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Regioselective Entry to Bromo-γ-hydroxybutenolides: Useful Building Blocks for Assemblying Natural Product-Like Libraries

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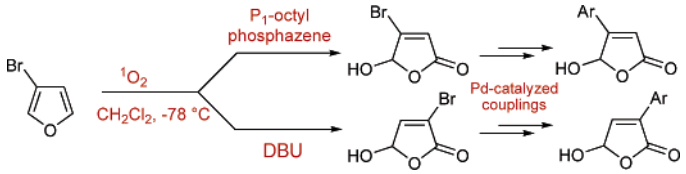
ABSTRACT



We report a regioselective entry to 3-bromo- and 4-bromo-5-hydroxy-5*H*-furan-2-ones by photooxidation of 3-bromofuran with a singlet oxygen in the presence of a suitable base. By this procedure, a variety of 3-substituted γ-hydroxybutenolides have become for the first time easily accessible. Strategies employing these highly functionalized building blocks for the preparation of focused libraries of natural-like molecules are also discussed.

Natural products containing a γ-hydroxybutenolide moiety have gained considerable attention from the chemical and biological communities by virtue of the wide spectrum of biological activities they display. Relevant examples include dysidiolide,[1] manoalide,[2] cacospongionolides,[3] and petrosaspongiolides[4] (Figure 1).

Total syntheses have also been reported for some of these products,[5] and in the case of dysidiolide, focused libraries have been prepared to explore structure−activity relationships and to shed light on the biological importance of the intriguing and densely functionalized butenolide moiety.[6]

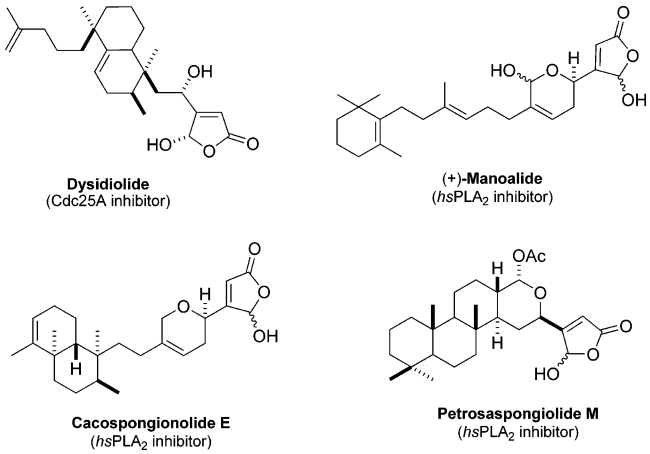


Figure 1. Examples of biologically active natural products bearing a 5-hydroxy-furan-2-one (γ-hydroxybutenolide) moiety.

[†] Deceased.

(1) (a) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759. (b) Takahashi, M.; Dodo, K.; Sugimoto, Y.; Aoyagi, Y.; Yamada, Y.; Hashimoto, Y.; Shirai, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2571.

(2) (a) De Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett.* **1980**, *21*, 1611. (b) Potts, B. C. M.; Faulkner, D. J. *J. Nat. Prod.* **1992**, *55*, 1701. (c) Potts, B. C. M.; Faulkner, D. J.; De Carvalho, M. S.; Jacobs, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 5093.

(3) (a) De Rosa, S.; Crispino, A.; De Giulio, A.; Iodice, C. *J. Nat. Prod.* **1995**, *58*, 1776. (b) Soriente, A.; Crispino, A.; De Rosa, M.; De Rosa, S.; Scettri, A.; Scognamiglio, G.; Villano, R.; Sodano, G. *Eur. J. Org. Chem.* **2000**, 947. (c) Garcia Pastor, P.; De Rosa, S.; De Giulio, A.; Paya', M.; Alcarza, M. J. *Brit. J. Pharm.* **1999**, *126*, 301.

(4) (a) Randazzo, A.; Debitus, C.; Pastor, P. G.; Alcaraz, M. J.; Paya, M.; Gomez-Paloma, L. *J. Nat. Prod.* **1998**, *61*, 571. (b) Pastor, P. G.; Randazzo, A.; Gomez-Paloma, L.; Alcaraz, M. J.; Paya, M. *J. Pharmacol. Exp. Ter.* **1999**, *289*, 166.

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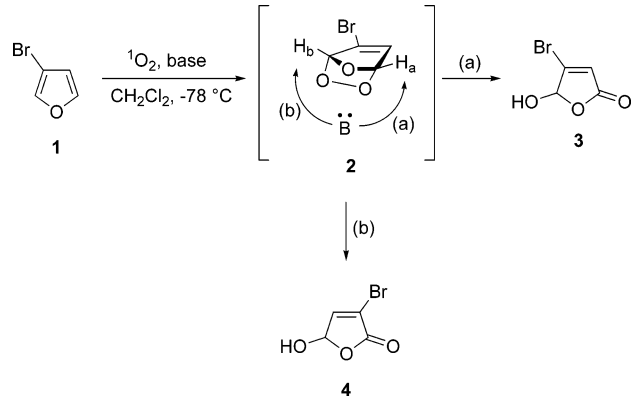
Typically, these products have been obtained by addition of 3-furanyllithium to a suitably functionalized terpenoidic molecule followed by photooxidation of the furan to the hydroxybutenolide.[5]

The simple one-pot, singlet-oxygen photooxidation of furans to γ-hydroxybutenolides, in the presence of rose-bengale as the photosensitizer, is known to suffer from relatively low yields and is limited by the sole access to 4-substituted butenolides. Faulkner and co-workers reported good yields and regioselectivities submitting naturally occurring 3-alkylfuran models to an improved process based on exposing the endoperoxide intermediate to a base.[7] However, when this oxidation protocol was applied in the course of several total syntheses, the results were not so satisfactory.[8] Moreover, all these synthetic schemes invariably required the use of experimental conditions, such as the handling of 3-furanyllithium, which is hardly suitable for combichem.

We envisaged that an alternative route to chemical diversity around the butenolide scaffold might employ an appropriate 3-bromofuran derivative for Pd-catalyzed coupling reactions. Two alternative paths emerge from this concept, differing for the sequence of the coupling and oxidation maneuvers. The route in which the bromofuran **1** was first coupled to one building block and then photooxidized was soon discarded due to the incompatibility of **1**, which is very prone to polymerization, to the coupling conditions. Once ascertained that the oxidation of **1** followed by Pd coupling was feasible, we worked on the optimization of the photooxidation step, so as to be able to access both 3-bromo- (**3**) and 4-bromobutenolides (**4**) (Scheme 1). This

Scheme 1. Base-Promoted Photooxidation of 3-Bromofuran



reaction gave satisfactory results on small substrate amounts (1 mmol) as well as on the gram scale (6.8 mmol). The availability of **3** and **4**, in fact, further enhanced the chemical diversity potentially attainable, by allowing access to two regioisomeric series of products.

The serendipitous observation that by using DBU as base only the 3-substituted vinyl bromide **4** was formed prompted us to probe the matter of base-promoted regiocontrol, as this result was in striking contrast to the literature reports in which DIPEA was employed instead. In the beginning, a regioselective photooxidation of 3-bromofuran appeared to us as a quite challenging task, as the bromine atom is the only element of regiodifferentiation.

In practice, however, it was shown that, in fact, a wise selection of the base allowed effective regiocontrol, as indicated by the entries of Table 1, even if a convincing

Table 1. Yields and Regioisomeric Ratios Observed in the Base-Promoted Photooxidation of 3-Bromofuran

entry	base	yield[a]	time (h)	ratio (**3**/**4**)
1	$(TMS)_3N$	nd[b]	6.0	–
2	2,6-di-*tert*-Bu-pyr	nd[b]	5.3	–
3	pempidine	64	5.0	67:33
4	DIPEA	82	4.5	50:50
5	phosphazene	70	5.3	80:20
6	DBU	78	4.3	0:100

[a] Calculated after C-18 reverse-phase HPLC purification. [b] A complex mixture of oxidized products was observed.

explanation of how the observed regioisomeric ratios are related to the nature of the base employed is not easy to grasp.

However, two remarks can be made: (a) a complex mixture of byproducts is observed in the absence of relatively strong bases (entries 1 and 2); (b) strong and particularly bulky bases, such as the phosphazene of Figure 2, lead to

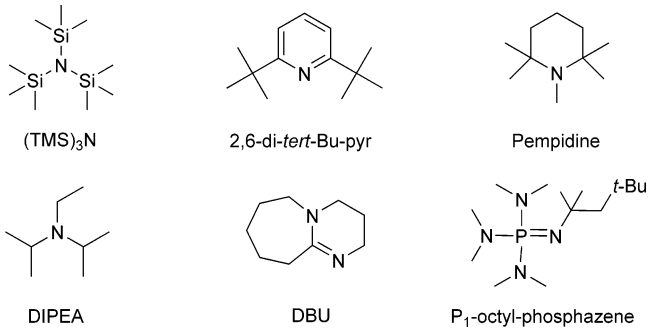


Figure 2. Different bases tested in the photooxidation of **1**.

the preferential formation of precursor **3**. In fact, we observe

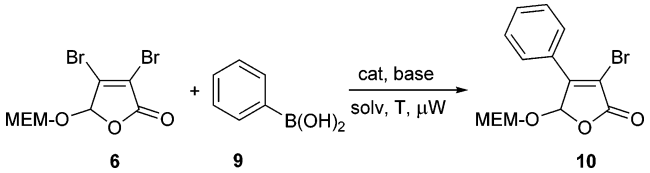
(5) (a) Katsumura, S.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 5827. (b) Coombs, J.; Lattmann, E.; Hoffmann, H. M. R. *Synthesis* **1998**, 1367. (c) Soriente, A.; De Rosa, M.; Apicella, A.; Scettri, A.; Sodano, G. *Tetrahedron: Asymmetry* **1999**, *10*, 4481. (d) Cheung, A. K.; Murelli, R.; Snapper, M. L. *J. Org. Chem.* **2004**, *69*, 5712.

(6) (a) Brohm, D.; Philippe, N.; Metzger, S.; Bhargava, A.; Müller, O.; Lieb, F.; Waldmann, H. *J. Am. Chem. Soc.* **2002**, *124*, 13171. (b) Brohm, D.; Metzger, S.; Bhargava, A.; Müller, O.; Lieb, F.; Waldmann, H. *Angew. Chem.* **2002**, *114*, 319. (c) Brohm, D.; Metzger, S.; Bhargava, A.; Müller, O.; Lieb, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 307.

(7) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773.

(8) (a) Sodano, G.; Payà, M. et al. *J. Med. Chem.* **1998**, *41*, 3232. (b) Koch, M. A.; Wittenberg, L.-O.; Basu, S.; Jeyaraj, D. A.; Gourzoulidou, E.; Reinecke, K.; Odermatt, A.; Waldmann, H. *PNAS* **2004**, *101*, 16721. (c) Cheung, A. K.; Snapper, L. M. *J. Am. Chem. Soc.* **2002**, *124*, 11584.

Table 2. Different Experimental Conditions Investigated for the Suzuki-Type Coupling of **6** with Phenyl Boronic Acid (**9**)



entry	**6** (equiv)	**9** (equiv)	catalyst (mol %)	base (equiv)	solvent	temp (°C)	μW (W)	time (min)	conversion % of **6**[a]
1	1	2	$PdCl_2(PPh_3)_2$, (5)	CsF (4)	toluene/H_2O	60	200	5	–
2	1	2	$Pd(PPh_3)_4$, (2)	Na_2CO_3 (4)	DME	80	200	5	–
3	1	2	$Pd(PPh_3)_4$, (2)	CsF (4)	toluene/H_2O	60	150	5	–
4	1	2	$PdCl_2 + PPh_3$, (1.2)	CsF (2.4)	DME	80	150	5	trace
5	1	1	$Pd(OAc)_2$, (0.4)	CsF (4)	H_2O	120	60	5	48
6	1	1.2	$Pd(OAc)_2$, (0.4)	CsF (2.4)[b]	H_2O	120	60	5	73[c]
7	1	1.5	$Pd(OAc)_2$, (0.4)	CsF (4)[b]	H_2O	120	60	6	90[c]
8	1	1.5	$Pd(OAc)_2$, (0.4)	CsF (4)	H_2O[d]	120	60	5	100[c]
9	1	1.5	$PdCl_2$(dppf), (0.03)	CsF (4)[b]	H_2O/THF	100	200	5	63
10	1	1.5	$PdCl_2$(dppf), (0.03)	CsF (4)[b]	H_2O/THF	120	200	6	98

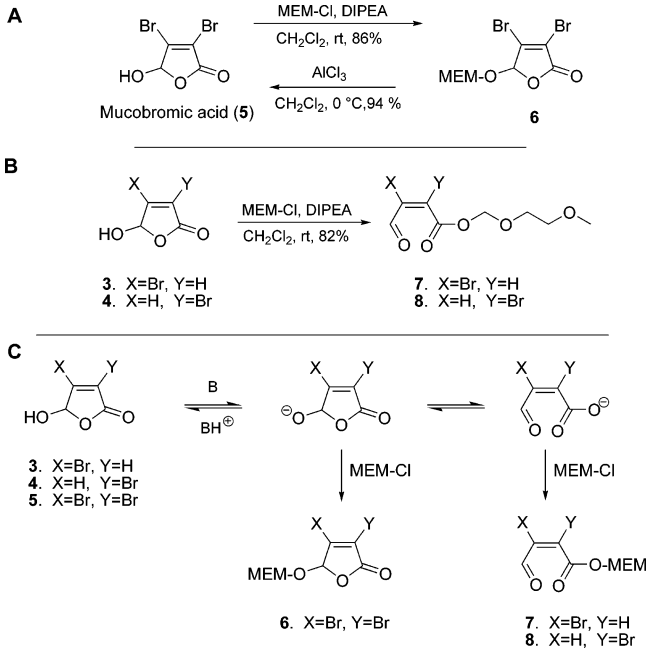
[a] Conversions are based on the ratio beween areas of H-5 NMR signals of compounds **10** and **6**. [b] In the presence of 1 equiv of TBAB. [c] These good to excellent conversions are accompanied by significant decomposition of the reaction product. [d] In the presence of 0.2 equiv of $BMIM^+$ BF_4^-.

inverted **3**/**4** ratios on going from DBU to phosphazene, with DIPEA and pempidine giving intermediate results. It should be noted that, to the best of our knowledge, this is the first synthetic procedure that allows one to selectively obtain 3-substituted γ-hydroxybutenolides.

Our next goal was to find an appropriate scheme of protection and deprotection of the hydroxy group to render the butenolide portion compatible with the experimental conditions required by Pd-catalyzed couplings.[9] Because we had decided to rely on the versatile Suzuki coupling to decorate the butenolide scaffold, we needed a protecting group that would be stable to basic conditions.

Suzuki couplings on the related mucochloric and mucobromic acids (**5**) have been investigated by Zhang and coworkers.[10] Their study highlighted the instability of the butenolide portion in the presence of classical bases such as AcO^-, CO_3^{2-}, and PO_4^{3-} and established the beneficial use of CsF under phase-transfer conditions. As for protection of the 5-hydroxy (hemiacetal) group, our choice fell on MEM which appeared sufficiently stable but also easily removable. MEM protection (MEM-Cl, DIPEA in DCM, rt, 86%) and deprotection ($AlCl_3$, DCM, 0 °C, 94%)[11] procedures were preliminarily optimized on the commercially available mucobromic acid (Scheme 2A).[12] To our surprise, when we attempted to extend the same conditions to monobrominated **3** and **4**, we witnessed the selective formation of acyclic MEM esters **7** and **8** in good yields (Scheme 2B). Under basic conditions, the cyclic hemiacetal is in equilibrium with the carboxylate open form. Apparently, the kinetics of carboxylate formation are faster relative to MEM ether formation for the monobrominated compounds **3** and **4**, and the opposite applies for the dibrominated **5** (Scheme 2C). We finally resorted to THP protection,[13] which proceeded

Scheme 2. Outcomes of MEM Protection Procedures of Mucobromic Acid **5** and of the Two Regioisomers **3** and **4**



(9) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.

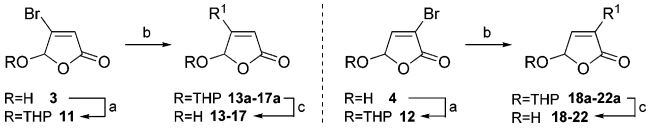
(10) Zhang, J.; Blazecka, P. G.; Belmont, D.; Davidson, J. G. *Org. Lett.* **2002**, *25*, 4559.

(11) Typical MEM deprotection conditions based on milder Lewis acids, such as PPTS or $TiCl_4$, did not work well in our hands.

(12) (a) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *11*, 809. (b) Monti, H.; Leandri, G.; Klos-Ringuet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021.

(13) Grieco, P. A.; Yoshikoshi, A.; Miyashita, M. *J. Org. Chem.* **1977**, *42*, 3772, and references therein.

Table 3. Suzuki Coupling of **3** and **4** with Different Boronic Acids along with Their THP Protection and Deprotection Procedures[a]



entry	substrate	$R^1-B(OH)_2$	product, yield
1	11	phenyl boronic acid	**13a**, 74%
2	11	benzothiophene-2-boronic acid	**14a**, 87%
3	11	3-formylphenyl boronic acid	**15a**, 83%
4	11	4-methoxyphenyl boronic acid	**16a**, 88%
5	11	1-naphthalene boronic acid	**17a**, 91%
6	12	phenyl boronic acid	**18a**, 60%
7	12	benzothiophene-2-boronic acid	**19a**, 75%
8	12	3-formylphenyl boronic acid	**20a**, 80%
9	12	4-methoxyphenyl boronic acid	**21a**, 79%
10	12	1-naphthalene boronic acid	**22a**, 77%

[a] Key: (a) DHP, *p*-TosOH, CH_2Cl_2, 0 to 25 °C, 1.5 h; (b) $R^1-B(OH)_2$, $Pd(dppf)Cl_2$, TBAB, CsF, H_2O/THF, μW, 120 °C; (c) HCl 1 N, THF, 20 min.

smoothly and fast (1.5 h) affording THP−butenolides **11** and **12** in good yields (95% and 87%, respectively) (Table 3, a).

The last stage of our study consisted of the optimization of the Suzuki-type coupling reaction. We selected as the model reaction the coupling of **6** (the MEM ether of **5**) with phenylboronic acid to seek optimal experimental conditions. We also decided to take advantage of microwave irradiation to speed up reaction times in conformity with the principles of diversity oriented synthesis.[14] Accordingly, several schemes that varied solvent composition, catalyst, and base were examined, allowing us to gather the results described in Table 2. Entry 10 displays the best experimental conditions we found. This protocol was then applied to the case of **11** and **12** affording THP-protected coupled products **13a**−**22a** in satisfactory yields (up to 60%). To generate this small collection of products, we chose several boronic acids with different steric bulk and electronic properties to demonstrate the general utility of the proposed strategy (Table 3). Finally, the deprotection of the latter by exposure to HCl (1 N) in THF furnished the desired 3- and 4-substituted γ-hydroxybutenolides **13**−**22** (Table 3, c).[15]

A final remark is that the use of other Pd-catalyzed reactions, such as Heck or Sonogashira couplings, may further expand the potential molecular diversity around this densely functionalized scaffold. Along these lines, the exploration of additional synthetic processes, taking advantage of the building blocks **3** and **4**, are currently underway in our laboratory.

In conclusion, the base-promoted regioselective photooxidation of 3-bromofuran allows a convenient entry to 3-bromo- and 4-bromo-γ-hydroxybutenolides (**3** and **4**) which may be employed to prepare a wide variety of synthetic products bearing the same pharmacophoric moiety of several biologically active natural products.

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Supporting Information Available: Spectroscopic and analytical data and experimental procedures for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219. (b) Varma, R. S.; Namboodiri, V. V. *Pure Appl. Chem.* **2001**, *73*, 1309.

(15) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7485.