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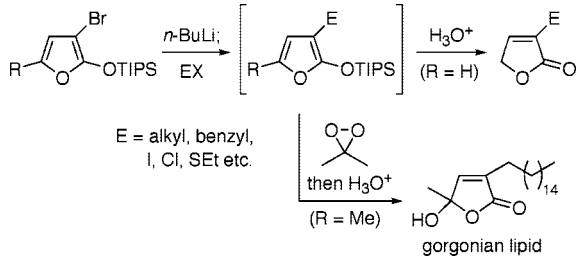
General, Regiodefined Access to α-Substituted Butenolides through Metal−Halogen Exchange of 3-Bromo-2-silyloxyfurans. Efficient Synthesis of an Anti-inflammatory Gorgonian Lipid

John Boukouvalas* and Richard P. Loach

Département de Chimie, Université Laval, Quebec City, Quebec G1K 7P4, Canada

john.boukouvalas@chm.ulaval.ca

Received July 18, 2008



A variety of α-substituted butenolides were efficiently prepared from 3-bromo-2-triisopropylsilyloxyfuran via lithium−bromine exchange and in situ quench with carbon or heteroatom electrophiles. The inherent flexibility of this methodology is illustrated by a short and efficient synthesis of an anti-inflammatory marine natural product.

The α-alkylbutenolide substructure is found in a variety of pharmacologically active natural products, as represented by the antileukemic/neuroprotective labdane pinusolide (**1**),[1] the novel antimalarial clerodane gomphostinin (**2**),[2] a potent antitumor acetogenin (annomolon A, **3**),[3] and the anti-inflammatory gorgonian lipid **4**[4] (Figure 1). In addition, α-substituted butenolides are valuable intermediates in the synthesis of other important targets,[5] including a host of antimicrobial[6] and herbicidal lactones.[7] Consequently, a great amount of effort has been directed at their construction[8] from both acyclic[9] and oxacyclic precursors.[10] Perhaps the most appealing methods are those relying on homologation of a suitable synthon for carbanion **A**,[8,10e] such as the lithiated Diels−Alder adduct **6**[11] and lithiofuryl diamidophosphate **7**[12] (Figure 2). However, these methods have some serious limitations. For instance, the requisite retro-Diels−Alder reaction in the synthesis of **5** from **6** is reportedly achievable only through flash vacuum pyrolysis at 500 °C.[11] Also, while lithiofuran **7** reacts with good electrophiles (e.g., MeI and BnBr), alkylation fails with the less reactive ethyl iodide.[12b] Hence, a direct and practical means for joining the butenolide ring to a carbon chain is lacking, thereby hampering the use of this linchpin approach (cf. **A**→**5**) in natural product synthesis.

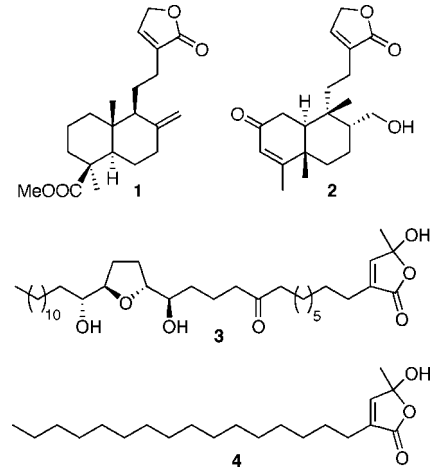


FIGURE 1. Naturally occurring α-substituted butenolides.

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10.1021/jo8015924 CCC: $40.75 © 2008 American Chemical Society
Published on Web 09/18/2008

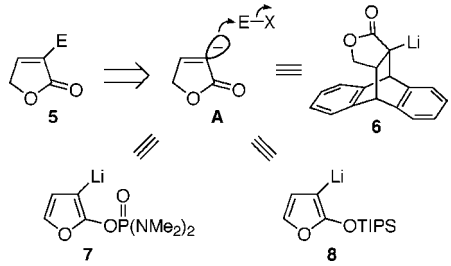
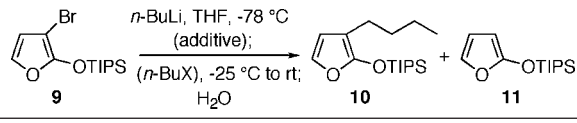


FIGURE 2. Selected synthons for carbanion **A**.

TABLE 1. Butylation of 3-Bromo-2-triisopropylsilyloxyfuran[a]



entry	*n*-BuX	additive	**10** (%)[b]	**11** (%)[b]
1	*n*-BuI		91	9
2	*n*-BuI	HMPA	81	19
3	*n*-BuI	DMPU	86	14
4	*n*-BuBr		40	60
5			<2[c]	>98

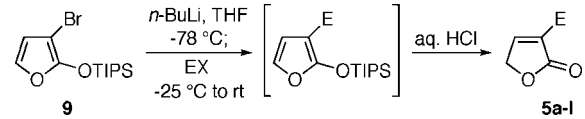
[a] All reactions were run using 1.1 equiv of *n*-BuLi; in entries 1−4, 1.3 equiv of *n*-BuX was used, and 1.0 equiv of the indicated additive in entries 2 and 3. [b] **10/11** ratios were determined by ^{1}H NMR; the starting material (**9**) was completely consumed in all cases. [c] See text.

We have recently reported a new synthon for **A**, namely 3-lithio-2-triisopropylsilyloxyfuran (**8**, Figure 2), which is rapidly quenched with aldehydes at −78 °C to provide 3-(1-hydroxyalkyl)-2-silyloxyfurans in excellent yields.[13] Encouraged by the high efficiency of this process, when compared to similar reactions of **7**,[12a] we decided to explore the behavior of **8** toward less reactive electrophiles with a view to establishing a general route to α-substituted butenolides. Reported herein is the successful accomplishment of this goal along with an efficient four-step synthesis of the anti-inflammatory lipid **4** from commercially available starting materials.

Our work began with an investigation of the butylation of **8**, generated in situ by metal−halogen exchange of the easily prepared 3-bromo-2-triisopropylsilyloxyfuran **9**[14] (Table 1). Gratifyingly, alkylation proceeded smoothly in THF by using a small excess of *n*-BuI (1.3 equiv), to give 3-*n*-butyl-2-silyloxyfuran **10** in high yield (entry 1). Although additives such as HMPA or DMPU are known to be beneficial to the alkylation of the parent 3-lithiofuran,[15] their use had a slightly negative impact on the yield of **10** (entries 2 and 3).[16] Replacement of *n*-butyl iodide with the less reactive *n*-BuBr, which is also produced by Li−Br exchange,[17] led to a substantially reduced yield of **10** (entry 4). In the absence of added *n*-BuBr, however, no alkylation product was detected (entry 5).

The scope and preparative value of this reaction were then explored by application to the synthesis of a range of α-substituted butenolides. Thus, the initially formed 3-substituted-2-silyloxyfurans were not isolated but hydrolyzed in situ with aq HCl to the corresponding lactones (Table 2). Yields with carbon electrophiles are generally high (entries 1−6) except for the modest 41% with homoallyl iodide (entry 4), presumably due to competing β-elimination.

TABLE 2. One-Pot Synthesis of α-Substituted Butenolides[a]



entry	electrophile (EX)	equiv	E	% yield of **5**[b]
1	*n*-BuI	1.3	*n*-Bu	85 (**5a**)
2	MeI	1.3	Me	83 (**5b**)
3	CH_2=$CHCH_2Br$	1.3	CH_2=$CHCH_2$	84 (**5c**)
4	CH_2=$CHCH_2CH_2I$	1.5	CH_2=$CH(CH_2)_2$	41 (**5d**)
5	$PhCH_2Br$	1.3	$PhCH_2$	85 (**5e**)
6	*m*-MeO-$PhCH_2Br$	1.3	*m*-MeO-$PhCH_2$	88 (**5f**)
7	ICH_2CH_2I	1.5	I	80 (**5g**)
8	C_2Cl_6	1.2	Cl	87 (**5h**)
9	$(PhSO_2)_2NF$ (NFSi)	1.05	F	37[c] (**5i**)
10	EtSSEt	1.3	EtS	86 (**5j**)
11	PhSeSePh	1.1	PhSe	72 (**5k**)
12	TMSCl	1.3	TMS	70 (**5l**)

[a] All reactions were run with 1.1 equiv of *n*-BuLi. [b] Yields refer to chromatographically purified products. [c] The low yield of **5i** is attributed, in part, to its high volatility.

Heteroatom electrophiles are equally well-behaved, allowing a variety of α-functionalized butenolides to be efficiently prepared from **9** in a single operation (entries 7−12). An exception within this group is the volatile fluorobutenolide **5i**,[18] whose low yield is attributed to inadvertent loss during solvent removal (37%, entry 9). Of particular interest is the high yield of the crystalline iodobutenolide **5g** (80%, entry 7), a potentially useful cross-coupling reagent that is notoriously difficult to prepare by existing methods.[9d,10d]

To further illustrate the usefulness of this chemistry, lipid **4** was chosen as a target. This compound typifies a small family of anti-inflammatory fatty acid γ-hydroxybutenolides isolated by Yamada and co-workers from the Japanese gorgonian *Euplexaura flava* (Nutting).[4] At the same time, **4** can be regarded as a viable model for the right-hand portion of the antitumor acetogenin annomolon A (**3**, Figure 1).[3] Notwithstanding a recent surge of interest in the construction of α-substituted γ-hydroxybutenolides,[19] there have been no reported syntheses of **3** or **4** to date.

Our route to **4** commenced with the conversion of commercially available ynamine **12** and propylene oxide to bromobutenolide **13**[20] using the method of Jacobsen[21] (Scheme 1). Silylation of **13** provided the key building block **14** in excellent

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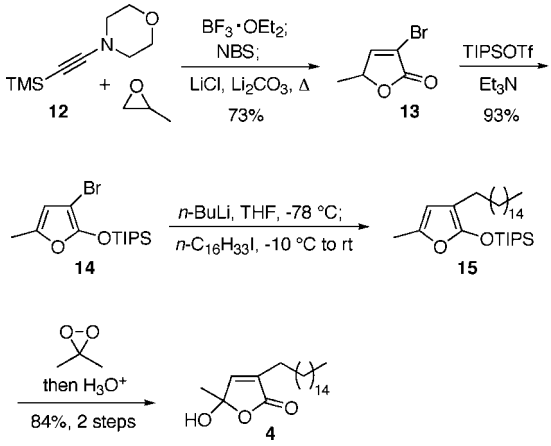
SCHEME 1. Synthesis of Gorgonian Lipid 4



yield. Subsequent lithium−bromine exchange and quenching with 1-iodohexadecane afforded silyloxyfuran **15**, which was subjected to our oxyfunctionalization protocol[22] without prior chromatographic purification, to deliver lipid **4** in 84% yield over two steps.

To conclude, a general and efficient one-pot protocol for converting 3-bromo-2-silyloxyfurans into α-substituted butenolides has been developed. Furthermore, the intermediate 3-substituted 2-silyloxyfurans can be exploited for installing an additional butenolide substituent at the γ-position,[23] as demonstrated by a short and efficient synthesis of the anti-inflammatory gorgonian lipid **4** (4 steps, 57% overall yield). Efforts to apply this methodology to the synthesis of more complex natural products are currently underway and will be reported in due course.

Experimental Section

General Procedure for the Preparation of α-Substituted Butenolides: Synthesis of 3-(3-Methoxybenzyl)-2(5*H*)-furanone (5f). To 125.9 mg of **9** (0.394 mmol) in 4 mL of THF under nitrogen at −78 °C was added *n*-BuLi (174 μL, 2.5 M in hexanes, 1.1 equiv). After stirring for 2 h then warming to −25 °C, 3-methoxybenzyl bromide (71.8 μL, 0.512 mmol, 1.3 equiv) was added. The temperature was kept at −25 °C for 30 min, then at −10 °C for 2 h. The mixture was warmed to rt and aq HCl (1 M, 2 mL) was added. Stirring was continued for 1 h, then Et_2O (5 mL) was added. After separation of the organic layer, the aqueous phase was washed with Et_2O (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexanes−ethyl acetate, 3:1, v:v) to give **5f** as a light orange oil (71.0 mg, 88%): R_f 0.36 (hexanes/AcOEt, 1:1); FTIR (NaCl, film) 3491, 3040, 2837, 1751, 1600, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.58 (d, J = 1.9 Hz, 2H), 3.80 (s, 3H), 4.76 (m, 2H), 6.77−6.84 (m, 3H), 6.96 (m, 1H), 7.22−7.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.8, 55.2, 70.2, 112.0, 114.7, 121.2, 129.7, 134.1, 138.9, 145.6, 159.8, 173.9. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.81; H, 6.19.

5-Methyl-3-bromo-2(5*H*)-furanone (13). To 95.5 mg of ynamine **12** (0.521 mmol, 1.4 equiv) in CH_2Cl_2 (2.5 mL) at 0 °C were added successively BF_3·Et_2O (66.0 μL, 1.4 equiv), propylene oxide (26.1 μL, 0.372 mmol, 1.0 equiv), and after 30 min NBS (212 mg, 3.2 equiv). The resulting dark brown mixture was kept at 0 °C for 20 min, then warmed to rt for a further 20 min and diluted with CH_2Cl_2 (2.5 mL), then aq HCl (1M, 2.5 mL) was added and the resulting mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting orange oil was dissolved in DMF (1 mL), then LiCl (78.5 mg, 1.86 mmol, 5.0 equiv) and Li_2CO_3 (28.0 mg, 0.372 mmol, 1.0 equiv) were added. The mixture was heated at 70 °C for 10 min, then cooled to rt, and partitioned between pentanes−Et_2O (1:1, 15 mL) and water (15 mL). The aqueous layer was extracted with pentanes−Et_2O (1:1, 3 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (hexanes/AcOEt, 4:1, v:v) afforded **13** (48.2 mg, 73%) as a yellow oil: R_f 0.42 (Et_2O/hexanes, 2:1); FTIR (NaCl, film) 2984, 1767, 1608, 1451 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, J = 6.8 Hz, 3H), 5.09 (qd, J = 6.8, 2.0 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 79.2, 113.0, 153.8, 168.3. Spectral data are consistent with those reported in the literature.[20c]

5-Methyl-3-bromo-2-triisopropylsilyloxyfuran (14). To a solution of 45.9 mg of **13** (0.259 mmol) in CH_2Cl_2 (2 mL) at 0 °C were added NEt_3 (90.6 μL, 1.3 equiv) and TIPSOTf (47.0 μL, 1.3 equiv). After stirring for 30 min, aq 5% $NaHCO_3$ (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a brown oil. Flash chromatography on silica gel (hexanes/NEt_3, 99:1) provided **14** (80.4 mg, 93%) as a colorless oil: R_f 0.85 (hexanes/NEt_3, 200:1); FTIR (NaCl, film) 2946, 2869, 1643, 1464, 1385, 1258, 1127, 1057, 1002 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (d, J = 7.2 Hz, 18H), 1.25 (m, 3H), 2.15 (d, J = 1.2 Hz, 3H), 5.83 (q, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3, 13.6, 17.5, 72.8, 109.1, 140.9, 151.6; HRMS (ESI) exact mass calcd for $C_{14}H_{25}O_2BrSi$ $[M + H]^+$ 333.0880, found 333.0895.

5-Hydroxy-5-methyl-3-(*n*-hexadecyl)-2(5*H*)-furanone (4). To 99.1 mg of **14** (0.297 mmol) in 3 mL of THF at −78 °C was added *n*-BuLi (130 μL, 2.5 M in hexanes, 1.1 equiv) then the solution was stirred for 2 h. After slowly warming to −10 °C, 1-iodohexadecane (186.7 μL, 2.0 equiv) was added and the mixture was stirred for 2 h at −10 °C, then slowly warmed to rt. Water (5 mL) and Et_2O (8 mL) were added, the aqueous layer was separated and extracted with Et_2O (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The yellow residue was dissolved in hexane (3 mL) and filtered through a plug of NEt_3-neutralized silica gel. The hexane was evaporated and the resulting colorless oil was dissolved in 5 mL of anhydrous Et_2O and cooled to 5 °C. Dimethyldioxirane (8.1 mL, ca. 0.06–0.11 M in acetone)[24] was added and the mixture was warmed to rt over

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1 h. Evaporation of the volatiles gave a white waxy solid, which was dissolved in 5 mL of Et_2O. Water (3 drops) and Amberlyst-15 (50 mg) were added, the mixture was stirred for 90 min, and then water (5 mL) was added and the ether layer was separated. The aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the resulting white solid (SiO_2, hexanes/AcOEt, 40:1 to 20:1 v:v) furnished lipid **4** (84.9 mg, 84%) as colorless crystals: mp 68−69 °C (lit.[4] mp 67 °C); R_f 0.28 (hexanes/AcOEt, 3:1); FTIR (NaCl, film) 3430 (br), 3089, 2917, 2850, 1756, 1725, 1657, 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 6.8 Hz, 3H), 1.24−1.37 (m, 26H), 1.54 (m, 2H), 1.69 (s, 3H), 2.25 (td, J = 8.0, 1.2 Hz, 2H), 6.80 (t, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.7, 24.8, 24.9, 27.2, 29.2, 29.3, 29.4, 29.5, 29.6, 29.65 (2C), 29.7 (4C), 31.9, 104.2, 136.4, 146.5, 171.3. Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H, 11.31. Found: C, 74.45; H, 11.56. The NMR data of **4** are in excellent agreement with those of the natural product.[4]

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council (NSERC) of Canada for financial support. We also thank HydroQuébec for a postgraduate scholarship to R.P.L.

Supporting Information Available: Experimental details, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8015924

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