A New, Highly Stereoselective Synthesis of β-Unsubstituted (*Z*)-γ-Alkylidenebutenolides Using Bromine as a Removable Stereocontrol Element

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Abstract: Several β-unsubstituted (*Z*)-γ-alkylidenebutenolides have been prepared in highly stereocontrolled fashion by implementing a steric directing group stratagem in the vinylogous aldol condensation of butenolides with aldehydes. Applications to the synthesis of the antitumor heptene (*S*)-melodorinol and a thiophenelactone from *Chamaemelum nobile* L. are described.

Key words: aldol reaction, bromobutenolides, dehalogenation, 2-silyloxyfurans, stereoselectivity

The stereoselective construction of γ-alkylidenebutenolides continues to stand as an important objective in synthetic organic chemistry due to the diverse structures and biological activities of many members of this class.[1,2] Most naturally occurring γ-alkylidenebutenolides have the *Z*-configuration, and many of them lack a β-substituent, as represented by eremolactone (**1**),[1a] the antitumor heptene (*S*)-melodorinol (**2**),[3] and the noncytotoxic cholesterol biosynthesis inhibitor xerulin[4] (**3**; Figure 1).

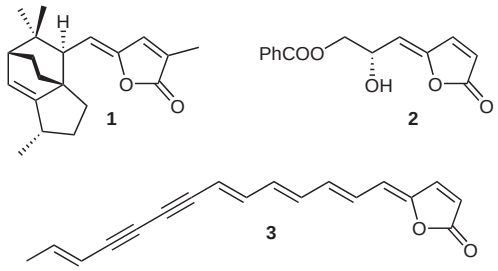
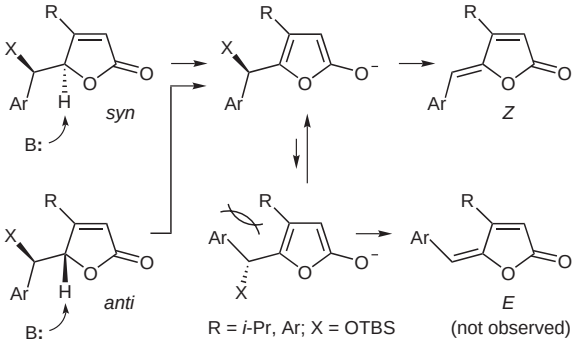


Figure 1

Although the *Z*-isomers are generally more stable than their *E*-counterparts, in the absence of a β-substituent the preference for formation of the *Z*-isomer is usually small.[1] As a consequence, traditional synthetic approaches involving alkylidenation of preformed oxacycles, such as butenolides and 2-silyloxyfurans, are notoriously nonstereoselective.[1a,5,6] Useful solutions to this problem include the inherently stereospecific *anti*-elimination of diastereomerically pure *syn*-γ-(α-hydroxyalkyl)butenolides,[1b,2c] the metallocyclization–protolysis of (*Z*)-2-en-4-ynoic acids,[1a,d] and the Stille coupling of (*Z*)-halomethylidenebutenolides with organotin reagents.[7] While these methods offer stereochemical predictability and high levels of selectivity, they all require access to stereodefined precursors that may involve several steps and/or the separation of diastereoisomers.[1b,8]



Scheme 1

In the course of our work on the total synthesis of nostoclides and rubrolides,[9] we found that mixtures of *syn*- and *anti*-γ-(α-silyloxyalkyl)butenolides bearing a β-isopropyl or aryl substituent readily undergo β-elimination in the presence of DBU to afford solely (*Z*)-γ-alkylidenebutenolides. The consistently high stereoselectivity seen in these reactions[9,10] can best be explained by an E1cb mechanism[9a] whereby the formation of the *Z*-isomer is favored due to the steric bias provided by the β-substituent (Scheme 1).[11] We now report an extension of the mechanistic principle to the synthesis of β-unsubstituted (*Z*)-γ-alkylidenebutenolides by using bromine as a removable steric directing group.[12]

The serviceability of this strategy was initially demonstrated by the preparation of benzylidenebutenolide **7a** from silyloxyfuran **4**[13] (Scheme 2). In accord with a general trend,[9a,14] the TBSOTf-mediated Mukaiyama aldol reaction of **4** with benzaldehyde delivered a 3.3:1 mixture of the *syn*- and *anti*-bromobutenolides **5** in 91% yield.[15] Treatment of this mixture with DBU in dichloromethane provided (*Z*)-ylidenebutenolide **6a** as the only detectable isomer in 94% yield after chromatography. Smooth debromination to **7a** was achieved by either Pd(0)-catalyzed reduction with tri-*n*-butyltin hydride (Bu_3SnH)[16] or Brückner's procedure (Zn, AcOH–THF, sonication).[7a] While the former method gave the highest yield (97%), the latter was cleaner making product purification easier.

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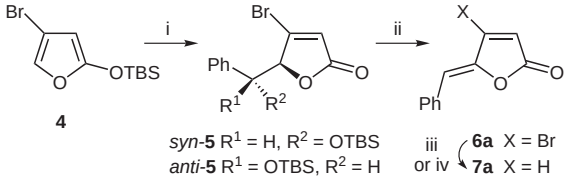
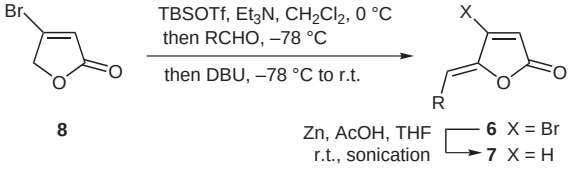


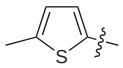
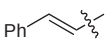
Scheme 2 *Reagents and conditions*: (i) PhCHO (1 equiv), TBSOTf (1.1 equiv), CH_2Cl_2, –78 °C, 2 h, 91%; (ii) DBU (2 equiv), CH_2Cl_2, r.t., 1 h, 94%; (iii) Bu_3SnH (1.4 equiv), $(Ph_3P)_4Pd$ (0.02 equiv), CH_2Cl_2, r.t., 1 h, 97%; (iv) Zn dust, AcOH, THF, r.t., sonication, 45 min, 85–88%.

The promise of this approach was further manifested by the direct alkylidenation of β-bromobutenolide **8** using a new variant of the one-pot procedure that we had previously developed for condensing β-arylbutenolides with aromatic aldehydes.[9b] Thus, sequential treatment of **8** with TBSOTf–triethylamine, the appropriate aldehyde and DBU,[17] delivered the corresponding γ-alkylidene-β-bromobutenolides **6** with excellent stereocontrol (Table 1). Attempts to condense the parent, non-brominated α,β-butenolide with benzaldehyde or *p*-anisaldehyde under the same conditions led to complex mixtures containing little, if any, of the desired product (**7a**: 0%; **7b**: ca. 5–10%). These results suggest that in addition to performing the intended steric directing role, the β-bromine also provides a strong accelerating effect to the condensation process.

Using this protocol, lactone **7c**, a constituent of *Chamaemelum nobile* L. and popular target for testing new methodology,[18] was prepared from 5-methylthiophene-2-carboxaldehyde in 76% yield over two steps (Table 1). Likewise, (*E*)-cinnamaldehyde was easily converted into **7d**,[19] which has only recently been prepared stereoselectively by Stille coupling.[7a]

Table 1 Stereocontrolled Access to (*Z*)-γ-Alkylidenebutenolides from β-Bromo-α,β-butenolide (**8**)

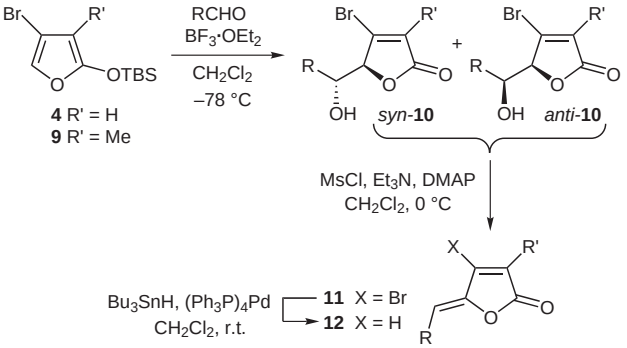


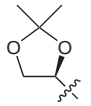
R	Yield (%)[a,b] of **6**	Yield (%)[a] of **7**
Ph	68[c] (**6a**)	86[d] (**7a**)
p-MeOPh	85 (**6b**)	87 (**7b**)
	83 (**6c**)	91 (**7c**)
	70 (**6d**)	77[d] (**7d**)

[a] Yields refer to chromatographically purified products.
[b] The *Z*/*E* ratio was over 40:1 according to ^{1}H NMR.
[c] A second portion of TBSOTf (1.1 equiv) was added after the aldehyde.
[d] Data from ref. 7a.

In contrast to aromatic aldehydes, simple alkanals did not undergo condensation with **8** under these conditions. Their conversion to (*Z*)-alkylidenebutenolides could be achieved with little additional effort through Mukaiyama aldol reaction with silyloxyfuran **4**[13] or **9**[20] (Table 2). Dehydration of the so obtained mixtures of *syn*- and *anti*-alcohols **10**[15] with mesyl chloride in the presence of triethylamine–DMAP (0 °C) or pyridine (r.t.) furnished **11** (*Z*:*E* > 40:1) in good to excellent yields.[21]

Table 2 Preparation of (*Z*)-γ-Alkylidenebutenolides from 4-Bromo-2-(*tert*-butyldimethylsilyloxy)furans

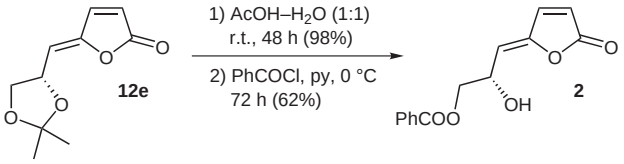


R	R′	Yield (%)[a] of **10** (*syn*:*anti*)	Yield (%)[a,b] of **11**	Yield (%)[a,b] of **12**
$Me(CH_2)_3$	H	91 (**10a**; 5.0:1)	98 (**11a**)	96 (**12a**)
$Me(CH_2)_3$	Me	87 (**10b**; 5.2:1)	91 (**11b**)	97 (**12b**)
$Ph(CH_2)_2$	H	82 (**10c**; 5.5:1)	99 (**11c**)	89 (**12c**)
$PhCH_2$	H	75 (**10d**; 4.2:1)	76[d] (**11d**)	77 (**12d**)
	H	–[c]	65[d] (**11e**)	93 (**12e**)

[a] Yields refer to chromatographically purified products. Aldols **10a**–**d** were obtained as diastereomeric mixtures after chromatography on silica gel.
[b] The *Z*/*E* ratio was over 40:1 according to ^{1}H NMR.
[c] Not determined; see text.
[d] Dehydration was carried out using MsCl in pyridine at r.t.

The crude diastereomeric aldol products can be carried forward without chromatographic purification, as illustrated by the entirely stereoselective conversion of (*R*)-2,3-isopropylidene glyceraldehyde to **11e** (65%, 2 steps) in the context of a new synthesis of (*S*)-melodorinol (**2**). Debromination of **11e** provided the requisite relay acetonide **12e**[3a] (93%, Table 2) whose hydrolysis and ensuing benzoylation afforded **2** as a pale yellow oil {$[\alpha]^{26}_D$ +91.0, (*c* = 0.98, $CHCl_3$); Lit. $[\alpha]_D$ +86.4,[3a] $[\alpha]_D$ +92.5[3b]} in 61% yield for the two steps (Scheme 3).

In summary, this new methodology enables stereocontrolled access to a variety of β-unsubstituted (*Z*)-γ-alkylidenebutenolides from readily available, non-stereodefined precursors. Moreover, the intermediate (*Z*)-γ-alkylidene-β-bromobutenolides are interesting in their



Scheme 3

own right since they can be transformed to a range of β-substituted homologues by cross-coupling reactions,[7a,9b,22] and also due to the recent discovery that certain members of this class are potent quorum sensing (QS) inhibitors[23] with potential utility for the treatment of anthrax and other bacterial infections.[24] Such applications are under study and the results will be reported in due course.

Acknowledgment

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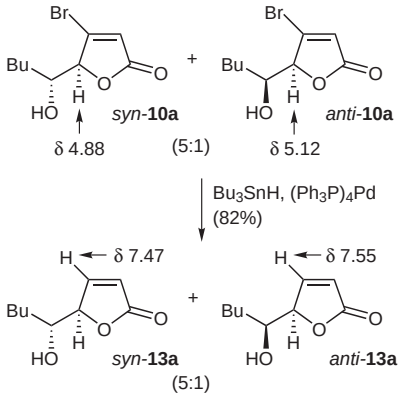
(15) The major isomers (*syn*) of all aldol products described herein (**5** and **10a**–**d**) were clearly distinguished from their *anti* counterparts by the upfield shift of their γ-proton ($\Delta\delta \approx 0.2$–0.3 ppm). Their stereochemistry was deduced by debromination of *syn*-**10a**/*anti*-**10a** to the corresponding butenolides *syn*-**13a**/*anti*-**13a** whose stereostructures were unambiguously assigned from the diagnostic shift of the β-proton[5a] (Scheme 4).



Scheme 4

(16) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965.

(17) **Typical Procedure**: To a solution of **8**[13] (147 mg, 0. 903 mmol) in anhyd CH_2Cl_2 (3 mL) at 0 °C were successively added TBSOTf (207 μL, 0. 903 mmol) and Et_3N (125 μL, 0. 903 mmol). The mixture was stirred for 30 min at 0 °C, then cooled to –78 °C, and then *p*-anisaldehyde (100 μL, 0.821 mmol) was added. After stirring at –78 °C for 1 h,

DBU (251 μL, 1.64 mmol) was added and the resulting dark purple solution was allowed to warm to r.t. and stirred for an additional 1.5 h before quenching with 15% aq tartaric acid. The aqueous phase was extracted with CH_2Cl_2 (3 ×) and the combined organic layers were washed with sat. aq $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel; EtOAc–CH_2Cl_2–hexanes, 1:3:10) to afford **6b** (196 mg, 85%) as a pale red-brown solid; mp 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 6.33 (s, 1 H), 6.35 (s, 1 H), 6.95 (d, *J* = 8.6 Hz, 2 H), 7.79 (d, *J* = 8.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2, 113.5, 114.3, 117.4, 124.8, 132.7, 138.1, 145.0, 160.9, 167.3. MS (CI): *m*/*z* = 281 [MH^+]. Anal. Calcd for $C_{12}H_9BrO_3$: C, 51.27; H, 3.23. Found: C, 51.29; H, 2.99.
Data for **6c**: yellow solid; mp 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (br d, *J* = 1.0 Hz, 3 H), 6.33 (s, 1 H), 6.55 (s, 1 H), 6.78 (dq, *J* = 3.7, 1.0 Hz, 1 H), 7.26 (d, *J* = 3.7 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7, 107.6, 117.7, 126.6, 133.0, 133.5, 136.7, 144.2, 147.8, 166.8. MS (CI): *m*/*z* = 271 [MH^+]. Anal. Calcd for $C_{10}H_7BrO_2S$: C, 44.30; H, 2.60; S, 11.83. Found: C, 44.25; H, 2.43; S, 12.19.
Compounds **6a** (white solid; mp 84–85 °C) and **6d** (yellow oil) exhibited NMR data commensurate with those reported by Brückner.[7a]

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Data for **9**: colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 (s, 6 H), 0.97 (s, 9 H), 1.80 (s, 3 H), 6.86 (s, 1 H).). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.5, 7.4, 17.9, 25.4, 94.0, 104.3, 129.2, 152.4. HRMS (EI): *m*/*z* calcd for $C_{11}H_{19}BrO_2Si$: 290.0338; found: 290.0331.

(21) Data for **11a**: orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3 H), 1.37 (m, 2 H), 1.49 (m, 2 H), 2.41 (q, *J* = 7.6 Hz, 2 H), 5.62 (dt, *J* = 0.5, 8.0 Hz, 1 H), 6.34 (d, *J* = 0.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 22.3, 26.1, 30.8, 117.3, 119.6, 136.9, 148.1, 167.0. HRMS (EI): *m*/*z* calcd for $C_9H_{11}BrO_2$: 229.9942; found: 229.9938.
Data for **11b**: orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.1 Hz, 3 H), 1.31–1.50 (m, 4 H), 1.96 (s, 3 H), 2.37 (q, *J* = 7.4 Hz, 2 H), 5.47 (t, *J* = 7.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.2, 13.7, 22.3, 25.8, 31.0, 114.5, 128.1, 132.2, 147.0, 167.9. HRMS (EI): *m*/*z* calcd for $C_{10}H_{13}BrO_2$: 244.099; found: 244.0098.
Data for **11c**: yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.65 (m, 2 H), 2.72 (m, 2 H), 5.54 (t, *J* = 7.6 Hz, 1 H), 6.25 (s, 1 H), 7.11–7.25 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0, 34.7, 115.7, 119.8, 126.2, 128.2, 128.4, 136.9, 140.3, 148.3, 166.8. HRMS (EI): *m*/*z* calcd for $C_{13}H_{11}BrO_2$: 277.9942; found: 277.9938.
Data for **11d**: white solid; mp 66–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (d, *J* = 8.1 Hz, 2 H), 5.76 (t, *J* = 8.1 Hz, 1 H), 6.40 (s, 1 H), 7.22–7.36 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.6, 114.9, 120.3, 126.8, 128.6, 128.8, 137.1, 137.9, 148.2, 166.8. Anal. Calcd for $C_{12}H_9BrO_2$: C, 54.55; H, 3.44. Found: C, 54.76; H, 3.53.
Data for **11e**: white solid; mp 29–31 °C; $[\alpha]_D^{23}$ +32.5 (*c* = 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.47 (s, 3 H), 3.73 (dd, *J* = 6.7, 8.2 Hz, 1 H), 4.23 (dd, *J* = 6.7, 8.2 Hz, 1 H), 5.12 (dt, *J* = 6.7, 8.2 Hz, 1 H), 5.64 (d, *J* = 8.2 Hz, 1 H), 6.43 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4, 26.5, 69.0, 70.6, 110.0, 112.8, 121.2, 137.0, 148.9, 165.9. HRMS (CI): *m*/*z* calcd for $C_{10}H_{11}BrO_4$: 274.9919; found: 274.9915.

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