Application on Novel Fragmentation Reaction: A Concise Synthesis of 2,3,5-Trisubstituted Furans from Butenolides

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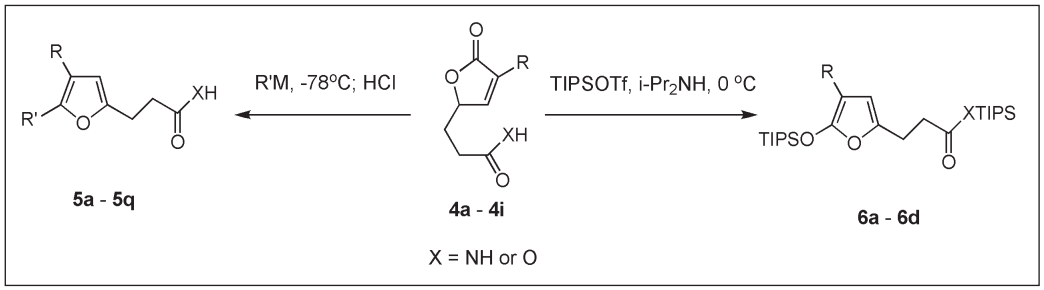

Butenolides **4**, generated from a novel fragmentation reaction, function as excellent precursors to 2,3,5-trisubstituted furans **5** by additions of alkyl or aryl metallic reagents. It can also be converted into siloxyfurans **6** by treatment with silylating reagents.

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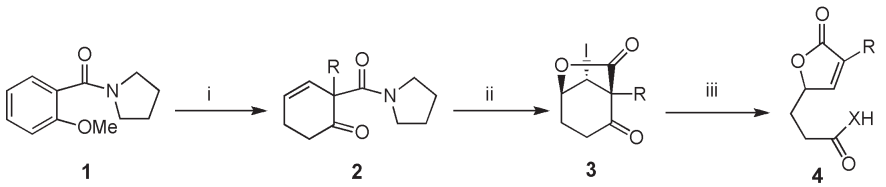
Introduction.

Polysubstituted furans are of great current interest because they are useful and versatile synthetic intermediates of a variety of heterocyclic and acyclic organic compounds. Several different preparative methods for polysubstituted furans have been reported in the literature [1]. The classical synthesis involves the intramolecular dehydration of acyclic precursors, such as 1,4-diketones [2], the tandem Diels-Alder cycloaddition – retro Diels-Alder reaction using oxazole derivatives and dienophiles [3], or the introduction of a substituent into the furan ring, usually through metalation [4]. Several new approaches to the regioselective synthesis of polysubstituted furans using transition metal -catalyzed cyclization strategies have been developed [5]. Kano and Dikshit reported a 1,2-addition and elimination sequence on converting butenolides to polysubstituted furans [6]. This method is straightforward but somewhat limited to substrate structures. It is necessary to develop this method on some common substrates with a variety of functional groups. As part of our program directed toward the development of the fragmentation reaction of 2-alkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones **3**, we were attracted to conduct this butenolide-furan transformation on a different set of structures readily available from a novel fragmentation process developed recently from our group [7,8]. The current study describes a concise synthesis of 2,3,5-trisubstituted furans from benzamide **1** *via* corresponding butenolide amides or acids **4**. The scope of this transformation and the limitation are also discussed.

Results and Discussion.

The preparation of 2-alkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones **3** has been well studied and reported in our earlier publications [7,8]. Birch reduction-alkylation of benzamide **1** with variable alkylating agents followed by enol ether hydrolyses gave the corresponding cyclohexenones **2**. Iodolactonizations of **2** afforded the 2-alkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones **3** (Scheme 1).

Scheme 1



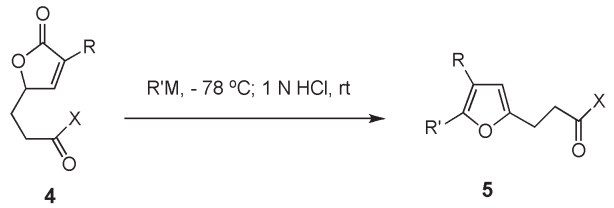
Reagents and conditions: (i) a) K, NH_3, *t*-BuOH and RX, -78 °C; b) 6 N HCl, MeOH; (ii) I_2, THF: H_2O (1:1); (iii) Liquid ammonia, - 78°C, when X = NH; LiOH, r.t., when X = O

Fragmentations of **3** with liquid ammonia in THF at –78 °C afforded butenolide amides **4a**-**4f** as only products in excellent yields [7]. To our satisfaction, additions of ~ 4.0 eq. alkyl or aryl lithium or Grignard reagents to

4a-**4f** at –78 °C for 2 hours, followed by acidic work-up afforded 2,3,5-trisubstituted furan amides **5a**- **5o** in moderate to good yields. The amide group in the butenolides **4** is compatible with metallic reagent addition. The results are summarized in Table 1. Whereas Grignard reagents (entry 7 and 10) was modestly reactive for additions to butenolide carbonyl groups, treatment of the butenolide amides with lithium reagents afforded the corresponding furans in higher yields. It is documented that butenolides can be good Michael acceptors by the addition of organic copper reagents [9]. However, the adducts from conjugated additions of nucleophiles to these butenolide amides were not observed, suggesting 1,2-additions were preferred by using either lithium or Grignard reagents. Attempting DIBAL reductions of the butenolide amide **4b** at –78 °C resulted in no conversion [10], probably due to steric hindrance of aluminum salt species formed before reduction could take place at the butenolide carbonyl group (entry 6).

Steric effect plays a crucial role to control the efficiency of organic metallic reagent additions. To evaluate the steric effect of the reagents in the butenolide carbonyl addition process, *n*-BuLi, *s*-BuLi and *t*-BuLi were employed with the same substrate **4a** under the same reaction conditions (entry 2, 3 and 4). *n*-BuLi addition resulted 81% yield of the corresponding **5b**, while *s*-BuLi and *t*-BuLi additions only afforded the corresponding **5c** and **5d** in 67% and 61% yields. The additions of ~ 2.0 eq. of the nucleophiles only led to starting material recovered. It may suggest that dianionic amidate species were involved in the reaction process before nucleophilic additions to butenolide carbonyl groups. Kaiser and coworkers reported that an intermediate - trilithioamide was involved in the conversions of phenyl and diphenylacetamides into the corresponding nitriles [11]. It was also discovered by Cooke and coworkers that yields of conjugated addition reactions of α–silylated-α,β-unsaturated primary amides were progressively improved when larger quantities of organometallic reagents were added [12], suggesting that additional reagents may be consumed in the formation of a dimetallated amide species which may also undergo addition reactions giving trianionic species. It is feasible to combine two organometallic reagents into this reaction. Thus, addition of 2.0 eq. MeLi into **4c** at –78 °C followed by 2.0 eq. PhLi afforded **5l** in

Table 1



4 **5**

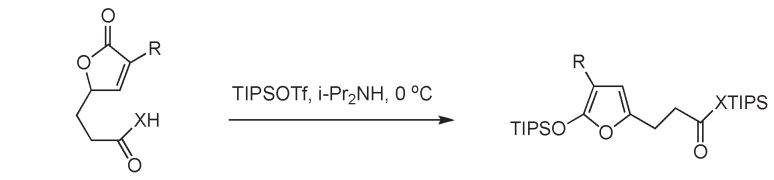
Entry	X	R	Substrate	R'M	Product	Yield (%)
1	NH	*n*-Bu	**4a**	MeLi	**5a**	82
2	NH	*n*-Bu	**4a**	*n*-BuLi	**5b**	81
3	NH	*n*-Bu	**4a**	*s*-BuLi	**5c**	67
4	NH	*n*-Bu	**4a**	*t*-BuLi	**5d**	60
5	NH	*n*-Bu	**4a**	PhLi	**5e**	64
6	NH	$(CH_2)_3Cl$	**4b**	DIBAL		0[a]
7	NH	$(CH_2)_3Cl$	**4b**	MeMgBr	**5f**	51
8	NH	$(CH_2)_3Cl$	**4b**	MeLi	**5f**	84
9	NH	$(CH_2)_3Cl$	**4b**	*t*-BuLi	**5g**	58
10	NH	$(CH_2)_3Cl$	**4b**	PhMgBr	**5h**	45
11	NH	$(CH_2)_3Cl$	**4b**	PhLi	**5h**	75
12	NH	$(CH_2)_3OBn$	**4c**	MeLi	**5i**	82
13	NH	$(CH_2)_3OBn$	**4c**	*n*-BuLi	**5j**	72
14	NH	$(CH_2)_3OBn$	**4c**	*s*-BuLi	**5k**	70
15	NH	$(CH_2)_3OBn$	**4c**	PhLi	**5l**	65
16	NH	$(CH_2)_3OBn$	**4c**	PhLi[b]	**5l**	61
17	NH	$CH_2O(CH_2)_2OTMS$	**4d**	MeLi	**5m**	82
18	NH	CH_2Ph	**4e**	MeLi	**5n**	80
19	NH	CH_2Ph	**4e**	*n*-BuLi	**5o**	61
20	O	$(CH_2)_3Cl$	**4g**	MeLi	**5p**	79
21	O	$(CH_2)_3OBn$	**4h**	MeLi	**5q**	79

[a] The procedure was followed in the reference 10. [b] 2.0 eq. MeLi and 2.0 eq. PhLi was added into the reaction mixture at –78 °C sequentially.

61% yield (entry 16). This procedure is more interesting since it can avoid using a large amount of precious lithium or Grignard reagents that are not commercially available. The butenolide carboxylic acids **4g** and **4h**, prepared from the corresponding iodolactones by treatment with LiOH [7], were transformed into 2,3,5-trisubstituted furan acids **5p** and **5q** in good yields by additions of ~ 3.0 eq. of organometallic reagents (Table 1, entry 20 and 21).

Siloxyfurans are employed as key intermediates for the synthesis of a variety of functional butenolides. Some transformations, for examples, vinylogous Mukaiyama Aldol and Michael additions, have been documented in the literatures [13]. A method of preparing siloxyfurans from butenolides comprises reacting a butenolide with a silylating agent in the presence of a base to provide a siloxyfuran ring [14]. To further test the utility of the butenolide amides and acids, we have transformed them into siloxyfuran substrates. Thus, treatment of butenolide amide **4b** and **4f** with TIPSOTf in the presence of diisopropyl amine furnished the corresponding siloxyfurans (84% and 71%). Under the same conditions, butenolide acids **4g** and **4h** could be transformed into siloxyfurans **6c** and **6d** in good yields.

Scheme 2



X = NH, R = $(CH_2)_3Cl$, **4b**
X = NH, R = CH_2(*o*-Br-Ph), **4f**
X = O, R = (CH_2)OBn, **4g**
X = O, R = CH_2(*o*-Br-Ph), **4h**

X = NH, R = $(CH_2)_3Cl$, **6a**, 84%
X = NH, R = CH_2(*o*-Br-Ph), **6b**, 71%
X = O, R = (CH_2)OBn, **6c**, 77%
X = O, R = CH_2(*o*-Br-Ph), **6d**, 72%

In summary, a concise approach to 2,3,5-trisubstituted furans from their corresponding precursors – readily available butenolide amides or acids **4** is described. This procedure is expected to be useful in the synthesis of complex molecules with furan moiety in the core nucleus.

EXPERIMENTAL

General.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 500 at 500 and 125 MHz respectively, with chloroform as the internal standard. Infrared spectra were obtained from a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Low resolution chemical ionization mass spectra were obtained using a Hewlett-Packard 5987A GC-MS system with isobutene as the ionizing gas. High resolution mass spectra were performed at the Mass Spectrometry Laboratory (School of Chemical Science) at the University of Illinois at Urbana-Champaign. Elemental analyses were performed at the Atlantic Microlab, Inc., Norcross, Georgia. Thin-layer chromatography was performed with Merck Kieselgel 60 F-254 precoated glass plates. Tetrahydrofuran was distilled from benzophenone sodium ketyl under nitrogen in a standing still. Reagents were purchased from Aldrich Chemical Company at the highest commercial quality and used without further purification unless otherwise stated.

General Procedure for Preparation of 2,3,5-Trisubstituted Furan Amides by Organic Lithium or Grignard Additions.

A solution of furan amide (1.0 eq.) in dry THF (C = 0.05 *M*) was cooled to –78 °C, and R'M (4.0 eq.) was added dropwise. The reaction mixture was stirred at –78 °C for two hours. The reaction was quenched with a 2 *N* HCl solution and slowly warmed to room temperature. Stirring was continued for an additional 30 min. The THF was removed *in vacuo* and the product was extracted with ethyl acetate several times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude material, which was purified by flash column chromatography (1:2 hexanes: EtOAc as eluent) to give the desired product as a white solid.

3-(4-Butyl-5-methylfuran-2-yl)propanamide (**5a**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89-0.92 (t, *J* = 7.3 Hz, 3H), 1.29-1.34 (m, 2H), 1.42-1.48 (m, 2H), 2.16 (s, 3H), 2.24-2.27 (t, *J* = 7.6 Hz, 2H), 2.88-2.91 (t, *J* = 7.6 Hz, 2H), 5.50 (br, s, 2H), 5.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.6, 14.1, 22.5, 24.1, 24.7, 32.7, 34.6, 120.0, 145.8, 151.3, 174.5; IR (neat) 3361, 3200, 2922, 1634 cm^{-1}. HR MS Calcd. for $C_{12}H_{19}NO_2$: 209.1416; Found 209.1418.

Anal. Calcd. For $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15. Found: C, 68.72; H, 9.11.

3-(4-Butyl-5-butylfuran-2-yl)propanamide (**5b**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90-0.93 (t, 3H, *J* = 7.3 Hz), 0.90-0.93 (t, 3H, *J* = 7.3 Hz), 1.28-1.36 (m, 4H), 1.42-1.48 (m, 2H), 1.52-1.58 (m, 2H), 2.24-2.27 (t, 2H, *J* = 7.8 Hz), 2.48-2.51 (m, 2H, *J* = 7.8 Hz), 2.53-2.56 (t, 2H, *J* = 7.8 Hz), 5.56 (br, s, 1H), 5.69 (br, s, 1H), 5.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ14.0, 14.1, 22.5, 22.6, 24.2, 25.8, 31.2, 33.0, 34.5, 107.6, 119.7, 150.9, 151.2, 174.8; IR (neat) 3370, 3200, 2955, 2927, 1659, 1575, 1421 cm^{-1}. HR MS Calcd. for $C_{15}H_{25}NO_2$: 251.1885; Found 251.1884.

Anal. Calcd. For $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02. Found: C, 71.54; H, 9.92.

3-(4-Butyl-5-*sec*-butylfuran-2-yl)propanamide (**5c**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76-0.79 (t, *J* = 7.3 Hz, 3H), 0.88-0.91 (t, *J* = 7.3 Hz, 3H), 1.16-1.18 (d, *J* = 6.8

Hz, 3H), 1.27-1.35 (m, 2H), 1.41-1.48 (m, 2H), 1.49-1.62 (m, 2H), 2.24-2.27 (t, *J* = 7.3 Hz, 2H), 2.51-2.54 (t, *J* = 7.3 Hz, 2H), 2.62-2.67 (m, 1H), 2.86-2.89 (t, *J* = 7.3 Hz, 2H), 5.73 (br, s, 1H), 5.81 (s, 1H), 6.12 (br, s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.4, 14.1, 19.8, 22.5, 24.2, 24.4, 29.1, 33.1, 34.5, 107.3, 119.3, 151.0, 153.0, 175.2; IR (neat) 3387, 3195, 2959, 1651, 1577cm^{-1}. HR MS Calcd. for $C_{15}H_{25}NO_2$: 251.1885; Found 251.1881.

Anal. Calcd. For $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02. Found: C, 71.60; H, 9.96.

3-(4-Butyl-5-*tert*-butylfuran-2-yl)propanamide (**5d**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91-0.94 (t, *J* = 7.3 Hz, 3H), 1.30 (s, 1H), 1.30-1.38 (m, 2H), 1.45-1.51 (m, 2H), 2.41-2.44 (t, *J* = 7.6 Hz, 2H), 2.41-2.44 (t, *J* = 7.1 Hz, 2H), 2.88-2.90 (t, *J* = 7.6 Hz, 2H), 5.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 22.9, 24.0, 25.6, 30.0, 33.6, 34.1, 34.4, 109.0, 118.4, 149.8, 155.3, 175.0; IR(neat) 3361, 3184, 2956, 1661 cm^{-1}. HR MS Calcd. for $C_{15}H_{25}NO_2$: 251.1885; Found 251.1892.

Anal. Calcd. For $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02. Found: C, 71.52; H, 9.89.

3-(4-Butyl-5-phenylfuran-2-yl)propanamide (**5e**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93-0.98 (t, *J* = 7.3 Hz, 3H), 1.35-1.48 (m , *J* = 7.3 Hz, 2H), 1.56-1.66 (m, 2H), 2.59-2.64 (m, 4H), 2.98-3.03 (t, *J* = 7.6 Hz, 2H), 5.71 (br, s, 1H), 5.99 (br, s, 1H), 6.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 22.8, 24.2, 25.8, 32.3, 34.3, 109.9, 112.8, 122.8, 125.5, 126.7, 128.7, 132.1, 147.2, 152.7, 174.7; IR (neat) 3407, 3186, 2950, 1653 cm^{-1}. HR MS Calcd. for $C_{17}H_{21}NO_2$: 271.1572; Found 271.1573.

Anal. Calcd. For $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80. Found: C, 75.16; H, 7.76.

3-[4-(3-Chloropropyl)-5-methylfuran-2-yl]propanamide (**5f**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.93 (p, *J* = 7.1 Hz, 2H), 2.18 (s, 3H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.48 (t, *J* = 7.6 Hz, 2H), 2.85 (t, *J* = 7.3 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2 H), 5.41 (br, s, 1H), 6.61 (br, s, 1H), 5.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.5, 21.8, 23.9, 32.9, 34.5, 44.4, 108.3, 127.8, 146.5, 151.8, 174.8; IR (neat) 3644, 3340, 1667 cm^{-1}. HR MS Calcd. for $C_{11}H_{16}NO_2Cl$: 229.0870; Found 229.0873.

Anal. Calcd. for $C_{11}H_{16}O_2NCl$: C, 57.22; H, 7.02; Found, C, 57.31; H, 6.98.

3-[4-(3-Chloropropyl)-5-*tert*-butylfuran-2-yl]propanamide (**5g**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 9H), 1.90 (p, *J* = 6.6 Hz, 2H), 2.45 (t, *J* = 7.8 Hz, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 2.81 (t, *J* = 7.3 Hz, 2H), 3.47 (t, *J* = 6.3 Hz, 2H), 5.72 (s, 1H), 5.55 (br, s, 1H), 5.69 (br, s, 1H), 5.72 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.0, 23.9, 29.8, 30.0, 34.0, 34.1, 34.3, 44.7, 108.6, 116.4, 155.9, 174.8; IR (neat) 3648, 3348, 1670 cm^{-1}. MS (CI): *m/z* = 272 [M$^+$+1].

Anal. Calcd. for $C_{14}H_{22}O_2NCl{\cdot}1/2H_2O$: C, 59.89; H, 8.26; Found, C, 59.85; H, 8.21.

3-[4-(3-Chloropropyl)-5-phenylfuran-2-yl]propanamide (**5h**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.00 (m, 2H), 2.41 (t, *J* = 6.6 Hz, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 3.60 (t, *J* = 6.1 Hz, 2H), 5.22 (br, s, 1H), 5.53 (br, s, 1H), 6.44 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.86 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.2, 29.8, 32.3, 38.1, 43.9, 126.0, 128.7, 128.9, 129.1, 133.8, 134.7, 156.7; IR (neat) 3648, 3203, 1667 cm^{-1}. MS (CI): *m/z* = 292 [M$^+$+1].

Anal. Calcd. for $C_{16}H_{18}O_2NCl$: C, 65.86; H, 6.22; Found, C, 65.91; H, 6.15.

3-[4-(3-Benzyloxypropyl)-5-methylfuran-2-yl]propanamide (**5i**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.78 (m, *J* = 6.6 Hz, 2H), 2.14 (s, 3H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.51 (t, *J* = 7.8 Hz, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 3.45 (t, *J* = 5.4 Hz, 2H), 4.49 (s, 2H), 5.50 (br, s, 1H), 5.59 (br, s, 1H), 5.81 (s, 1H), 7.28 (m, 1H), 7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.2, 21.2, 23.7, 30.1, 34.2, 69.4, 72.8, 107.3, 118.7, 127.4, 127.5, 128.2, 138.5, 145.7, 151.1, 174.2; IR (neat) 3354, 3210, 1668 cm^{-1}. MS (CI): *m/z* = 302 [M$^+$+1].

Anal. Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; Found, C, 71.69; H, 7.56.

3-[4-(3-Benzyloxypropyl)-5-butylfuran-2-yl]-propanamide (**5j**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, *J* = 7.6 Hz, 3H), 1.31 (m, *J* = 7.6 Hz, 2H), 1.54 (m, *J* = 7.5 Hz, 2H), 1.78 (m, *J* = 6.8 Hz, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.49 (q, *J* = 7.1 Hz, 4H), 2.87 (t, *J* = 7.1 Hz, 2H), 3.46 (t, *J* = 6.4 Hz, 2H), 4.49 (s, 2H), 5.69 (br, s, 1H), 5.81 (s, 1H), 6.08 (br, s, 1H), 7.28 (m, 1H), 7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7, 21.1, 22.1, 23.7, 25.4, 30.3, 30.8, 34.1, 69.4, 72.9, 107.0, 118.4, 127.3, 127.5, 127.9, 128.2, 138.4, 149.9, 151.1, 174.6; IR (neat) 3348, 3197, 1668 cm^{-1}. MS (CI): *m/z* = 344 [M$^+$+1].

Anal. Calcd. for $C_{21}H_{29}O_3N{\cdot}1/4H_2O$: C, 72.49; H, 8.55; Found, C, 72.61; H, 8.65.

3-[4-(3-Benzyloxypropyl)-5-*sec*-butylfuran-2-yl]propanamide (**5k**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.73 (t, *J* = 7.3 Hz, 3H), 1.13 (d, *J* = 7.1 Hz, 3H), 1.48 (m, 1H), 1.57 (m, 1H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.65 (m, *J* = 8.3 Hz, 1H), 2.80 (t, *J* = 8.3 Hz, 2H), 3.58 (s, 2H), 5.41 (br, s, 1H), 5.63 (br, s, 1H), 7.10 (m, 3H), 7.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.5, 19.8, 24.1, 29.1, 31.1, 33.2, 34.4, 107.8, 117.8, 126.1, 128.5, 128.6, 141.4, 151.5, 153.8, 174.7; IR (neat) 3341, 3190, 1669 cm^{-1}. MS (CI): *m/z* = 344 [M$^+$+1].

Anal. Calcd. for $C_{21}H_{29}O_3N$: C, 73.44; H, 8.51; Found, C, 73.42; H, 8.49.

3-[4-(3-Benzyloxypropyl)-5-phenylfuran-2-yl]propanamide (**5l**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.60 (t, *J* = 8.1 Hz, 2H), 3.01 (t, *J* = 7.3 Hz, 2H), 4.06 (s, 2H), 5.22 (br, s, 1H), 5.53 (br, s, 1H), 5.90 (s, 1H), 7.14 (m, 1H), 7.17 (m, 2H), 7.25 (m, 2H), 7.30 (m, 1H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.1, 32.8, 34.3, 110.4, 125.6, 127.2, 127.8, 128.2, 128.9, 130.3, 133.0, 153.4; IR (neat) 3345, 3192, 1666 cm^{-1}. MS (CI): *m/z* = 364 [M$^+$+1].

Anal. Calcd. for $C_{23}H_{25}O_3N$: C, 76.01.; H, 6.93; Found, C, 76.11; H, 6.89.

3-[4-(2-Trimethylsilanylethoxymethyl)-5-methylfuran-2-yl]propanamide (**5m**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.01 (s, 9H), 0.94 (t, *J* = 8.3 Hz, 2H), 2.13 (s, 3H), 2.52 (t, *J* = 7.8 Hz, 2H), 2.89 (t,

J = 7.5 Hz, 2H), 3.50 (t, *J* = 8.3 Hz, 2H), 4.18 (s, 2H), 5.53 (br, s, 1H), 5.60 (br, s, 1H), 5.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -1.90, 11.4, 18.0, 23.6, 34.0, 63.5, 67.2, 107.3, 116.9, 148.0, 151.7, 174.1; IR (neat) 3344, 3198, 1667 cm^{-1}. HRMS calcd. for $C_{14}H_{25}O_3NSi$: 283.1604; Found, 283.1599.

Anal. Calcd. for $C_{14}H_{25}O_3NSi$: C, 59.32; H, 8.89; Found, C, 59.25; H, 8.81.

3-(4-Benzyl-5-methylfuran-2-yl)propanamide (**5n**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.22 (s, 3H), 2.53-2.56 (t, *J* = 7.3 Hz, 2H,), 2.88-2.90 (t, 2H, *J* = 7.1 Hz), 3.64 (s, 2H), 5.68 (br, s, 2H), 5.80 (s, 1H), 7.16-7.21 (m, 3H), 7.27-7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.6, 24.0, 31.3, 34.4, 108.0, 118.5, 126.2, 128.5, 128.6, 141.1, 146.4, 151.7, 174.7; IR (neat) 3346, 3200, 2906, 1660 cm^{-1}. HR MS Calcd. for $C_{15}H_{17}O_2N$: 243.1259; Found 243.1259.

Anal. Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; Found, C, 73.98; H, 6.95.

3-(4-Benzyl-5-butylfuran-2-yl)-propanamide (**5o**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90-0.93 (t, 3H, *J* = 7.3 Hz), 1.32-1.36 (m, 2H), 1.55-1.61 (m, 2H), 2.51-2.58 (m, 4H), 2.87-2.90 (t, *J* = 7.3 Hz, 2H), 3.65 (s, 1H), 5.55 (br, s, 2H), 5.78 (s, H), 7.16-7.21 (m, 3H), 7.27-7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ14.0, 22.5, 24.0, 25.9, 31.1, 31.2, 34.3, 107.9, 118.2, 126.1, 128.5, 141.2, 150.7, 151.7, 175.0; IR (neat) 3359, 3187, 3028, 2928, 1660, 1574 cm^{-1}. HR MS Calcd. for $C_{18}H_{23}O_2N$: 285.1729; Found 285.1728.

Anal. Calcd. for $C_{18}H_{23}O_2N$: C, 75.76; H, 8.12; Found, C, 75.80; H, 8.11.

General Procedure for Preparation of 2,3,5-Trisubstituted Furan Acids by Organic Lithium Additions.

A solution of butenolide acid (1.0 eq.) in dry THF (C = 0.05 *M*) was cooled to –78 °C and R'Li (3.0 eq.) was added dropwise. The reaction mixture was stirred at –78 °C for two hours. The reaction was quenched with a 2 *N* HCl solution and slowly warmed to room temperature. Stirring was continued for an additional 30 min. THF was removed *in vacuo* and the product was extracted with ethyl acetate several times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude material, which was purified by flash column chromatography (1:1 hexanes: EtOAc as eluent) to give the desired product as a white solid.

3-[4-(3-Chloropropyl)-5-methylfuran-2-yl]propanoic Acid (**5p**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.86 (t, *J* = 6.8 Hz, 2H), 2.12 (s, 3H), 2.36 (t, *J* = 7.1 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.80 (t, *J* = 7.3 Hz, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 5.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.5, 21.9, 23.3, 32.7, 33.0, 44.4, 107.2, 117.8, 146.6, 151.3, 178.8; IR (neat) 3648, 1713 cm^{-1}. MS (CI): *m/z* = 231 [M$^+$+1].

Anal. Calcd. for $C_{11}H_{15}O_3Cl{\cdot}H_2O$: C, 53.12; H, 6.89; Found, C, 53.44; H, 6.80.

3-[4-(3-Benzyloxypropyl)-5-methylfuran-2-yl]propanoic Acid (**5q**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.71 (t, *J* = 6.9 Hz, 2H), 2.06 (s, 3H), 2.28 (t, *J* = 7.3 Hz, 2H), 2.58 (m, 2H), 2.79 (t, *J* = 6.9 Hz, 2H), 3.38 (t, *J* = 6.3 Hz, 2H), 4.42 (s, 2H), 5.72 (s, 1H), 7.21 (m, 1H), 7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.5, 21.5, 23.4, 30.4, 69.7, 73.1, 107.5, 119.0, 127.8, 127.9, 128.6, 138.7, 146.1, 151.1; IR (neat) 3532, 1711 cm^{-1}. MS (CI): *m/z* = 303 [M$^+$+1].

Anal. Calcd. for $C_{18}H_{22}O_4{\cdot}1/2H_2O$: C, 69.43; H, 7.45; Found, C, 69.65; H, 7.40.

General Procedure for Preparation of 2,3,5-Trisubstituted Siloxyfurans.

Triisopropylsilyl triflate (2.5 eq.) was added dropwise into a solution of butenolide amide or butenolide acid and *i*-Pr_2NH (5.0 eq.) in CH_2Cl_2 (C = 0.1 *M*) at 0 °C. The reaction mixture was stirred for 30 min. and then warmed to room temperature. CH_2Cl_2 and water were added and then reaction mixture was partitioned between CH_2Cl_2 and water. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give clear oil. The crude material was subjected to flash column chromatography purification using 4:1 hexanes: EtOAc as eluent. The pure product was obtained as colorless oil.

3-[4-(3-Chloropropyl)-5-triisopropylsilanyloxyfuran-2-yl]-*N*-triisopropylsilanylpropanamide (**6a**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (m, 36H), 1.25 (m, 6H), 1.91 (p, *J* = 7.3 Hz, 2H), 2.34 (t, *J* = 7.3 Hz, 2H), 2.49 (t, *J* = 7.3 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 4.76 (br, s, 1H), 5.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.5, 12.5, 12.6, 17.5, 17.8, 17.9, 18.0, 18.4, 21.0, 24.6, 32.9, 36.6, 44.7, 86.6, 94.8, 108.3, 142.4, 177.7; IR (neat) 3323, 1718 cm^{-1}. MS (CI): *m/z* = 544 [M$^+$+1].

Anal. Calcd. for $C_{28}H_{54}O_3NClSi_2$: C, 61.78; H, 10.00; Found, C, 61.65; H, 9.88.

3-[4-(2-Bromo-benzyl)-5-triisopropylsilanyloxyfuran-2-yl]-*N*-triisopropylsilanylpropanamide (**6b**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.09 (m, *J* = 3.7 Hz, 36H), 1.25 (m, *J* = 6.1 Hz, 6H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.78 (t, *J* = 7.1 Hz, 2H), 3.67 (s, 2H), 5.75 (s, 1H), 7.02 (m, 1H), 7.18 (d, *J* = 4.2 Hz, 2H), 7.51 (d, *J* =7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1, 12.2, 12.6, 17.8, 17.9, 24.2, 30.3, 34.5, 94.0, 95.0, 108.2, 124.6, 127.5, 127.7, 130.6, 132.7, 140.8, 142.4, 172.8; IR (neat) 3340, 1720 cm^{-1}. MS (CI): *m/z* = 637 [M$^+$+1].

Anal. Calcd. for $C_{32}H_{54}O_3NBrSi_2$: C, 60.35; H, 8.55; Found, C, 60.22; H, 8.65.

3-[4-(3-Benzyloxypropyl)-5-triisopropylsilanyloxyfuran-2-yl]propanoic Acid triisopropylsilanyl ester (**6c**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99 (m, 36H), 1.15 (m, 6H), 1.70 (t, *J* = 7.3 Hz, 2H), 2.20 (t, *J* = 7.3 Hz, 2H), 2.51 (t, *J* = 8.1 Hz, 2H), 2.70 (t, *J* = 7.1 Hz, 2H), 3.40 (t, *J* = 6.4 Hz, 2H), 4.42 (s, 2H), 5.67 (s, 1H), 7.19 (m, 1H), 7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.2, 12.6, 14.6, 17.4, 17.8, 18.0, 18.2, 30.1, 70.3, 127.6, 127.8, 128.5, 14.5; IR (neat) 1718 cm^{-1}. MS (CI): *m/z* = 617 [M$^+$+1].

Anal. Calcd. for $C_{35}H_{60}O_5Si_2$: C, 68.13; H, 9.80; Found, C, 68.28; H, 9.65.

3-[4-(2-Bromo-benzyl)-5-triisopropylsilanyloxyfuran-2-yl]propanoic Acid Triisopropylsilanyl Ester (**6d**).

Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01 (m, 36H), 1.18 (m, 6H), 2.52 (t, *J* = 6.3 Hz, 2H), 2.70 (t, *J* = 6.6 Hz, 2H), 3.59 (s, 2H), 5.67 (s, 1H), 6.96 (t, *J* = 8.1 Hz, 1H), 7.12 (m, 2H),

7.44 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1, 12.6, 17.8, 17.9, 18.4, 24.2, 41.1, 108.3, 127.5, 127.7, 132.7, 174.6; IR (neat) 1718 cm^{-1}. MS (CI): m/z = 638 [M$^+$+1].

Anal. Calcd. for $C_{32}H_{53}O_4BrSi_2$: C, 60.26; H, 8.38; Found, C, 60.45; H, 8.19.

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