 or 3 mmol as shown in Table 1) was added to the mixture of powdered K_2CO_3 (1.11 g, 4 mmol), tetrabutylammonium bromide (0.32 g, 1 mmol) and acetonitrile (6 mL). The mixture was stirred for 20 min. Then chiral synthon **4** (0.317 g, 1 mmol) was added and the mixture was stirred at room temperature for 1—4 d until TLC analysis indicated that the chiral synthon **4** had been completely consumed. After the addition of acetonitrile (50 mL), the mixture was filtered and the salts were washed with acetonitrile. The organic layer was dried, evaporated, and purified by column chromatography to give **6a—6f**.

Table 4 Main bond lengths (nm) of compound **6h**

O(1)—C(7)	0.1395(3)	C(8)—C(9)	0.1340(4)	C(14)—C(20)	0.1511(5)
O(1)—C(6)	0.1465(3)	N(1)—C(11)	0.1329(4)	C(15)—C(17)	0.1525(5)
O(2)—C(10)	0.1366(4)	N(2)—C(11)	0.1328(4)	C(15)—C(16)	0.1534(4)
O(2)—C(7)	0.1447(3)	N(1)—C(12)	0.1349(4)	C(1)—C(6)	0.1522(4)
O(3)—C(10)	0.1216(4)	C(12)—C(13)	0.1383(5)	C(1)—C(2)	0.1536(4)
S(1)—C(8)	0.1725(3)	C(12)—C(19)	0.1494(5)	C(1)—C(15)	0.1550(4)
S(1)—C(11)	0.1775(3)	C(13)—C(14)	0.1369(5)	C(2)—C(3)	0.1521(4)
C(7)—C(8)	0.1515(4)	C(14)—N(2)	0.1357(4)	C(3)—C(4)	0.1525(4)

Table 5 Main bond angles (°) of compound **6h**

C(8)-S(1)-C(11)	106.9(2)	C(8)-C(9)-C(10)	108.5(3)	N(2)-C(11)-S(1)	121.3(2)
C(7)-O(1)-C(6)	114.2(2)	O(3)-C(10)-O(2)	121.0(3)	N(1)-C(12)-C(13)	119.7(3)
C(10)-O(2)-C(7)	108.7(2)	O(3)-C(10)-C(9)	129.4(3)	N(1)-C(12)-C(19)	116.1(4)
C(6)-C(1)-C(15)	112.4(2)	O(2)-C(10)-C(9)	109.6(3)	C(13)-C(12)-C(19)	124.2(3)
C(9)-C(8)-S(1)	137.5(3)	N(1)-C(11)-N(2)	129.2(3)	C(14)-C(13)-C(12)	120.0(3)
C(7)-C(8)-S(1)	113.9(2)	N(1)-C(11)-S(1)	109.5(3)	N(2)-C(14)-C(13)	121.1(3)

5-(*R*)-[(1*R*,2*S*,5*R*)-(－)-Menthyloxy]-4-pyrrolidinyl-2(5*H*)-furanone (**6a**): Yield 0.39 g (85 %), as a white crystal, m.p. 149—150 ℃ [EtOAc/petroleum ether (30—60 ℃)]; $[\alpha]_D^{20}$ －174.8 (*c* 1.15, $CHCl_3$); UV (C_2H_5OH) λ_{max}: 273.0 (ε 1.509), 233.1 (ε 0.069) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.78 (d, *J*＝6.9 Hz, 3H, CH_3), 0.83 (d, *J*＝7.1 Hz, 3H, CH_3), 0.92 (d, *J*＝6.6 Hz, 3H, CH_3), 0.94—1.10 (m, 3H, CH_2, CH), 1.16—1.30 (m, 1H, CH), 1.34—1.50 (m, 1H, CH), 1.59—1.66 (m, 2H, 2CH), 1.96—1.97 (m, 4H, CH_2CH_2), 2.15—2.19 (m, 2H, 2CH), 3.18—3.31 (m, 3H, CH_2CHN), 3.58—3.66 (m, 1H, CHN), 3.63 (ddd, *J*＝10.7, 9.8, 4.2 Hz, 1H, OCH), 4.42 (s, 1H, H-3), 5.82 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.4, 20.8, 22.1, 22.8, 24.3, 24.9, 25.6, 31.2, 34.0, 39.5, 47.5, 47.7, 49.3, 77.7, 81.3, 94.7, 163.5, 172.6; IR (KBr) *v*: 1748 (C＝O), 1620 (C＝C), 1330 (N－C), 1120 (COC, v_{as}), 990 (COC, v_s) cm^{-1}; FABMS *m/z* (%): 308 (MH^+, 100), 307 (M^+, 10), 170 ($M^+-C_{10}H_{17}O$, 10), 152 ($M^+-C_{12}H_{19}O$, 25), 83 ($C_4C_3O_2^+$, 10). Anal. calcd for $C_{18}H_{29}NO_3$: C 70.32, H 9.51, N 4.56; found C 70.33, H 9.78, N 4.78.

5-(*R*)-[(1*R*,2*S*,5*R*)-(－)-Menthyloxy]-4-piperidinyl-2(5*H*)-furanone (**6b**): Yield 0.35 g (78%), as a light yellow crystal, m.p. 172—174 ℃ [EtOAc/petroleum ether (30—60 ℃)]; $[\alpha]_D^{20}$ －103.5 (*c* 0.9, $CHCl_3$); UV (C_2H_5OH) λ_{max}: 274.2 (ε 1.474), 229.9 (ε 0.006) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.79 (d, *J*＝6.9 Hz, 3H, CH_3), 0.84 (d, *J*＝7.1 Hz, 3H, CH_3), 0.93 (d, *J*＝6.5 Hz, 3H, CH_3), 0.99—1.04 (m, 3H, CH_2, CH), 1.14—1.26 (m, 1H, CH), 1.30—1.48 (m, 1H, CH), 1.54—1.72 (m, 8H, 3CH_2, 2CH), 2.11—2.21 (m, 2H, 2CH), 3.14—3.40 (m, 4H, 2CH_2N), 3.69 (ddd, *J*＝10.7, 9.8, 4.2 Hz, 1H, OCH), 4.54 (s, 1H, H-3), 5.84 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.8, 20.8, 22.2, 22.8, 23.1, 23.7, 23.7, 25.2, 31.3, 34.2, 39.3, 47.9, 47.9, 48.0, 77.4, 81.4, 94.0, 165.6, 172.8; IR (KBr) *v*: 3115 (C＝C—H), 1792 (C＝O), 1610 (C＝C), 1350 (N—C), 1140 (COC, v_{as}), 924 (COC, v_s) cm^{-1}; FABMS *m/z* (%): 322 (MH^+, 100), 321 (M^+, 20), 184 ($M^+-C_{10}H_{17}$, 95), 166 ($M^+-C_{10}H_{19}O$, 50), 138 ($C_{10}C_{18}^+$, 10), 83 ($C_4C_3O_2^+$, 90), 69 ($C_5H_9^+$, 16). Anal. calcd for $C_{19}H_{31}NO_3$: C 70.99, H 9.72, N 4.36; found C 70.91, H 10.03, N 4.53.

5-(*R*)-[(1*R*,2*S*,5*R*)-(－)-Menthyloxy]-4-morpholinyl-2(5*H*)-furanone (**6c**): **4** (4 mmol)/morphline (12 mmol). Yield 1.16 g (90%), as a light yellow crystal, m.p. 150—151 ℃ [EtOAc/petroleum ether (30—60 ℃)]; $[\alpha]_D^{20}$ －174.78 (*c* 1.15, $CHCl_3$); UV (C_2H_5OH) λ_{max}: 272.3 (ε 1.357), 227.4 (ε 0.016) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.75 (d, *J*＝6.9 Hz, 3H, CH_3), 0.82 (d, *J*＝7.1 Hz, 3H, CH_3), 0.89 (d, *J*＝6.5 Hz, 3H, CH_3), 0.91—1.05 (m, 3H, CH_2, CH), 1.09—1.25 (m, 1H, CH), 1.17—1.18 (m, 1H, CH), 1.58—1.63 (m, 2H, 2CH), 2.07—2.18 (m, 2H, 2CH), 3.19—3.30 (m, 4H, 2CH_2N), 3.15—3.71 (m, 4H, 2CH_2O), 3.68 (ddd, *J*＝10.3, 9.4, 4.7 Hz, 1H, OCH), 4.58 (s, 1H, H-3), 5.84 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.6, 20.6, 22.0, 22.9, 25.1, 31.2, 34.0, 39.2, 47.2, 47.2, 47.7, 65.8, 65.8, 77.4, 83.1, 93.8, 165.6, 171.9; IR (KBr) *v*: 3105 (C＝C—H), 1759 (C＝O), 1635 (C＝C), 1310 (N—C), 1128 (COC, v_{as}), 990 (COC, v_s) cm^{-1}; FABMS *m/z* (%): 324 (MH^+, 100), 323 (M^+, 6), 186 ($M^+-C_{10}H_{17}$, 45), 168 ($M^+-C_{10}H_{19}O$, 12), 83 ($C_4C_3O_2^+$, 12). Anal. calcd for $C_{18}H_{29}NO_4$: C 66.84, H 9.04, N 4.33; found C 66.76, H 9.28, N 4.72.

5-(*R*)-[(1*R*,2*S*,5*R*)-(－)-Menthyloxy]-4-(2'-naphthoxy)-2(5*H*)-furanone (**6d**): Yield 0.24 g (63%), as a light yellow crystal, m.p. 67.5—68.5 ℃ [EtOAc/petroleum ether (30—60 ℃)]; $[\alpha]_D^{20}$ －49.4 (*c* 0.939, $CHCl_3$); UV (C_2H_5OH) λ_{max}: 221 (ε 2.164) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.73 (d, *J*＝6.6 Hz, 3H, CH_3), 0.84 (d, *J*＝6.4 Hz, 3H, CH_3), 0.86 (d, *J*＝6.6 Hz, 3H, CH_3), 0.95—1.07 (m, 3H, CH_2, CH), 1.38—1.46 (m, 2H, 2CH), 1.65—

1.69 (m, 2H, 2CH), 1.89—1.94 (m, 1H, CH), 2.07—2.11 (m, 1H, CH), 4.84 (ddd, J=10.2, 10.2, 4.1 Hz, 1H, OCH), 6.31 (d, J=11.9 Hz, 1H, H-3), 6.46 (s, 1H, H-5), 7.35 (d, J=8.7 Hz, 1H, H-3′), 7.47 (d, J=3.6 Hz, 2H, H-6′, H-7′), 7.66 (s, 1H, H-1′), 7.80—7.88 (m, 3H, H-4′, H-5′, H-8′); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.2, 20.8, 21.9, 23.2, 26.1, 31.3, 34.2, 40.5, 46.9, 75.7, 77.5, 118.5, 120.9, 125.8, 126.5, 127.7, 129.1, 19.4, 131.0, 131.1, 133.7, 147.9, 163.9, 164.6; IR (KBr) v: 3050 (C=C—H), 1750 (C=O), 1730 (C=C), 1170 (COC, v_{as}), 980 (COC, v_s) cm^{-1}; FABMS *m/z* (%): 381 (MH^+, 45), 243 ($M^+-C_{10}H_{17}$, 60), 144 ($C_{10}H_8O^+$, 100), 139 ($C_{10}H_{19}^+$, 10), 133 ($C_{10}H_{13}^+$, 70), 83 ($C_4C_3O_2^+$, 58). Anal. calcd for $C_{24}H_{28}O_4$: C 75.81, H 7.42; found C 75.84, H 7.62.

5-(*R*)-[(1*R*,2*S*,5*R*)-(－)-Menthyloxy]-4-(8'-quinolinoxy)-2(5*H*)-furanone (**6e**): Yield 0.22 g (58%), as a light yellow crystal, m.p. 116—117 ℃ [EtOAc/petroleum ether (30—60 ℃)]; $[\alpha]_D^{20}$ −70.4 (c 1.11, $CHCl_3$); UV (C_2H_5OH) λ_{max}: 288.2 (ε 0.393), 225.1 (ε 2.532) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.67 (d, J=7.0 Hz, 3H, CH_3), 0.73 (d, J=7.0 Hz, 3H, CH_3), 0.81 (d, J=7.1 Hz, 3H, CH_3), 0.96—1.06 (m, 3H, $2CH_2$, CH), 1.41—1.45 (m, 2H, 2CH), 1.63—1.65 (m, 2H, 2CH), 1.90—2.07 (m, 2H, 2CH), 4.81 (ddd, J=10.9, 10.9, 4.4 Hz, 1H, OCH), 6.44 (s, 1H, H-5), 6.70 (d, J=12.0 Hz, 1H, H-3), 7.42 (dd, J=8.0, 4.0 Hz, 1H, H-6′), 7.56 (dd, J=7.8, 3.0 Hz, 1H, H-3′), 7.65 (d, J=7.2 Hz, 1H, H-5′), 7.72 (d, J=7.9 Hz, 1H, H-7′), 8.16 (d, J=8.0 Hz, 1H, H-4′), 8.91 (d, J=3.0 Hz, 1H, H-2′); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.0, 21.7, 22.9, 24.1, 26.8, 32.2, 35.0, 41.4, 47.8, 76.6, 77.8, 122.4, 122.9, 127.0, 127.3, 130.1, 130.4, 132.1, 137.3, 147.3, 151.3, 164.8, 165.6; IR (KBr) v: 3050 (C=C—H), 1750 (C=O), 1740 (C=C), 1150 (COC, v_{as}), 990 (COC, v_s) cm^{-1}; FABMS *m/z* (%): 382 (MH^+, 1), 251 ($M^+-C_9H_7NH$, 90), 171 ($C_{10}C_{19}O_2^+$, 100), 146 ($C_9H_7ONH^+$, 45), 133 ($C_{10}H_{13}^+$, 85), 83 ($C_4C_3O_2^+$, 23). Anal. calcd for $C_{23}H_{27}NO_4$: C 72.41, H 7.14, N 3.67; found C 72.43, H 7.32, N 4.03.

5-(*R*)-[(1*R*,2*S*,5*R*)-(－)-Menthyloxy]-4-(4'-methyl-2'-thiazolylamino)-2(5*H*)-furanone (**6f**): Yield 0.30 g (43%), as a white crystal, m.p. 64—65 ℃ [EtOAc/petroleum ether (30—60 ℃)]; $[\alpha]_D^{20}$ −154.4 (c 0.95, $CHCl_3$); UV (C_2H_5OH) λ_{max}: 256.3 (ε 2.71)nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.80 (d, J=6.8 Hz, 3H, CH_3), 0.87—0.88 (m, 1H, CH-10), 0.90 (d, J=7.1 Hz, 3H, CH_3), 0.97 (d, J=6.5 Hz, 3H, CH_3), 0.98—1.02 (m, 2H, 2×CH), 1.22—1.28 (m, 1H, CH), 1.39—1.50 (m, 1H, CH), 1.66—1.70 (m, 2H, CH_2), 2.14—2.32 (m, 2H, 2×CH), 2.32 (s, 3H, CH_3), 3.65 (ddd, J=10.9, 6.8, 4.2 Hz, 1H, OCH), 3.66 (s, 1H, NH), 3.96 (d, J=4.1 Hz, 1H, CH-5′), 5.76 (s, 1H, CH-3), 6.56 (s, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.6, 20.8, 22.2, 23.1, 25.4, 31.4, 34.2, 40.0, 47.3, 78.1, 98.7, 110.8, 118.0, 131.0, 168.0; IR (KBr) v: 3191 (C=C—H), 1799 (C=O), 1610 (C=C), 1531, 1147 (COC, v_{as}), 930 (COC, v_s) cm^{-1}; MS *m/z* (%): 350 (M^+, 37), 213 ($M^+-C_{10}H_{17}$, 64), 156 ($C_{10}H_{20}O^+$, 50), 139 ($C_{10}H_{19}^+$, 71), 137 ($C_{10}H_{17}^+$, 36), 83 ($C_4C_3O_2^+$, 96), 67 ($C_5H_7^+$, 66), 55 ($C_4H_7^+$, 91), 43 ($C_3H_7^+$, 100). Anal. calcd for $C_{18}H_{26}N_2O_3S$: C 61.69, H 7.48, N 7.99; found C 61.71, H 7.34, N 7.63.

General procedure for preparation of 6g and 6h

2 mmol of nucleophilic reagent **5g** or **5h** was dissolved in 8 mL of freshly distilled DMF. After cooling to r.t., 0.56 mL (4 mmol) of triethylamine and 2 mmol of chiron **4** were added and the mixture was stirred at room temperature for 6 days, as monitored by TLC analysis. The solution was extracted with CH_2Cl_2 (2× 30 mL), and then washed with water until pH=7. The organic layer was dried, evaporated, and purified by column chromatography on silica gel to give **6g** or **6h**.

5-(*R*)-[(1*R*,2*S*,5*R*)-(－)-Menthyloxy]-4-(1'-imidazolyl)-2(5*H*)-furanone (**6g**): Yield 0.44 g (72%), as a white crystal, m.p. 114—115 ℃ [EtOAc/petroleum ether (30—60℃)]; $[\alpha]_D^{20}$ −185.0 (c 1.15, $CHCl_3$); UV (C_2H_5OH) λ_{max}: 255.2 (ε 3.538) nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.83 (d, J=6.9 Hz, 3H, CH_3), 0.89 (d, J=7.1 Hz, 3H, CH_3), 0.93—0.98 (m, 1H, CH), 1.02 (d, J=6.6 Hz, 3H, CH_3), 1.07—1.16 (m, 2H, 2×CH), 1.28—1.33 (m, 2H, 2×CH), 1.70—1.73 (m, 2H, 2×CH), 2.11—2.34 (m, 2H, 2×CH), 3.89 (ddd, J=10.7, 6.6, 4.2 Hz, 1H, OCH), 6.00 (s, 1H, CH-3), 6.34 (s, 1H, H-5), 7.26 (d, J=13.1, 1H, H-4′), 7.26 (d, J=13.1, 1H, H-5′), 8.02 (s, 1H, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.6, 20.8, 22.2, 23.1, 25.2, 31.5, 34.1, 39.7, 47.9, 79.4, 95.6, 102.7, 117.2, 131.9, 136.0, 153.6, 168.5; IR (KBr) v: 3112, 1795 (C=O), 1766 (C=C), 1655 (C=C), 1120 (COC, v_{as}), 975 (COC, v_s) cm^{-1}; EIMS *m/z* (%): 304 (M^+, 65), 168 ($M^+-C_{10}H_{18}$, 32), 167 ($M^+-C_{10}H_{17}$, 100), 150 ($C_{10}H_{14}O^+$, 75), 149 ($C_{10}H_{13}O^+$, 75), 95 ($C_7H_{11}^+$, 66), 81 ($C_6H_9^+$, 83), 43 ($C_3H_7^+$, 86). Anal. calcd for $C_{17}H_{24}N_2O_3$: C 67.08, H 7.95, N 9.20; found C 66.85, H 7.46, N 9.04.

5-(*R*)-[(1*R*,2*S*,5*R*)-(－)-Menthyloxy]-4-(4',6'-dimethyl-2'-pyrimidinethio)-2(5*H*)-furanone (**6h**): Yield 0.31 g (41%), as a white crystal, m.p. 100—101 ℃ [EtOAc/petroleum ether (30—60 ℃)]; $[\alpha]_D^{20}$ −81.2 (c 0.815, $CHCl_3$); UV (C_2H_5OH) λ_{max}: 248.7 (ε 0.66) nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.83 (d, J=6.9 Hz, 3H, CH_3), 0.88 (d, J=7.1 Hz, 3H, CH_3), 0.94 (d, J=6.5 Hz, 3H, CH_3), 0.96—1.02 (m, 2H, CH_2),1.20—1.32 (m, 2H, CH_2), 1.37—1.47 (m, 1H, CH), 1.67—1.69 (m, 2H, CH_2), 2.05—2.09 (m, H, CH), 2.18—2.26 (m, H, CH), 2.80 (s, 6H, 2×CH_3),3.67 (ddd, J=10.6, 6.4, 4.2 Hz, 1H, OCH), 6.16 (s, 1H, CH-3), 6.92 (s, 1H, H-5), 7.07 (s, 1H, H-4′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.7, 20.8, 22.2, 23.5, 25.2, 31.5, 34.1, 34.1, 40,4, 40,4, 47.6, 80.1, 100.6, 117.8, 117.9, 118.1, 159.3, 166.1, 168.1, 170.0; IR (KBr) v: 3116, 1759 (C=O), 1131 (COC, v_{as}), 959 (COC, v_s) cm^{-1}; EIMS *m/z* (%): 376 (M^+, 60), 239 ($M^+-C_{10}H_{17}$, 25), 221 ($M^+-C_{10}H_9O$, 63), 193 ($C_9H_{11}N_2OS^+$, 100), 165 ($C_8H_{11}N_2OS^+$, 66), 140 ($C_6H_8N_2OS^+$, 32), 83 ($C_4H_3O_2^+$, 24), 67 ($C_5H_7^+$, 53), 55 ($C_4H_7^+$, 43), 43 ($C_3H_7^+$, 50), 41 ($C_3H_5^+$, 53). Anal. calcd for $C_{20}H_{28}N_2O_3S$: C 63.80, H 7.80, N 7.44; found C 63.71, H 7.39, N 7.28.

General procedure for preparation of 6i and 6j

1 mmol of nucleophilic reagent **5i** or **5j** was warmly dissolved at 40 ℃ in freshed DMSO as a solvent. 0.28 mL (2 mmol) of freshly distilled triethylamine and 1 mmol of chiron **4** were added and the mixture was stirred at room temperature for 4 d, up to the time when TLC analysis indicated that the chiral synthon **4** had been completely consumed. The solution was extracted with CH_2Cl_2 (2×30 mL), and then washed with water to pH=7. The organic layer was dried, evaporated, and purified by column chromatography on silica gel to give **6i** or **6j**

5-(*R*)-[(1*R*,2*S*,5*R*)-(－)-Menthyloxy]-4-(9'-adeninyl)-2(5*H*)-furanone (**6i**): **4** (2 mmol) and adenine (2 mmol) were used. Yield 0.45 g (50%), as a light yellow crystal, m.p. 121—122 ℃ (acetone); $[\alpha]_D^{20}$ －121.4 (*c* 1.04, $CHCl_3$); UV (C_2H_5OH) λ_{max}: 296.2 (ε 0.798), 280.5 (ε 0.624), 264.7 (ε 2.471), 261.0 (ε 1.872), 258.6 (ε 2.311), 254.8 (ε 1.452), 252.1 (ε 2.185), 249.0 (ε 1.474), 247.2 (ε 1.824) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.81 (d, *J*=7.3 Hz, 3H, CH_3), 0.89 (d, *J*=7.2 Hz, 3H, CH_3), 1.02 (d, *J*=7.7 Hz, 3H, CH_3), 1.05—1.41(m, 3H, $2CH_2$, CH), 1.43—1.63 (m, 1H, CH), 1.64—1.80 (m, 2H, CH_2), 2.00—2.20 (m, 2H, 2CH), 2.30—2.46 (m, 1H, CH), 3.89 (ddd, *J*=10.5, 10.5, 5.5 Hz, 1H, OCH), 6.05 (s, 2H, NH_2), 6.48 (s, 1H, H-5), 7.09 (s, 1H, H-3), 8.14 (s, 1H, H-8′), 8.47 (s, 1H, H-2′); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.5, 20.6, 22.1, 22.7, 24.9, 31.8, 33.6, 40.8, 47.2, 78.8, 96.3, 103.9, 116.8, 137.4, 149.5, 152.8, 154.2, 156.3, 169.2; IR (KBr) *v*: 3300 (NH_2), 1760 (C=O), 1640 (C=C), 1158 (COC, v_{as}), 962 (COC, v_s) cm^{-1}; EIMS *m/z* (%): 371 (MH^+, 1), 232 ($M^+-C_{10}H_{18}O$, 68), 217 ($M^+-C_{10}H_{18}O$, 100), 161 ($C_9C_{10}O_2^+$, 61), 139 ($C_{10}H_{19}^+$, 5), 138 ($C_{10}H_{18}^+$, 34), 95 ($C_5C_3O_2^+$, 95), 81 (C_5H_5O, 65). Anal. calcd for $C_{19}H_{25}N_5O_3$: C 61.43, H 6.78, N 18.86; found C 61.15, H 7.05, N 18.61.

5-(*R*)-[(1*R*,2*S*,5*R*)-(－)-Menthyloxy]-4-[9'-(8'-azaguaninyl)]-2(5*H*)-furanone (**6j**): Yield 0.44 g (68%), as a light yellow crystal, m.p. 207—208 ℃ (acetone); $[\alpha]_D^{20}$ ＋145.2 (*c* 0.49, CH_3COCH_3); UV (C_2H_5OH) λ_{max}: 351.8 (ε 0.239), 247.0 (ε 0.561), 291.6 (ε 0.096) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.75 (d, *J*=6.6 Hz, 3H, CH_3), 0.89 (d, *J*=7.1 Hz, 3H, CH_3), 1.02 (d, *J*=6.6 Hz, 3H, CH_3), 1.00—1.17 (m, 3H, CH_2, CH), 1.30—1.45 (m, 3H, CH_2, CH), 2.03—2.51 (m, 3H, 3CH), 3.34 (s, 1H, H-3′), 3.71 (ddd, *J*=10.3, 10.3, 3.4 Hz, 1H, OCH), 6.68 (s, 1H, H-5), 6.84 (s, 1H, H-3), 6.95 (d, *J*=1.8 Hz, 1H, NH=C-2′), 11.31 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.9, 20.9, 22.4, 23.0, 25.1, 31.1, 34.0, 38.9, 47.4, 79.8, 97.2, 104.0, 124.3, 153.2, 156.3, 160.8, 158.9, 169.4; IR(KBr) *v*: 3400 (br, s, OH), 1720 (C=O), 1660 (C=C), 1140 (COC, v_{as}), 980 (COC, v_s) cm^{-1}; FABMS *m/z* (%): 389 (MH^+, 100), 250 ($M^+-C_{10}H_{19}$, 65), 233 ($M^+-C_{10}H_{18}OH$, 30), 83 ($C_4C_3O_2^+$, 18). Anal. calcd for $C_{18}H_{24}N_6O_4$: C 55.65, H 6.23, N 21.64; found C 55.23, H 6.53, N 21.36.

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