ORGANIC LETTERS

2007
Vol. 9, No. 2
195−198

Base-Assisted Regio- and Diastereoselective Conversion of Functionalized Furans to Butenolides Using Singlet Oxygen

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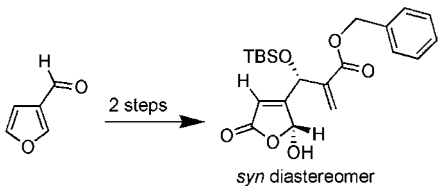
Received October 17, 2006

ABSTRACT



A facile synthesis of β-functionalized γ-hydroxybutenolides was achieved using a Baylis–Hillman reaction followed by singlet oxygen oxidation. The conversion from 3-furfural was regio- and diastereoselective.

Butenolides are prevalent structural motifs in bioactive natural products that have shown a wide range of activities as antibiotic, antifungal, antifouling, and anticancer agents.[1] General and efficient synthetic methods for accessing diverse structures of this class of compounds as useful synthons continue to be of interest.[2] One attractive approach with generality is to transform 2-oxyfurans that are already at the oxidation level of butenolides. Recent examples[3] include a conversion from 2-siloxyfuran using an enantioselective vinylogous Michael reaction,[3a] a diastereoselective synthesis of γ-butenolides via a phosphine-catalyzed allylic alkylation,[3b] an enantioselective synthesis of γ-butenolides using a Mukaiyama−Michael reaction,[3c] a conversion of 2-methoxyfurans to butenolides catalyzed by iodide anion,[3d] and a synthesis of spirocyclic butenolides using 2-(trimethylsilyloxy)furan as a dianion equivalent.[3e]

Another well-known strategy is to use furans as precursors in mild photooxidation reactions that mimic the biogenic process, although stereocontrol in this approach is more difficult.[4] In this paper, we report a base-assisted, regio- and diastereoselective conversion of 3-hydroxyacrylate furans to

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[1] For recent representative examples of cytotoxic, antibiotic, and antifungal butenolides, see: (a) Wright, A. D.; Nys, R. D.; Angerhofer, C. K.; Pezzuto, J. M.; Gurrath, M. *J. Nat. Prod.* **2006**, *69*, 1180−1187. (b) Husain, A.; Khan, M. S. Y.; Hasan, S. M.; Alam, M. M. *Eur. J. Med. Chem.* **2005**, *40*, 1394−1404. (c) Mansoor, T. A.; Hong, J.; Lee, C. O.; Sim, C. J.; Im, K. S.; Lee, D. S.; Jung, J. H. *J. Nat. Prod.* **2004**, *67*, 721−724. (d) Braun, M.; Hohmann, A.; Rahematpura, J.; Buehne, C.; Grimme, S. *Chem. Eur. J.* **2004**, *10*, 4584−4593. (e) Grossmann, G.; Poncioni, M.; Bornand, M.; Jolivet, B.; Neuburger, M.; Sequin, U. *Tetrahedron* **2003**, *59*, 3237−3251.

[2] For reviews of synthetic routes to butenolides, see: (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625−694. (b) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287−315. (c) Brückner, R. *Curr. Org. Chem.* **2001**, *5*, 679−718. (d) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2324−2342.

[3] (a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 1192−1194. (b) Cho, C. W.; Krische, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689−6691. (c) Barluenga, J.; Prado, A. D.; Santamaria, J.; Tomas, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6583−6585. (d) Ma, S.; Lu, L.; Lu, P. *J. Org. Chem.* **2005**, *70*, 1063−1065. (e) Maulide, N.; Marko, I. E. *Org. Lett.* **2006**, *8*, 3705−3707.

[4] For initial work in photooxidative conversion of furans to γ-hydroxybutenolides, see: (a) Grimminger, W.; Kraus, W. *Liebigs Ann. Chem.* **1979**, *10*, 1571−1576. (b) Brownbridge, P.; Chan, T. H. *Tetrahedron Lett.* **1980**, *21*, 3431−3434. (c) Katsumura, S.; Hori, K.; Fugiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 4625−4628. (d) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773−2776. For a very recent example of regioselective synthesis of γ-hydroxybutenolides, see: (e) Aqunio, M.; Riccio, B. R.; Gomez-Paloma, L. *Org. Lett.* **2006**, *8*, 4831−4834. For use of other oxidants, see: (f) Clive, D. L. J.; Minaruzzaman; Ou, L. *J. Org. Chem.* **2005**, *70*, 3318−3320 and refs 4a−h therein.

10.1021/ol062551l CCC: $37.00

β-substituted γ-hydroxybutenolides using singlet oxygen. Many active natural products containing β-substituted γ-hydroxybutenolides, such as manoalide,[5] tend to be epimerized at the γ-carbon, although stereospecificity at this center is occasionally observed such as in dysidiolide, the first known natural product inhibitor of protein phosphatase cdc25A (Figure 1).[6] In our approach, the functionalities installed by the Baylis−Hillman (BH) reaction between 3-furfural and a range of acrylates are compatible with the singlet oxygen oxidation conditions,[7] which allows for an expedient and mild synthesis of a variety of functionalized γ-hydroxybutenolides with stereocontrol at the γ-carbon for the first time.

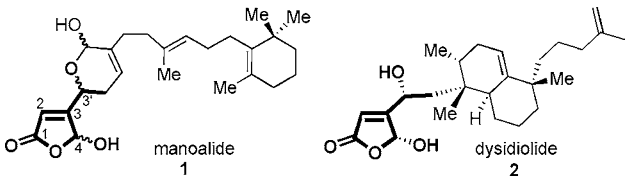
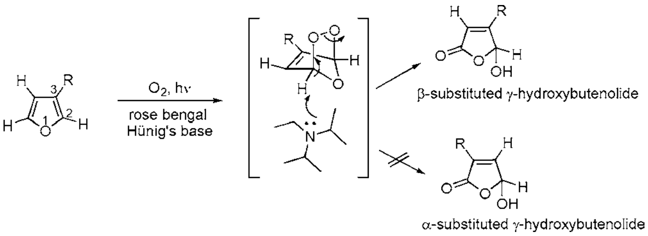


Figure 1. Examples of β-substituted γ-hydroxybutenolides containing natural products.

Although 3-hydroxyacrylate furans have not been used prior to this study in singlet oxygen oxidation reactions for synthesizing functionalized butenolides, it is well recognized that 3-alkyl- or 3-hydroxyalkylfurans are useful synthons for accessing butenolides with regioselectivity in a base-dependent manner.[4d] This approach has been applied in a number of total syntheses of bioactive γ-hydroxybutenolide natural products such as cacospongionolides and cladocorans.[8] The use of Hünig's base as the key reagent for controlling the regioselective opening of the endoperoxide intermediate to specifically access the β-substituted, rather than the α-substituted, γ-hydroxybutenolides was consistently observed (Scheme 1). Base-assisted diastereoselective synthesis of γ-hydroxybutenolides has not been previously reported. In the case of dysidiolide, one diastereomer (as specified in Figure 1) could be selectively obtained through crystallization.[6a,b]

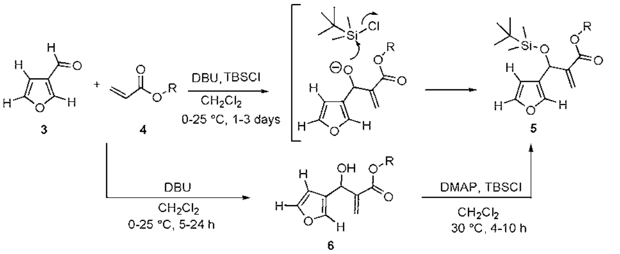
Scheme 1. Base-Assisted Singlet Oxygen Oxidation of Furans[4d]



We sought to examine the applicability of this singlet oxygen oxidation reaction to 3-hydroxyacrylate furan skeletons generated from 3-furfural using the BH reaction. The BH reaction is known as an effective method for preparing highly functionalized molecules from simple synthons with expediency.[9] Typically, the 3′-hydroxy group, as seen in manoalide and dysidiolide, can be produced using the addition reaction between lithiated furans and aldehydes.[5,6] The mild BH approach has not been previously used to install the 3′-hydroxy group frequently observed in butenolide natural products.

In our approach, 3-furfural (**3**) was treated with a series of readily available acrylates (**4a−g**) to provide the *tert*-butyldimethylsilyl (TBS)-protected 3-siloxyacrylate furan skeletons (**5a−g**) in 30−40% overall yields in one pot or over two steps (Scheme 2). It was hypothesized that a bulky substituent, such as a TBS group, could facilitate the chemoselectivity of this transformation. Mechanistically, the silyl protection was envisioned to proceed in one pot during

Scheme 2. Synthesis of 3-Hydroxyacrylate Furans **5a−g** Using the Baylis−Hillman Reaction



R = Methyl (**5a**), Ethyl (**5b**), Butyl (**5c**), Benzyl (**5d**), Cinnamyl (**5e**), Allyl (**5f**), 2-Chloroethyl (**5g**)

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(5) First isolation and structural elucidation of manoalide: (a) De Silva, D. E.; Scheuer, P. J. *Tetrahedron Lett.* **1980**, *21*, 1611−1614. First total synthesis of manoalide: (b) Katsumura, S.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 5827−5830.

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(7) For a summary of initial applications of singlet oxygen in the synthesis of bioactive compounds, see (a) Wasserman, H. H.; Lipshutz, B. H. *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; Chapter 9. For a recent summary of the use of singlet oxygen in biomimetic syntheses, see: (b) Margaros, I.; Montagnon, T.; Tofi, M.; Pavlakos, E.; Vassilikogiannakis, G. *Tetrahedron* **2006**, *62*, 5308−5317.

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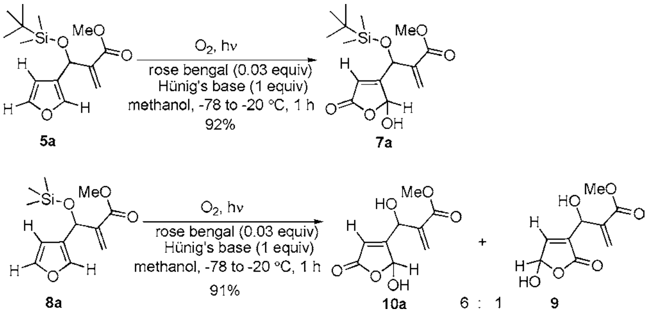
(9) For a recent reveiew of the Baylis−Hillman (BH) reaction, see: Basavaiah, D.; Rao, A. J.; Satyanarayana T. *Chem. Rev.* **2003**, *103*, 811−891. For a recent example of using BH adducts as butenolide precursors, see ref 3b.

the BH reaction after the formation of the alkoxide intermediate from the addition step between the acrylate and the furfural. In the cases of methyl, ethyl, butyl, and benzyl acrylates, the silyl protection was successfully introduced using the one-pot approach. In the other instances, the silyl protection was required to be installed in a separate step.

The TBS-protected BH adduct of 3-furfural and methyl acrylate, **5a**, was used as the model compound to examine the following singlet oxygen oxidation step in the presence of Hünig's base (Scheme 3). Both nonpolar and polar protic solvents were investigated as they are known to affect the efficiency of singlet oxygen oxidation due to their different abilities in stabilizing singlet oxygen.[7] Reactions in general were complete in 1−3 h in high yields, with methanol providing the fastest rate of reaction. The conversion was completely regioselective in the presence of Hünig's base as indicated by ^{1}H NMR spectroscopy of the resulting butenolide, which is consistent with the case reported for 3-alkylfurans.[4d] The regioselectivity was dependent on the presence of the TBS group. When trimethylsilyl (TMS) protection was used instead, the regioselectivity was diminished to 6:1 with loss of the TMS group during workup, although the yield remained comparable at 91%.

Scheme 3. Regioselective Conversion of **5a** to Butenolide **7a** by Singlet Oxygen Oxidation



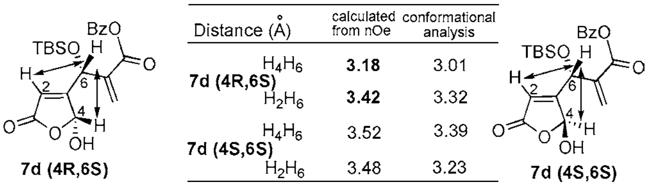
Initially, the oxidation reaction of **5a** to **7a** would provide the γ-hydroxybutenolide as a diastereomeric mixture under standard conditions of workup and purification.) Given the easily epimerizable γ-hydroxy carbon center, we used neutral silica gel to examine if mildly acidic silica gel may be attributable to the apparent epimerization. When the crude reaction mixture was purified on neutral silica gel, a single diastereomer of **7a** was obtained in 92% yield. The TBS-protected BH adducts were then subjected to this Hünig's base-assisted singlet oxygen oxidation reaction and returned excellent yields of the butenolides with regio- and diastereoselectivity under neutral conditions for base removal (Table 1).

Table 1. Diastereoselective Conversion of **5a−g** to Butenolides **7a−g**

entry	furan	ester	product	yield^a (%)
1	**5a**	methyl	**7a**	92
2	**5b**	ethyl	**7b**	90
3	**5c**	butyl	**7c**	91
4	**5d**	benzyl	**7d**	86
5	**5e**	cinnamyl	**7e**	86
6	**5f**	allyl	**7f**	96
7	**5g**	2-chloroethyl	**7g**	76

^{a} Isolated yields.

Conformational analysis combined with 2D NOESY spectroscopy was performed to tentatively assign the relative configurations of the observed diastereoselectivity (Supporting Information), as efforts to crystallize these highly flexible butenolides were unsuccessful. The NOE results obtained from the diastereomeric mixture of **7d** were compared with those of the selectively formed single diastereomer of **7d** to confirm that the NOEs are comparable. The distances between H4−H6 and H2−H6 were calculated using the observed NOE data as potentially distinguishing factors for the two diastereomers (Figure 2). Conformational searches were performed for both the (4*S*,6*S*) and (4*R*,6*S*) diastereomers using MacroModel[10] to examine the average distances of H4−H6 and H2−H6 from conformers within 2 kcal/mol of the global minimum.



Distance (Å)		calculated from nOe	conformational analysis
7d (4R,6S)	H_4H_6	**3.18**	3.01
	H_2H_6	**3.42**	3.32
7d (4S,6S)	H_4H_6	3.52	3.39
	H_2H_6	3.48	3.23

Figure 2. Distances of H4−H6 and H2−H6 of the diastereomers of **7d**. The distances derived from the NOEs of the selectively formed diastereomer are shown in bold.

The NOE-based calculation indicated that, while the distances of H2−H6 in the two diastereomers are similar, the distance between H4 and H6 would be significantly smaller in the preferentially formed diastereomer. The conformational analysis reproduced this relative relationship where the distance between H4 and H6 in the (4*R*,6*S*), or *syn*, diastereomer, was found to be smaller than that in the (4*S*,6*S*) diastereomer, while the H2−H6 average distances in the two diastereomers were found to be similar. A *syn*, or (4*R*,6*S*), assignment for the preferred diastereomer of **7d** would therefore be consistent with the observed NOE and modeling results.

The TBS protecting group of **7d** was removed using tetrabutylammonium fluoride (TBAF) in THF in 2 h without any sign of epimerization, and the deprotected butenolide **10d** exhibited a similar NOE pattern for these two sets of protons, indicating that the diastereoselectivity was maintained. This method was able to provide deprotected buteno-

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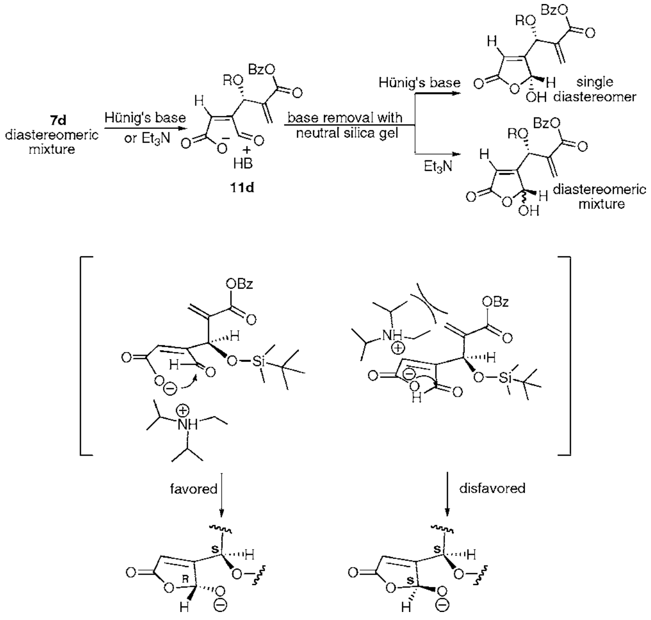
(10) Mohamadi, F.; Richard, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

lides **10a**−**g** as a single diastereomer in each case in 24−60% yields (Supporting Information).

Scheme 4. Base-Dependent Recovery of Diastereoselectivity in the Formation of **7d** and a Proposed Transition State Leading to the Observed Diastereoselectivity



Further investigation confirmed that this diastereoselectivity was base-dependent (Scheme 4). Upon treatment with acidic $CDCl_3$ (stored without molecular sieves), the selectively formed diastereomer of **7d** rapidly epimerized to two diastereomers as expected. Surprisingly, when this diastereomeric mixture of **7d** was treated with Hünig's base followed by purification using neutral silica gel, the diastereomeric mixture reverted back to the previous single diastereomer. NMR spectroscopy indicated that in the presence of Hünig's base, the deprotonated γ-hydroxybutenolide would be in the "ring-open" form (**11d**). The closing of the butenolide ring upon removal of this base was diastereoselective, depending on the bulkiness of the counterion of the carboxylate of the butenolide, and this selectivity was maintained under neutral conditions for base removal. This is consistent with the observation that the deprotecting step using TBAF, which also provides a bulky counterion, does not result in loss of diastereoselectivity. The presence of Hünig's base was essential in recovering the diastereoselectivity as triethylamine, a less bulky base, was not able to return the single diastereomer after acidic epimerization and base removal under neutral conditions. A proposed transition state leading to this selectivity is shown in Scheme 4. The selectivity could be due to the bulkiness of the base in selecting the less hindered *Re* face of the intermediate for stabilizing the carboxylate.

In conclusion, this work illustrates for the first time the utility of using the mild Baylis−Hillman reaction to prepare 3-hydroxyacrylate furans as precursors for facile and diastereoselective access of β-substituted, γ-hydroxybutenolide moieties frequently observed in bioactive natural products. The role of a bulky base in conferring the diastereoselectivity is revealed, allowing for these densely functionalized butenolides to be considered as useful synthons for further transformations. Investigations on the scope of this base-assisted approach with BH adducts from other activated alkenes are underway and will be reported in due course.

Acknowledgment. This work is supported by an Australian Research Council Discovery Project Grant to F.L. (ARC-DP055068). S.N.P. is supported by a predoctoral research fellowship from Macquarie University. We thank Peter Karuso of Macquarie University for helpful discussions and technical assistance in securing the 2D NOESY spectra.

Supporting Information Available: Experimental procedures and spectra of key transformations, characterization data for compounds **5**−**11**, details of the conformational analysis, and 2D NOESY spectra of compounds **7d** and **10d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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