Efficient Synthesis of (*E*)-3-Alkylidene-2(3*H*)-furanones from 3-(1-Hydroxyalkyl)-2-silyloxyfurans

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Abstract: Several unsubstituted (*E*)-3-alkylmethylidene- and (*E*)-3-(arylmethylidene)-2(3*H*)-furanones have been synthesized in highly stereoselective fashion by mesylation–elimination of 3-(1-hydoxyalkyl)-2-silyloxyfurans. The latter were prepared from 2-triisopropylsilyloxy-3-bromofuran by halogen–lithium exchange and reaction of the in situ generated 3-lithiated silyloxyfuran with aldehydes.

Key words: 2-silyloxyfurans, bromination, lithiation, lactones, stereoselectivity

The 3-ylidene-2(3*H*)-furanone unit characterizes a small but pharmacologically important group of natural products and semi-synthetic derivatives, comprising the highly selective EGF receptor kinase inhibitor BE-23372M (**1**),[1] the andrographolide-derived potent anti-HIV agents DASM (cf. **2**),[2] and the medicinal plant constituents peronemin D_1 (**3**)[3] and guttoside (**4**, Figure 1).[4]

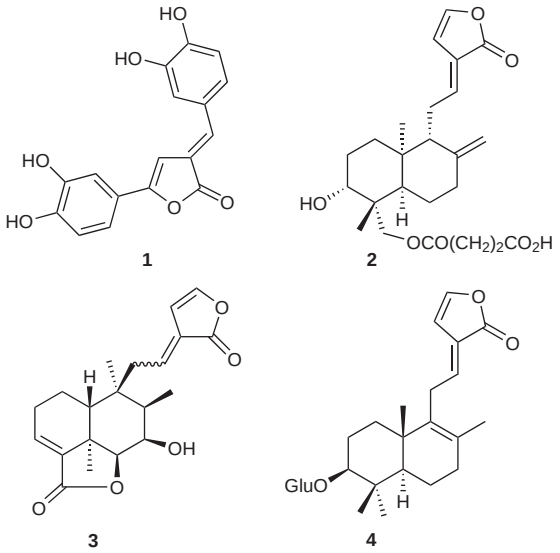
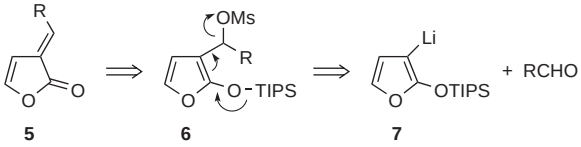


Figure 1

Conceivably, these substances may produce their biological effects by acting as alkylating agents in Michael-type reactions with thiol-containing bionucleophiles.[5] Furthermore, 3-ylidene-2(3*H*)-furanones are valuable intermediates in the synthesis of other compounds,[6,7] including coumarins,[6] naphthalenes[8] and 3-ylidene-3*H*-pyrrolin-2-ones.[9]

Traditionally, 3-ylidene-2(3*H*)-furanones have been prepared by cyclodehydration of γ-keto acids and ensuing aldol condensation with aromatic aldehydes. Although this process has been widely used,[6] it is restricted to the preparation of 5-substituted derivatives,[10] and even then its utility can be hampered by poor *E*/*Z* stereoselectivity and overall efficiency,[6] as noted during the synthesis of BE-23372M.[1c] In recent years, several alternative routes have been reported,[11–16] most of them involving transition-metal-catalyzed cyclization or cyclocarbonylation of appropriately functionalized acetylenic or allenic substrates.[13–16] All of these methods, however, also involve de novo construction of the lactone ring and are only applicable to furanones bearing a C5 substituent[11–15] and/or a disubstituted methylidene appendage.[12,16]

We report here a fundamentally different approach that overcomes these limitations and enables expedient access to a range of hitherto unknown, unsubstituted (*E*)-3-alkylidene-2(3*H*)-furanones **5** from readily available starting materials (Scheme 1).



Scheme 1

The strategy we followed relies on an unprecedented elimination of silyloxyfurylcarbinol mesylates **6**, envisioned to arise by addition of 3-lithio-2-silyloxyfuran **7** to aldehydes (Scheme 1). 3-Bromo-2-triisopropylsilyloxyfuran (**10**) was viewed as a stable precursor of **7** and also as a key building block, obtainable in two steps from commercially available furanone **8** (Scheme 2). Thus, bromination of **8** and subsequent dehydrohalogenation of the crude dibromide adduct[17] provided the known 3-bromo-2(5*H*)-furanone (**9**) in 91% yield.[18] Exposure of **9** to TIPSOTf/Et_3N in dichloromethane[19,20] afforded bromosilyloxyfuran **10** in 89% yield after flash chromatography.[21]

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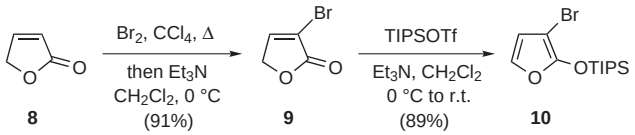


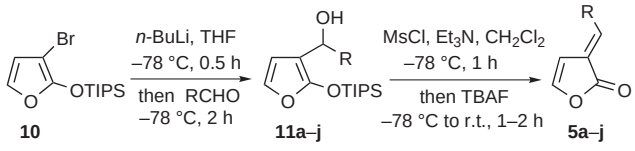
Scheme 2

The requisite 3-(1-hydroxyalkyl)-2-silyloxyfurans **11** were prepared from **10** by halogen–metal exchange with *n*-butyllithium, followed by in situ reaction of the resulting 2-lithio-3-triisopropylsilyloxyfuran with aldehydes (Table 1).[20,22] With the exception of *p*-nitrobenzaldehyde (entry 7), all of the aliphatic and aromatic aldehydes tried gave excellent carbinol yields although the quality of aldehyde proved to be critical for optimal results.[22]

Treatment of alcohol **11a** with MsCl/Et_3N in dichloromethane (–78 °C to r.t.) accomplished mesylation and ensuing elimination to furnish 3-hexylidenefuranone **5a** (*E*:*Z* = 17:1) which was obtained essentially free from its *Z*-isomer after purification on silica gel (42% yield, >97% *E*).[23] The yield of **5a** was only slightly improved when TBAF was used in conjunction with MsCl/Et_3N (52%; entry 1).[24] Nonetheless, higher yields of 3-alkylidenefuranones were obtained from furylcarbinols with branched alkyl substituents (entries 2–4).

The smooth conversion of isovaleraldehyde-derived carbinol **11b** to furanone **5b** (96%, entry 2) is especially noteworthy since the latter can be regarded as a simplified analogue of diterpene lactones **2**–**4** (Figure 1). Likewise, furylcarbinols bearing an α-aryl, biaryl or heteroaryl substituent (cf. **11e**–**j**) were transformed to the corresponding 3-arylmethylidenefuranones in consistently excellent yields (entries 5–10). Significantly, elimination proceeds with high *E*-stereoselectivity, regardless of the nature of the R group.[23] This can best be explained by considering conformers **6A** and **6B** which may undergo elimination by a concerted mechanism or via formation of the corresponding carbocations **12A** and **12B** (Figure 2). Conformers **6A** and **12A** are favored over **6B** and **12B** on steric grounds since the latter are substantially destabilized by allylic 1,3-strain[25] between the triisopropylsilyloxy (TIPSO) and R substituents.

Table 1 Preparation of 3-(*E*)-Alkylidene-2(*3H*)-furanones



Entry	R	Yield (%) of **11**[a]	Yield (%) of **5**[a]	*E*:*Z*[b]
1	$Me(CH_2)_4$	92 (**11a**)	52 (**5a**)[c]	17:1
2	Me_2CHCH_2	93 (**11b**)	96 (**5b**)	17:1
3	*i*-Pr	99 (**11c**)	73 (**5c**)	23:1
4	*t*-Bu	96 (**11d**)	61 (**5d**)	>30:1
5	Ph	98 (**11e**)	93 (**5e**)	>30:1
6	*p*-MeO-Ph	82 (**11f**)	97 (**5f**)	>30:1
7	*p*-NO_2-Ph	58 (**11g**)	90 (**5g**)	>30:1
8	*m*-Cl-Ph	91 (**11h**)	97 (**5h**)	>30:1
9	*p*-Ph-Ph	80 (**11i**)	96 (**5i**)	>30:1
10	2-Furyl	98 (**11j**)	91 (**5j**)	>30:1

[a] All yields refer to chromatographically purified products.
[b] Ratios were determined by ^1H NMR.
[c] The yield of **5a** was 42% when the experiment was performed without using TBAF.

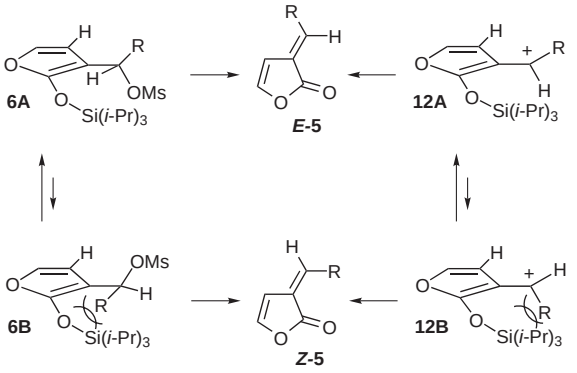
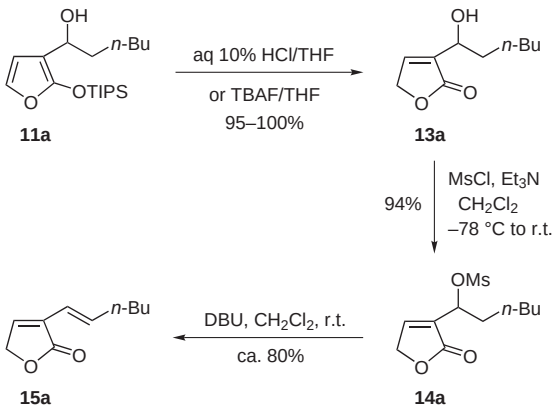


Figure 2

It is worthy of note that the propensity of silyloxyfurylcarbinol mesylates **6** to undergo in situ elimination to **5** (Scheme 1), sharply contrasts the behavior of their unmasked furanone counterparts which have been isolated on several occasions and shown to undergo nucleophilic displacement with high efficiency.[26] Indeed, mesylation of alcohol **13a**, obtained by hydrolysis of silyloxyfuran **11a**, proceeded smoothly to furnish mesylate **14a** in high yield (Scheme 3). Moreover, exposure of **14a** to DBU did not provide 3-hexylidenefuranone **5a** but led to 3-(*E*)-hexenylfuranone **15a** instead as the main reaction product.[27]



Scheme 3

In conclusion, the first synthesis of unsubstituted (*E*)-3-alkylidene-2(3*H*)-furanones has been achieved by a highly regio- and stereocontrolled pathway from 3-bromo-2-triisopropylsilyloxyfuran. The simplicity and inherent flexibility of this new methodology set the stage for the synthesis of several natural and unnatural products of biomedical importance.

Acknowledgment

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(21) Data for **10**: colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (18 H, d, *J* = 7.2 Hz), 1.29 (3 H, m), 6.27 (1 H, d, *J* = 2.4 Hz), 6.80 (1 H, d, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3, 17.4, 73.3, 114.1, 131.7, 153.4. HRMS: *m/z* calcd: 318.0651 [M^+]; found: 318.0656.

(22) **Typical Procedure.**
To a solution of bromofuran **10** (0.720 g, 2.26 mmol) in anhyd THF (30 mL) stirred at –78 °C under nitrogen was added *n*-BuLi (2.5 M in hexane, 1.08 mL, 2.49 mmol). After 30 min at –78 °C, a solution of freshly distilled *n*-hexanal (0.450 g, 4.53 mmol) in THF (10 mL) was added dropwise and the mixture was stirred at –78 °C for 2 h. Then, H_2O was added (150 mL) and the solution was extracted twice with EtOAc. The combined extracts were washed with H_2O, aq sat. NaCl, dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (95:5:1, hexane–Et_2O–Et_3N) afforded furylcarbinol **11a** (0.708 g, 92%). All furylcarbinols **11a–j** were obtained as oils and characterized by ^{1}H NMR, ^{13}C NMR, and HRMS; data for representative compounds are provided below.
Data for **11a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87–1.80 (32 H, m), 2.17 (1 H, m), 4.60 (1 H, m), 6.27 (1 H, d, *J* = 1.9 Hz), 6.76 (1 H, d, *J* = 1.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 14.0, 17.7, 22.7, 25.6, 31.7, 37.4, 65.9, 99.7, 109.7, 131.3, 152.3. HRMS: *m/z* calcd: 297.1886 [$M - C_3H_7$]$^+$; found: 297.1891.
Data for **11e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (18 H, m), 1.27 (3 H, m), 2.05 (1 H, d, *J* = 3.0 Hz), 5.75 (1 H, d, *J* = 3.0 Hz), 6.12 (1 H, d, *J* = 2.4 Hz), 6.71 (1 H, d, *J* = 2.4 Hz), 7.30 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 17.8, 67.9, 99.9, 110.5, 126.2, 127.3, 128.5, 131.6, 143.8, 153.5. HRMS: *m/z* calcd: 346.1964 [M^+]; found: 346.1961.
Data for **11f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (18 H, m), 1.27 (3 H, m), 2.17 (1 H, d, *J* = 3.6 Hz), 3.73 (3 H, s), 5.71 (1 H, s), 6.16 (1 H, d, *J* = 2.2 Hz), 6.71 (1 H, d, *J* = 2.2 Hz), 6.85 (2 H, d, *J* = 8.4 Hz), 7.31 (2 H, d, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 17.8, 55.4, 67.6, 100.1, 110.6, 113.8, 127.5, 131.6, 136.2, 153.3, 158.9. HRMS: *m/z* calcd: 333.1522 [$M - C_3H_7^+$]; found: 333.1518.
Data for **11g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (18 H, m), 1.26 (3 H, m), 2.42 (1 H, br s), 5.81 (1 H, s), 6.04 (1 H, d, *J* = 2.2 Hz), 6.71 (1 H, d, *J* = 2.2 Hz), 7.54 (2 H, d, *J* = 9.1 Hz), 8.14 (2 H, d, *J* = 9.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 17.8, 67.0, 98.9, 110.0, 123.7, 126.9, 132.1, 147.2, 151.3, 153.8. HRMS: *m/z* calcd: 392.1893 [MH^+]; found: 392.1890.

(23) The *E*-stereochemistry of compounds **5a–j** was determined by NOESY experiments. The *Z*-isomers of **5a–c** are clearly distinguished by ^{1}H NMR from their *E*-isomers by the upfield shift of the three olefin protons (Δδ ca. 0.1–0.3 ppm).

(24) **Typical Procedure.**
To a solution of furylcarbinol **11e** (0.190 g, 0.55 mmol) in anhyd CH_2Cl_2 (5 mL) stirred at –78 °C under nitrogen was

added Et_3N (0.056 g, 0.55 mmol) and MsCl (0.063 g, 0.55 mmol). The mixture was stirred at –78 °C for 1 h and TBAF (1.0 M in THF, 0.55 mL, 0.55 mmol) was added. The mixture was slowly warmed to r.t. with stirring over 1 h. Purification by column chromatography (4:1, hexane–Et_2O) provided furanone **5e** (0.088 g, 93%).

Data for **5a**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (3 H, t, *J* = 7.1 Hz), 1.28 (4 H, m), 1.48 (2 H, m), 2.31 (2 H, m), 6.12 (1 H, dd, *J* = 4.0, 1.0 Hz), 6.74 (1 H, m), 6.94 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.3, 30.7, 31.6, 105.4, 126.2, 144.1, 145.4, 168.3. HRMS: *m/z* calcd: 166.0994 [M^+]; found: 166.0991.

Data for **5b**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (6 H, d, *J* = 6.8 Hz), 1.85 (1 H, m), 2.24 (2 H, t, *J* = 6.4 Hz), 6.15 (1 H, dd, *J* = 3.6, 0.8 Hz), 6.78 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7, 38.6, 39.7, 105.5, 126.9, 143.0, 145.6, 168.3. HRMS: *m/z* calcd: 152.0837 [M^+]; found: 152.0842.

Data for **5c**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (6 H, d, *J* = 6.4 Hz), 2.70 (1 H, m), 6.15 (1 H, dd, *J* = 3.6, 0.8 Hz), 6.61 (1 H, dq, *J* = 10.0, 0.8 Hz), 6.97 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 30.5, 105.4, 124.1, 145.4, 150.0, 168.8. HRMS: *m/z* calcd: 138.0681 [M^+]; found: 138.0676.

Data for **5d**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (9 H, s), 6.34 (1 H, dd, 3.8, 0.8 Hz), 6.77 (1 H, dd, *J* = 1.9, 0.8 Hz), 6.99 (1 H, dd, *J* = 3.8, 1.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9, 35.6, 105.8, 122.4, 145.4, 153.7, 169.9. HRMS: *m/z* calcd: 152.0837 [M^+]; found: 152.0833.

Data for **5e**: yellow solid, mp 190–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (1 H, dd, *J* = 3.6, 1.0 Hz), 7.12 (1 H, dd, *J* = 3.6, 2.0 Hz), 7.43 (4 H, m), 7.53 (2 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 106.4, 123.3, 129.3, 130.4, 130.8, 134.8, 137.9, 147.5, 169.6. HRMS: *m/z* calcd: 172.0524 [M^+]; found: 172.0519.

Data for **5f**: yellow solid, mp 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (3 H, s), 6.55 (1 H, dd, *J* = 3.4, 0.8 Hz), 6.92 (2 H, dd, *J* = 7.0, 1.8 Hz), 7.08 (1 H, dd, *J* = 3.4, 2.0 Hz), 7.37 (1 H, m), 7.51 (2 H, dd, *J* = 7.0, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7, 106.4, 114.9, 120.7, 127.6, 132.4, 137.8, 146.5, 161.9, 170.1. HRMS: *m/z* calcd: 202.0630 [M^+]; found: 202.0624.

Data for **5g**: yellow solid, mp 212–213 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (1 H, dd, *J* = 3.7, 1.0 Hz), 7.25 (1 H, dd, *J* = 3.7, 1.6 Hz), 7.44 (1 H, m), 7.68 (2 H, dd, *J* = 6.9, 1.6 Hz), 8.28 (2 H, dd, *J* = 6.9, 1.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 106.0, 124.5, 126.7, 130.7 (2×), 134.1, 140.8, 149.8, 168.5. Anal. Calcd for $C_{12}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.56; H, 3.05; N, 6.38.

Data for **5h**: yellow solid, mp 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (1 H, dd, *J* = 3.5, 0.8 Hz), 7.17 (1 H, dd, *J* = 3.5, 1.8), 7.40 (4 H, m), 7.51 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 106.2, 124.6, 128.5, 129.8, 130.6 (2×), 135.3, 135.9, 136.5, 148.3, 169.1. HRMS: *m/z* calcd: 206.0135 [M^+]; found: 206.0129.

Data for **5i**: yellow solid, mp 222–223 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.63 (1 H, dd, *J* = 3.4, 0.8 Hz), 7.15 (1 H, dd, *J* = 3.4, 1.8 Hz), 7.44 (4 H, m), 7.64 (6 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 106.5, 123.1, 127.3, 127.9, 128.4, 129.2, 131.0, 133.8, 137.4, 140.0, 143.5, 147.4, 169.7. Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 81.97; H, 4.66.

Data for **5j**: yellow solid, mp 191–192 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (1 H, dd, *J* = 3.4, 1.6 Hz), 6.80 (2 H, m), 7.07 (1 H, dd, *J* = 3.4, 1.6 Hz), 7.12 (1 H, m), 7.63 (1 H, d, *J* = 1.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 108.1, 113.4, 119.3, 120.3, 122.1, 146.0, 146.8, 151.9, 169.9. HRMS: *m/z* calcd: 162.0317 [M^+]; found: 162.0322.

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