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A Short Entry to α-Substituted γ-Alkylidene Pentenolides. Synthesis and Preliminary Biological Evaluation of Novel Gelastatin Analogues

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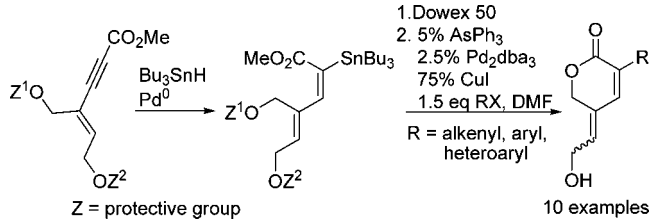

Biologically interesting 2-substituted 4-alkylidene pentenolides were prepared with complete control of regio- and stereoselectivity from 2-iodo allylic alcohols via an array of Pd-catalyzed processes, including alkynylation with methyl propiolate, tributyltin hydride addition, and α-functionalization. Some of the compounds possess selective cytostatic activity against ovarian carcinoma HeLa S3 and leukemia CCRF-CEM cell lines.

Introduction

The development of novel drugs inspired by natural products (NP) has been particularly successful in the advancement of new antineoplastic and antiinfective agents into the clinic.[1] This approach, i.e., the synthesis and biological evaluation of small series of NP analogues, may prove to be a more rational approach towards novel medicinal agents than the production of large combinatorial libraries. Accordingly, the goal of a synthetic medicinal chemist pursuing an NP lead should be the development of a short synthetic route that would allow access to a maximum number of possible analogues.

Bioactive γ-alkylidene butenolides are widely distributed throughout the plant kingdom and have inspired many synthetic efforts.[2,3] Surprisingly though, the synthesis of pentenolide analogues, i.e., 4-alkylidene pentenolides, has been virtually unexplored, probably because most of the biologically active pentenolides comprise the α,β-unsaturated δ-lactone unit with a structurally complex substituent attached at C5.[4] Our interest in 4-alkylidene pentenolides stems from a few recent reports on the activity of pentenolide natural products against a range of biological targets suggesting that they may be privileged structures for drug development. By way of example, gelastatins A and B (Figure 1) are structurally unique inhibitors[5] of matrix metalloproteases (MMPs) responsible for tissue remodeling and degradation of the extracellular matrix. These enzymes are involved in malignant pathologies and constitute promising

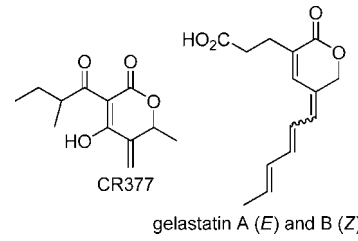

FIGURE 1. Structures of the gelastatins and CR377.

(1) Cho, Y. S.; Wu, K.-D.; Moore, M. A. S.; Chou, T.-C.; Danishefsky, S. J. *Drugs Future* **2005**, *30*, 737.

(2) For reviews on γ-alkylidene butenolide synthesis, see: (a) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. (b) Brückner, R. *Curr. Org. Chem.* **2001**, *5*, 679.

(3) For the most recent examples of γ-alkylidene butenolide synthesis, see: (a) Fáková, H.; Pour, M.; Kuneš, J.; Šenel, P. *Tetrahedron Lett.* **2005**, *46*, 8137. (b) Xu, H.-W.; Wang, J.-F.; Liu, G.-Z.; Hong, G.-F.; Liu, H.-M. *Org. Biomol. Chem.* **2007**, *5*, 1247. (c) Boukouvalas, J.; Beltrán, P. P.; Lachance, N.; Côté, S.; Maltais, F.; Pouliot, M. *Synlett* **2007**, 219. (d) Novák, P.; Pour, M.; Špulák, M.; Votruba, I.; Kotora, M. *Synthesis* **2008**, 3465.

(4) For a review on isolation and biological activity, see: (a) Collett, L. A.; Davies-Coleman, M. T.; Rivett, D. E. A. *Prog. Chem. Org. Nat. Prod.* **1998**, *75*, 181. (b) For a recent review on synthesis, see: Boucard, V.; Broustal, G.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, 225.

(5) Lee, H.-J.; Chung, M.-C.; Lee, C.-H.; Yun, B.-S.; Chun, H.-K.; Kho, Y.-H. *J. Antibiot.* **1997**, *50*, 357.

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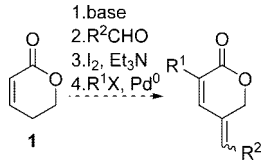
targets for anticancer therapy.[6] CR 377 is another natural product[7] with potent antifungal activity against *Candida albicans*.

Given the biological effects of the above NPs and apparent analogy to biologically active alkylidene butenolides, the 2-substituted 4-alkylidene pentenolide skeleton was believed to be an interesting scaffold for the preparation and biological evaluation of a small library. Since the published syntheses of the gelastatins[8] and their 4-benzylidene analogues[9] involve 13 and 12 steps, respectively, that are not readily adjusted to the preparation of analogues, we set out to develop a general pathway to this class of compounds that would enable the attachment of a broad array of substituents to both positions.

Results and Discussion

The easiest possible path to 2-substituted 4-alkylidene pentenolides, outlined in Scheme 1, is based on the sequential functionalization of the commercially available 5,6-dihydro-2*H*-pyran-2-one (**1**). As is the case with the analogous butenolide core, the γ position can be functionalized via enolate formation and subsequent reaction with aldehydes[10] (steps 1 and 2), and Johnson α-iodination[11] followed by a coupling process (steps 3 and 4) would introduce a substituent into the α position.

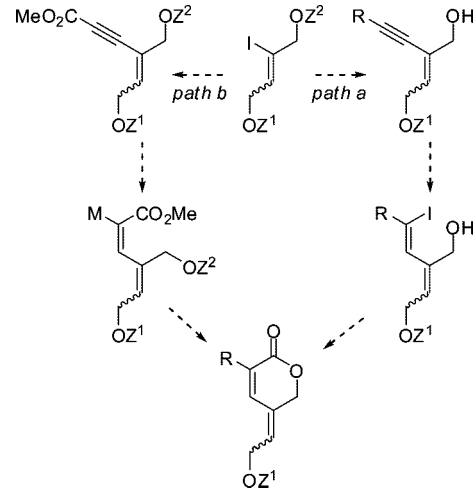
SCHEME 1. Direct Functionalization of the Pentenolide Core



In practice, all attempts to introduce the alkylidene moiety into position 4, including simple enolate generation/quenching with an aldehyde,[10a] as well as treatment[10b] of **1** with an aldehyde in the presence of TBDMSOTf/DIPEA followed by DBU-induced elimination, resulted in the decomposition of the unsaturated pyranone. NMR spectra of the crude reaction mixtures indicated that under basic conditions, the pentenolide ring is much more prone to opening than its butenolide congener. It quickly became apparent that de novo construction of the pentenolide core with the desired substitution already in place would be preferable to repeating reactions from the butenolide system.

(*E*)- and (*Z*)-2-iodobut-2-en-1,4-diols were considered[12] as suitable four-carbon synthons in this approach. The structure of each contains the 4-alkylidene unit as well as vinyl iodide and hydroxymethyl groups that are integral for the construction of the six-membered ring (Scheme 2). In addition, the Z^1-protected OH group should facilitate production of compound libraries at this position. Apparently though, the Z^1-protected OH group is not crucial for the strategy and can be replaced by other substituents.

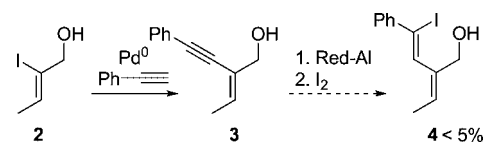
SCHEME 2. Proposed Pathways to 2-Substituted γ-Alkylidene Pentenolides



Thus, Sonogashira coupling with an alkyne, followed by *trans*-hydrometalation/iodination of the triple bond, would deliver an iodo alcohol that would be subjected to carbonylation in the last step (path a). Alternatively, attachment of a propiolic acid ester via a suitable coupling would deliver the remaining portion of the pentenolide ring. A stereoselective *cis*-hydrometalation of the conjugated triple bond would set the stage for another coupling process in the α-position as well as the ring closure (path b).

The preparation of 2,5-disubstituted pentenolides from homopropargylic alcohols through OH group-directed *trans*-hydroalumination/iodination followed by Pd-catalyzed carbonylative lactonization has been described[13] recently by us. However, this sequence is limited to substrates with a stable aryl group on the triple bond due to the harsh hydrometalation conditions. Thus, simple (*E*)-2-(2-phenylethynyl)-but-2-en-1-ol (**3**) was prepared via standard Sonogashira coupling first and subjected to sequential treatment[14] with Red-Al and I_2 in order to assess the influence of the alkylidene moiety on the hydrometalation process (Scheme 3). However, the reaction gave an inseparable mixture of the starting material with less than 5% of the product as judged by NMR, and increasing both temperature and time led to complete decomposition.

SCHEME 3. Attempted Hydroalumination of 3



(6) For reviews on MMPs, see: (a) Gupta, S. G. *Chem. Rev.* **2007**, *107*, 3042. (b) Verma, R. P.; Hansch, C. *Bioorg. Med. Chem.* **2007**, *15*, 2223.

(7) Brady, S. F.; Clardy, J. *J. Nat. Prod.* **2000**, *63*, 1447.

(8) Lee, H.-Y.; Tae, H. S.; Kim, B. G.; Choi, H.-M. *Tetrahedron Lett.* **2003**, *44*, 5803.

(9) (a) Cho, J.-H.; Ko, S. Y.; Oh, E.; Park, J. C.; Yoo, J. U. *Helv. Chim. Acta* **2002**, *85*, 3994. (b) Kim, E. J.; Ko, S. Y. *Bioorg. Med. Chem.* **2005**, *13*, 4103.

(10) For recent examples, see: (a) Pohmakotr, M.; Tuchinda, P.; Premkaisorn, P.; Reutrakul, V. *Tetrahedron* **1998**, *54*, 11297–11304. (b) Boukouvalas, J.; Lachance, N.; Ouellet, M.; Trudeau, M. *Tetrahedron Lett.* **1998**, *39*, 7665–7668. (c) Bellina, F.; Anselmi, Ch.; Viel, S.; Mannina, L.; Rossi, R. *Tetrahedron* **2001**, *57*, 9997–10007. (d) Boukouvalas, J.; Pouliot, M. *Synlett* **2005**, 343. (e) Bellina, F.; Anselmi, Ch.; Rossi, R. *Tetrahedron Lett.* **2002**, *43*, 2023–2027. (f) Bellina, F.; Anselmi, Ch.; Martina, F.; Rossi, R. *Eur. J. Org. Chem.* **2003**, 2290–2302.

(11) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.

(12) For recent synthetic applications of these synthons, see: (a) Schiller, R.; Pour, M.; Fáková, H.; Kuneš, J.; Císařová, I. *J. Org. Chem.* **2004**, *69*, 6761. (b) Reference 3a.

(13) Šnajdr, I.; Pavlík, J.; Schiller, R.; Kuneš, J.; Pour, M. *Collect. Czech. Chem. Commun.* **2007**, *72*, 1472.

(14) (a) Marshall, J.; Shearer, B.; Crooks, S. *J. Org. Chem.* **1987**, *52*, 1236. (b) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595. (c) Crousse, B.; Alami, M.; Linstrumelle, G. *Synlett* **1997**, 992.

The poor results led us to explore the alternative route whereby the iodo alcohols **5** and **6** were prepared by protecting the known (*Z*)-4-*tert*-butylsilyloxy-3-iodobut-2-en-1-ol[15] and (*E*)-3-iodobut-2-en-1,4-diol[16] as THP-ethers followed by coupling with methyl propiolate (path b) to afford the enyne esters **7** and **8** (Scheme 4).

SCHEME 4. Negishi Coupling of Iodides 5 and 6

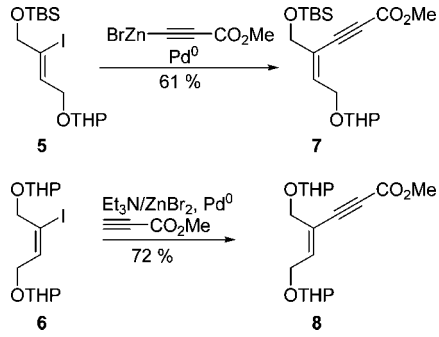


TABLE 1. Catalyst Screening for the Coupling of 5 and 6

SM	catalyst	product	yield (%)
5	5% $Pd(PPh_3)_4$	**7**	30
5	5% Pd_2dba_3, 20% (Biphenyl-2-yl)Cy_2P	**7**	35
5	**5% Pd_2dba_3, 20% TFP**	**7**	**61**
5	5% $(TFP)_2PdCl_2$	**7**	56
5	10% PEPPSI-iPr[a]	**7**	10
6	5% Pd_2dba_3, 20% Cy_3P	**8**	14
6	5% Pd_2dba_3, 20% (Biphenyl-2-yl)Cy_2P	**8**	20
6	5% Pd_2dba_3, 20% $(t\text{-Bu})_2CH_3P$	**8**	37
6	5% Pd_2dba_3, 20% dppf	**8**	16
6	5% Pd_2dba_3, 20% TFP	**8**	25
6	**10% (TFP) $_2PdCl_2$/20% BuLi**	**8**	**72**

[a] [1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)-palladium(II) dichloride.

Using Negishi's conditions A[17] for the coupling of electron-deficient alkynes [i.e., zincated methyl propiolate, $Pd(PPh_3)_4$] gave a low yield (30%) of **7**. Fortunately, subsequent catalyst screening (Table 1) revealed that switching the ligand to tris(2-furyl)phosphine[18] (TFP) led to a satisfactory isolated yield of 61%. The (*E*)-isomer **6** coupled much more reluctantly, since a mere 25% of **8** together with a substantial amount of methyl (*Z*)-3-diisopropylaminopropenoate (68%) were obtained when the same conditions were applied. Hence, the formation of the aminopropenoate was avoided by in situ generation of the coupling partner from $HCCCO_2Me$ with $ZnBr_2/Et_3N$ (referred to as Negishi's conditions B[17]) in the presence of the more reactive $Pd(TFP)_2$ catalyst. This species is produced[19] by the in situ reduction of $PdCl_2TFP_2$ with BuLi and secured a synthetically useful yield of **8** (72%). The higher reactivity of **5** compared to **6** is probably the result of chelation of the organopalladium intermediate by the OTHP group (**9**, Figure 2), which facilitated oxidative addition step. Similar chelation (**10**) has been recently shown[12a] to influence Pd-catalyzed carbonylative lactonization.

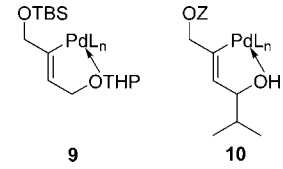
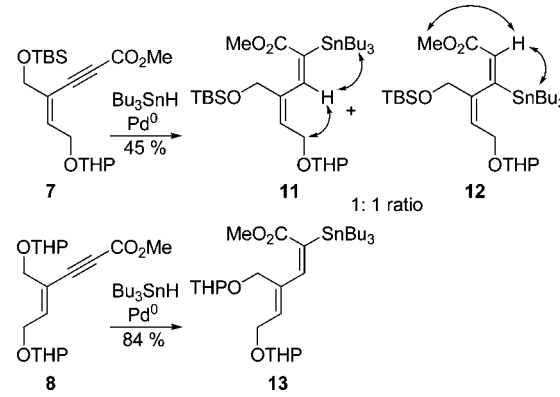


FIGURE 2. Structures of O to Pd chelates.

Pd-catalyzed hydrostannation[20,21] of enyne esters **7** and **8** was explored during the next stage of the scaffold synthesis (Scheme 5). In both cases, we expected the electronic effect of the ester group to steer the course of the addition.[22] Accordingly, ester **8** underwent a smooth stereo- and regioselective addition, while a somewhat surprising loss of regioselectivity was observed in the hydrostannation of **7**; the identity of both regioisomers **11** and **12** was established from NOE connectivities, as depicted in Scheme 5.

SCHEME 5. Pd-Catalyzed Hydrostannation of Enyne Esters 7 and 8



Even though chelation of the organopalladium intermediate might again be invoked to explain this result, Alami et al. have recently reported[23] that the regioselectivity of Pd-catalyzed hydrostannation of (*Z*)-enynols analogous to **7** is controlled by the geometry of the double bond (*Z*- or *syn*-directing effect) rather than the nature of the substituents. Hence, the formation of both regioisomers in the hydrostannation of **7** is more likely the result of the competition between the electronic effect of the ester group (favoring **11**) and the *syn*-directing effect arising from the geometry of the double bond (favoring **12**). Because **11** and **12** formed an inseparable mixture, the last step of the sequence was investigated with ester **13** as the starting material.

Although preliminary experiments have shown a good ability of ester **13** to cross-couple, subsequent hydrolysis/ring closure was surprisingly difficult. For example, **13** underwent smooth cross-coupling reactions with ethyl (*Z*)-3-iodoacrylate and methyl (*E*)-3-iodoacrylate[24] mediated by $Pd(PPh_3)_4$/CuI in DMF[25] to produce triene esters **14** (55%) and **15** (63%). The former did not cyclize under a variety of acidic conditions, while

(15) Pour, M.; Negishi, E.-i. *Tetrahedron Lett.* **1996**, *37*, 4679.
(16) Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc.* **2004**, *126*, 8569.
(17) Negishi, E.-i.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597.
(18) (a) Farina, V.; Baker, S. R.; Sapino, C., Jr. *Tetrahedron Lett.* **1991**, *32*, 4453. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (c) For a review on TFP as ligand for transition metal-mediated organic synthesis, see: Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997.
(19) Pour, M.; Negishi, E. *Tetrahedron Lett.* **1997**, *38*, 525.
(20) (a) Trost, B. M.; Chao, J.-L. *Synthesis* **1994**, 1267. (b) Alami, M.; Fabiola, F. *Synlett* **1996**, 755.
(21) For recent reviews on metal-catalyzed hydrostannations, see: (a) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257. (b) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853.
(22) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
(23) Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *J. Org. Chem.* **2007**, *72*, 3868.
(24) Cox, L. R.; DeBoos, G. A.; Fullbrook, J. J.; Percy, J. M.; Spencer, N. *Tetrahedron: Asymmetry* **2005**, *16*, 347.
(25) Bellina, F.; Carpita, A.; De Mantis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029.

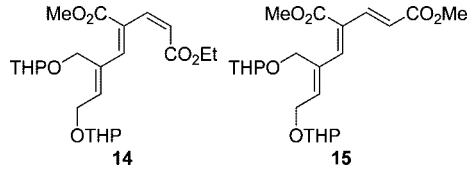
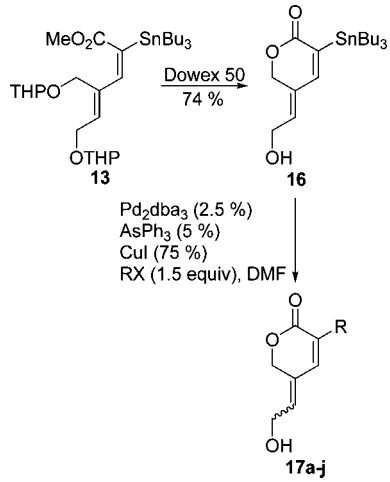


FIGURE 3. Structures of the coupling products of **13** with iodo acrylates.

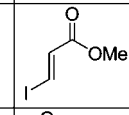
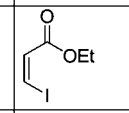
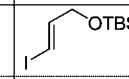
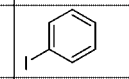
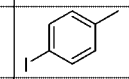
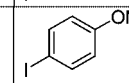
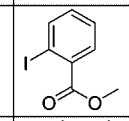
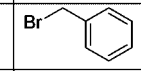
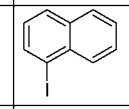
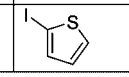
SCHEME 6. Preparation of the Target Alkylidene Pentenolides



the latter cyclized to the corresponding pentenolide (**17a**, vide infra) on Dowex 50 in a moderate yield of 45% (Figure 3).

For this reason, compound **13** was subjected to treatment with Dowex 50 to give 2-tributylstannyl pentenolide **16** in 74% yield (Scheme 6). Subsequent coupling reactions again confirmed that cycloalkenylstannanes in general, and especially those with the trialkylstannyl group in the α-position to a carbonyl, do not readily undergo Pd-catalyzed cross-coupling.[26] Even though Sweeney et al. were able[27] to effect cross-coupling of the analogous 2-tributylstannyl butenolides with aryl iodides using $PdCl_2(PPh_3)_2$ in boiling toluene, we had to resort[28] to a system composed of Pd_2dba_3/$AsPh_3$/CuI and NMP in order to cross-couple 5-ethyl-3-tributylstannyl-2,5-dihydrofuran-2-one with various heteroaryl iodides. Similarly, variation of the reaction conditions using methyl (*E*)-3-iodoacrylate[24] revealed that $Pd(PPh_3)_4$/CuI in DMF[25] successfully employed for the coupling of stannyl ester **13** (vide supra) led to a mere 10% yield of lactone **17a**, and replacement of the ligand on Pd with $AsPh_3$ was necessary to achieve reasonable isolated yields[29] of lactones **17** (Scheme 6, Table 2). In this context, the following observations should be mentioned. First, the conditions allowed the couplings to proceed at room temperature, which was important because of the sensitive nature of lactone **16**. This compound was stable at −18 °C, but suffered from limited stability at temperatures above 0 °C. Hence, the moderate to good isolated yields (33−55%) achieved in the cross-coupling step resulted from the limited stability of this coupling partner rather than from the reaction conditions having not been fully optimized. Second, since only *Z*-isomers were detected in the NMR spectra of the crude reaction mixtures, the *E*/*Z* isomerization reported for the phenyl- and thienyl-substituted final compounds **17** must have occurred during subsequent operations. The ease of isomerization clearly depends on the substitution in position 3 and is not unexpected, since the gelastatins were also isolated as an inseparable mixture of *E*/*Z* isomers. [5] Unfortunately, none of the catalysts and/or selected conditions including those reported by Fu[30] allowed coupling with methyl 3-iodopropenoate, and hence attachment of the saturated side chain of the gelastatins could not be achieved.

TABLE 2. Overview of the Target 2-Substituted 4-Alkylidene Pentenolides 17

Compound	R-X	t (h)	yield[a] (%)	*E*/*Z* ratio[b]
17a		8	42	*Z*
17b		8	45	*Z*
17c		8	51	*Z*
17d		12	55	1/2
17e		12	43	1/4
17f		12	38	1/2.5
17g		8	33	1/1.5
17h		8	52	*Z*
17i		12	47	*Z*
17j		8	55	1/1.5

[a] Isolated yields after two cycles of column chromatography. [b] Only (*Z*)-isomers were observed in the crude reaction mixtures.

All final compounds **17** were subjected to a preliminary screening against a panel of antineoplastic cell lines, including the mouse lymphocytic leukemia L1210 cells (ATCC CCL 219), CCRF-CEM T lymphoblastoid cells (human acute lymphoblastic leukemia, ATCC CCL 119), human promyelocytic leukemia HL-60 cells (ATCC CCL 240), and human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2). Interestingly, compounds **17a**,

(26) (a) Farina, V.; Baker, S. R.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, *29*, 6043. (b) Reference 18b. (c) Pour, M.; Negishi, E.-i. *Tetrahedron Lett.* **1996**, *37*, 4679. (d) Negishi, E.-i.; Pour, M.; Cederbaum, F. E.; Kotora, M. *Tetrahedron* **1998**, *54*, 7057.

(27) Hollingworth, G. J.; Perkins, G.; Sweeney, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, *16*, 1913.

(28) Kuneš, J.; Balšánek, V.; Pour, M.; Buchta, V. *Collect. Czech. Chem. Commun.* **2001**, *66*, 1809.

(29) (a) Because biological screening of the target compounds was planned, isolated yields after two rounds of column chromatography are reported. (b) Attempts to attach halogenated aryl moieties were also successful, but the corresponding (*E*/*Z*)-3-(halogenated aryl)-5-(2-hydroxyethylidene)-5,6-dihydro-2*H*-pyran-2-ones were unstable.

(30) (a) Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718. (b) Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 5079. (c) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 674.

17b, and **17d** displayed selective activity against the HeLa S3 and CCRF-CEM cells, with the most active compound **17a** having IC_{50} values of 3.50 ± 0.39 and 1.80 ± 0.07 μmol/L, respectively.

Conclusion

In summary, we have shown that a viable route to 2-substituted 4-alkylidene pentenolides analogous to the gelastatins and CR 377 leads to the assembly of a few suitably substituted building blocks, namely, a 2-iodo allylic alcohol, methyl propiolate, and an electrophile (RX). Notably, the preparation of α-alkenylated and arylated δ-lactones has been explored for the first time. The presence of OH groups both in the alkylidene moiety and the C3 substituent (**17c**) enables further modifications as well as attachment to the solid phase to facilitate the production of further series of analogues and combinatorial libraries. The preliminary screening results suggest that the synthesis of compound libraries based on the pentenolide scaffold should be a worthwhile endeavor.

Experimental Section

(*E*)-2-(2-Phenylethynyl)but-2-en-1-ol (3). $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and copper(I) iodide (19.5 mg, 0.1 mmol) were added to a solution of phenylacetylene (0.22 mL, 2 mmol) and iodide **2**[31] (198 mg, 1.0 mmol) in pyrrolidine (4.6 mL) under Ar atmosphere. The mixture was stirred at ambient temperature for 10 min, then diluted with ethyl acetate (20 mL) and washed with saturated aqueous NH_4Cl solution (20 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 8:2). Yield 93%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.38 (m, 2H, H2′, H6′), 7.30−7.25 (m, 3H′, H3′, H4′, H5′), 6.18−6.09 (m, 1H, CH), 4.26 (t, 2H, J = 0.8 Hz, OCH_2), 1.92 (bs, 1H, OH), 1.79 (d, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 131.5, 128.3, 128.1, 123.4, 123.1, 88.9, 88.6, 59.8, 14.0; IR ($CDCl_3$) ν_{max} 1443, 1490, 1597, 1682, 2250, 2873, 2925, 2958, 3604 cm^{-1}; LRMS *m*/*z* (relative intensity) 173.2 $[M + H]^+$ (100), 161.0 (8), 151.3 (51), 135.3 (8), 123.4 (42), 119.5 (12), 107.4 (8), 87.3 (5); HRMS $[M + H]^+$ calcd for $C_{12}H_{13}O$, 173.0966, found 173.0968.

(*E*)-Methyl 4-(*tert*-Butyldimethylsilyloxymethyl)-6-(tetrahydropyran-2-yloxy)hex-4-en-2-ynoate (7). Solution A: Zinc bromide (2.79 g, 12.38 mmol) was melted under high vacuum, then allowed to cool down to room temperature under Ar atmosphere and dissolved in dry THF (9.1 mL). **Solution B:** A solution of 1.5 M LDA (7.88 mL, 11.38 mmol) was added to a stirred solution of methyl propiolate (1.067 mL, 11.90 mmol) in dry THF (9.1 mL) under Ar atmosphere at −78 °C. The resultant mixture was stirred for 30 min, solution **A** was added via cannula at −78 °C, and the mixture was gradually warmed to room temperature over 1 h. $Pd_2(dba)_3$ (124.2 mg, 0.12 mmol), tris(2-furyl)phosphine (111.5 mg, 0.48 mmol), and iodide **5** (1.0 g, 2.42 mmol) were subsequently added, and the reaction mixture was stirred for another 12 h. The mixture was diluted with ethyl acetate (50 mL) and washed with a saturated aqueous NH_4Cl solution (50 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 9:1). Yield 61%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48−6.39 (m, 1H, CH), 4.68−4.61 (m, 1H, OCH), 4.52−4.41 (m, 1H, OCH_2), 4.38−4.28 (m, 1H, OCH_2), 4.22−4.16 (m, 2H, OCH_2), 3.92−3.82 (m, 1H, OCH_2), 3.78 (s, 3H, OCH_3), 3.57−3.47 (m, 1H, OCH_2), 1.89−1.45 (m, 6H, CH_2), 0.9 (s, 9H, CH_3), 0.07 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 138.6, 122.2, 98.5, 86.1, 81.9, 65.2, 64.2, 62.2, 52.7, 30.5, 25.8, 25.4, 19.4, 18.3, −5.4; IR ($CDCl_3$) ν_{max} 1436, 1463, 1471, 1711, 2212 2247, 2857, 2930, 2954 cm^{-1}; LRMS *m*/*z* (relative intensity) 369.1 $[M + H]^+$ (22), 337.4 (5), 285.2 (12), 249.2 (37), 203.4 (8), 177.0 (100), 153.4 (4); HRMS $[M + H]^+$ calcd for $C_{19}H_{33}O_5Si$, 369.2097, found 369.2089.

(*Z*)-Methyl 6-(Tetrahydropyran-2-yloxy)-4-[(tetrahydropyran-2-yloxy)methyl]hex-4-en-2-ynoate (8). Solution A: Zinc bromide (3.29 g, 14.6 mmol) was melted under high vacuum, then allowed to cool down to room temperature under Ar atmosphere and dissolved in dry THF (26 mL). Triethylamine (8.22 mL, 59.0 mmol) was then added, with the reaction mixture having turned red after stirring for 1−3 min at ambient temperature. **Solution B:** $(TFP_3)_2PdCl_2$ (418.4 mg, 0.65 mol) was suspended in dry THF (5 mL) under Ar atmosphere, and the mixture cooled down to −78 °C. A solution of 2.5 M BuLi (0.52 mL, 1.30 mmol) was added, and the mixture was allowed to gradually warm to −30 °C over 30 min. Iodide **6** (2.49 mg, 6.52 mmol) was then added, the reaction mixture was warmed to 0 °C, and freshly prepared solution **A** (via cannula) and methyl propiolate (1.1 mL, 12.3 mmol) were added. After 4 h of stirring at room temperature, the reaction mixture was diluted with ethyl acetate (50 mL), and washed with saturated aqueous NH_4Cl solution (50 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 9:1). Yield 72%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49−6.43 (m, 1H, CH), 4.67−4.63 (m, 1H, OCH), 4.63−4.58 (m, 1H, OCH), 4.43−4.32 (m, 1H, OCH_2), 4.29−4.09 (m, 3H, OCH_2), 3.89−3.74 (m, 2H, OCH_2), 3.76 (s overlapped, 3H, OCH_3), 3.55−3.45 (m, 2H, OCH_2), 1.88−1.45 (m, 12H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 144.1, 119.2, 98.1, 97.5, 86.4, 79.4, 63.2, 63.0, 62.1, 61.9, 52.6, 30.4, 30.2, 25.3, 25.3, 19.1, 18.9; IR ($CDCl_3$) ν_{max} 1436, 1454, 1709, 2215, 2248, 2853, 2874, 2948 cm^{-1}; LRMS *m*/*z* (relative intensity) 339.2 $[M + H]^+$ (2), 305.2 (14), 271.3 (7), 249.2 (63), 219.2 (4), 205.3 (8), 177.0 (100), 169.4 (7), 130.1 (6); HRMS $[M + H]^+$ calcd for $C_{18}H_{27}O_6$, 339.1808, found 339.1814.

(2*E*,4*E*)-Methyl 2-(Tributylstannyl)-4-(*tert*-butyldimethylsilyloxymethyl)-6-(tetrahydropyran-2-yloxy)hexa-2,4-dienoate (11) and (2*E*,4*E*)-Methyl 3-(Tributylstannyl)-4-(*tert*-butyldimethylsilyloxymethyl)-6-(tetrahydropyran-2-yloxy)hexa-2,4-dienoate (12). To a solution of **7** (228 mg, 0.62 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) in dry THF (3.5 mL) under Ar atmosphere was slowly added tributyltinhydride (0.165 mL, 0.62 mmol). After 5 min of stirring, the reaction mixture was diluted with ethyl acetate (10 mL) and washed with brine (10 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 95:5). Yield 45% (mixture of **11** + **12**, 1:1); yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 1H, CH, A), 5.98 (s, 1H, CH, B), 5.81−5.73 (m, 1H, CH, A), 5.49−5.39 (m, 1H, CH, B), 4.61−4.53 (m, 1H, OCH, A+B), 4.26−4.01 (m, 2H, OCH_2, A+B), 4.18 (s overlapped, 2H, OCH_2, A+B), 3.88−3.73 (m, 1H, OCH_2, A+B), 3.62 (s, 3H, OCH_3, A+B), 3.50−3.37 (m, 1H, OCH_2, A+B), 1.86−1.40 (m, 12H, CH_2, A+B), 1.38−1.21 (m, 6H, CH_2, A+B), 1.03−0.93 (m, 6H, CH_2, A+B), 0.92−0.81 (m, 12H, CH_3, A+B), 0.05 (s, 6H, CH_3, A), 0.04 (s, 6H, CH_3, B); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 167.1, 163.8, 145.0, 141.1, 140.9, 140.4, 129.3, 123.8, 114.3, 97.9, 97.8, 64.6, 64.6, 64.3, 63.6, 62.1, 61.9, 51.3, 51.0, 30.6, 28.9, 28.8, 28.8, 28.7, 27.3, 27.2, 26.0, 25.9, 25.5, 25.5, 19.5, 18.5, 18.3, 13.6, 13.6, 10.5, 10.4, −5.4 (A+B); IR ($CDCl_3$) ν_{max} 1434, 1464, 1588, 1701, 1719, 2246, 2258, 2855, 2872, 2930, 2956 cm^{-1}; LRMS *m*/*z* (relative intensity) 659.3 $[M + H]^+$ (1), 599.3 (100), 581.3 (9), 551.3 (1), 427.3 (1), 415.3 (4), 291.2 (3), 235.1 (1), 177.1 (15), 89.3 (6). Anal. Calcd for $C_{31}H_{60}O_5SiSn$: C, 56.45; H, 9.17. Found: C, 56.50; H, 9.26

(2*E*,4*Z*)-Methyl 2-(Tributylstannyl)-6-(tetrahydropyran-2-yloxy)-4-[(tetrahydropyran-2-yloxy)methyl]hexa-2,4-dienoate (13). Tributyltinhydride (1.27 mL, 4.72 mmol) was slowly added under Ar

(31) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404.

atmosphere to a solution of **8** (1.59 g, 4.72 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in dry THF (24.1 mL). After 5 min of stirring at room temperature, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with brine (30 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 92:8). Yield 84%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (t, 1H, $J_{H,Sn}$ = 30.2 Hz, CH), 5.87 (t, 1H, J = 6.5 Hz, CH), 4.63 (s, 1H, OCH), 4.55 (s, 1H, OCH), 4.43−4.13 (m, 4H, OCH_2), 3.91−3.77 (m, 2H, OCH_2), 3.67 (s, 3H, OCH_3), 3.55−3.44 (m, 2H, OCH_2), 1.88−1.44 (m, 18H, CH_2) 1.37−1.23 (m, 6H, CH_2), 1.02−0.94 (m, 6H, CH_2), 0.88(t, 9H, J = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 143.4, 138.4, 137.1, 133.2, 98.0, 97.0, 63.3, 62.5, 62.0, 51.2, 30.6, 30.3, 28.7, 28.6, 27.2, 25.4, 25.4, 19.4, 19.3, 13.6, 10.5; IR (KBr pellet) ν_{max} 1261, 1341, 1456, 1582, 1706, 2851, 2870, 2924 cm^{-1}; LRMS *m*/*z* (relative intensity) 629.3 $[M + H]^+$ (6), 540.7 (7), 458.5 (16), 431.2 (31), 373.3 (100), 307.4 (24), 177.1 (8), 89.4 (16). Anal. Calcd for $C_{30}H_{54}O_6Sn$: C, 57.24; H, 8.65. Found: C, 57.31; H, 8.66.

(5*Z*)-3-(Tributylstannyl)-5-(2-hydroxyethylidene)-5,6-dihydro-2*H*-pyran-2-one (16). Compound **13** (630 mg, 1.0 mmol) was dissolved in methanol (5 mL), and Dowex 50 (0.6 g) was added to the solution. The resultant mixture was stirred for 2 h at room temperature, and the acidic resin filtered off. The solvent was removed under reduced pressure, the residue was diluted with ethyl acetate (20 mL), and the solution washed with brine (20 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 8:2). Yield 74%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (t, 1H, $J_{H,Sn}$ = 22.0 and 19.5 Hz, CH), 5.89−5.80 (m, 1H, CH), 5.07 (s, 2H, OCH_2), 4.27 (t, 2H, J = 5.8 Hz, OCH_2), 1.56−1.43 (m, 6H, CH_2), 1.39−1.22 (m, 6H, CH_2), 1.14−0.97 (m, 6H, CH_2), 0.88 (t, 9H, J = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 153.7, 136.9, 132.0, 129.6, 66.5, 58.9, 29.2, 27.5, 13.9, 10.2; IR ($CDCl_3$) ν_{max} 1456, 1464, 1569, 1682, 1698, 2252, 2854, 2872, 2826, 2958 cm^{-1}; LRMS *m*/*z* (relative intensity) 429.5 $[M + H]^+$ (32), 332.7 (53), 304.7 (100), 262.6 (7), 238.5 (8), 216.6 (4), 186.6 (8), 118.5 (25), 102.6 (43). Anal. Calcd for $C_{19}H_{34}O_3Sn$: C, 53.17; H, 7.98. Found: C, 53.18; H, 8.01.

General Procedure for Preparation of Compounds 17a−17j. Triphenylarsine (7.4 mg, 0.025 mmol), $Pd_2(dba)_3$ (12.9 mg, 0.0125 mmol) and copper(I) iodide (72.4 mg, 0.38 mmol) were added to a solution of **16** (214.6 mg, 0.50 mmol) and appropriate halogenide (0.75 mmol) in dry DMF (2 mL) under Ar atmosphere. The reaction mixture was stirred for 8−12 h at room temperature, then diluted with ethyl acetate (20 mL), and washed with brine (20 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography.

(2*E*)-Methyl 3-[(*Z*)-5-(2-Hydroxyethylidene)-2-oxo-5,6-dihydro-2*H*-pyran-3-yl]acrylate (17a). Reaction details: halogenide = (*E*)-methyl 3-iodoacrylate, time = 8 h, mobile phase = petroleum ether/ethyl acetate 1:1. Yield 42%; white crystals, mp 84.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, 1H, J = 15.9 Hz, CH), 7.17 (s, 1H, CH), 6.79 (d, 1H, J = 15.9 Hz, CH), 6.17−6.08 (m, 1H, CH), 5.17−5.11 (m, 2H, OCH_2), 4.44−4.31 (m, 2H, OCH_2), 3.77 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 161.9, 144.4, 138.2, 137.2, 129.3, 123.8, 122.7, 66.0, 59.1, 51.8; IR (KBr pellet) ν_{max} 1201, 1363, 1436, 1457, 1653, 1718, 1733, 2341, 2359 cm^{-1}; LRMS *m*/*z* (relative intensity) 225.1 $[M + H]^+$ (16), 207.2 (12), 197.1 (3), 181.3 (4), 175.2 (2), 165.2 (100), 147.3 (4), 135.2 (2), 119.4 (1). Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.84; H, 5.31.

(2*Z*)-Ethyl 3-[(*Z*)-5-(2-Hydroxyethylidene)-2-oxo-5,6-dihydro-2*H*-pyran-3-yl]acrylate (17b). Reaction details: halogenide = (*Z*)-ethyl 3-iodoacrylate, time = 8 h, mobile phase = petroleum ether/ethyl acetate 1:1. Yield 45%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1H, CH), 6.83 (d, 1H, J = 12.6 Hz, CH), 6.11−6.04 (m, 1H, CH), 6.00 (d, 1H, J = 12.6 Hz, CH), 5.14 (d, 2H, J = 1.8 Hz, OCH_2), 4.36−4.28 (m, 2H, OCH_2), 4.15 (q, 2H, J = 7.2 Hz, OCH_2), 1.26 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 163.1, 144.5, 136.8, 136.3, 128.9, 123.4, 122.8, 66.1, 60.1, 58.9, 14.1; IR ($CDCl_3$) ν_{max} 1177, 1369, 1389, 1450, 1459, 1655, 1710, 1719, 2875, 2925, 3401 cm^{-1}; LRMS *m*/*z* (relative intensity) 239.3 $[M + H]^+$ (7), 221.2 (10), 211.2 (23), 193.2 (8), 165.2 (100), 147.3 (3), 135.3 (2), 119.3 (1); HRMS $[M + H]^+$ calcd for $C_{12}H_{15}O_5$, 239.0919, found 239.0916.

(5*Z*)-3-[(*E*)-3-(*tert*-Butyldimethylsilyloxy)prop-1-enyl]-5-(2-hydroxyethylidene)-5,6-dihydro-2*H*-pyran-2-one (17c). Reaction details: halogenide = (*E*)-3-(*tert*-butyldimethylsilyloxy)-1-iodoprop-1-ene, time = 8 h, mobile phase = petroleum ether/ethyl acetate 1:1. Yield 51%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48−6.29 (m, 2H, CH), 6.19 (t, 1H, J = 6.3 Hz, CH), 5.97 (s, 1H, CH), 4.99 (s, 2H, OCH_2), 4.42−4.26 (m, 4H, OCH_2), 0.93 (s, 9H, CH_3), 0.098 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 150.9, 139.1, 132.6, 129.2, 122.4, 113.5, 65.9, 62.9, 58.8, 25.9, 18.4, −5.3; IR (KBr pellet) ν_{max} 1126, 1253, 1378, 1406, 1462, 1701, 2855, 2928, 2953, 3400 cm^{-1}; LRMS *m*/*z* (relative intensity) 311.4 $[M + H]^+$ (15), 247.4 (1), 211.4 (2), 179.4 (17), 161.4 (3), 133.4 (4), 102.6 (100), 74.6 (4); HRMS $[M + H]^+$ calcd for $C_{16}H_{27}O_4Si$, 311.1679, found 311.1691.

5-(2-Hydroxyethylidene)-3-phenyl-5,6-dihydro-2*H*-pyran-2-one (17d). Reaction details: halogenide = iodobenzene, time = 12 h, mobile phase = petroleum ether/ethyl acetate 1:1. Yield 55%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.45 (m, 2H, H2′, H6′A+B), 7.45−7.30 (m, 4H, H3′, H4′, H5′, A+B, CH, A), 7.07 (s, 1H, CH, B), 6.04−5.88 (m, 1H, CH, A+B), 5.18−5.09 (m, 2H, OCH_2, A), 4.93−4.90 (m, 2H, OCH_2, B), 4.40−4.23 (m, 2H, OCH_2, A), 4.28 (d, 2H, J = 6.3 Hz, OCH_2, B), 2.94 (bs, 1H, OH, A+B); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 163.6, 156.0,141.3, 136.8, 135.1, 134.9, 134.5, 132.2, 130.0, 129.2, 128.8, 128.7, 128.7, 128.5, 128.5, 128.3, 128.2, 70.8, 66.4, 58.5, 58.2 (A+B); IR ($CDCl_3$) ν_{max} 1152, 1401, 1446, 1693, 2885, 2924, 3025, 3401 cm^{-1}; LRMS *m*/*z* (relative intensity) 217.2 $[M + H]^+$ (19), 199.2 (42), 181.2 (9), 171.2 (100), 155.2 (15), 128.3 (10), 115.3 (2), 105.4 (1). Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.36; H, 5.67.

5-(2-Hydroxyethylidene)-3-(4-methylphenyl)-5,6-dihydro-2*H*-pyran-2-one (17e). Reaction details: halogenide = 4-iodotoluene, time = 12 h, mobile phase = petroleum ether/ethyl acetate 1:1. Yield 43%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.43 (m, 2H, AA′BB′, H2′, H6′,A), 7.43−7.37 (m, 2H, AA′BB′, H2′, H6′, B), 7.27−7.21 (m.2H, AA′BB′, H3′, H5′, A), 7.23 (s, 1H, CH, A), 7.21−7.14 (m.2H, AA′BB′, H3′, H5′, B), 7.04 (s, 1H, CH, B), 6.06 −5.85 (m, 1H, CH, A+B), 5.18−5.05 (m, 2H, OCH_2, A), 4.94−4.90 (m, 2H, OCH_2, B), 4.42−4.31 (m, 2H, OCH_2, A), 4.31−4.23 (m, 2H, OCH_2, B), 2.61 (bs, 1H, OH, A), 2.49 (bs, 1H, OH, B), 2.39 (s, 3H, CH_3, B), 2.36 (s, 3H, CH_3, A); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 163.6, 156.0, 140.6, 138.8, 138.6, 136.7, 134.3, 134.0, 132.0, 131.7, 129.4, 129.3, 128.9, 128.9, 128.4, 128.3, 115.0, 70.8, 66.4, 58.6, 58.2, 21.3, 21.2 (A+B); IR ($CDCl_3$) ν_{max} 1160, 1215, 1400, 1456, 1512, 1702, 2875, 2929, 3020, 3400 cm^{-1}; LRMS *m*/*z* (relative intensity) 231.2 $[M + H]^+$ (14), 213.2 (44), 203.2 (17), 195.2 (8), 185.2 (100), 167.2 (6), 157.3 (40), 142.3 (9), 129.3 (3), 119.3 (1). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.12; H, 6.15.

5-(2-Hydroxyethylidene)-3-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran-2-one (17f). Reaction details: halogenide = 4-iodoanisole, time = 12 h, mobile phase = petroleum ether/ethyl acetate 1:1. Yield 38%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.43 (m, 3H, AA′BB′, H2′, H6′, A, CH, A), 7.33−7.25 (m, 2H, AA′BB′, H2′, H6′, B), 7.01 (s, 1H, CH, B), 6.94−6.85 (m, 2H, AA′BB′, H3′, H5′, A+B), 6.09−5.84 (m, 1H, CH, A+B), 5.14 (s, 2H, OCH_2, A), 4.90 (s, 2H, OCH_2, B), 4.41−4.21 (m, 2H, OCH_2, A+B), 3.82 (s, 3H, OCH_3, B), 3.80 (s, 3H, OCH_3, A); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 163.9, 161.5, 160.2, 155.8, 140.0, 136.8, 133.7, 133.6, 131.4, 130.7, 130.2, 130.1, 129.9, 114.7, 114.5, 114.0, 113.9, 71.1, 66.7, 66.4, 58.9, 58.5, 55.7 (A+B); IR ($CDCl_3$) ν_{max} 1150,

1178, 1246, 1289, 1401, 1457, 1510, 1604, 1697, 2928, 2955, 3401 cm^{-1}; LRMS *m/z* (relative intensity) 247.3 $[M + H]^+$ (15), 229.2 (29), 219.2 (31), 201.3 (100), 189.2 (4), 173.3 (16), 158.3 (8), 147.3 (1), 123.3 (29). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.09; H, 5.67.

Methyl 2-[5-(2-Hydroxyethylidene)-2-oxo-5,6-dihydro-2*H*-pyran-3-yl]benzoate (17g). Reaction details: halogenide = methyl-2-iodobenzoate, time = 8 h, mobile phase = petroleum ether/ethyl acetate 1:1. Yield 33%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03−7.96 (m, 1H, CH, A+B), 7.60−7.40 (m, 2H, CH, A+B), 7.34−7.27 (m, 2H, CH, A+B, CH, A), 6.91 (s, 1H, CH, B), 6.00−5.84 (m, 1H, CH, A+B), 5.21 (s, 2H, OCH_2, A), 5.00 (s, 2H, OCH_2, B), 4.36 (d, 2H, J = 6.4 Hz, OCH_2, B), 4.28 (d, 2H, J = 6.4 Hz, OCH_2, A), 3.83 (s, 3H, OCH_3, A+B), 2.37 (bs, 1H, OH, A+B); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 167.2, 164.1, 163.7, 138.9, 137.2, 136.7, 134.0, 133.7, 132.5, 132.4, 132.1, 131.4, 130.7, 130.3, 130.4, 130.1, 130.0, 129.9, 129.4, 129.1, 128.7, 128.6, 128.3,66.5, 66.4, 58.6, 58.3, 52.3, 52.2 (A+B); IR (KBr pellet) ν_{max} 1263, 1284, 1401, 1434, 1450, 1596, 1702, 1708, 2853, 2923, 2952, 3401 cm^{-1}; LRMS *m/z* (relative intensity) 275.2 $[M + H]^+$ (16), 257.2 (36), 247.1 (100), 231.1 (66), 219.2 (29), 211.2 (21), 203.2 (23), 197.2 (9), 183.2 (13), 175.3 (8), 173.2 (2), 157.4 (1). Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.81; H, 5.21.

(5*Z*)-3-Benzyl-5-(2-hydroxyethylidene)-5,6-dihydro-2*H*-pyran-2-one (17h). Reaction details: halogenide = benzylbromide, time = 8 h, mobile phase = petroleum ether/ethyl acetate 1:1. Yield 52%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.16 (m, 5H, CH), 6.55 (s, 1H, CH), 5.76 (t, 1H, J = 6.3 Hz, CH), 5.05 (s, 2H, OCH_2), 4.20 (d, 2H, J = 6.3 Hz, OCH_2), 3.65 (s, 2H, CH_2), 2.34 (bs,1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 140.8, 137.9, 132.6, 130.0, 129.2, 129.1, 128.6, 126.7, 66.4, 58.4, 36.5; IR (KBr pellet) ν_{max} 1196, 1249, 1405, 1453, 1494, 1691, 2872, 2920, 3027, 3401 cm^{-1}; LRMS *m/z* (relative intensity) 231.2 $[M + H]^+$ (9), 216.3 (100), 203.4 (30), 171.2 (6), 162.3 (24), 153.3 (32), 109.5 (4). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.22; H, 6.19.

(5*Z*)-5-(2-Hydroxyethylidene)-3-(naphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (17i). Reaction details: halogenide = 1-iodonaphthalene, time = 12 h, mobile phase = petroleum ether/ethyl acetate 1:1. Yield 47%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.80 (m, 2H, CH), 7.78−7.71 (m, 1H, CH), 7.50−7.34 (m, 4H, CH), 7.00 (s, 1H, CH), 5.93−5.84 (m, 1H, CH), 5.26−5.23 (m, 2H, OCH_2), 4.18 (d, 2H, J = 6.3 Hz, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 144.6, 135.3, 133.5, 133.0, 131.9, 129.4, 129.3, 128.7, 128.3, 127.8, 127.4, 126.6, 126.4, 125.4, 67.1, 58.8; IR (KBr pellet) ν_{max} 1154, 1189, 1247, 1402, 1453, 1508, 1693, 2855, 2923, 2954, 3055, 3400 cm^{-1}; LRMS *m/z* (relative intensity) 267.2 $[M + H]^+$ (2), 249.2 (100), 239.2 (24), 231.2 (14), 221.2 (74), 205.2 (17), 193.3 (23), 181.3 (11), 165.2 (2), 139.3 (2), 121.4 (1); HRMS $[M + H]^+$ calcd for $C_{17}H_{15}O_3$, 267.1021, found 267.1029.

5-(2-Hydroxyethylidene)-3-(thiophen-2-yl)-5,6-dihydro-2*H*-pyran-2-one (17j). Reaction details: halogenide = 2-iodothiophene, time = 8 h, mobile phase = petroleum ether/ethyl acetate 1:1. Yield 55%; yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (m, 1H, CH, A), 7.60−7.52 (m, 1H, CH, A+B), 7.40−7.33 (m, 1H, CH, A+B), 7.24 (s, 1H, CH, B), 7.07−7.02 (m, 1H, CH, A+B), 6.10−5.99 (m, 1H, CH, A), 5.96−5.88 (m, 1H, CH, B), 5.17−5.13 (m, 2H, OCH_2, A), 4.93−4.89 (m, 2H, OCH_2, B), 4.44 (bs, 2H, OCH_2, B), 4.32 (bs, 2H, OCH_2, A), 2.16 (bs, 1H, OH, A), 2.11 (bs, 1H, OH, B); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 162.7, 136.9, 136.7, 134.0, 131.8, 130.6, 129.7, 129.2, 128.4, 128.3, 127.8, 127.3, 127.3, 126.9, 124.3, 122.8, 122.2, 66.2, 66.2, 58.8, 58.5 (A+B); IR (KBr pellet) ν_{max} 1223, 1250, 1337, 1360, 1422, 1458, 1653, 1708, 2854, 2926, 2952 cm^{-1}; LRMS *m/z* (relative intensity) 223.3 $[M + H]^+$ (4), 205.2 (85), 191.2 (8), 177.3 (100), 163.2 (4), 149.3 (19), 135.3 (1), 111.4 (3), 97.6 (1); HRMS $[M + H]^+$ calcd for $C_{11}H_{11}O_3S$, 223.0429, found 223.0426.

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Supporting Information Available: General experimental section, copies of ^{1}H NMR spectra for compounds **3**, **7**, **8**, **13**, **16**, **17a**−**j** and copies of ^{13}C NMR spectra for compounds **17a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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