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Electrohydrocyclization of alkoxy tether substituted mixed enone/enoate and bisenone systems: retention versus elimination

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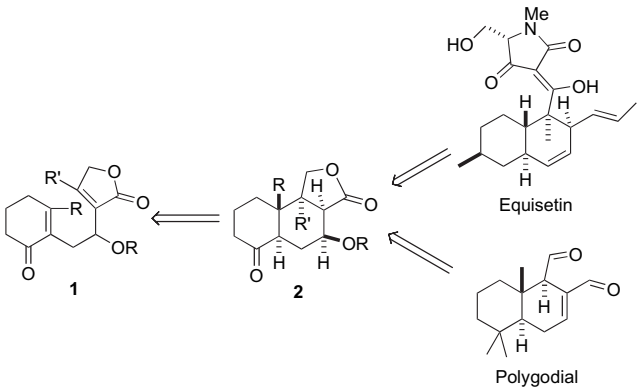
Abstract—The electrohydrocyclization of tethered enone/enoate or bisenone systems which contain an alkoxyl substituent in the tether was studied. Rather surprisingly, the cyclization of these compounds afforded very different products depending upon the alkoxy substituent. This behavior and its potential applications will be discussed.

1. Introduction

The hydrodimerization reaction remains an important transformation in organic chemistry.[1] Although the intermolecular reaction is well appreciated and finds a number of different applications from the academic to the industrial scale, the intramolecular version (henceforth called the electrohydrocyclization) has received much less attention. At the same time, it does have some particularly attractive features, including the rapid increase in molecular complexity resulting from the formation of one new ring and up to four new stereocenters.[2] In an effort directed at harnessing the power of the electrohydrocyclization, we have recently reported our results of a more detailed study of the effect of ring size, tether length, β-substitution, and reaction conditions on the electrohydrocyclization of cyclic five- and six-membered ring enones.[3]

Encouraged by these initial results, we were interested in exploring the electrohydrocyclization of tether substituted systems such as **1** (Scheme 1). This tether substituent can be of value in several different ways. First, it provides a means of differentiating between the two carbonyls, particularly in cases where both are ketones or esters. Second, it provides a convenient handle for functionalization of the newly formed ring. Third, and perhaps most importantly, it provides a possible entry into the generation of optically pure cyclization materials and thereby an entry into asymmetric electrohydrocyclization reactions. Ultimately, the electrohydrocyclization of these alkoxy tether substituted enone/enoate systems could be a versatile route to the basic skeleton of a variety of biologically active sesquiterpene natural products such as equisetin and polygodial.[4]



Scheme 1. Tether substituted cyclization system and potential applications.

2. Results and discussion

As an initial exploration of these tether substituted cyclization reactions, two simple systems were explored: bisenone **4** and enone/enoate **3**. The most obvious route to such cyclization substrates is via a Baylis–Hillman reaction. Beyond the advantage of convergency, this approach also has potential for the preparation of asymmetric cyclization substrates via the growing number of asymmetric catalysts for Baylis–Hillman reactions that have been reported in recent years.[5]

Keywords: Hydrodimerization; Reduction; Electrochemistry; Cyclization; Elimination.
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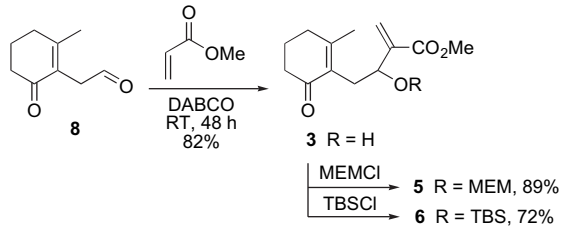
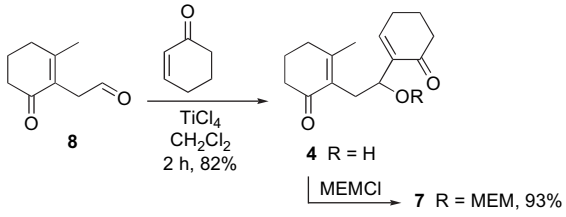
In keeping with this approach, the synthesis of enone/enoate cyclization precursor **3** involved a Baylis–Hillman reaction between known aldehyde **8** with methyl acrylate in the presence of DABCO at room temperature[6] (Scheme 2). The solvent used for this reaction proved to be an important variable, since typical solvent systems such as water/dioxane, methanol or acetonitrile did not afford good yields, even after prolonged reaction times.[7] Neat reaction conditions, however, afforded enone/enoate system **3** in 82% yield after 48 h.



Scheme 2. Synthesis of enone/enoate cyclization precursor **3**.

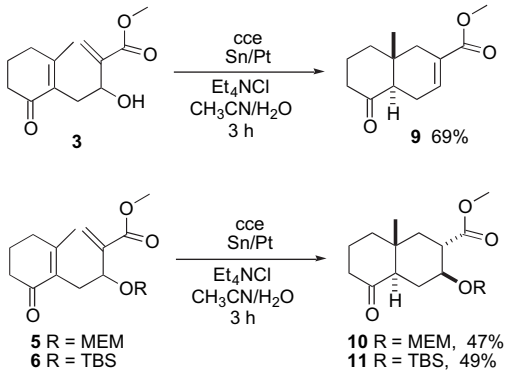
In addition to the hydroxy-substituted compound, two ether-substituted cyclization substrates (**5** and **6**) were prepared simply by treating alcohol **3** with MEMCl and TBSCl, respectively, under standard reaction conditions.

For the preparation of bisenone system **4**, another Baylis–Hillman reaction was employed, this time between aldehyde **8** and 2-cyclohexenone (Scheme 3). Standard conditions (including neat reaction conditions) completely failed to afford any of the desired products. Indeed, extensive optimization of the reaction conditions eventually determined that the more reactive Lewis-acid catalyzed conditions reported by Li were the only ones that afforded significant amounts of the desired product.[8] Fortunately, these conditions did work quite well, affording **4** in 82% yield. Treatment of **4** with MEMCl under standard conditions then afforded the MEM-protected compound **7** in 93% yield.



Scheme 3. Synthesis of bisenone cyclization precursor **4**.

With the cyclization substrates in hand, electrohydrocyclization was first explored under electrochemical conditions. Compound **3** was subjected to a constant current (cce) of 100 mA for 5 h using a tin anode and a platinum cathode in an undivided cell under an inert atmosphere of argon with 0.1 M tetraethylammonium chloride as the supporting electrolyte in aqueous acetonitrile[9] (Scheme 4). The reaction afforded cyclization product **9** in 69% yield. Although we were somewhat surprised to observe the elimination product, it was initially suspected that the intermediate enolate formed during the electrohydrocyclization underwent elimination of hydroxide to yield the α,β-unsaturated cyclic ester (vide infra). With respect to the product stereochemistry, the trans ring fusion was initially proposed based upon the results of previous cyclizations in this group and was supported by the absence of any NOE between the angular methyl group and the bridgehead proton.[3b] Further evidence for the stereochemical outcome of this reaction came from the structural studies of the cyclization products of the ether-substituted compounds **5** and **6** (vide infra).



Scheme 4. Electrochemical cyclizations of enone/enoate systems.

On the basis of that assumption, the electrohydrocyclizations of the two ether-substituted substrates **5** and **6** were expected to also afford the same elimination product **9**. Interestingly, they did not follow the same pattern. Instead, both of these compounds afforded cyclization products with retention of the alkoxy substituents (**10** and **11**). Moreover, a single isomer of the retention product was observed, indicating that the pre-existing stereocenter in the tether served to direct the facial selectivity of the cyclization. Presumably this occurs with the substituent assuming a pseudo-equatorial position in a chair-like transition state **12** (Fig. 1). In keeping with this proposed transition state and the results of our previous electrohydrocyclizations, the relative stereochemistry of the four stereocenters in product **11** was determined to be as shown.[3b] This stereochemistry was determined by the use of a NOESY spectrum of **11**, which revealed key cross-peaks between the angular methyl group and H^c and between H^a and H^b, but not between the angular methyl group and H^b or H^a. Compound **10** is also formed as a single isomer, presumably with the same stereochemical result as compound **11**.

The next stage was to determine if the bisenone systems would behave similarly. Cyclization of systems **4** and **7** under the same electrochemical conditions proceeded as expected with compound **4**, containing an unprotected alcohol in the tether, affording the elimination product **13** and compound **7**, with a MEM ether in the tether, affording retention product **14** (Scheme 5). In this latter case, the product was once again obtained as a single isomer.

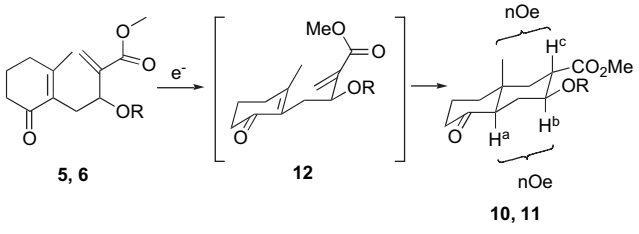
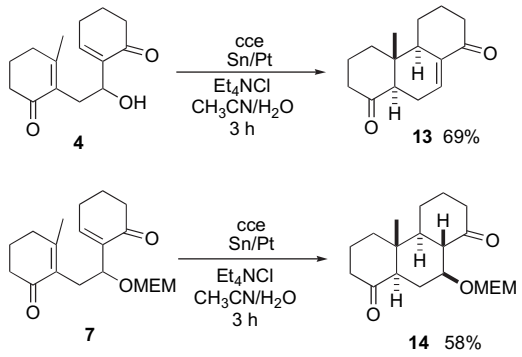


Figure 1. Proposed conformation for cyclization.



Scheme 5. Electrochemical cyclizations of bisenone systems.

The stereochemistry of these cyclization products was determined via extensive NMR studies. For compound **14**, a NOESY revealed key correlations between the angular methyl group and H^b on one face of the newly formed ring and H^a, H^c, and H^d on the other face, which is consistent with the proposed stereochemistry (Fig. 2). This outcome is also consistent with previous cyclizations by Mandell and in this group of tethered biscyclohexenones, which have cleanly afforded the trans/*anti*/trans isomer as the sole reaction product.[3b,10] From this assignment, the stereochemistry of **13** is predicted to be the same at the remaining three stereocenters.[11]

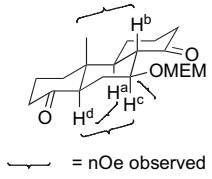
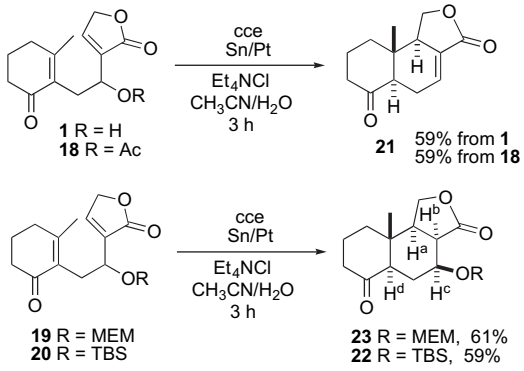


Figure 2. Stereochemistry of product **14**.

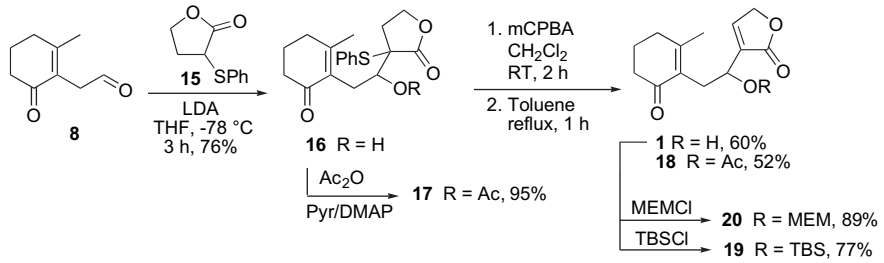
On the basis of these encouraging results, the preparation of enone/enoate **1**, which would be more directly applicable to the synthesis of drimane-type natural products, was undertaken (Scheme 6). Initial attempts using a Baylis–Hillman reaction between 2(5*H*)-furanone and the aldehyde **8** were not successful under a variety of conditions.[12] As a result, more traditional methods for the synthesis of these types of compounds were employed, in particular the use of α-thio-γ-lactones.[13] With that in mind, 3-phenylsulfanyl-dihydrofuran-2-one **15** was synthesized in two steps starting from γ-butyrolactone in 78% yield overall.[14] Formation of the enolate of **15** and condensation with aldehyde **8** then afforded aldol product **16**. This product was converted to the corresponding acetate **17** by treatment with acetic anhydride in pyridine. Either compound **16** or **17** could be converted into the furanone systems by oxidation to the sulfoxide with *m*-CPBA followed by thermal elimination in toluene at reflux. From alcohol **1**, the corresponding TBS and MEM ethers **19** and **20** were prepared as before.

With the desired cyclization precursors in hand, cyclization of **1** afforded elimination product **21** as expected (Scheme 7). Not too surprisingly, acetate protected compound **18** also afforded the same elimination product in essentially the same yield. The two ether substrates, **19** and **20**, afforded the retention products **22** and **23**, respectively, as single isomers. Assignment of the stereochemistry of these products was more difficult than in previous cases, since no NOE was observed between the angular methyl group and H^a, H^b, H^c or H^d. This favors the stereochemistry as shown, but is clearly not definitive. Further support for the depicted stereochemistry comes from previous cyclizations in this group, which have afforded trans ring fusions for [6.6] systems and cis ring fusions for [6.5] systems and have always afforded the *anti* relationship between the two pre-existing rings (in this case the angular methyl group and H^a).[3]



Scheme 7. Electrochemical cyclizations of enone/enoate systems.

In an effort to compare the electrochemical results with conventional synthetic methods, the cyclizations of the four substrates in Scheme 7 were investigated using samarium diiodide as the reducing agent[15] (Table 1). Treatment with 4 equiv of freshly prepared samarium diiodide at room temperature in THF under argon afforded the anticipated elimination product **21** from substrates **1** and **18**. Similarly, substrates **19** and **20** afforded alkoxy-retention cyclization products **22** and **23** in keeping with those observed under electrochemical conditions. The yields in all cases are slightly lower than those obtained under the electrochemical



Scheme 6. Synthesis of 2(5*H*)-furanone-containing substrates.

Table 1. Cyclizations under electrochemical and SmI_2 conditions

Substrate	Product	Yield, electrochemical conditions	Yield, SmI_2 conditions
1	**21**	59	45
18	**21**	59	40
19	**22**	59	50
20	**23**	61	39

conditions, but are similar. Further, no change in product stereochemistry was observed.

One clear question in all of these tether substituted cyclizations is why some afford elimination products and some retention products. One possible explanation is based on the pK_a (and thus leaving group ability) of the conjugate acid of the potential leaving group as seen in Table 2. The two cases that afford elimination (acetoxy and hydroxy groups) have the two lowest pK_a values, while the MEM alcohol and silanol cases afford retention of the substituent and have higher pK_a values.[16] Other issues, such as the ability of the initial products to adopt a configuration suitable for elimination, may also contribute to this difference in reaction outcome.

Table 2. Reaction outcome versus substituent and substituent pK_a

Substituent	pK_a	Product type
Acetate	4.7	Elimination
Hydroxyl	15	Elimination
OMEM	19	Retention
OTBS	21.5	Retention

3. Conclusion

In conclusion, we have noted that alkoxy tether substituted enone/enoate and dienone systems can successfully undergo the electrohydrocyclization. Either the elimination or the retention product can be formed, with the product type being determined by whether the oxygen group on the tether is a simple hydroxyl or an ether. Further studies of the mechanism of this reaction and applications in synthesis are underway and will be reported in due course.

4. Experimental

4.1. General

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM 360 MHz spectrometer as a solution in deuterochloroform. NOESY spectra were collected on a JEOL ECA-500 500 MHz spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane. Infrared (IR) spectra were recorded on a Perkin–Elmer Spectrum Bx spectrophotometer. All solvents were of reagent grade unless stated otherwise. Reactions were monitored by thin layer chromatography (TLC) with precoated silica gel plates. Silica gel (100–200 mesh) was used for all chromatographic purifications. All reactions were performed under an argon atmosphere unless noted otherwise.

4.1.1. 3-Hydroxy-2-methylene-4-(2-methyl-6-oxo-cyclohex-1-enyl)-butyric acid methyl ester [3]. A mixture of aldehyde **8** (1.40 g, 9.20 mmol), methyl acrylate (2.48 mL, 27.6 mmol), and 1,4-diazabicyclo[2.2.2]octane (1.03 g, 9.20 mmol) was stirred at room temperature for 48 h. The mixture was diluted with 30 mL of methylene chloride and extracted with 10% aqueous HCl (2×20 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (30% ethyl acetate/hexanes as eluent) to obtain 1.80 g (82%) of **3** as a clear oil.

IR ($CDCl_3$) 3310, 2923, 2848, 1722, 1645, 1438; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.95 (s, 1H), 4.47–4.44 (m, 1H), 3.74 (s, 3H), 2.71–2.67 (m, 1H), 2.57–2.55 (m, 1H), 2.41–2.35 (m, 4H), 2.01–1.99 (m, 5H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.3, 167.0, 160.1, 142.7, 132.4, 125.2, 77.1, 51.8, 37.7, 33.4, 33.2, 22.2, 21.7. HRMS (EI) calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1203.

4.1.2. 3-(2-Methoxy-ethoxymethoxy)-2-methylene-4-(2-methyl-6-oxo-cyclohex-1-enyl)-butyric acid methyl ester [5]. A mixture of **3** (100 mg, 0.42 mmol), DMAP (10 mg, 0.08 mmol), and diisopropylethyl amine (330 μL, 1.89 mmol) in methylene chloride (4 mL) was cooled to 0 °C and 2-methoxyethoxymethyl chloride (98 μL, 0.84 mmol) was added. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was diluted with 10 mL methylene chloride and washed successively with water, 10% HCl, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (30% ethyl acetate/hexanes as eluent) to afford 122 mg (89%) of **5** as a light yellow oil.

IR ($CDCl_3$) 2935, 2887, 1720, 1664, 1627, 1436, 1379; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.24 (s, 1H), 5.82 (s, 1H), 4.81 (s, 2H), 4.61–4.52 (m, 1H), 3.74 (s, 3H), 3.72–3.68 (m, 2H), 3.54–3.49 (m, 2H), 3.36 (s, 3H), 2.8–2.61 (m, 2H), 2.35–2.29 (m, 3H), 2.15 (s, 3H), 2.02–1.86 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.4, 166.7, 158.3, 141.4, 132.1, 126.1, 93.7, 74.5, 71.8, 67.1, 59.2, 51.9, 37.9, 33.3, 31.5, 22.3, 22.0. HRMS (EI) calcd for $C_{17}H_{26}O_6$ 326.1729, found 326.1730.

4.1.3. 3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methylene-4-(2-methyl-6-oxo-cyclohex-1-enyl)-butyric acid methyl ester [6]. To a solution of **3** (200 mg, 0.839 mmol) in 0.8 mL DMF was added imidazole (172 mg, 2.53 mmol) followed by *tert*-butyldimethylsilyl chloride (380 mg, 2.53 mmol). The reaction mixture was stirred overnight at room temperature and then was diluted with 15 mL of methylene chloride and washed with water. The aqueous layer was extracted with 15 mL of methylene chloride and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude oil was purified by flash column chromatography (30% ethyl acetate/hexanes as eluent) to afford 210 mg (72%) of **6** as a light yellow oil.

IR ($CDCl_3$) 2993, 2851, 1752, 1721, 1660, 1620, 1465; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.15 (s, 1H), 5.87 (s, 1H), 4.68 (t, J=6.6 Hz, 1H), 3.75 (s, 3H), 2.62–2.54 (m, 2H), 2.34–2.27

(m, 4H), 1.98–1.85 (m, 5H), 0.85 (d, J=21.6 Hz, 9H), 0.05 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 166.7, 157.5, 144.8, 132.0, 124.3, 69.9, 51.6, 37.6, 34.3, 33.0, 25.7, 25.6, 22.0, 21.9, 17.9, 14.1, −3.7, −5.2. HRMS (EI) calcd for $C_{19}H_{32}O_4Si$ 352.2070, found 352.2069.

4.1.4. 2-[2-Hydroxy-2-(6-oxo-cyclohex-1-enyl)-ethyl]-3-methyl-cyclohex-2-enone [4]. In a dry vial, aldehyde **8** (150 mg, 1 mmol), freshly distilled methylene chloride (1.5 mL), and cyclohexenone (195 μL, 2 mmol) were cooled to 0 °C and titanium tetrachloride (165 μL, 1.5 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h, then diluted with methylene chloride, and extracted with saturated aqueous sodium bicarbonate. The organic layer was separated and dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (20% ethyl acetate/hexanes as eluent) to afford 200 mg (82%) of **4** as a clear oil.

IR ($CDCl_3$) 3473, 2857, 1779, 1716, 1698, 1471; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.01 (t, J=4.7 Hz, 1H), 4.42–4.36 (m, 1H), 3.98 (br, J=5.4 Hz, 1H, OH), 2.66 (dd, J=14.3, 4.0 Hz, 1H), 2.48–2.34 (m, 10H), 2.03 (s, 3H), 1.98–1.89 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.1, 200.1, 160.0, 145.5, 141.4, 132.9, 70.4, 38.8, 37.8, 33.7, 33.2, 25.8, 22.9, 22.3, 21.8. HRMS (EI) calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1414.

4.1.5. 2-[2-(2-Methoxy-ethoxymethoxy)-2-(6-oxo-cyclohex-1-enyl)-ethyl]-3-methyl-cyclohex-2-enone [7]. A mixture of **4** (100 mg, 0.40 mmol), DMAP (10 mg, 0.08 mmol), and diisopropylethyl amine (316 μL, 1.80 mmol) in methylene chloride (4 mL) was cooled to 0 °C and 2-methoxyethoxymethyl chloride (92 μL, 0.80 mmol) was added. The reaction mixture was warmed to room temperature and stirred overnight at room temperature. The mixture was diluted with 10 mL methylene chloride and washed successively with H_2O, 10% HCl, saturated aqueous sodium bicarbonate, and brine. Organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (25% ethyl acetate/hexanes as eluent) to afford 125 mg (93%) of **7** as a light yellow oil.

IR ($CDCl_3$) 2934, 1773, 1663, 1627, 1109, 1038; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.96 (t, J=4.4 Hz, 1H), 4.63–4.52 (m, 3H), 4.67–4.62 (m, 1H), 3.55–3.46 (m, 3H), 3.35 (s, 3H), 2.81–2.75 (m, 1H), 2.59–2.53 (m, 1H), 2.41–2.28 (m, 10H), 2.02 (s, 3H), 1.95–1.85 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.1, 199.0, 158.2, 146.8, 140.2, 132.7, 94.3, 73.2, 72.4, 67.6, 59.7, 39.3, 38.5, 33.8, 31.6, 26.5, 23.4, 22.9, 22.6. HRMS (EI) calcd for $C_{19}H_{28}O_5$ 336.1937, found 336.1936.

4.1.6. 3-[1-Hydroxy-2-(2-methyl-6-oxo-cyclohex-1-enyl)-ethyl]-3-phenylsulfanyl-dihydro-furan-2-one [16]. Diisopropylamine (130 μL, 0.93 mmol) in THF (0.56 mL) was cooled to −78 °C and *n*-BuLi (372 μL, 0.93 mmol) was added. Then the 3-phenylsulfanyl-dihydro-furan-2-one **15** (193 mg, 0.93 mmol) in THF (1.0 mL) was added and the reaction warmed to −50 °C and stirred for 1 h. Then aldehyde **7**[17] (170 mg, 1.11 mmol) in THF (0.67 mL) was added and the reaction stirred for another 3 h at −50 °C. At this point, the reaction was poured onto cold saturated aqueous ammonium chloride (20 mL). The organic layer was separated and the aqueous layer was extracted twice with ether (2×10 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (30% ethyl acetate/hexanes as eluent) to obtain 251 mg (76%) of **16** as a light yellow oil.

IR ($CDCl_3$) 3426, 3058, 2924, 1776, 1651, 1573, 1472, 1139; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.64–7.56 (m, 2H), 7.37–7.29 (m, 3H), 4.24–4.17 (m, 1H), 3.99–3.90 (m, 1H), 3.80–3.77 (m, 1H), 3.63 (br s, 1H, OH), 3.12–2.82 (m, 1H), 2.73–2.49 (m, 1H), 2.40–2.33 (m, 6H), 2.12 (d, J=6.0 Hz, 2H), 1.95–1.85 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.6, 175.1, 159.7, 137.2, 136.7 (2C), 132.2, 130.0, 129.2 (2C), 72.1, 65.2, 59.1, 37.4, 33.0, 29.1, 27.9, 22.8, 21.5. HRMS (EI) calcd for $C_{19}H_{22}OS$ 347.1239, found 347.1236.

4.1.7. Acetic acid 2-(2-methyl-6-oxo-cyclohex-1-enyl)-1-(2-oxo-3-phenylsulfanyl-tetrahydro-furan-3-yl)-ethyl ester [17]. To a mixture of **16** (100 mg, 0.28 mmol) in pyridine (0.56 mL) was added acetic anhydride (43 μL, 0.42 mmol) followed by DMAP (17 mg, 0.14 mmol). The reaction was stirred overnight at room temperature and then was diluted with methylene chloride (20 mL) and extracted with 1 N HCl (10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (20% ethyl acetate/hexanes as eluent) to afford 105 mg (95%) of **17** as a light yellow oil.

IR ($CDCl_3$) 3067, 2937, 2870, 1780, 1663, 1629, 1583, 1227; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.61 (d, J=7.3 Hz, 2H), 7.42–7.32 (m, 3H), 5.34 (dd, J=11.0, 3.7 Hz, 1H), 4.27 (dd, J=8.4, 3.7 Hz, 2H), 3.05–2.98 (m, 1H), 2.83–2.66 (m, 2H), 2.53 (s, 1H), 2.35–2.26 (m, 4H), 2.20–2.13 (m, 1H), 1.95–1.87 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 173.0, 170.0, 159.1, 137.3 (2C), 137.0, 130.1, 129.1, 128.9 (2C), 73.2, 71.6, 65.1, 37.4, 32.9, 30.5, 25.8, 21.9, 21.5, 20.6. HRMS (EI) calcd for $C_{21}H_{24}O_5S$ 389.1345, found 389.1348.

4.1.8. 3-[1-Hydroxy-2-(2-methyl-6-oxo-cyclohex-1-enyl)-ethyl]-5*H*-furan-2-one [1]. To a solution of **16** (600 mg, 1.6 mmol) in methylene chloride (16 mL), was added *m*-chloroperbenzoic acid (578 mg, 3.3 mmol). The reaction was stirred for 2 h at room temperature and then was diluted with 15 mL methylene chloride and washed with 20 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with 10 mL of methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in 5 mL of toluene and refluxed 1 h. The solvent was then evaporated and the crude mixture was purified by flash column chromatography (50% ethyl acetate/hexanes as eluent) to afford 250 mg (60%) of **1** as a light yellow oil.

IR ($CDCl_3$) 3390, 2926, 2870, 1732, 1660, 1509, 1446; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38 (t, J=1.8 Hz, 1H), 4.76 (t, J=2.2 Hz, 2H), 4.41–4.38 (m, 1H), 4.33 (br s, 1H, OH),

2.82 (d, J=14.6 Hz, 1H), 2.52 (dd, J=15.0, 9.8 Hz, 1H), 2.41–2.33 (m, 4H), 2.00 (9s, 3H), 1.95–1.85 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.4, 172.9, 160.9, 145.3, 137.0, 131.8, 70.5, 67.9, 37.4, 33.0, 32.2, 21.9, 21.5. HRMS (EI) calcd for $C_{13}H_{16}O_4$ 236.1049, found 236.1048.

4.1.9. Acetic acid 2-(2-methyl-6-oxo-cyclohex-1-enyl)-1-(2-oxo-2,5-dihydro-furan-3-yl)-ethyl ester [18]. To a solution of **17** (240 mg, 0.6 mmol) in methylene chloride (6 mL), was added *m*-chloroperbenzoic acid (207 mg, 1.2 mmol). The reaction was stirred for 2 h at room temperature and then was diluted with 15 mL methylene chloride and washed with 20 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with 10 mL of methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in 5 mL of toluene and refluxed 1 h. The solvent was then evaporated and the resulting mixture purified by flash column chromatography (50% ethyl acetate/hexanes as eluent) to afford 91 mg (54%) of **18** as a light yellow oil.

IR ($CDCl_3$) 2937, 2869, 1760, 1661, 1629, 1227, 1031; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.36 (s, 1H), 5.63–5.59 (m, 1H), 4.76–4.75 (m, 2H), 2.87–2.85 (m, 2H), 2.36–2.29 (m, 3H), 2.04–1.86 (m, 7H), 1.29–1.19 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.2, 172.0, 170.3, 159.4, 147.0, 133.0, 129.3, 70.1, 67.7, 37.4, 33.0, 28.7, 21.9, 21.6, 20.8. HRMS (EI) calcd for $C_{15}H_{18}O_5$ 278.1154, found 278.1155.

4.1.10. 3-[1-(*tert*-Butyl-dimethyl-silanyloxy)-2-(2-methyl-6-oxo-cyclohex-1-enyl)-ethyl]-5*H*-furan-2-one [19]. To a solution of **1** (30 mg, 0.12 mmol) in 0.5 mL DMF was added imidazole (25 mg, 0.36 mmol) followed by *tert*-butyldimethylsilyl chloride (55 mg, 0.36 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was then diluted with 15 mL of methylene chloride and washed with water. The aqueous layer was extracted with 15 mL of methylene chloride and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude oil was purified by flash column chromatography (30% ethyl acetate/hexanes as eluent) to afford 34 mg (77%) of **19** as a light yellow oil.

IR ($CDCl_3$) 2939, 2847, 1755, 1663, 1464, 1379, 1248; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.31 (t, J=1.5 Hz, 1H), 4.73–4.71 (m, 2H), 4.59 (t, J=5.9 Hz, 1H), 2.68–2.65 (9m, 2H), 2.34–2.26 (m, 4H), 1.92 (s, 3H), 1.90–1.85 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 172.2, 157.7, 145.4, 138.3, 131.1, 70.1, 66.8, 37.5, 33.3, 32.9, 25.6 (3C), 21.9, 21.7, −5.1 (2C). HRMS (EI) calcd for $C_{19}H_{30}O_4Si$ 350.1936, found 350.1936.

4.1.11. 3-[1-(2-Methoxy-ethoxymethoxy)-2-(2-methyl-6-oxo-cyclohex-1-enyl)-ethyl]-5*H*-furan-2-one [20]. A mixture of **1** (250 mg, 1.0 mmol), DMAP (22 mg, 0.2 mmol), and diisopropylethyl amine (786 μL, 4.5 mmol) in methylene chloride (1 mL) was cooled to 0 °C and 2-methoxyethoxymethyl chloride (229 μL, 2.0 mmol) was added. The reaction mixture was warmed to room temperature and stirred overnight at room temperature. The mixture was diluted with 10 mL methylene chloride and washed successively with water, 10% HCl, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (30% ethyl acetate/hexanes as eluent) to afford 305 mg (89%) of **20** as a light yellow oil.

IR ($CDCl_3$) 2930, 1718, 1673, 1629, 1440, 1367, 1248; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33 (s, 1H), 4.73 (s, 2H), 4.62–4.57 (m, 2H), 4.51 (t, J=6.6 Hz, 1H), 3.63–3.44 (m, 4H), 3.29 (s, 3H), 2.85–2.68 (m, 2H), 2.31–2.27 (m, 4H), 1.96 (s, 3H), 1.88–1.82 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.4, 172.4, 158.8, 146.8, 134.6, 130.7, 93.9, 71.5, 70.6, 70.1, 67.0, 58.9, 37.5, 32.9, 30.0, 21.9, 21.7. HRMS (EI) calcd for $C_{17}H_{24}O_6$ 324.1573, found 324.1573.

4.2. General procedure for preparative electrolysis

A solution of enone/enoate or bisenone compound (50 mg, 1 equiv) and tetraethylammonium chloride (0.1 N, 1.31 g, 36 equiv) in 70 mL of acetonitrile and 9 mL of water was degassed by bubbling argon through it for 1 h. A constant current of 100 mA was applied by using tin foil (2 cm^2) as the sacrificial anode and platinum (2 cm^2) as the cathode. The reaction progress was monitored by thin layer chromatography. Then the reaction mixture was poured into a separatory funnel along with 20 mL of ether and extracted with 20 mL of 5% aqueous sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (20% ethyl acetate/hexanes as eluent) to afford the cyclization products as light yellow oils.

4.2.1. 8a-Methyl-5-oxo-1,4,4a,5,6,7,8,8a-octahydro-naphthalene-2-carboxylic acid methyl ester [9]. The cyclization product **9** was obtained as a yellow oil (32 mg, 69%). IR ($CDCl_3$) 2922, 1705, 1652, 1271, 1253; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.00–6.97 (m, 1H), 3.73 (s, 3H), 2.37–2.12 (m, 14H) 1.96–1.75 (m, 1H), 1.55 (s, 1H), 1.29–1.24 (m, 5H), 0.94–0.85 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 211.4, 167.9, 138.0, 136.9, 52.1, 51.8, 41.8, 40.2, 39.9, 37.6, 31.2, 28.1, 22.8. HRMS (EI) calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1255.

4.2.2. 3-(2-Methoxy-ethoxymethoxy)-8a-methyl-5-oxo-decahydro-naphthalene-2-carboxylic acid methyl ester [10]. The cyclization product **10** was obtained as a light yellow oil (23.5 mg, 47%). IR ($CDCl_3$) 2929, 2888, 1715, 1663, 1456, 1150; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.79–4.75 (m, 2H), 4.47–4.41 (m, 1H), 3.78–3.66 (m, 4H), 3.58–3.53 (m, 3H), 3.39 (s, 3H), 2.78–2.67 (m, 1H), 2.56–2.36 (m, 2H), 2.22–2.09 (m, 1H), 2.05–1.90 (m, 4H), 1.56 (s, 3H), 1.34–1.22 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 215.8, 164.0, 95.3, 81.2, 73.3, 71.8, 71.6, 67.0, 58.9, 51.6, 48.7, 43.3, 39.0, 29.3, 27.8, 26.9, 18.8. HRMS (EI) calcd for $C_{17}H_{28}O_6$ 326.1885, found 326.1888.

4.2.3. 3-(*tert*-Butyl-dimethyl-silanyloxy)-8a-methyl-5-oxo-decahydro-naphthalene-2-carboxylic acid methyl ester [11]. The cyclization product **11** was obtained as a light yellow oil (24.5 mg, 49%). IR ($CDCl_3$) 2927, 2855, 1741, 1725, 1443; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.48–4.46 (m, 1H), 3.65 (s, 3H), 3.03–2.99 (d, J=16.1 Hz, 1H), 2.64–2.60 (dd, J=14.6, 3.0 Hz, 1H), 2.33–2.29 (d, J=15.0 Hz, 1H),

2.09–1.94 (m, 3H), 1.84–1.75 (m, 1H), 1.61–1.54 (m, 5H), 1.24 (s, 3H), 0.79 (s, 9H), 0.04 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.7, 173.9, 71.2, 66.9, 51.4, 44.6, 39.9, 32.1, 30.8, 30.4, 27.8, 26.9, 25.5 (3C), 20.1, 17.8, −4.5, −5.3. HRMS (EI) calcd for $C_{19}H_{34}O_4Si$ 354.2226, found 354.2225.

4.2.4. 4b-Methyl-2,3,4,4a,4b,5,6,7,8a,9-decahydro-phenanthrene-1,8-dione [13]. The cyclization product **13** was obtained as a yellow oil (28.5 mg, 61%). IR ($CDCl_3$) 2929, 1715, 1652, 1253; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.17 (s, 1H), 2.44–2.21 (m, 4H), 1.98–1.83 (m, 1H), 1.58–1.47 (m, 9H), 1.33–1.25 (m, 3H), 0.92–0.84 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 212.6, 191.5, 148.7, 133.2, 55.5, 50.0, 48.9, 48.2, 40.9, 40.1, 38.0, 37.2, 30.5, 22.1, 14.1. HRMS (EI) calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1465.

4.2.5. 9-(2-Methoxy-ethoxymethoxy)-4a-methyl-dodecahydro-phenanthrene-1,8-dione [14]. The cyclization product **14** was obtained as a yellow oil (29 mg, 58%). IR ($CDCl_3$) 2925, 2880, 1718, 1658, 1437, 1260; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.78 (d, J=22.3 Hz, 2H), 3.73–3.54 (m, 5H), 3.38 (s, 3H), 2.38–2.11 (m, 3H), 2.00–1.72 (m, 4H), 1.63–1.45 (m, 5H), 1.37–1.24 (m, 6H), 0.86 (t, J=6.2 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 211.0, 200.7, 93.7, 76.8, 72.4, 67.5, 61.2, 59.6, 56.6, 50.4, 49.4, 40.5, 38.1, 36.0, 30.3, 27.1, 25.9, 23.0, 14.5. HRMS (EI) calcd for $C_{19}H_{30}O_5$ 338.2093, found 338.2093.

4.2.6. 9a-Methyl-1,5,5a,7,8,9,9a,9b-octahydro-naphtho[1,2-*c*]furan-3,6-dione [21]. The cyclization product **21** was obtained as a light yellow oil (28 mg, 59%). IR ($CDCl_3$) 2929, 1701, 1648, 1253; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.87 (t, J=3.6 Hz, 1H), 4.45 (t, J=10.0 Hz, 1H), 3.96 (t, J=8.1 Hz, 1H), 3.17–3.09 (m, 1H), 2.51–2.31 (m, 5H), 2.01–1.87 (m, 2H), 1.76–1.71 (m, 1H), 1.24–1.21 (m, 1H), 0.98 (t, J=13.9 Hz, 1H), 0.69 (s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.4, 169.8, 135.3, 134.4, 67.1, 53.3, 48.3, 41.5, 40.3, 37.9, 23.2, 22.7, 13.3. HRMS (EI) calcd for $C_{13}H_{16}O_3$ 220.1100, found 220.1098.

4.2.7. 4-(*tert*-Butyl-dimethyl-silanyloxy)-9a-methyl-decahydro-naphtho[1,2-*c*]furan-3,6-dione [22]. The cyclization product **22** was obtained as a yellow oil (29 mg, 59%). IR ($CDCl_3$) 2930, 2830, 1740, 1715, 1450, 1420, 1220; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.42 (dd, J=19.4, 2.6 Hz, 1H), 4.27 (dd, J=16.5, 8.4 Hz, 1H), 4.13 (dd, J=11.4, 8.2 Hz, 1H), 2.89 (t, J=13.5 Hz, 1H), 2.78–2.66 (m, 1H), 2.18 (d, J=19.1 Hz, 1H), 1.95–1.67 (m, 1H), 1.69–1.55 (m, 6H), 1.25 (t, J=7.3 Hz, 1H), 1.13–1.06 (m, 1H), 0.94 (d, J=7.4 Hz, 2H), 0.88–0.81 (m, 9H), 0.11–0.06 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 211.1, 175.5, 66.9, 64.2, 51.4, 44.7, 44.3, 35.6, 35.5, 32.6, 29.9, 25.6 (3C), 21.2, 19.9, 17.9, −4.9, −5.1. HRMS (EI) calcd for $C_{19}H_{32}O_4Si$ 352.2070, found 352.2069.

4.2.8. 4-(2-Methoxy-ethoxymethoxy)-9a-methyl-decahydro-naphtho[1,2-*c*]furan-3,6-dione [23]. The cyclization product **23** was obtained as a yellow oil (31 mg, 61%). IR ($CDCl_3$) 2928, 2812, 1716, 1663, 1449, 1362; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.81–4.64 (m, 4H), 4.23–3.99 (m, 1H), 3.70–3.63 (m, 2H), 3.54–3.48 (m, 2H), 3.35 (s, 3H), 2.30–2.19 (m, 2H), 2.14–2.05 (m, 4H), 1.97–1.74 (m, 3H), 1.59–1.39 (m, 1H), 1.26–1.08 (m, 3H), 0.79–0.76 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 212.6, 174.6, 81.5, 72.8, 68.8, 60.5, 57.0, 55.8, 52.7, 49.0, 42.0, 41.1, 37.5, 31.7, 27.0, 22.8, 14.2. HRMS (EI) calcd for $C_{17}H_{26}O_6$ 326.1729, found 326.1732.

References and notes

1. Lund, H.; Hammerich, O. *Organic Electrochemistry*, 4th ed.; Marcel Dekker: New York, NY, 1991, Chapter 21; Fry, A. J. *Synthetic Organic Electrochemistry*, 2nd ed.; John Wiley and Sons: New York, NY, 1989; pp 208–232; Bastida, R. M.; Brillas, E.; Costa, J. M. *J. Electroanal. Chem.* **1987**, *227*, 55–66; Baizer, M. M.; Anderson, J. D. *J. Electrochem. Soc.* **1964**, *111*, 223–226.
2. Little, R. D.; Schwaebe, M. K. *Top. Curr. Chem.* **1997**, *185*, 2–48.
3. (a) Handy, S. T.; Omune, D. *Org. Lett.* **2005**, *7*, 1553–1555; (b) Handy, S. T.; Omune, D. *Tetrahedron* **2007**, *63*, 1366–1371.
4. Polygodial: (a) Urones, J. G.; Marcos, I. S.; Perez, B. G.; Lithgow, A. M.; Diez, D.; Gomez, P. M.; Basabe, P.; Garrido, N. M. *Tetrahedron* **1995**, *51*, 1845–1860; (b) Barrero, A. F.; Alvarezmanzaneda, E.; Altarejos, J.; Salido, S.; Ramos, J. M. *Tetrahedron Lett.* **1994**, *35*, 2945–2948; (c) Jansen, B. J. M.; Kreuger, J. A.; DeGroot, A. *Tetrahedron* **1989**, *45*, 1447–1452; (d) Razmilic, I.; Lopez, J.; Sierra, J.; Cortes, M. *Synth. Commun.* **1987**, *17*, 95–103; (e) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 273–281; (f) Guillerm, D.; Delarue, M.; Jalalinaini, M.; Lemaitre, P.; Lallemand, J. Y. *Tetrahedron Lett.* **1984**, *25*, 1043–1046; (g) Holliinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Ratcliffe, N. M.; Worthington, P. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1579–1586; Equisetin: (h) Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Org. Biomol. Chem.* **2005**, 274–280; (i) Yuki, K.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2001**, *42*, 2517–2519; (j) Turos, E.; Audia, J. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8231–8236.
5. For more recent examples, see: (a) Wei, S. W.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Catal. Today* **2007**, *121*, 151–157; (b) Shi, M.; Liu, Y. H.; Chen, L. H. *Chirality* **2007**, *19*, 124–128; (c) Xu, J. Y.; Guan, Y. Y.; Yang, S. H.; Ng, Y. R.; Peh, G. R.; Tan, C. H. *Chem. Asian J.* **2006**, 724–729; (d) Vasbinder, M. M.; Imbriglio, J. E.; Miller, S. J. *Tetrahedron* **2006**, *62*, 11450–11459; (e) Berkessel, A.; Roland, K.; Neudorfl, J. M. *Org. Lett.* **2006**, *8*, 4195–4198; (f) Wang, J.; Li, H.; Yu, X. H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005**, *7*, 4293–4296; (g) Matsui, K.; Takizawa, S.; Sasai, H. *Tetrahedron Lett.* **2005**, *46*, 1943–1946; (h) Hayashi, Y.; Tamura, T.; Shoji, M. *Adv. Synth. Catal.* **2004**, *346*, 1106–1110; (i) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231–1240; (j) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589–5592; (k) Krishna, P. R.; Kannan, V.; Reddy, P. V. N. *Adv. Synth. Catal.* **2004**, *346*, 603–606; (l) Mocquet, C. M.; Warriner, S. L. *Synlett* **2004**, 356–358; (m) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094–12095.
6. Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413–5418.
7. For example, the use of water/dioxane (1:1) afforded 8% yield after two days, while methanol afforded 34% yield after two days.
8. Li, G.; Wei, H. X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1–5.

9. Conditions were adapted from those reported by Kise and co-workers and are not optimized. Kise, N.; Iitaka, S.; Iwasaki, K.; Ueda, N. *J. Org. Chem.* **2002**, *67*, 8305–8315.
10. Mandell, L.; Daley, R. F.; Day, R. A. *J. Org. Chem.* **1976**, *41*, 4087–4089.
11. Indeed, subjection of MEM ether compound **12** to elimination afforded compound **11**, further supporting the stereochemical assignment of compound **11**.
12. Baylis–Hillman reactions of furanones most likely proceed via aldolization mechanisms and thus afford mixtures of α and γ products, with the γ product often being major. For an example, see: Franck, X.; Figadere, B. *Tetrahedron Lett.* **2002**, *43*, 1449–1451.
13. (a) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2324–2342; (b) Evans, P.; Leffray, M. *Tetrahedron* **2003**, *59*, 7973–7981.
14. Calderon, A.; March, P. D.; Arrad, M.; Font, J. *Tetrahedron* **1994**, *50*, 4201–4214.
15. (a) Cabrera, A.; Lagadec, R. L.; Sharma, P.; Arias, J. L.; Toscano, R. A.; Velasco, L.; Gavino, R.; Alvarez, C.; Salmon, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3609–3617; (b) Wu, H.; Ding, J. *J. Chem. Res.* **2002**, 461–462; (c) Banik, B. M.; Venkatraman, M. S.; Bnik, I.; Basu, M. K. *Tetrahedron Lett.* **2004**, *45*, 4737–4739; (d) Zhou, L.; Zhang, Y. *Synth. Commun.* **2000**, *30*, 597–607; (e) Cabrera, A.; Rosas, N.; Sharma, P.; Le Lagadec, R.; Velasco, L.; Salmon, M. *Synth. Commun.* **1998**, *28*, 1103–1108.
16. Zhang, S.; Zhang, X.; Bordwell, F. G. *J. Am. Chem. Soc.* **1995**, *117*, 602–606.
17. Ho, P.-T.; Lee, S. F.; Chang, D.; Wiesner, K. *Experientia* **1971**, *27*, 1377–1379.