JOC Article

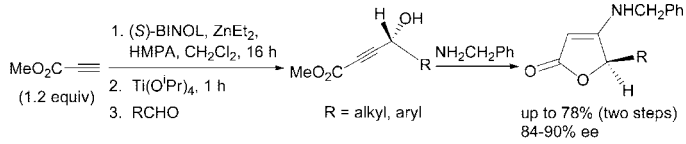
Reactivity of γ-Hydroxy-α,β-acetylenic Esters with Amines: Facile Synthesis of the Optically Active 4-Amino-2(5*H*)-furanones

Li-Hong Zhou,[†,‡] Xiao-Qi Yu,*[,‡] and Lin Pu*[,†]

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319, and Department of Chemistry, Key Laboratory of Green Chemistry and Technology (Ministry of Education), Sichuan University, Chengdu, China 610064

lp6n@virginia.edu

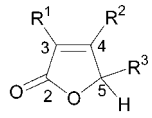
Received November 21, 2008



A convenient synthesis of the optically active 4-amino-2(5*H*)-furanones is discovered by combining an asymmetric alkyne addition to aldehydes and a subsequent aliphatic amine addition. Both steps can be conducted at room temperature and the products are obtained with high enantioselectivity (84−90% ee). The 4-amino-2(5*H*)-furanones are also found to undergo very facile electrophilic substitution reactions.

Introduction

2(5*H*)-Furanone (or γ-butenolide) structures are found to exist in many natural and unnatural products. Derivatives of 2(5*H*)-furanones have exhibited very diversebiological functions and



2(5H)-furanones

are important in the development of therapeutic agents.[1] For example, a few 4-substituted 2(5*H*)-furanones are found to be potent antibiotics and have shown cytotoxicity against human colon carcinoma and human melanoma.[2] Extensive studies on the synthesis of both chiral and achiral derivatives of 2(5*H*)-furanones have been conducted.[3,4] We are interested in the synthesis of chiral 4-amino-2(5*H*)-furanones. Previously, the intramolecular Wittig reaction[4a−e] and [2,3]-Wittig rearrangement[4f] have been used to prepare 4-amino-2(5*H*)-furanones. Other methods such as the addition of an ester enolate to a nitrile,[4g] condensation of an amine with a tetronic ester,[4h] addition of an amine to a γ-silyloxy-α,β-acetylenic ester,[4h] and reaction of an amine with a 4-bromo-2(5*H*)-furanone[4i] have also been used. Among the reported syntheses, we consider the most direct method to be the addition of amines to γ-hydroxy-α,β-acetylenic esters.[4j,k] In this reaction, the β-amine addition is followed by γ-lactonization to readily generate the 4-amino-2(5*H*)-furanone products. Although racemic or achiral 4-amino-2(5*H*)-furanones have been prepared from this route,[4j,k] the optically active products have not been obtained by using this reaction.

[†] University of Virginia.
[‡] Sichuan University.

(1) Examples: (a) Van Quaquebeke, E.; Simon, G.; Andre', A.; Dewelle, J.; El Yazidi, M.; Bruyneel, F.; Tuti, J.; Nacoulma, O.; Guissou, P.; Decaestecker, C.; Braekman, J.-C.; Kiss, R.; Darro, F. *J. Med. Chem.* **2005**, *48*, 849–856. (b) Bousserouel, H.; Litaudon, M.; Morleo, B.; Martin, M.-T.; Thoison, O.; Nosjean, O.; Boutin, J. A.; Renard, P.; Sévenet, T. *Tetrahedron* **2005**, *61*, 845–851. (c) Dai, S.-J.; Tao, J.-Y.; Liu, K.; Jiang, Y.-T.; Shen, L. *Phytochemistry* **2006**, *67*, 1326–1330.

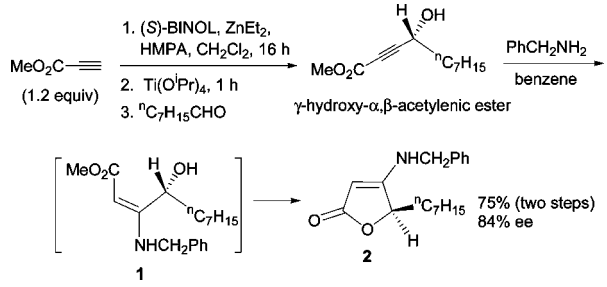
(2) Ortega, M. J.; Zubia, E.; Ocanã, G. M.; Naranjo, S.; Salvà, J. *Tetrahedron* **2000**, *56*, 3963–3967.

(3) Selected reports and reviews: (a) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2324–2342. (b) Brückner, R. *Curr. Org. Chem.* **2001**, *5*, 679–718. (c) Raju, R.; Allen, L. J.; Le, T.; Taylor, C. D.; Howell, A. R. *Org. Lett.* **2007**, *9*, 1699–1701. (d) Patil, S. N.; Liu, F. *Org. Lett.* **2007**, *9*, 195–198. (e) Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 778–779. (f) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194. (g) Cho, C. W.; Krische, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689–6691. (h) Barleuenga, J.; Prado, A. D.; Santamaria, J.; Tomas, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6583–6585. (i) Ma, S.; Lu, L.; Lu, P. *J. Org. Chem.* **2005**, *70*, 1063–1065. (j) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055–5072. (k) Feringa, B. L.; de Lange, B.; Jansen, J. F. G. A.; de Jong, J. C.; Lubben, M.; Faber, W. S.; Schudde, E. P. *Pure Appl. Chem.* **1992**, *64*, 1865–1871.

(4) (a) Ireland, R. E.; Brown, F. R., Jr. *J. Org. Chem.* **1980**, *45*, 1868–1880. (b) Niwa, H.; Miyachi, Y.; Osamu Okamoto, O.; Uosaki, Y.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4605–4608. (c) Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y. *J. Org. Chem.* **1987**, *52*, 2941–2943. (d) Hart, D. J.; Sun, L.-Q.; Kozikowski, A. P. *Tetrahedron Lett.* **1995**, *36*, 7787–7790. (e) Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449–2458. (f) Li, Y.-J.; Lee, P.-T.; Yang, C.-M.; Chang, Y.-K.; Weng, Y.-C.; Liu, Y.-H. *Tetrahedron Lett.* **2004**, *45*, 1865–1868. (g) Hiyama, T.; Oishi, H.; Suetsugu, Y.; Nishide, K.; Saimoto, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2139–2150. (h) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1988**, *29*, 1489–1492. (i) Basler, B.; Schuster, O.; Bach, T. *J. Org. Chem.* **2005**, *70*, 9798–9808. (j) Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1949**, 1423–1430. (k) Mavrov, M. V.; Konyushkin, L. D.; Simirskaya, N. I.; Zlotin, S. G. *Russ. Chem. Bull. Int. Ed.* **2005**, *54*, 2857–2866.

10.1021/jo802592h CCC: $40.75 © 2009 American Chemical Society
Published on Web 02/05/2009

SCHEME 1. Asymmetric Synthesis of an 4-Amino-2(5*H*)-furanone



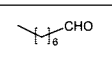
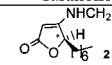
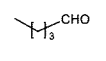
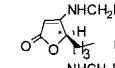
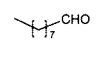
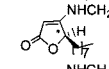
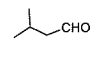
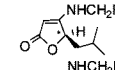
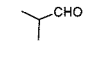
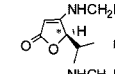
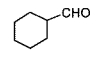
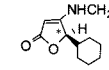
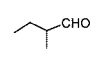
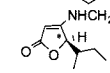
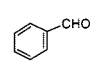
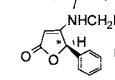
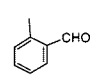
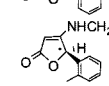
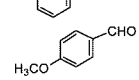
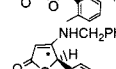
Recently, we discovered a highly enantioselective reaction of methyl propiolate with aldehydes by using 1,1′-bi-2-naphthol (BINOL) in combination with $ZnEt_2$, $Ti(O^iPr)_4$, and HMPA at room temperature.[5,6] This reaction allows the synthesis of γ-hydroxy-α,β-acetylenic esters under very mild conditions with excellent enantiomeric purity. We find that treatment of the γ-hydroxy-α,β-acetylenic esters with aliphatic amines leads to the facile synthesis of the optically active 4-amino-2(5*H*)-furanones. These 4-amino-2(5*H*)-furanones are also found to undergo electrophilic substitution under very mild conditions. Herein, these results are reported.

Results and Discussion

We have conducted the reaction of methyl propiolate with octanal in the presence of (*S*)-BINOL, $ZnEt_2$, $Ti(O^iPr)_4$, and HMPA to generate the corresponding γ-hydroxy-α,β-acetylenic ester (Scheme 1).[5b] When this γ-hydroxy-α,β-acetylenic ester is treated with 1.2 equiv of benzylamine in benzene at room temperature, upon removal of the solvent, the ^{1}H NMR spectrum of the residue indicates the formation of the amine addition product **1** as the major product. After chromatography on silica gel eluted with 50% ethyl acetate in hexanes, compound **1** undergoes an intramolecular cyclization to form the 4-amino-2(5*H*)-furanone **2**. TLC analysis with silica gel plate shows that the polarity of **2** is much greater than that of **1** and **1** is not converted to **2** during the TLC analysis. Increasing the amount of benzylamine to 1.4 equiv allows the lactonization to take place immediately after the amine addition before column chromatograph and it also reduces the overall reaction time. Changing the solvent to THF gives lower yield and using methanol gives similar yield as the use of benzene. Increasing the reaction temperature or addition of DABCO as a catalyst shows little influence on the reaction time and the product yield. Thus, the combination of the asymmetric alkyne addition to octanal with the subsequent treatment with 1.4 equiv of benzylamine at room temperature gives the 4-amino-2(5*H*)-furanone product **2** in 75% yield in two steps and with 84% ee. Although the γ-hydrogen of the γ-hydroxy-α,β-acetylenic ester is of significant acidity, no racemization is observed in the presence of the amine base.

We have examined the two-step reaction of methyl propiolate with a variety of aldehydes and then with benzylamine to generate optically active 4-amino-2(5*H*)-furanones. As the results summarized in Table 1 show, the desired products are obtained in good yields (all the yields are the total of the two steps) and high enantiomeric purity. The reaction works well for linear and branched aliphatic aldehydes. Good enantioselectivity is also observed for a few aromatic aldehydes. In entry 7, a racemic chiral aldehyde is used that gives a 1:1 mixture of two diastereomers with good enantiomeric purity for each diastereomer. No optically active 4-amino-2(5*H*)-furanones were prepared by the reaction of amines with chiral propargylic alcohols before, although the racemic or achiral products were obtained from the reaction of amines with achiral or racemic γ-hydroxy-α,β-acetylenic esters.[4j,k]

TABLE 1. Results for the Asymmetric Methyl Propiolate Addition to Various Aldehydes Followed by Treatment with Benzylamine

entry	aldehyde	4-amino-2(5H)-furanone	Yield[a] (%)	ee (%)
1			75	84
2			70	87
3			31	83
4			51	85
5			62	84
6			69	86
7			53	84; 87
8			78	87
9			57	90
10			67	90

[a] The total yield of the two steps.

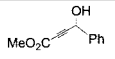
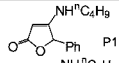
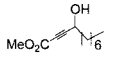
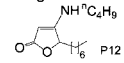
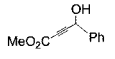
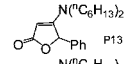
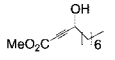
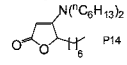
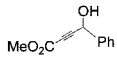
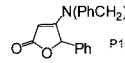
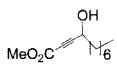
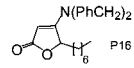
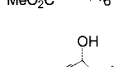
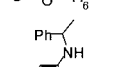
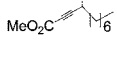
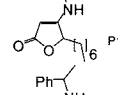
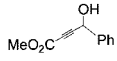
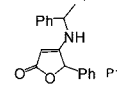
As shown in Table 1, the enantiomeric purity of the products generated from the asymmetric methyl propiolate addition to the aliphatic and aromatic aldehydes is maintained in the subsequent reaction with benzylamine to form the 4-amino-2(5*H*)-furanones. However, we find that the reaction of benzylamine with the γ-hydroxy-α,β-acetylenic esters derived from other aromatic aldehydes such as 1-naphthaldehyde and 2-furaldehyde led to the racemized 4-amino-2(5*H*)-furanones. It is not clear yet what contributes to the racemization and formation of free radicals during the amine addition might be involved.

We have also studied the reactivity of racemic alkyl- and aryl-substituted γ-hydroxy-α,β-acetylenic esters in the presence of a variety of primary and secondary amines. The results are summarized in Table 2. Entries 1−6 show that both primary and secondary amines can react with the γ-hydroxy-α,β-acetylenic esters to generate the 4-amino-2(5*H*)-furanones with good yields. In entries 7 and 8, a racemic chiral amine is used that gives the products in good yields with 1.1−1.4:1 diastereomeric ratio. In entry 9, the optically pure amino ester is used, which gives the product with 1.3:1 diastereomeric ratio.

(5) (a) Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 122–125. (b) Rajaram, A. R.; Pu, L. *Org. Lett.* **2006**, *8*, 2019–2021.

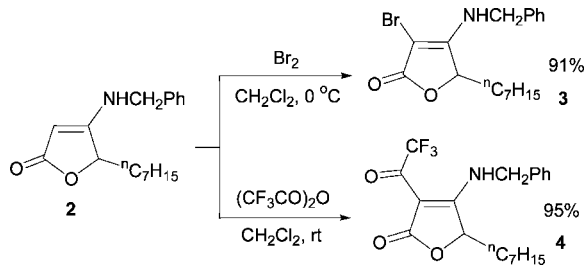
(6) Other reports on the asymmetric propiolate addition to aldehydes: (a) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8–9. (b) Yang, F.; Xi, P.; Yang, L.; Lan, J.; Xie, R.; You, J. S. *J. Org. Chem.* **2007**, *72*, 5457–5460. (c) Lebel, H.; Parmentier, M. *Org. Lett.* **2007**, *9*, 3563–3566.

TABLE 2. Results for the Reaction of γ-Hydroxy-α,β-acetylenic Esters with Various Amines

entry	γ-hydroxy-α,β-acetylenic ester[a]	amine	4-amino-2(5H)-furanone	Yield[b] (%)
1		$^nC_4H_9NH_2$	 P11	81
2		$^nC_4H_9NH_2$	 P12	75
3		$(^nC_6H_{13})_2NH$	 P13	87
4		$(^nC_6H_{13})_2NH$	 P14	88
5		$(PhCH_2)_2NH$	 P15	87
6		$(PhCH_2)_2NH$	 P16	89
7			 P17	86 (1.1:1)[c]
8			 P18	80 (1.4:1)[c]
9			 P19	71 (1.3:1)[c]

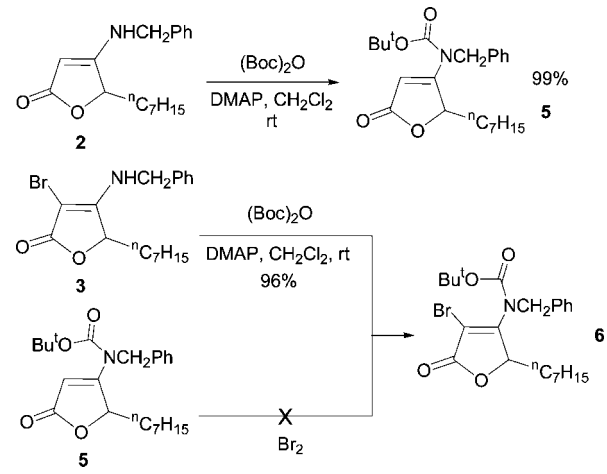
[a] Prepared from the treatment of methyl propiolate with ^{n}BuLi at −78 °C followed by the addition of the aldehyde.[7] [b] The total yield of the alkyne addition and the amine addition. [c] The diasteromeric ratio.

SCHEME 2. Reactions of 2 with Br_2 and $(CF_3CO)_2O$



We have investigated the reactivity of the 4-amino-2(5*H*)-furanones. When the racemic compound **2** is treated with Br_2 in methylene chloride solution at 0 °C, the 3-brominated product **3** is obtained in 91% yield (Scheme 2). Previously, the bromination of 4-amino-2(5*H*)-furanones with NBS[8a] as well as the iodination with ICl or $I(py)_2BF_4$[8b−d] were conducted to give the 3-halogenated products, but the direct bromination with Br_2 was not reported. We have also studied the reaction of compound **2** with trifluoroacetic anhydride. At room temperature in methylene chloride solution, **2** reacts with trifluoroacetic anhydride to give a C-acylated product **4** in 95% yield rather than an N-acylated product (Scheme 2). The ^{1}H NMR spectra of both **3** and **4** show the disappearance of the vinyl proton singlet of **2** at δ 4.67 for the substitution at the 3-position. The acylation at the 3-position of a 4-amino-2(5*H*)-furanone is unprecedented and it allows the direct construction of a new

SCHEME 3. Reactions with Boc_2O



C−C bond on a 4-amino-2(5*H*)-furanone ring under very mild conditions. These halogenation and acylation of **2** demonstrate that the 3-position of the 4-amino-2(5*H*)-furanone is very electron rich and susceptible to electrophilic substitution. Preparation of compounds **3** and **4** makes it possible to further derivatize the 4-amino-2(5*H*)-furanones on the ring.

In contrast to the reaction with trifluoroacetic anhydride, when **2** is treated with $(Boc)_2O$ in the presence of DMAP at room temperature, the N-protected product **5** is obtained in 99% yield (Scheme 3).[4i] When **3** is treated with $(Boc)_2O$ in the presence of DMAP at room temperature, it also gives the N-protected product **6** in 96% yield. However, the electron-withdrawing effect of the Boc group in **5** makes this compound unreactive toward bromine.

In summary, we have discovered a convenient synthesis of the optically active 4-amino-2(5*H*)-furanones by combining an asymmetric alkyne addition to aldehydes and a subsequent aliphatic amine addition. Both steps are conducted at room temperature and the products are obtained with high enantioselectivity. The 4-amino-2(5*H*)-furanones are also found to undergo very facile electrophilic substitution reactions.

Experimental Section

General Data. Dichloromethane was dried by passing through activated alumina columns under nitrogen. All solvents were stored over molecular sieves. All liquid aldehydes were distilled prior to use.

General Procedure for the Preparation of 4-Amino-5-substituted-2(5*H*)-furanones. (a) To a stirred solution of (*S*)-BINOL (0.243 g, 0.5 mmol, 40 mol %), HMPA (0.44 mL, 2.5 mmol), and methyl propiolate (0.425 mL, 5.0 mmol) in methylene chloride (15 mL) under nitrogen is slowly added $ZnEt_2$ (0.523 mL, 5.0 mmol). After the solution is stirred at room temperature for 16 h, $Ti(O^iPr)_4$ (0.370 mL, 1.25 mmol) is added and the stirring is continued for another hour. Then, an aldehyde (1.25 mmol, neat) is added in one portion and the reaction is allowed to proceed at room temperature for 4 h. Ammonium chloride (saturated aqueous) is added to quench the reaction, and the mixture is extracted with methylene chloride and dried with sodium sulfate. After column chromatography on silica gel eluted with 10% ethyl acetate in hexanes, an optically active γ-hydroxy-α,β-acetylenic ester product is isolated. (b) A solution of the optically active γ-hydroxy-α,β-acetylenic ester product prepared in step a (2 M in benzene) and an amine (1.4 equiv) is stirred under nitrogen at room temperature for 5−24 h. After the reaction is completed as shown by TLC, the solvent is evaporated and the product is obtained after column

(7) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28–29.

(8) (a) Schlessinger, R. H.; Pettus, T. R. R.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1994**, *59*, 3246–3247. (b) Matsuo, K.; Ishida, S.; Takund, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1149–1150. (c) Campos, P. J.; Arranz, J.; Rodriguez, M. A. *Tetrahedron Lett.* **1997**, *38*, 8397–8400. (d) Kim, J. M.; Na, J. E.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6317–6318.

chromatography on silica gel eluted with 50% ethyl acetate in hexanes. The enantiomeric purity of the product is determined by using HPLC-Chiralcel OD or AD column.

Characterization of the 4-Amino-5-substituted-2(5*H*)-furanones Products: 4-(Benzylamino)-5-heptylfuran-2(5*H*)-one, 2 (P1): 75% overall yield, and 84% ee determined by HPLC analysis: chiralcel AD-H column; solvent: 95:5 hexanes:isopropanol; flow rate: 1 mL/min; retention time: t_{minor} = 22.1 min and t_{major} = 27.0 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.15 (br, H), 4.77 (dd, J = 7.5, 3.3 Hz, 1H), 4.67 (s, 1H), 4.28 (d, J = 5.1 Hz, 2H), 1.85 (m, 1H), 1.61 (m, 1H), 1.45−1.26 (m, 10H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 170.9, 136.7, 128.6, 127.6, 127.3, 81.3, 78.6, 48.8, 33.0, 31.7, 29.2, 29.0, 23.9, 22.5, 14.0. HRMS (ESI) calcd for $C_{18}H_{25}NO_2 + H^+$ 288.1964, found 288.1967.

4-(Benzylamino)-5-butylfuran-2(5*H*)-one, P2: 70% overall yield, and 87% ee determined by HPLC analysis: chiralcel OD-H column; solvent: 90:10 hexanes:isopropanol; flow rate: 1 mL/min; retention time: t_{major} = 37.3 min and t_{minor} = 47.3 min. $[\alpha]^{21}_D$ 14.2 (c 0.30, THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 4.97 (br, 1H), 4.77 (dd, J = 7.8, 3.3 Hz, 1H), 4.70 (s, 1H), 4.29 (d, J = 5.4 Hz, 2H), 1.83 (m, 1H), 1.61 (m, 1H), 1.45−1.31 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 171.3, 136.7, 128.4, 127.3, 127.0, 80.5, 78.7, 48.5, 32.5, 25.9, 22.1, 13.7. HRMS (ESI) calcd for $C_{15}H_{19}NO_2 + H^+$ 246.1494, found 246.1497.

4-(Benzylamino)-5-octylfuran-2(5*H*)-one, P3: 31% overall yield, and 83% ee determined by HPLC analysis: chiralcel OD-H column; solvent: 90:10 hexanes:isopropanol; flow rate: 1 mL/min; retention time: t_{major} = 26.7 min and t_{minor} = 37.2 min. $[\alpha]^{21}_D$ 15.7 (c 0.20, THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.30 (m, 5H), 5.96 (br, 1H), 4.77 (m, 1H), 4.56 (s, 1H), 4.26 (d, J = 5.1 Hz, 2H), 1.87 (m, 1H), 1.60 (m, 1H), 1.36−1.24 (m, 12H), 0.87(m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 170.6, 136.6, 128.7, 127.7, 127.3, 81.6, 78.6, 48.9, 33.0, 31.8, 29.4, 29.3, 29.2, 24.0, 22.6, 14.1. HRMS (ESI) calcd for $C_{19}H_{27}NO_2 + H^+$ 302.2115, found 302.2118.

4-(Benzylamino)-5-isobutylfuran-2(5*H*)-one, P4: 51% overall yield, and 85% ee determined by HPLC analysis: chiralcel AD-H column; solvent: 90:10 hexanes:isopropanol; flow rate: 1 mL/min; retention time: t_{minor} = 18.2 min and t_{major} = 22.5 min. $[\alpha]^{21}_D$ 17.8 (c 0.20, THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.27 (m, 5H), 5.18 (br, 1H), 4.79 (dd, J = 6.3, 3.9 Hz, 1H), 4.65 (s, 1H), 4.27 (d, J = 5.4 Hz, 2H), 2.00 (m, 1H), 1.55 (m, 2H), 0.964 (d, J = 6.6 Hz, 3H), 0.957 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 170.9, 136.4, 128.9, 128.0, 127.5, 81.8, 77.1, 49.1, 42.7, 24.9, 23.5, 21.5. HRMS (ESI) calcd for $C_{15}H_{19}NO_2 + H^+$ 246.1494, found 246.1491.

4-(Benzylamino)-5-isopropylfuran-2(5*H*)-one, P5: 62% overall yield, and 84% ee determined by HPLC analysis: chiralcel OD-H column; solvent: 90:10 hexanes: isopropanol; flow rate: 1 mL/min; retention time: t_{minor} = 34.7 min and t_{major} = 38.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.26 (m, 5H), 4.86 (br, 1H), 4.76 (s, 1H), 4.69 (d, J = 2.4 Hz, 1H), 4.29 (d, J = 5.1 Hz, 2H), 2.03 (heptet d, J = 6.9, 2.7 Hz, 1H), 1.15 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H) (contains ∼9% impurity that cannot be removed). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 169.8, 136.7, 128.7, 127.7, 127.4, 82.6, 82.3, 49.0, 30.6, 19.4, 13.5. HRMS (ESI) calcd for $C_{14}H_{17}NO_2 + H^+$ 232.1332, found 232.1333.

4-(Benzylamino)-5-cyclohexylfuran-2(5*H*)-one, P6: 69% overall yield, and 86% ee determined by HPLC analysis: chiralcel OD-H column; solvent: 90:10 hexanes: isopropanol; flow rate: 1 mL/min; retention time: t_{major} = 34.7 min and t_{minor} = 38.3 min; $[\alpha]^{21}_D$ 14.2 (c 0.26, THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.37−7.29 (m, 5H), 5.16 (br, 1H), 4.69 (s, 1H), 4.65 (d, J = 1.8 Hz, 1H), 4.28 (d, J = 5.4 Hz, 2H), 1.71 (m, 6H), 1.47 (m, 1H), 1.20 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 169.8, 136.8, 128.5, 127.5, 127.2, 82.6, 81.7, 48.8, 40.1, 29.8, 26.3, 25.8, 25.6, 23.7. HRMS (ESI) calcd for $C_{17}H_{21}NO_2 + H^+$ 272.1651, found 272.1656.

4-(Benzylamino)-5-*sec*-butylfuran-2(5*H*)-one, P7: 53% overall yield, and 84% and 87% ee determined by HPLC analysis: chiralcel OD-H column; solvent: 90:10 hexanes:isopropanol; flow rate: 1 mL/min; retention time: t_{minor1} = 5.1 min, t_{minor2} = 31.8 min, t_{major1} = 36.9 min, and t_{major2} = 37.8 min. The NMR spectra show a mixture of two diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 5.10 (br, 1H), 4.81 (m), 4.72 (m), 4.28 (d, J = 5.4 Hz, 2H), 1.67−1.40 (m, 1H), 1.09 (d, J = 6.9 Hz), 0.96 (t, J = 7.5 Hz), 0.92 (t, J = 7.5 Hz), 0.77 (d, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 169.2, 168.8, 136.5, 128.9, 128.1, 127.6, 127.5, 83.6, 83.4, 82.7, 80.6, 49.2, 37.5, 37.4, 26.6, 21.4, 15.7, 11.9, 11.3. HRMS (ESI) calcd for $C_{15}H_{19}NO_2 + H^+$ 246.1494, found 246.1491.

4-(Benzylamino)-5-phenylfuran-2(5*H*)-one, P8: 78% overall yield, and 90% ee determined by HPLC analysis: chiralcel AD-H column; solvent ratio: 90:10 hexanes: isopropanol; flow rate: 1 mL/min; retention time: t_{minor} = 24.3 min and t_{major} = 29.1 min. $[\alpha]^{21}_D$ −26.7 (c 0.41, THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.12 (m, 10H), 5.61 (s, 1H), 4.80 (s, 1H), 4.72 (br, 1H), 4.24 (t, J = 5.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 169.2, 136.2, 134.9, 129.6, 129.1, 128.7, 127.9, 127.2, 127.1, 82.2, 80.3, 49.0. HRMS (ESI) calcd for $C_{17}H_{15}NO_2 + H^+$ 266.1181, found 266.1187.

4-(Benzylamino)-5-*o*-tolylfuran-2(5*H*)-one, P9: 57% overall yield, and 90% ee determined by HPLC analysis: chiralcel OD-H column; solvent: 90:10 hexanes: isopropanol; flow rate: 2 mL/min; retention time: t_{minor} = 33.4 min and t_{major} = 53.8 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.08 (m, 9H), 5.81 (s, 1H), 5.55 (br, 1H), 4.66 (s, 1H), 4.23 (d, J = 3.6 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 169.4, 137.4, 136.4, 132.6, 130.5, 129.0, 128.2, 127.2, 126.9, 126.0, 81.8, 77.4, 48.4, 18.6. HRMS (ESI) calcd for $C_{18}H_{17}NO_2 + H^+$ 280.1338, found 280.1338.

4-(Benzylamino)-5-(4-methoxyphenyl)furan-2(5*H*)-one, P10: 67% overall yield, and 90% ee determined by HPLC analysis: chiralcel AD-H column; solvent: 90:10 hexanes: isopropanol; flow rate: 1 mL/min; retention time: t_{minor} = 34.9 min and t_{major} = 44.3 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−6.89 (m, 9H), 5.58 (s, 1H), 4.80 (s, 1H), 4.70 (br, 1H), 4.25 (t, J = 5.4 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 169.3, 160.5, 136.3, 128.8, 128.7, 127.8, 127.3, 126.8, 114.4, 82.3, 80.1, 55.3, 49.0. HRMS (ESI) calcd for $C_{18}H_{17}NO_3 + H^+$ 296.1287, found 296.1279.

4-(Butylamino)-5-phenylfuran-2(5*H*)-one, P11: 81% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5H), 5.56 (s, 1H), 4.73 (s, 1H), 4.59 (br, 1H), 3.05 (p, 2H), 1.47 (sextet, 2H), 1.24 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 169.8, 135.3, 129.3, 128.8, 127.1, 80.2, 80.0, 44.8, 30.1, 19.7, 13.4. HRMS (ESI) calcd for $C_{14}H_{17}NO_2 + H^+$ 232.1338, found 232.1334.

4-(Butylamino)-5-heptylfuran-2(5*H*)-one, P12: 75% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (br, 1H), 4.74 (dd, J = 7.5, 3.3 Hz, 1H), 4.51 (s, 1H), 3.08 (m, 2H), 1.86 (m, 1H), 1.57 (m, 3H), 1.38−1.23 (m, 12H), 0.91 (t, J = 7.5 Hz, 3H), 0.84 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 171.0, 80.0, 78.5, 44.8, 33.1, 31.7, 30.4, 29.2, 29.1, 24.0, 22.5, 20.0, 14.0, 13.6. HRMS (ESI) calcd for $C_{15}H_{27}NO_2 + H^+$ 254.2122, found 254.2115.

4-(Dihexylamino)-5-phenylfuran-2(5*H*)-one, P13: 87% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.34 (m, 5H), 5.70 (s, 1H), 4.76 (s, 1H), 3.13−2.89 (m, 4H), 1.61−0.86 (m, 22H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 169.1, 135.6, 129.4, 129.0, 127.7, 82.0, 80.0, 50.9, 50.7, 50.6, 31.2, 28.0, 26.0, 22.3, 13.8. HRMS (ESI) calcd for $C_{22}H_{33}NO_2 + H^+$ 344.2590, found 344.2588.

4-(Dihexylamino)-5-heptylfuran-2(5*H*)-one, P14: 88% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (dd, J = 6.9, 2.4 Hz, 1H), 4.53 (s, 1H), 3.07 (m, 4H), 1.87 (m, 1H), 1.55−1.26 (m, 27H), 0.88 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 170.9, 82.5, 77.7, 50.6, 33.8, 31.7, 31.4, 29.2, 29.0, 26.4, 24.2, 22.54, 22.49, 14.0, 13.9. HRMS (ESI) calcd for $C_{23}H_{43}NO_2 + H^+$ 366.3372, found 366.3369.

4-(Dibenzylamino)-5-phenylfuran-2(5*H*)-one, P15: 87% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−6.98 (m, 15H), 5.85 (s, 1H), 5.01 (s, 1H), 4.34−4.17 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 169.9, 134.8, 129.4, 129.0, 128.5, 128.0, 127.6,

126.8, 84.4, 80.0, 53.4. HRMS (ESI) calcd for $C_{24}H_{21}NO_2 + H^+$ 356.1651, found 356.1646.

4-(Dibenzylamino)-5-heptylfuran-2(5*H*)-one, P16: 89% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.13 (m, 10H), 5.02 (dd, J = 7.5, 2.4 Hz, 1H), 4.81 (s, 1H), 4.42−4.25 (m, 4H), 2.00 (m, 1H), 1.65 (m, 1H), 1.47 (m, 2H), 1.30−1.21 (m, 8H), 0.86 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 171.8, 135.1, 128.9, 127.9, 127.0, 84.7, 77.8, 53.3, 33.8, 31.5, 28.9, 24.3, 22.4, 13.9. HRMS (ESI) calcd for $C_{25}H_{31}NO_2 + H^+$ 378.2433, found 378.2435.

5-Heptyl-4-(1-phenylethylamino)furan-2(5*H*)-one, P17: 86% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.22 (m, 5H), 5.97 (d, J = 5.7 Hz, 1H), 4.78 (dd, J = 4.2, 3.3 Hz, 1H), 4.39 (s, 1H), 4.34 (m, 1H), 1.89 (m, 1H), 1.60 (m, 1H), 1.56 (d, 3H), 1.27−1.23 (m, 10H), 0.87 (t, J = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 169.1, 142.1, 128.8, 127.7, 125.8, 82.9, 78.5, 55.2, 33.1, 31.7, 29.2, 29.1, 24.0, 22.9, 22.6, 14.0. HRMS (ESI) calcd for $C_{19}H_{27}NO_2 + H^+$ 302.2120, found 302.2115.

5-Phenyl-4-(1-phenylethylamino)furan-2(5*H*)-one, P18: 80% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.23 (m, 10H), 5.57 (s, 1H), 4.75 (br, 1H), 4.62 (s, 1H), 4.35 (p, 1H), 1.39 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 167.9, 142.0, 135.0, 129.7, 129.0, 128.7, 127.6, 127.4, 125.4, 83.6, 80.4, 55.1, 23.3. HRMS (ESI) calcd for $C_{18}H_{17}NO_2 + H^+$ 280.1338, found 280.1338.

Methyl 2-(2-heptyl-5-oxo-2,5-dihydrofuran-3-ylamino)-2-phenylacetate, P19: 71% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.33 (m, 5H), 5.83 (d, J = 5.4 Hz, 1H), 4.91 (d, J = 5.4 Hz, 1H), 4.78 (dd, J = 4.5, 3.0 Hz, 1H), 4.44 (s, 1H), 3.76 (s, 3H), 1.87 (m, 1H), 1.64 (m, 1H), 1.46 (m, 2H), 1.30−1.28 (m, 8H), 0.88 (t, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 170.6, 167.1, 134.7, 129.2, 127.0, 84.9, 78.4, 61.1, 53.3, 33.1, 31.7, 29.2, 29.0, 24.1, 22.6, 14.0. HRMS (ESI) calcd for $C_{20}H_{27}NO_4 + H^+$ 346.1055, found 346.2010.

Preparation and Characterization of 4-(Benzylamino)-3-bromo-5-heptylfuran-2(5*H*)-one, 3. To a stirred solution of 4-(benzylamino)-5-heptylfuran-2(5*H*)-one (0.3 mmol, 86 mg) in CH_2Cl_2 (20 mL) at 0 °C was added dropwise a solution of Br_2 (0.3 mmol, 0.015 mL) in CH_2Cl_2 (10 mL) over 10 min. After the reaction is completed by TLC, the solvent is evaporated and the product is obtained in 91% yield after column chromatography eluted with 50% ethyl acetate in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.27 (m, 5H), 5.40 (br, 1H), 4.86 (dd, J = 7.5, 2.7 Hz, 1H), 4.62 (d, J = 6.0 Hz, 2H), 1.93 (m, 1H), 1.62 (m, 1H), 1.42−1.24 (m, 10H), 0.86 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 164.3, 137.0, 129.0, 128.1, 127.1, 78.1, 74.0, 47.6, 33.1, 31.6, 29.02, 28.96, 23.9, 22.5, 14.0. MS calcd for $C_{18}H_{24}BrNO_2 + H^+$ 365.1, found 366.0.

Preparation and Characterization of 4-(Benzylamino)-5-heptyl-3-(2,2,2-trifluoroacetyl)furan-2(5*H*)-one, 4. To a stirred solution of 4-(benzylamino)-5-heptylfuran-2(5*H*)-one (0.3 mmol, 86 mg) in CH_2Cl_2 (20 mL) was added dropwise a solution of trifluoroacetic anhydride (0.4 mmol, 0.015 mL) in CH_2Cl_2 (10 mL) over 2 h. After the reaction is completed as shown by TLC, the solvent is evaporated, and the product is obtained in 95% overall yield after column chromatography eluted with 50% ethyl acetate in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.92 (br, 1H), 7.46−7.29 (m, 5H), 5.10 (dd, J = 7.5, 1.8 Hz, 1H), 4.62 (d, J = 6.3 Hz, 1H), 2.01 (m, 1H), 1.62 (m, 1H), 1.44−1.23 (m, 10H), 0.87 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 176.6 (q, J_{C-F} = 38 Hz), 167.1, 134.0, 129.4, 129.0, 127.0, 115.9 (q, J_{C-F} = 286 Hz), 92.6, 75.7, 49.3, 32.5, 31.5, 28.9, 28.8, 24.1, 22.4, 13.9. HRMS (ESI) calcd for $C_{20}H_{24}F_3NO_3 + H^+$ 384.1787, found 384.1784.

Preparation and Characterization of *tert*-Butyl Benzyl(2-heptyl-5-oxo-2,5-dihydrofuran-3-yl)carbamate, 5. To a stirred solution of 4-(benzylamino)-5-heptylfuran-2(5*H*)-one (0.3 mmol, 86 mg) and DMAP (0.36 mmol, 44 mg) in CH_2Cl_2 (20 mL) was added Boc_2O (0.36 mmol, 78 mg). After the reaction is completed as shown by TLC, the solvent is evaporated, and the product is obtained in 99% yield after column chromatography eluted with 25% ethyl acetate in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.15 (m, 5H), 5.68 (s, 1H), 5.21 (s, 2H), 4.94−4.68 (m, 2H), 1.93 (s, 1H), 1.58−1.25 (m, 20H), 0.87 (t, J = 5.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 167.0, 151.3, 135.6, 128.8, 127.7, 126.2, 98.4, 84.2, 81.4, 52.7, 33.5, 31.6, 29.1, 28.9, 27.8, 24.7, 22.5, 14.0. HRMS (ESI) calcd for $C_{23}H_{33}NO_4 + Na^+$ 410.2307, found 410.2301.

Preparation and Characterization of *tert*-Butyl Benzyl(4-bromo-2-heptyl-5-oxo-2,5-dihydrofuran-3-yl)carbamate, 6. To a stirred solution of 4-(benzylamino)-3-bromo-5-heptylfuran-2(5*H*)-one (**3**; 0.5 mmol, 183 mg) in CH_2Cl_2 (20 mL) was added DMAP (0.6 mmol, 73 mg) and Boc_2O (0.6 mmol, 131 mg). After the reaction is completed as shown by TLC, the solvent is evaporated, and the product is obtained in 96% yield after column chromatography eluted with 25% ethyl acetate in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.27 (m, 5H), 5.47 (dd, J = 8.7, 2.4 Hz, 1H), 5.06 (m, 2H), 1.47 (m, 9H), 1.29−1.16 (m, 12H), 0.86 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 161.4, 151.7, 136.8, 128.5, 127.9, 127.6, 83.9, 81.8, 77.2, 49.9, 32.2, 31.5, 28.8, 28.6, 27.8, 24.5, 22.4, 13.9. HRMS (ESI) calcd for $C_{23}H_{32}BrNO_4 + Na^+$ 488.1412, found 488.1401.

Acknowledgment. Partial support of this work from the U.S. National Science Foundation (CHE-0717995), the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation of China (Nos. 20725206 and 20732004), and the Specialized Research Fund for the Doctoral Program of Higher Education in China are gratefully acknowledged. L.H.Z. also thanks the fellowship from the China Scholarship Council [No.(2007)3020].

Supporting Information Available: The ^{1}H/^{13}C NMR, mass spectra, and HPLC plots of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802592H