JOC Article

Regioselective Synthesis and Structural Studies of Substituted γ-Hydroxybutenolides with Use of a Tandem Baylis−Hillman/Singlet Oxygenation Reaction

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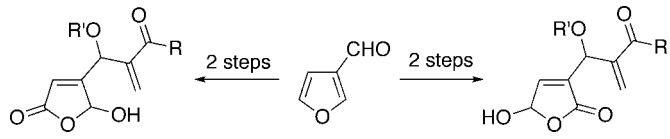


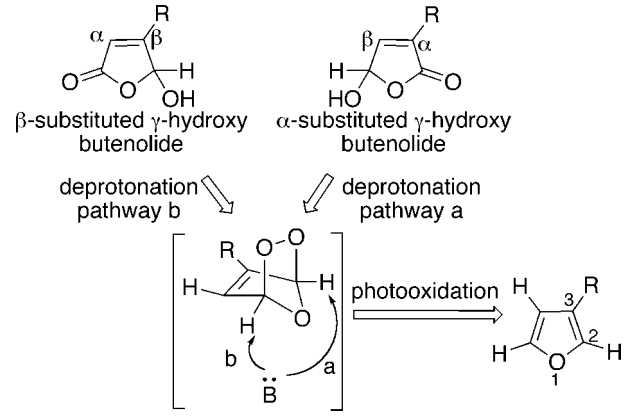
The scope and limitations of a regioselective synthesis of either α- or β-substituted γ-hydroxybutenolides from 3-furfural and enones are described. The sequence features a Baylis−Hillman reaction followed by singlet oxygen oxidation with use of either an amine base or TBAF as the regioselectivity switches. Structural studies in solution on some of the resulting γ-hydroxybutenolides are also reported.

Introduction

Bioactive natural products frequently contain a γ-hydroxybutenolide moiety that is substituted at either the α or β position. Many α-substituted γ-hydroxybutenolides are known antimicrobial compounds, and β-substituted γ-hydroxybutenolides are often used as anticancer or anti-inflammatory agents.[1] There has been on-going interest in developing facile and selective methods for synthesizing diverse and highly functionalized analogues of this class of structures from readily available starting materials.[2] Approaches such as photooxidative conversion of functionalized furans to α- or β-substituted γ-hydroxybutenolides with regioselectivity have been frequently employed particularly for practical convergent synthesis (Scheme 1).[3]

We have reported the use of a simple reagent to confer regioselectivity for either α- or β-substituted γ-hydroxybutenolides in this photooxidative transformation as a versatile strategy to access rapidly butenolides from readily available synthons such as furfural and acrylates.[4] The furans are functionalized by using a Baylis−Hillman reaction with acrylates and then subjected to endoperoxide formation under photochemical conditions. Mechanistically, the two deprotonation pathways of the endoperoxide intermediate (**3**), a and b, can be differentiated through consideration of steric and neighboring group effects (Scheme 2). When the functionalized furans are treated with a bulky Hünig's base, pathway b is preferred to provide the β-substituted γ-hydroxybutenolides. When TBAF is used instead of Hünig's base, pathway a is preferred to provide the

SCHEME 1



(1) For recent examples of α- or β-substituted, bioactive butenolides found in nature, see: (a) Wright, A. D.; de Nys, R.; Angerhofer, C. K.; Pezzuto, J. M.; Gurrath, M. *J. Nat. Prod.* **2006**, *69*, 1180–1187. (b) Keyzers, R. A.; Davies-Coleman, M. T. *Chem. Soc. Rev.* **2005**, *34*, 355–365. (c) Grossmann, G.; Poncioni, M.; Bornand, M.; Jolivet, B.; Neuburger, M.; Sequin, U. *Tetrahedron* **2003**, *59*, 3237–3251. (d) Charan, R. D.; McKee, T. C.; Boyd, M. R. *J. Nat. Prod.* **2001**, *64*, 661–663.

(2) For recent reviews of synthetic routes to butenolides, see:(a) Brückner, R. *Curr. Org. Chem.* **2001**, *5*, 679–718. (b) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 2324–2342.

(3) 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 recent summary of the use of singlet oxygen in biomimetic syntheses, see: (e) Margaros, I.; Montagnon, T.; Tofi, M.; Pavlakos, E.; Vassilikogiannakis, G. *Tetrahedron* **2006**, *62*, 5308–5317. For a very recent example of regioselective synthesis of γ-hydroxybutenolides, see: (f) Aquino, M.; Bruno, I.; Riccio, R.; Gomez-Paloma, L. *Org. Lett.* **2006**, *8*, 4831–4834.

(4) (a) Patil, S. N.; Liu, F. *Org. Lett.* **2007**, *9*, 195–198. (b) Patil, S. N.; Liu, F. *J. Org. Chem.* **2007**, *72*, 6305–6308.

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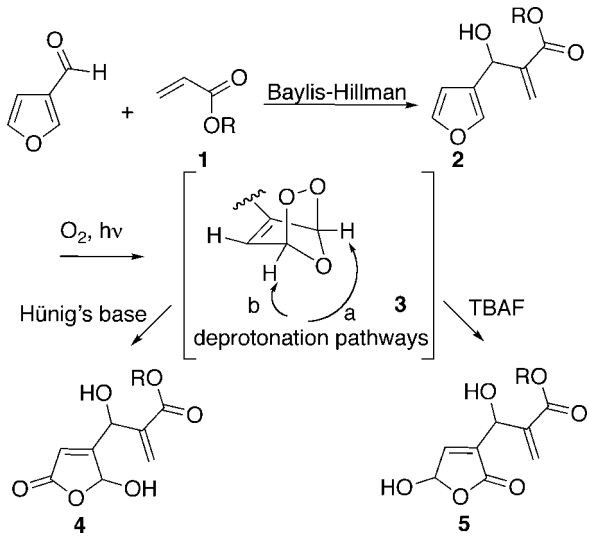
SCHEME 2. Regioselective Synthesis of α- or *β*-Substituted *γ*-Hydroxybutenolides from 3-Furfural and Acrylates



α-substituted γ-hydroxybutenolides due to H-bonding between the fluoride anion and the neighboring 3′-hydroxy group. Effectively, either α- or *β*- substituted γ-hydroxybutenolides can be readily synthesized by applying a different regioselectivity switch to the same furan intermediate by using the same method.

Herein we report the scope and limitation of this approach using 3′-furfural and a variety of enones. In addition, studies have also been performed with solution-based techniques, such as NMR or optical rotation spectroscopy, to address structural issues of representative butenolides given the presence of an epimerizable center at the γ-position.

Results and Discussion

Functionalization of 3-Furfural with the Baylis−Hillman (BH) Reaction. The Baylis−Hillman reaction was employed as an economic and mild method for synthesizing funtionalized furans with use of a variety of enones in moderate to good yields (50−70%). The BH reaction, although efficient, can be limited in scope. Hence optimization of conditions was performed for each substrate. Methods using DBU as the base[5] were successful for the cyclic enones (entries 2 and 3, Table 1), but failed for methyl vinyl ketone (**6a**). Changing DBU to DABCO did not improve the outcome. Finally, **7a** was successfully synthesized by using imidazole and proline as cocatalysts (entry 1, Table 1).[6] Aqueous trimethylamine was used for the synthesis of **7e** (entry 5, Table 1).[7] The yield of **7d** synthesized with use of DABCO in a mixture of dioxane and water (1:1) was low (26%), but improved significantly when the reaction was conducted in neat condition with DABCO and phenol as cocatalysts (entry 4, Table 1).[8] In general, DBU was found to be a BH catalyst with more generality and can be used for diverse alkenes such as electron deficient enones, sterically demanding acrylates (e.g., cholesterol acrylate), and cyclic enones.

The 3′-hydroxy group of the BH adducts (**7a**−**e**) was protected by using a bulky TBS group. The protection is not necessary for the singlet oxygenation but does enhance the regioselectivity for the formation of *β*-substituted γ-hydroxybutenolides. When the functionalized furan has a bulky side chain, such as **7f**, this protection is not required for complete regioselectivity in our method. This protection step was problematic in the case of **7a** where the use of imidazole with a highly activated enone led to a complex mixture of reaction products. However, an optimized method with TBSOTf and 2,6-lutidine was able to circumvent this problem. Reactions were monitored carefully as prolonged reaction time may result in lower yields.

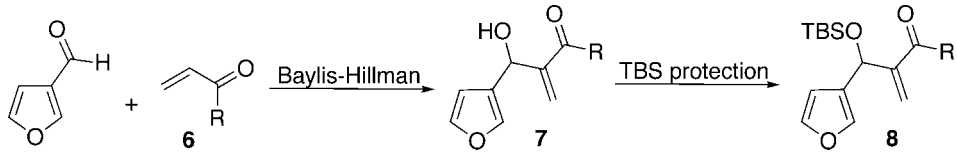
Synthesis of α- or *β*-Substituted *γ*-Hydroxybutenolides from the BH Adducts. With a diverse collection of BH adducts, the chemo- and regioselectivity scope of the singlet oxygenation reaction was examined. Following our previous studies of the photooxidation reaction of the 3-hydroxyacrylate furans (Scheme 2), these functionalized furans were treated with either Hünig's base or TBAF to investigate the generality of these regioselectivity switches (Tables 2 and 3).

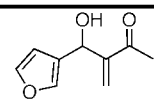
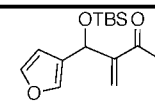
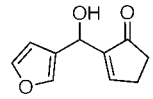
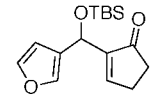
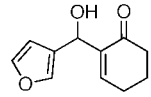
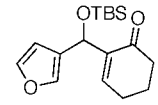
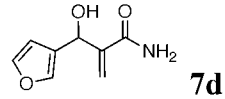
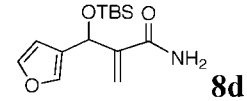
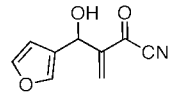
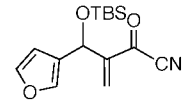
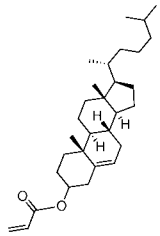
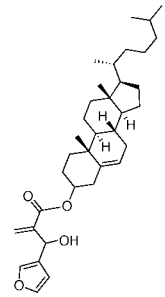
The TBS-protected BH adducts, **8a**−**8c** and **8e**, upon Hünig's base-mediated singlet oxygen oxidation, returned *β*-substituted γ-hydroxybutenolides with complete regioselectivity (entries 1−3 and 5, Table 2). The reaction with **8d** resulted in some formation of **9d** indicated by ^{1}H NMR spectroscopy of the crude reaction mixture. However, successful purification of **9d** could not be achieved. While methanol is the typical solvent to use, DCM was used in some cases for better solubility and purification outcomes. Overall the singlet oxygen oxidation is chemoselective with good to excellent isolated yields. The electron-deficient double bond in the substrates is inert in the oxidation, and regioselectivity remained uncompromised even for substrates with small side chains such as **8a** and **8e** (entries 1 and 5, Table 2). For **7f**, where the side chain is large, complete regioselectivity was achieved even without TBS protection of the 3′-hydroxy group of the furan (entry 6, Table 2). When TBAF was used instead of Hünig's base in singlet oxygen oxidation, complete reversal of selectivity for the α-substituted γ-hydroxybutenolides was observed (Table 3). The regioselectivity was unaffected even for **7f**, where the bulky side chain may potentially interfere with the deprotonation step. This mild and facile approach may find general applicability in the synthesis of natural products that contain both α- and *β*-substituted γ-hydroxybutenolide cores.

Strucutral Studies with NMR and Optical Rotation Spectroscopy. The γ-hydroxybutenolide core is known as the key pharmacophore of this class of compounds that usually exist as a mixture of epimers due to the γ-carbon center.[9] Normally, this epimeric mixture is readily indicated by NMR spectroscopy through the manifestation of doubled peaks. Occasionally, questions arose regarding the possibility of selectivity for one epimer in this equilibrium. The likely reasons are due to either conformational bias or trapping of the γ-hydroxy group, such as the case with *β*-substituted γ-hydroxybutenolide natural products dysidiolide or dictyodentrillolide.[10,11] In the case of

(5) (a) Aggarwal, V. K.; Mereu, A. *Chem. Ind.* **2001**, *82*, 595–600. (b) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311–2312.
(6) Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett.* **2001**, *43*, 127–130.
(7) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723–4725.
(8) Faltin, C.; Fleming, E. M.; Connon, S. J. *J. Org. Chem.* **2004**, *69*, 6496–6499.
(9) Glaser, K. B.; De Carvalho, M. S.; Jacobs, R. S.; Kernan, M. R.; Faulkner, D. J. *Mol. Pharm.* **1989**, *36*, 782–788.
(10) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759–8760.
(11) (a) Cambie, R. C.; Bergquist, P. R.; Karuso, P. *J. Nat. Prod.* **1988**, *51*, 1014–1016. (b) Cambie, R. C.; Craw, P. A.; Bergquist, P. R.; Karuso, P. *J. Nat. Prod.* **1988**, *51*, 331–334.

TABLE 1. Synthesis of Functionalized Furans



entry	enone[a]	yield (%)	furan (**7**)	yield (%) (from **7**)	silyl furan (**8**)
1	 **6a**	61[a]	 **7a**	87[f]	 **8a**
2	 **6b**	70[b]	 **7b**	36[g]	 **8b**
3	 **6c**	75[b]	 **7c**	81[g]	 **8c**
4	 **6d**	64[c]	 **7d**	36[g]	 **8d**
5	 **6e**	68[d]	 **7e**	85[f]	 **8e**
6	 **6f**	16[e]	 **7f**	-	-

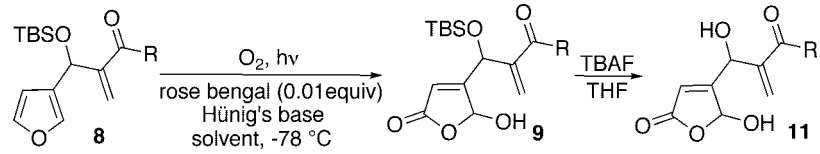
[a] **6a** (3 equiv), imidazole (0.3 equiv), proline (0.3 equiv), DMF, rt, 3 days.[4] [b] DBU (1 equiv), neat, rt, 12 h. [c] 3-Furfural (1.5 equiv), DABCO (1 equiv), **6d** (1 equiv), phenol (1 equiv), 45°C, 3 days. [d] Trimethylamine (1 equiv) with 20% recovered furfural. [e] DBU (1 equiv), DCM. [f] TBSOTf (2 equiv), 2,6-lutidine (3 equiv), anhydrous DCM 0 °C to rt. [g] TBSCl (1.3 equiv), imidazole (2.5 equiv).

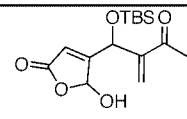
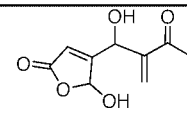
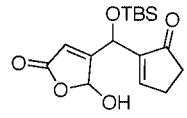
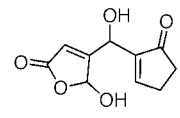
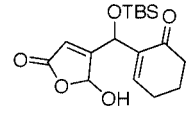
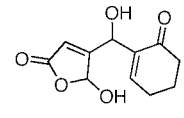
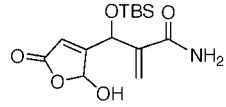
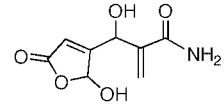
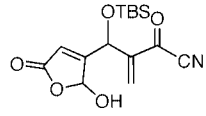
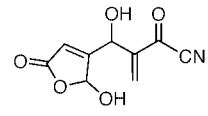
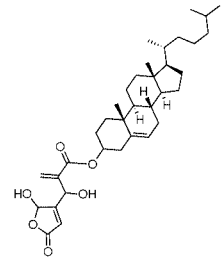
dysidiolide, broad peaks were obtained by NMR spectroscopy for this natural product, and X-ray crystallography provided the structure of a single epimer. However, as selective crystallization of one epimer cannot be excluded, it is not possible for this to be used as definitive evidence for a single epimer in solution with peak broadening due to conformational equilibrium. In the case of dictyodentrillolide, where the γ-hydroxy group is acetylated, NMR spectroscopy indicated the presence of one epimer with one set of broadened peaks, although it is unclear whether this broadening is due to long-range coupling or some conformational equilibrium. Most recently, Miles and co-workers reported the fast epimerization of γ-hydroxybutenolides such as manoalide by an alkyl amine.[12] With a catalytical amount of an amine base, the two γ-epimers exchange rapidly to provide only one set of peaks in the ^{1}H or ^{13}C NMR spectrum. These reports summarize the ambiguities frequently encountered in interpreting NMR spectroscopic data where processes can be obscured by either the inherent time scale or traces of impurity below the detection limit of this solution technique.

We have observed that our β-substituted acrylyl γ-hydroxybutenolides appeared as one set of peaks in the ^{1}H or ^{13}C NMR spectra when using Hünig's base in the oxygenation reaction but not triethylamine. Two possibilities can explain the apparent NMR pattern: one epimer (racemic) appearing as one set of peaks or two epimers (both racemic) in fast exchange (Scheme 3) catalyzed by a base. To ascertain which possibility is applicable requires solution techniques that are both time-dependent and time-independent for comparison to reach a definitive conclusion. With a facile method available to access

(12) Miles, W. H.; Duca, D. G.; Selfridge, B. R.; Palha De Sousa, C. A.; Hamman, K. B.; Goodzeit, E. O.; Freedman, J. T. *Tetrahedron Lett.* **2007**, *48*, 7809–7812.

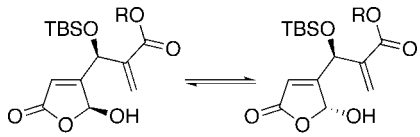
TABLE 2. Synthesis of β-Substituted γ-Hydroxybutenolides



entry	furan (**8**)	yield (%)	silyl butenolide (**9**)	butenolide (**11**)	yield (%) (from **9**)
1	**8a**	91	 **9a**	 **11a**	60
2	**8b**	90[a]	 **9b**	 **11b**	80
3	**8c**	88[a]	 **9c**	 **11c**	52
4	**8d**	-[a,b]	 **9d**	 **11d**	-
5	**8e**	95	 **9e**	 **11e**	54
6	**7f**	-	-	 **11f**	93[c]

[a] MeOH was the solvent instead of DCM. [b] A complex mixture was obtained. NMR spectrscopy of the crude mixture indicated characteristic signals of **9d** but purification was not successful. [c] From **7f**.

SCHEME 3. Epimerization of β-Siloxyacrylyl γ-Hydroxybutenolide (Racemic)



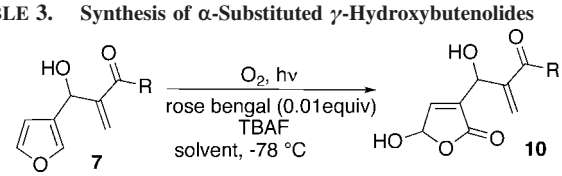
syn-12 *anti*-12

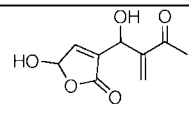
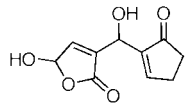
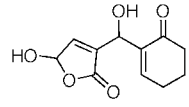
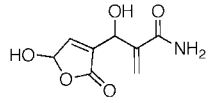
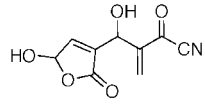
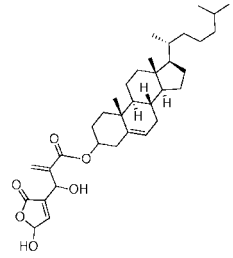
β-substituted γ-hydroxybutenolides, we proceeded to a comparative structural study using NMR and optical rotation spectroscopy.

β-Substituted γ-hydroxybutenolide **12a**, prepared by singlet oxygenation with Hünig's base, was subjected to a temperature-variant NMR study (Figure 1). The starting point was a room temperature ^{1}H spectrum (stack 1, Figure 1) showing one set of peaks between 5 and 7 ppm for the butenolide. As the temperature was lowered, the peaks continued to broaden until they clearly separated to two sets of peaks at −40 °C (stack 5). The starting set of peaks can be recovered by increasing the temperature again, showing no temperature-dependent degradation of the sample (stacks 6−9). However, the two sets of butenolide peaks in the spectrum at −40 °C (stack 5) did not align with those in the ^{1}H spectrum of **12a** obtained at room temperature from a sample of **12a** that was treated with a protic acid to ensure its complete epimerization. As there may be complications from potential conformational populations at lower temperatures, this demonstrates the difficulty in reaching a definitive conclusion on the epimerization state of **12a** with use of NMR.

We then proceeded to prepare the 3′(*S*) isomer of **12a**. In the absence of an enantiomeric specific method to synthesize chemically the BH precursor of **12a**, we resorted to esterase enzyme-catalyzed resolution of BH products.[13] While this method failed to apply to **12a** due to presumably the inability

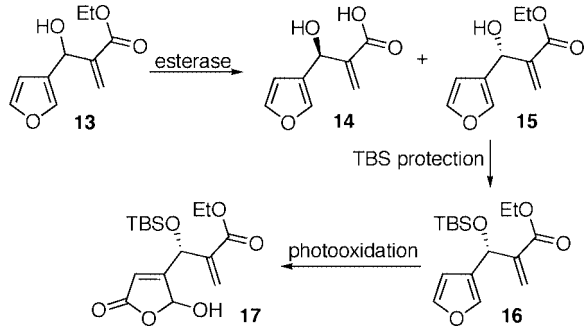
TABLE 3. Synthesis of α-Substituted γ-Hydroxybutenolides



entry	furan (**7**)	yield (%)	butenolide (**10**)
1	**7a**	82	 **10a**
2	**7b**	91	 **10b**
3	**7c**	90	 **10c**
4	**7d**	-[a]	 **10d**
5	**7e**	95	 **10e**
6	**7f**	80	 **10f**

[a] A complex mixture resulted without evidence of the presence of **10d**.

SCHEME 4. Synthesis of 3′(*S*)-Butenolide 17



of the reported esterase enzyme to use **12a** as a substrate, another BH adduct **13**, the ethyl ester analogue of **12a**, was accepted by the enzyme to give **15** in 97% ee with **14** being the hydrolysis product. Furan **15** was then converted to butenolide **17**, with an *S* configuration at the 3′-carbon, using singlet oxygen and Hünig's base (Scheme 4).

(13) Bhuniya, D.; Narayanan, S.; Lamba, T. S.; Krishna Reddy, K. V. S. R. *Synth. Commun.* **2003**, *33*, 3717–3726.

The epimerization state of 3′(*S*)-γ-hydroxybutenolide **17** was next investigated by optical rotation studies. If **17** existed as one epimer at the γ-hydroxy carbon, then its optical rotation would be a nonzero number for this enantiomerically pure sample while displaying one set of peaks in the NMR spectra. The epimerization of **17** from one to two after acid treatment will lead to an optical rotation value very different from that of the pure enantiomer along with two sets of peaks in the NMR spectra (possibility A).[14] If **17** is already a mixture of two epimers in rapid exchange at the γ-hydroxy carbon, then its optical rotation will not change before and after acid treatment and irrespective of changes of its NMR signals (possibility B). We have proposed previously that the observation of one set of peaks in the NMR of these butenolide using Hünig's base and neutral silica gel may favor one epimer of the γ-hydroxybutenolide (possibility A) without definitive evidence to exclude either possibility. The optical rotation studies now offer the opportunity to exclude one of the two possibilities with certainty, independent of the apparent NMR appearances. As shown in Figure 2, **17**, prepared by using Hünig's base in the singlet oxgenenation reaction and purified by neutral silica gel, recorded a specific optical rotation of 9.1° while presenting as one set of peaks in its ^{1}H NMR spectrum. Treatment of **17** under acidic conditions to ensure its epimerization led to two sets of peaks in the ^{1}H NMR spectrum, yet its specific optical rotation remained the same. This observation is consistent with only possibility B, not A. Furthermore, after a catalytic amount of Hünig's base (0.1 mol %) was added to the epimerized sample of **17** according to the Miles protocol, the ^{1}H NMR spectrum reverted back from two sets of peaks to one set of peaks, yet its specific optical rotation again remained unchanged. This clearly indicated that the base-catalyzed fast epimerization of the γ-center is operable here with exclusion of possibility A.[15] This also demonstrates that optical rotation can be used as a time-independent technique in solution to definitively clarify potentially ambiguous NMR interpretations for these γ-hydroxybutenolides.[16]

In conclusion, this work illustrates the scope and limitation of using simple regioselectivity switches to access either α- or β-substituted γ-hydroxybutenolides from enone functionalized furans by singlet oxygenation. Studies in solution using NMR and optical rotation spectroscopy of some of the γ-hydroxybutenolides also provided further information regarding the epimerization process at the γ-hydroxy carbon center of these butenolides.

Experimental Section

Preparation of Cholesterol Acrylate 6f ((8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl Acrylate). Acryloyl chloride was added dropwise to a stirred solution of cholesterol and triethylamine at 0 °C under nitrogen. The reaction

(14) The scenario of the two epimers with two stereocenters having identical optical rotation values is highly unlikely here, although it is possible for complex natural products with many stereocenters to exhibit indistinguishable optical rotation values for their epimers. For a recent example, see: Cecil, A. R. L.; Hu, Y.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368–3374.

(15) For a detailed study on the rates and mechanisms of acid- or base-catalyzed cyclic hemiacetal formation between an oxygen nucleophile and an aldehyde, see: Harron, H.; McClelland, R. A.; Thankachan, C.; Tidwell, T. T. *J. Org. Chem.* **1981**, *46*, 903–910.

(16) CD spectroscopy indicated a positive cotton effect for **17** both before and after acid treatment and no difference was discernable (spectra in the Supporting Information). See: Soriente, A.; Crispino, A.; De Rosa, M.; De Rosa, S.; Scettri, A.; Scognamiglio, G.; Villano, R.; Sodano, G. *Eur. J. Org. Chem.* **2000**, *6*, 947–953.

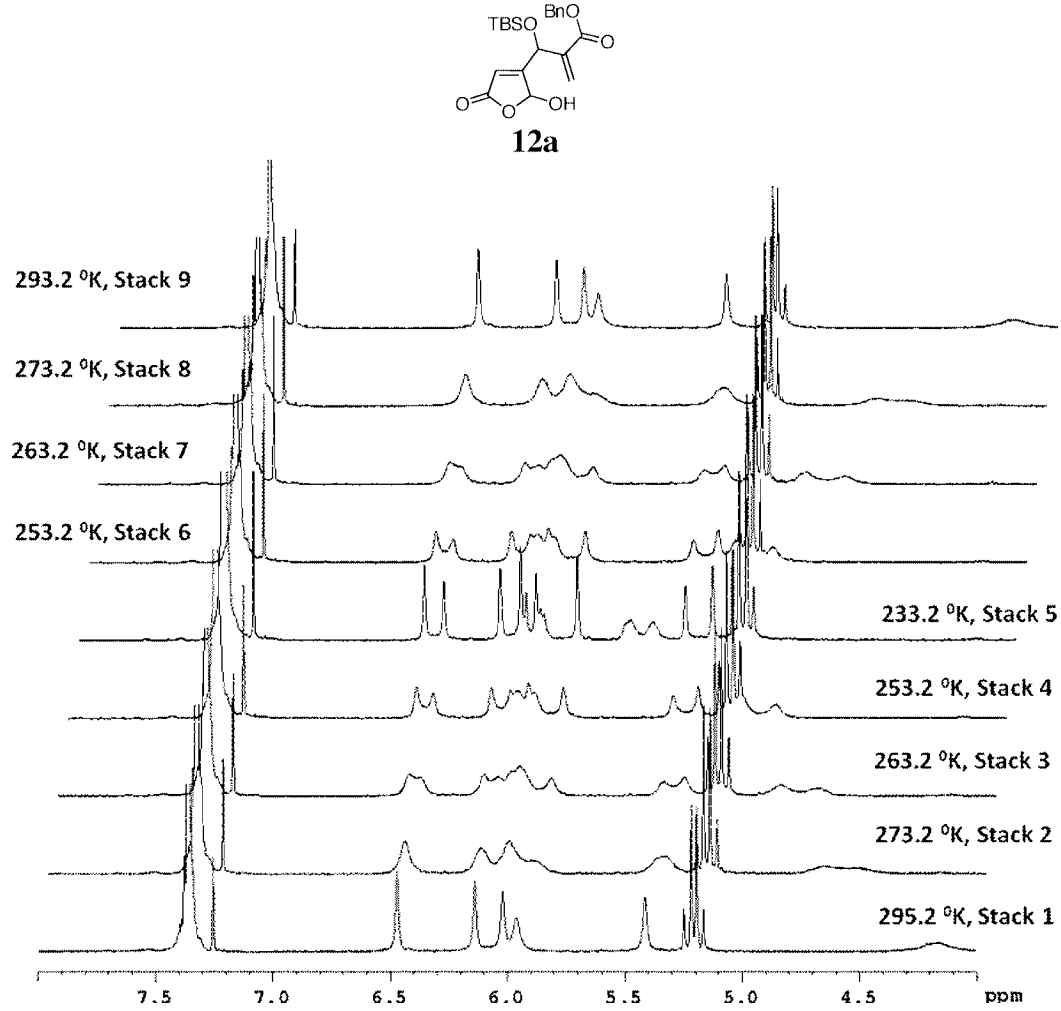


FIGURE 1. Stacked ^{1}H NMR spectra of **12a**.

mixture was allowed to warm to room temperature and stirred for 5 h to affod cholesterol acrylate as a white solid. Yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (s, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 2.5−1.0 (m, 31H), 5.35 (d, J = 4.6 Hz, 2H), 5.75 (dd, J = 10.42, 1.5 Hz, 1H), 6.07 (dd, J = 17.2, 10.4 Hz, 1H), 6.35 (dd, J = 17.27, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 19.2, 19.8, 21.5, 23.0, 23.3, 24.3, 24.7, 28.2, 28.4, 28.7, 32.3, 32.3, 50.4, 56.6, 57.1, 74.5, 123.2, 129.4, 130.7, 139.9, 166.0.

General Procedure for the Preparation of Baylis−Hillman Adducts. DBU (1.04 mmol) was added to a mixture of an activated alkene (1.04 mmol) and 3-furfural (1.04 mmol) being stirred at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred under nitrogen at room temperature until completion. Upon finishing, the reaction mixture was adsorbed onto silica and purified by flash column chromatography using petroleum ether/ethyl acetate (2:1) to afford the Baylis−Hillman adduct. For **7f**, DCM (400 μL per 1 mmol of cholesterol acrylate) was added to the reaction mixture to improve solubility.

3-(Furan-3-yl(hydroxy)methyl)but-3-en-2-one (7a). Yield 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.31 (br s, −OH), 5.55 (s, 1H), 6.04 (s, 1H), 6.15 (s, 1H), 6.29−6.30 (m, 1H), 7.33−7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 66.5, 109.5, 126.8, 140.2, 143.6, 149.8, 200.8; ESI [M + Na$^+$] 189.0523, calcd for $(C_9H_{10}O_3Na)^+$ 189.0528.

2-(Furan-3-yl(hydroxy)methyl)cyclopent-2-enone (7b). Yield 70%; ^{1}H NMR (400 MHz,$CDCl_3$) δ 2.47−2.49 (m, 2H), 2.60−2.64 (m, 2H), 3.35 (d, J = 4.7 Hz, −O*H*), 5.53 (s, 1H), 6.39 (s, 1H), 7.36−7.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 35.8, 63.5, 109.4, 126.7, 140.2, 143.9, 147.3, 159.6, 210.1; ESI [M + Na$^+$] 201.0530, calcd for $(C_{10}H_{10}O_3Na)^+$ 201.0528.

2-(Furan-3-yl(hydroxy)methyl)cyclohex-2-enone (7c). Yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88−1.99 (m, 2H), 2.30−2.42 (m, 4H), 3.7 (br s, −O*H*), 5.45 (s, 1H), 6.27 (t, J = 1.3 Hz, 1H), 6.88 (t, J = 4.1 Hz, 1H), 7.29−7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 25.9, 38.8, 66.0, 109.5, 127.2, 139.9, 140.5, 143.4, 147.4, 200.7; ESI [M + Na$^+$] 215.0677, calcd for $(C_{11}H_{12}O_3Na)^+$ 215.0678.

2-(Furan-3-yl(hydroxy)methyl)acrylamide (7d). Yield 64%; ^{1}H NMR (400 MHz, CD_3OD) δ 5.54 (s, 1H), 5.68 (s, 1H), 5.91 (s, 1H), 6.38 (s, 1H), 7.39−7.43 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 68.0 111.2, 121.1, 129.2, 141.9, 145.2, 148.1, 173.1; ESI [M + Na$^+$] 190.0482, calcd for $(C_8H_9NO_3Na)^+$ 190.0480.

2-(Furan-3-yl(hydroxy)methyl)acrylonitrile (7e). Yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (br s, −O*H*), 5.27 (s, 1H), 6.04 (s, 1H), 6.10 (s, 1H), 6.40−6.42 (m, 1H), 7.42 (s, 1H), 7.47−7.49 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 67.6, 108.9, 117.4, 125.2, 126.0, 130.7, 140.8, 144.5; ESI [M + Na$^+$] 172.0376, calcd for $(C_8H_7NO_2Na)^+$ 172.0374.

(8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 2-(Furan-3-yl(hydroxy)methyl)acrylate (7f). Yield 16%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (s, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.92 (s, 1H), 1.02 (s, 3H), 0.92−1.70 (m, 25 H), 1.70−2.05 (m, 2H), 3.15 (t, J = 6.2 Hz, 1H), 5.35−5.40 (m, 2H), 5.50 (d, J = 6.4 Hz, 1H), 5.83 (dd, J = 2.3, 2.3 Hz, 1H), 6.35−6.37 (m, 2H), 7.36−7.40 (m, 2H); ^{13}C NMR (100 MHz,

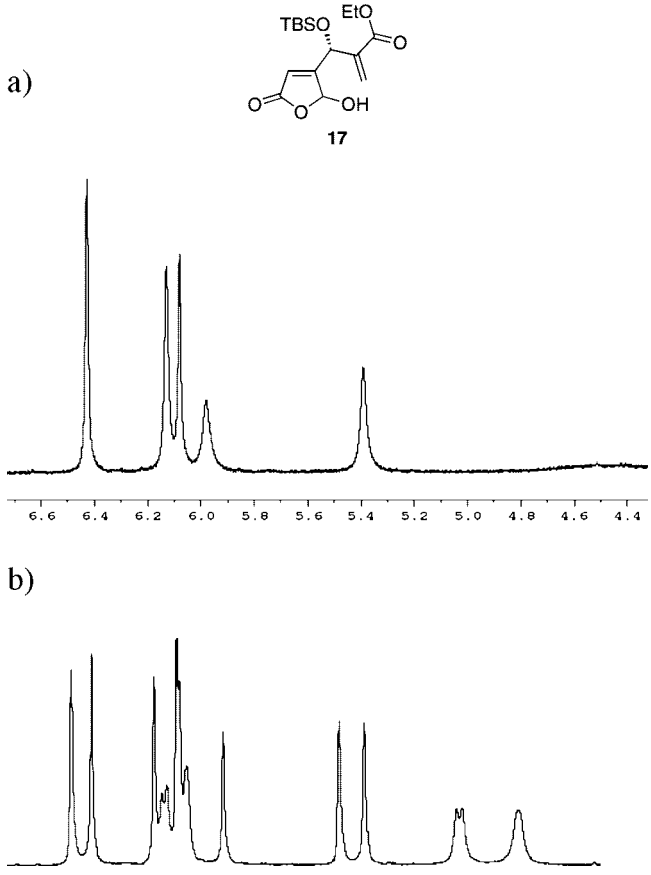


FIGURE 2. A comparative study of **17** with NMR and optical rotation spectroscopy: (a) ^{1}H NMR spectrum of **17** prepared by using Hünig's base and purified by neutral silica gel ($[\alpha]_D$ 9.1 at 23.2 °C) and (b) ^{1}H NMR spectrum of epimerized **17** ($[\alpha]_D$ 8.5 at 22.6 °C).

$CDCl_3$) δ 12.3, 19.2, 19.8, 21.5, 23.0, 23.3, 24.3, 24.8, 26.23, 3.15, 28.5, 28.7, 32.3, 32.4, 36.6, 37.1, 37.4, 38.4, 38.4, 39.9, 40.2, 42.8, 50.4, 56.6, 57.1, 67.5, 75.5, 109.8, 123.4, 126.1, 127.2, 139.8, 139.8, 140.2, 142.2, 143.8, 166.3; ESI [M + Na^+] 559.3741, calcd for $(C_{35}H_{52}O_4Na)^+$ 559.3763.

General Procedure for the Preparation of Protected Baylis−Hillman Adducts. TBSOTf (2.0 mmol) (or TBSCl (1.3 mmol)) was added to a stirring solution of Baylis−Hillman adducts (1.0 mmol) and 2,6-lutidine (3 mmol) (or imidazole (2 mmol)) in anhydrous DCM (100 μL) under nitrogen at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred under nitrogen. The reaction mixture was monitored by TLC for disappearance of starting material. In general, reactions were complete in 45 min with use of TBSOTf. Prolonged reaction time in the TBSOTf method may result in silylation of the enone in the case of **8a**. Upon finishing the reaction mixture was purified by passing through silica gel with petroleum ether/ethyl acetate (9:1) to afford the product as a colorless oil.

3-((*tert*-Butyldimethylsilyloxy)(furan-3-yl)methyl)but-3-en-2-one (8a). Yield 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.03 (s, 3H), 0.89 (m, 9H), 2.30 (s, 3H), 5.72 (s, 1H), 6.10 (s, 1H), 6.23−6.24 (m, 1H), 6.27−6.28 (m, 1H), 7.27 (s, 1H), 7.29−7.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −4.5, 18.7, 26.3, 26.9, 64.9, 109.5, 124.7, 128.7, 139.8, 143.0, 151.9, 199.1; ESI [M + Na^+] 303.1386, calcd for $(C_{15}H_{24}O_3SiNa)^+$ 303.1392.

2-((*tert*-Butyldimethylsilyloxy)(furan-3-yl)methyl)cyclopent-2-enone (8b). Yield 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 2.36−2.49 (m, 2H), 2.51−2.67 (m, 2H), 5.50 (s, 1H), 6.34−6.35 (m, 1H), 7.30 (t, J = 1.7 Hz, 1H), 7.35−7.36 (m, 1H), 7.59−7.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −4.5, 18.7, 26.2, 26.9, 35.9, 63.3, 109.4, 128.3, 139.6, 143.3, 149.8, 158.7, 207.9; ESI [M + Na^+] 315.1400, calcd for $(C_{16}H_{24}O_3SiNa)^+$ 315.1392.

2-((*tert*-Butyldimethylsilyloxy)(furan-3-yl)methyl)cyclohex-2-enone (8c). Yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.01 (s, 3H), 0.88 (s, 9H), 1.87−2.04 (m, 2H), 2.34−2.42 (m, 4H), 5.70 (s, 1H), 6.26−6.27 (m, 1H), 7.15 (t, J = 4.22 Hz, 1H), 7.24−7.26 (m, 1H), 7.29−7.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, 18.7, 23.2, 26.1, 26.3, 38.9, 63.7, 109.5, 129.4, 139.6, 142.6, 142.9, 145.4, 198.5; ESI [M + Na^+] 329.153939, calcd for $(C_{17}H_{26}O_3SiNa)^+$ 329.154342.

2-((*tert*-Butyldimethylsilyloxy)(furan-3-yl)methyl)acrylamide (8d). Yield 36%; ^{1}H NMR (400 MHz, $CDCl_3$) 0.10 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 5.52 (s, 1H), 5.59 (s, 1H), 6.09 (d, J = 1.3 Hz, 1H), 6.24−6.25 (m, 1H), 6.7 (br s, −NH_2), 7.30−7.31 (m, 1H), 7.32 (t, J = 1.74 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) −4.7, −4.5, 18.6, 26.1, 70.2, 109.4, 123.1, 128.0, 139.6, 143.7, 144.5 168.3; ESI [M + Na^+] 304.1342, calcd for $(C_{14}H_{23}NO_3SiNa)^+$ 304.1345.

2-((*tert*-Butyldimethylsilyloxy)(furan-3-yl)methyl)acrylonitrile (8e). Yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 5.24 (s, 1H), 5.95−5.97 (m, 1H), 6.03−6.05 (m, 1H), 6.34−6.73 (m, 1H), 7.39 (t, J = 1.8 Hz, 1H), 7.42−7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) −4.6, −4.5, 18.6, 26.1, 68.4, 108.9, 117.5, 126.1, 127.5, 129.2, 140.3, 144.1; ESI [M + Na^+] 286.1244, calcd for $(C_{14}H_{21}NO_2SiNa)^+$ 286.1239.

General Procedure for the Singlet Oxygen Oxidation Reaction with Hünig's Base. To a mixture of a Baylis−Hillman adduct (0.30 mmol) and rose bengal (3 mg, 0.003 mmol) in methanol or DCM (70 mL) was added Hünig's base (0.36 mmol). The reaction mixture was then exposed to singlet oxygen (generated from compressed air with a 150 W flood light) at −78 °C. The reaction mixture was then monitored for disappearance of starting material. Upon completion the reaction mixture was removed from the bath, and the solvent was removed under vacuum at room temperature and purified by flash column chromatography to afford the butenolide product.

4-(1-(*tert*-Butyldimethylsilyloxy)-2-methylene-3-oxobutyl)-5-hydroxyfuran-2(5*H*)-one (9a). Yield 91%, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 2.36 (s, 3H), 5.50 (s, 1H), 5.82−6.04 (m, 2H), 6.30−6.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 18.5, 26.1, 26.4, 26.7, 65.3, 66.4, 98.3, 118.6, 118.8, 128.5, 129.1, 148.5, 169.3, 170.3, 171.0, 171.4, 199.4, 199.9; ESI [M + H^+] 313.1469, calcd for $(C_{15}H_{25}O_5Si)^+$ 313.1471.

4-((*tert*-Butyldimethylsilyloxy)(5-oxocyclopent-1-enyl)methyl)-5-hydroxyfuran-2(5*H*)-one (9b). Yield 91%, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.94 (br s, −O*H*), 2.50−2.53 (m, 2H), 2.67−2.70 (m, 2H), 5.23−5.40 (m, 1H), 5.89−6.09 (m, 2H), 7.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, 18.6, 26.1, 27.6, 35.9, 64.5, 64.6, 97.9, 98.8, 118.4, 120.4, 146.3, 147.1, 162.5, 163.1, 168.2, 169.7, 170.5, 170.8, 208.8, 209.6; ESI [M + Na^+] 347.1284, calcd for $(C_{16}H_{24}O_5SiNa)^+$ 347.1291.

4-((*tert*-Butyldimethylsilyloxy)(6-oxocyclohex-1-enyl)methyl)-5-hydroxyfuran-2(5*H*)-one (9c). Yield 88%, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.98−2.04 (m, 2H), 2.45−2.49 (m, 4H), 5.48 (s, 1H), 5.91 (s, 1H), 6.03 (s, 1H), 7.24−7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.5, 18.6, 22.9, 26.1, 26.3, 38.6, 64.9, 98.7, 118.6, 139.4, 149.7, 170.9, 199.7; ESI [M + Na^+] 361.1444, calcd for $(C_{17}H_{26}O_5SiNa)^+$ 361.1441.

2-((*tert*-Butyldimethylsilyloxy)(2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl)methyl)acrylonitrile (9e). Yield 95%, solid; ^{1}H NMR (400 MHz, CD_3OD) δ 0.15 (s, 6H), 0.95 (s, 9H), 5.27 (s, 1H), 5.96−6.22 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ −4.2, −4.0, 19.8, 26.9, 71.9, 100.4, 117.8, 121.2, 125.9, 134.7, 169.6, 172.6; ESI [M + H^+] 296.1313, calcd for $(C_{14}H_{22}NO_4)^+$ 296.1318.

(8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl−17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 2-(Hydroxy(2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl)methyl)acrylate (11f). Yield 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (s, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.91(d, J = 6.5 Hz, 3H), 1.02 (s, 3H), 0.92−2.5 (m, 31H), 4.2−3.8 (br s, −O*H*), 4.75−4.60 (m, 1H), 5.34 (s,1H), 5.39 (d, J = 4.4 Hz, 1H), 5.9−6.2 (m, 3H), 6.42(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 19.2, 19.8, 21.5, 23.0, 23.3, 24.3, 24.8, 28.1, 28.5, 28.7, 32.3, 32.4, 36.3, 36.7, 37.0, 37.3, 38.4, 39.9, 40.2, 42.8, 50.4, 56.6, 57.1, 67.2, 76.2, 98.5, 119.3, 123.7, 139.2, 139.5, 165.8, 168.9, 171.1; ESI [M + Na^+] 591.3683, calcd for $(C_{35}H_{52}O_6Na)^+$ 591.3662.

General Procedure for the Singlet Oxygen Oxidation Reaction with TBAF. Tetrabutylammonium fluoride, 1.0 M solution in tetrahydrofuran (0.36 mmol), was added to the mixture of a Baylis−Hillman adduct (0.30 mmol) and rose bengal (3 mg, 0.003 mmol) in dichloromethane (70 mL). Methanol (70 mL) was used as the solvent for polar starting materials. The reaction mixture was then exposed to singlet oxygen (generated from compressed air with a 150 W flood light) at −78 °C for 5 h. The reaction mixture was then removed from the bath, and the solvent was removed under vacuum at room temperature. The crude mixture was dissolved in acetonitrile (2 mL), passed through Poly-Prep columns containing prefilled AG50W-X8 (H^+) resin of ion exchange capacity of 3.4 (nominal mequiv/2 mL of resin), and flushed with 8 mL of acetonitrile. The acetonitrile was removed and the residue, after the protonation step, was filtered through silica gel to remove trace impurities (silica gel 60 Å 0.06−0.2 mm, 70−230 mesh) and further purified by flash column chromatography to afford the butenolide as a colorless oil. In the case of polar butenolides, more than one protonation step may be necessary.

5-Hydroxy-3-(1-hydroxy-2-methylene-3-oxobutyl)furan-2(5*H*)-one (10a). Yield 82%; ^{1}H NMR (400 MHz, CD_3OD) δ 2.37 (s, 3H), 4.53−4.72 (br s, −O*H*), 5.38 (s, 1H), 6.19 (s, 1H), 6.39 (s, 1H), 7.07 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 27.1, 98.8, 128.9, 140.7, 148.6, 150.5, 172.8, 201.2; ESI [M + Na^+] 221.0418, calcd for $(C_9H_{10}O_5Na)^+$ 221.0426.

5-Hydroxy-3-(hydroxy(5-oxocyclopent-1-enyl)methyl)furan-2(5*H*)-one (10b). Yield 91%; ^{1}H NMR (400 MHz, CD_3OD) δ 2.40−2.48 (m, 2H), 2.61−2.70 (m, 2H), 5.15−5.19 (m, 1H), 6.10 and 6.11 (t, J = 0.9, 1.0, Hz, 1H), 7.16 and 7.18 (t, J = 1.3, 1.4 Hz, 1H), 7.69−7.73 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 28.6, 36.8, 62.2, 62.4, 99.8, 139.7, 139.9, 146.9, 147.1, 148.9, 149.0, 164.4, 172.6, 172.7, 210.9; ESI [M + Na^+] 233.0419, calcd for $(C_{10}H_{10}O_5Na)^+$ 233.0426.

5-Hydroxy-3-(hydroxy(6-oxocyclohex-1-enyl)methyl)furan-2(5*H*)-one (10c). Yield 90%; ^{1}H NMR (400 MHz, CD_3OD) δ 1.97−2.05 (m, 2H), 2.37−2.50 (m, 4H), 5.32 (S, 1H), 5.88 (s, 1H), 7.06−7.13 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 24.5, 27.7, 40.0, 64.3, 64.3, 105.0, 105.1, 140.5, 140.6, 141.6, 141.7, 146.7, 146.8, 150.6, 150.7, 172.2, 172.3, 200.7, 200.8; ESI [M + Na^+] 247.0573, calcd for $(C_{11}H_{12}O_5Na)^+$ 247.0582.

2-(Hydroxy(5-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)methyl)-acrylonitrile (10e). Yield 95%; ^{1}H NMR (400 MHz, CD_3OD) δ 5.06 (s, 1H), 6.04−6.24 (m, 4H), 7.32 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 68.6, 68.8, 99.9, 100.0, 118.2, 118.3, 126.1, 126.3, 134.1, 134.2, 134.6, 138.3, 149.9, 150.1, 172.1; ESI [M + Na^+] 204.0273, calcd for $(C_8H_7NO_4Na)^+$ 204.0273.

(8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 2-(Hydroxy(5-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)methyl)acrylate (10f). Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (s, 3H), 0.87 (d, J = 5.9 Hz, 3H), 0.87 (d, J = 5.9 Hz, 3H), 0.91 (d, J = 5.8 Hz, 3H), 1.02 (s, 3H), 0.92−2.5 (m, 28 H), 4.2−3.6 (br s, −O*H*), 4.68 (s, 1H), 5.31 (s, 1H), 5.39 (s, 1H), 6.00 (s, 1H), 6.12 (s, 1H), 6.40 (s, 1H), 7.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 19.2, 19.8, 21.5, 23.1, 23.3, 24.3, 24.8, 28.2, 28.5, 28.7, 32.3, 32.4, 36.7, 37.1, 37.4, 38.5, 40.0, 40.2, 42.8, 50.5, 56.6, 57.2, 67.0, 75.8, 97.6, 123.6, 123.8, 128.4, 138.3, 138.8, 139.7, 146.1, 165.8, 170.3; ESI [M + Na^+] 591.3661, calcd for $(C_{35}H_{52}O_6Na)^+$ 591.3662.

Deprotection of the Silylated Butenolides. To the TBS protected butenolide (0.3 mmol) in anhydrous DCM (100 μL) was added tetrabutylammonium fluoride, 1.0 M solution in tetrahydrofuran (0.3 mmol). The mixture was stirred under nitrogen and at room temperature for 6 h. The solvent was removed under vacuum, and the residue was then passed through silica gel to remove impurities (silica gel 60 Å 0.06−0.2 mm, 70−230 mesh) and further purified by flash column chromatography to afford the butenolide as a colorless oil.

5-Hydroxy-4-(1-hydroxy-2-methylene-3-oxobutyl)furan-2(5*H*)-one (11a). Yield 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 5.35 (s, 1H), 6.0 (s, 1H), 6.19 (s, 1H), 6.29 (s, 1H), 6.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 68.1, 100.0, 119.8, 129.7, 146.9, 167.7, 170.4, 200.6; ESI [M + Na^+] 221.0422, calcd for $(C_9H_{10}O_5Na)^+$ 221.0426.

5-Hydroxy-4-(hydroxy(5-oxocyclopent-1-enyl)methyl)furan-2(5*H*)-one (11b). Yield 80%; ^{1}H NMR (400 MHz, CD_3OD) δ 2.41−2.5 (m, 2H), 2.64−2.74 (m, 2H), 4.6 (br s, −O*H*), 5.29 (s, 1H), 5.99 (br s, 1H), 6.11 (br s, 1H), 7.77 (t, J= 2.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 28.8, 36.7, 64.0, 100.7, 119.5, 146.6, 165.2, 172.6, 173.6, 210.8; ESI [M + Na^+] 233.0427, calcd for $(C_{10}H_{10}O_5Na)^+$ 233.0426.

5-Hydroxy-4-(hydroxy(6-oxocyclohex-1-enyl)methyl)furan-2(5*H*)-one (11c). Yield 52%; ^{1}H NMR (400 MHz, CD_3OD) δ 1.96−2.05 (m, 2H), 2.40−2.51 (m, 4H), 4.6 (br s, −O*H*), 5.42 (s, 1H), 5.86−6.11 (m, 2H), 7.16 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 24.5, 27.1, 27.8, 40.0, 65.8, 66.5, 100.7, 119.2, 140.3, 15 0.9, 152.4, 172.6, 173.8, 200.6, 201.2; ESI [M + Na^+] 247.0575, calcd for $(C_{11}H_{12}O_5Na)^+$ 247.0576.

2-(Hydroxy(2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl)methyl)acrylonitrile (11e). Yield 54%; ^{1}H NMR (400 MHz, CD_3OD) δ 4.51 (br s, −O*H*), 5.09 (br s, 1H), 6.09−6.19 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 68.7, 98.7, 116.3, 119.1, 123.9, 132.8, 167.7, 171.2; ESI [M + Na^+] 204.0265, calcd for $(C_8H_7NO_4Na)^+$ 204.0273.

Preparation of 3′(*S*)-17. The esterase enzyme (11 mg, ≥15 units/mg solid) was added to a mixture of phosphate buffer (pH 7.1, 41 mL), **13** (94 mg, 0.48 mmol), and DMSO (3 mL). The solution was stirred at 37−39 °C. After 4 h, HPLC (analytical column: (*S*,*S*) Welko, 25 cm × 4.6 cm; mobile phase: isopropanol/hexane (3:97); flow rate: 0.3 mL/min) indicated 97% ee for **15** (unhydrolyzed **13**). The reaction mixture was then acidified to pH 2 and extracted with ethyl acetate. Removal of ethyl acetate followed by flash column chromatography afforded **15** in 97% ee (32 mg, 34% yield). The synthesis and characterization of 3′(*S*)-**17** was followed as previously reported.[4]

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Supporting Information Available: NMR spectra of compounds **6a**,**7a**−**f**, **8a**−**e**, **9a**−**c**, **9e**, **10a**−**c**, **10e**−**f**, **11a**−**c**, and **11e**−**f**, chiral HPLC chromatogram of **15**, CD spectra of **17**, and full ^{1}H NMR spectra of **12a** at various temperatures. This material is available free of charge via the Internet at http://pubs.acs.org.

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