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Development of new Wittig reagent, silylfuranmethylid, and its reactivity

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Abstract—New Wittig reagents, furanmethylids **b**-**e** were successfully developed. Their preparation, reactivity, and application toward the natural products synthesis are described in detail.

1. Introduction

A γ-hydroxybutenolide moiety is found in various biologically active natural products, such as manoalide,[1] dysidiolide,[2] and spongianolide A,[3] and it is also regarded as a useful intermediate for the synthesis of (*Z*)-1,2-dicarbonylethylene derivatives.

The α-silylfuran derivatives substituted at the 3- or 4-positions are recognized as the appropriate precursors of the corresponding regioisomeric γ-hydroxybutenolide synthesis, because they can be regiospecifically oxidized with singlet oxygen (Fig. 1).[4] Thus, the silyl group directs the formation of the carbonyl group.

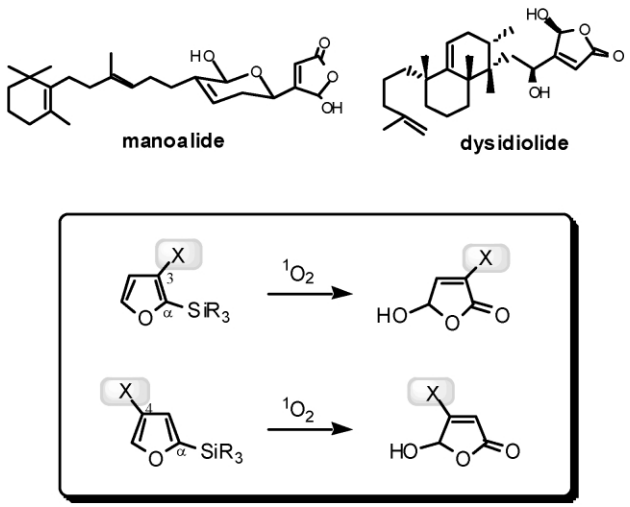

Figure 1. Regiospecific synthesis of γ-hydroxybutenolides.

Keywords: silylfuranmethylide; new Wittig reagent; γ-hydroxybutenolide; conjugated silylfuran.

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During our program on the synthesis of new phospholipase A_2 (PLA_2) inhibitors and the elucidation of their inhibitory mechanism,[5] it was required to synthesize the γ-hydroxybutenolide derivative **3**, and hence, the corresponding α-silylfuran derivative **2** conjugated at the 3-position (Fig. 2(a)). However, **2** could not be easily prepared from the sterically hindered aldehyde **1** and unstable 3-furylmethyl anion equivalents under the conventional Julia coupling or aldol-dehydration conditions. Also, in our synthetic study of a cytotoxic sesterterpenoid, (−)-spongianolide A, it was necessary to develop an efficient method for introduction of the α-silylfuran moiety conjugated at the 4-position toward the sterically hindered aldehyde of the tricyclic terpene skeleton such as **4** (Fig. 2(b)).[6] We successfully overcame these problems by applying the Wittig olefination reaction of 3-(2- or 5-trimethylsilylfuryl)triphenylphosphonium methylids **b** and **d** with the aldehydes **1** and **4**, respectively. Thus, silylfuranmethylids **b**-**e**, and hence the corresponding Wittig salts **B**-**E** seemed to be very useful for the synthesis of these conjugated furan derivatives. In this paper, we disclose the novel furanmethylids **b**-**e** and their preparation in detail, and discuss their reactivity toward aldehydes correlated with the silyl substituents on the furan ring, in comparison with that of a simple non-silyl substituted furanmethylid **a**.[7]

2. Results and discussion

The Wittig salts **B**-**E** were prepared by the standard procedure as shown in Scheme 1. The 2-trimethylsilyl (TMS) derivative **B** was prepared in 47% yield on a 500 mg scale from the corresponding 3-(2-TMS)furylmethanol, which was obtained from 3-furanmethanol **6**.[4,8] Thus, 3-(2-TMS)furylmethanol was reacted with phosphorus tribromide in the presence of a catalytic amount of pyridine to give the allylbromide intermediate, which was not

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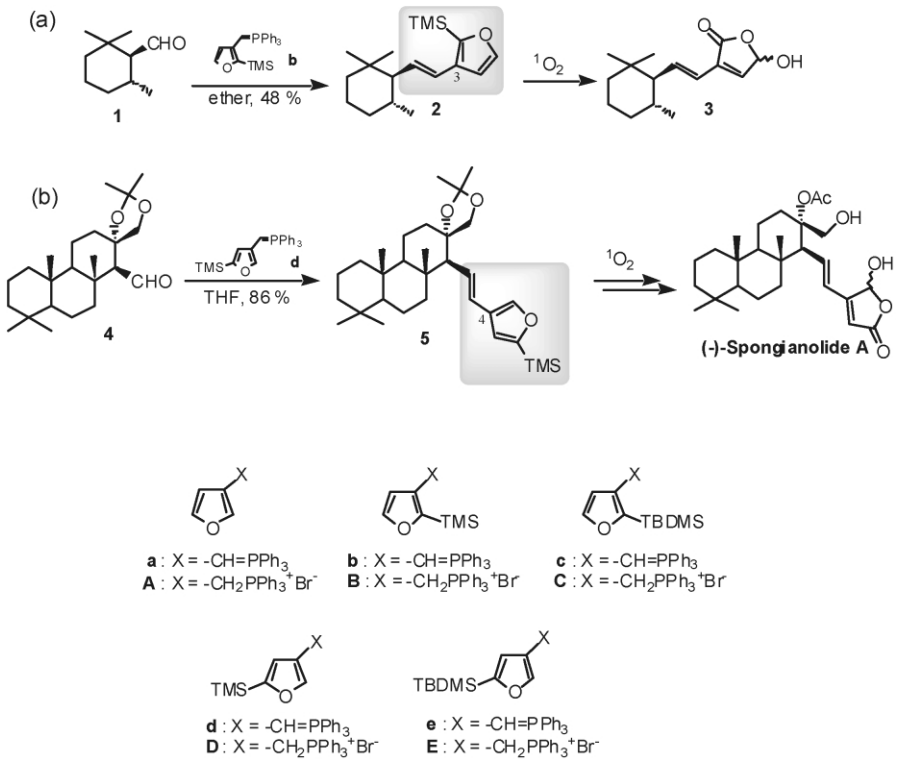
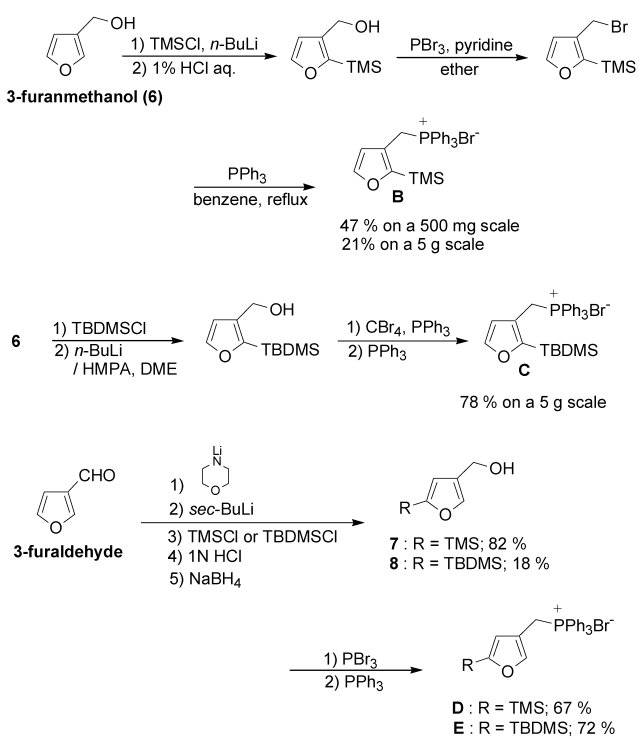


Figure 2.

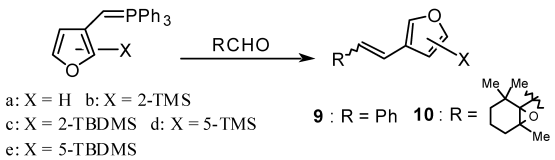
purified, and then treated with triphenylphosphine in benzene at 80°C to provide the desired **B** as a white solid. However, the 5 g scale preparation of **B** by this method resulted in only a 21% yield at most. On the other hand, the corresponding 2-*tert*-butyldimethylsilyl (TBDMS) derivative **C** was successfully synthesized from 3-(2-TBDMS)-furylmethanol in a substantially improved yield even on a 5 g scale. Thus, 3-(2-TBDMS)furylmethanol, which was obtained from **6** by an O-silylation followed by the retro-Brook rearrangement,[9] was treated with carbon tetrabromide and triphenylphosphine to give the allylbromide intermediate, which was then immediately reacted with triphenylphosphine at 80°C to afford the desired **C** in 78% yield. Presumably, a bulkier alkyl group of the silyl substituent at the 2-position of the furan ring would contribute to the stabilization of the 3-furylmethyl bromide intermediate.



Scheme 1.

The corresponding 5-TMS and 5-TBDMS derivatives **D** and **E** were also prepared from 3-furaldehyde as shown in Scheme 1. According to the literature procedure,[8,10] 3-(5-TMS)furaldehyde was obtained in one-pot by the treatment of 3-furaldehyde with lithium morpholinium, followed by lithiation and trimethylsilylation at the 5-position of the furan ring, and then by an acidic workup. After reduction of the aldehyde group with sodium borohydride, the corresponding 3-(5-TMS)furylmethanol **7** was obtained in 82% overall yield from 3-furaldehyde. Disappointedly, the preparation of the corresponding TBDMS-substituted furanmethanol **8** by the same procedure resulted in only an 18% yield due to the low reactivity of the lithium anion intermediate of the furan toward *tert*-butyldimethylsilyl chloride. Further trials to improve the yield under the various reaction conditions, such as increasing the reaction temperature or using more reactive TBDMSOTf were unsuccessful. Despite the problem regarding the preparation of **8**, both of the obtained 3-furanmethanols **7** and **8** were successfully converted to the corresponding Wittig salts **D** and **E** in 70–80% yields by bromination with phosphorus tribromide followed by the reaction with

Table 1. Reactivity of furanmethylids **a**-**e** toward aldehydes **9** and **10**



Entry	Aldehyde	Ylid	Product	Yield (%)	*E*/*Z*[a]
1	**9**	**a**	**9a**	82	4:5
2	**9**	**b**	**9b**	99	10:7
3	**9**	**c**	**9c**	93	10:7
4	**9**	**d**	**9d**	88	1:1
5	**9**	**e**	**9e**	quant.	1:1
6	**10**	**a**	**10a**	46	*E* only
7	**10**	**b**	**10b**	53	*E* only
8	**10**	**c**	**10c**	73	*E* only
9	**10**	**d**	**10d**	20	*E* only
10	**10**	**e**	**10e**[b]	95	*E* only

The Wittig salts **A**-**E** were treated with *n*-butyllithium in ether at 0°C for 15 min, and prepared furanmethylids **a**-**e** were reacted with aldehydes **9** and **10** at the same temperature.

[a] Determined by ^{1}H NMR (400 MHz).

[b] Produced **10e** was gradually transformed into unidentified products in $CDCl_3$.

triphenylphosphine, respectively. In contrast to the synthesis of the 2-TMS derivative **B**, the 5-TMS derivative **D** was successfully prepared in 67% yield even on a 5 g scale.

In order to test the reactivity of the newly developed furanmethylids **b**-**e** and to compare their reactivity with that of non-silyl substituted furanmethylid **a**, they were reacted with the selected aldehydes **9** and **10**, respectively. These results are shown in Table 1. The Wittig salts **A**-**E** were treated with *n*-butyllithium in ether at 0°C for 15 min, and the resulting red solutions of the corresponding furanmethylids **a**-**e** were reacted with each aldehyde at the same temperature. All of the reactions between the furanmethylids **a**-**e** and benzaldehyde **9** smoothly provided the corresponding conjugated furan derivatives **9a**-**9e** in 82–100% yields as almost equal mixtures of (*E*)- and (*Z*)-stereoisomers (entries 1–5). Meanwhile, the differences in reactivity of the ylids **a**-**e** were clearly observed toward the aldehyde **10** as shown in entries 6–10. We previously experienced that the reaction between the epoxyaldehyde **10** and alkyl lithium or Grignard reagents did not provide the expected alcohols, but resulted in the decomposition of **10**. Apparently, the steric hindrance around the aldehyde group by the neighboring *gem*-dimethyl substituent and the base sensitive epoxide moiety retarded the addition reaction of anion species toward this aldehyde. However, the ylids **a**-**e** successfully produced the desired conjugated furan derivatives, and showed their individual reactivity of one another. Thus, the silyl-free furanmethylid **a** provided the corresponding coupling product **10a** as a single (*E*)- stereoisomer in only 46% yield (entry 6). Similarly, 2-TMS-furanmethylid **b** gave **10b** in only 53% yield, accompanied by unidentified products due to the decomposition of the starting material (entry 7). However, the utilization of the 2-TBDMS derivative **c** substantially improved the product formation, and **10c** was obtained in 73% yield (entry 8). A similar phenomenon was observed for the reactions of the 5-silyl substituted furanmethylids **d** and **e** with aldehyde **10**. Thus, the reaction of the 5-TMS derivative **d** gave a complex mixture of products from which only a small amount of **10d** was detected by observation of the characteristic signals in its ^{1}H NMR (yield of **10d** was less than 20%, entry 9). On the contrary, 5-TBDMS furanmethylid **e** successfully provided **10e** in 95% yield (entry 10).[11] Based on these results, it was suggested that the bulky TBDMS group on the furan ring stabilized the benzylic anion of furanmethylid,[12] and it would also protected the coupling products from their decomposition. Thus, the bulky TBDMS group effected the production of the conjugated furan derivatives even toward the notorious aldehyde **10**.

The application of these developed furanmethylids is shown in Figures 2 and 3. In addition to the examples in Figure 2, the tricyclic furan derivative **12** was obtained in 84% yield as a single (*E*)-stereoisomer by the reaction of **d** with the epoxyaldehyde **11** (Fig. 3(a)).[6] Furthermore, in our synthesis of the peridinin, nor-carotenoid, the

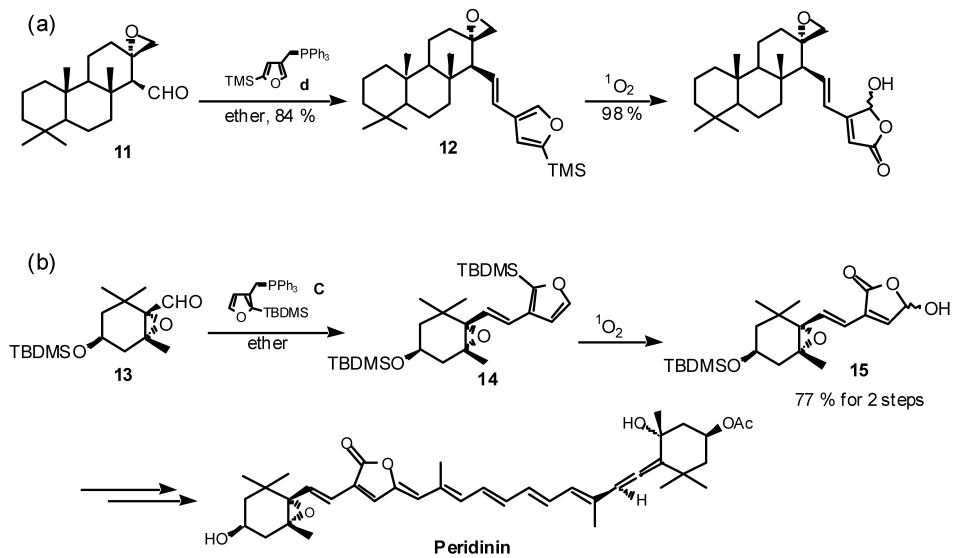


Figure 3.

epoxyaldehyde **13** was reacted with the ylid **c** to produce the corresponding furan derivative **14** in excellent yield (Fig. 3(b)).[13] The obtained silylfuran derivatives **2**, **5**, **12**, and **14** were then regiospecifically oxidized with singlet oxygen to provide the corresponding γ-hydroxybutenolide derivatives as a 1:1 mixture of stereoisomers at the hydroxy group in the butenolide ring. Thus, the efficient method for the regiospecific synthesis of the conjugated γ-hydroxybutenolide derivatives was realized.

In summary, we developed new Wittig reagents, the 3-furylmethyltriphenylphosphonium methylids **b**-**e**, which are very useful for the synthesis of the conjugated furan derivatives, and hence, the regiospecific synthesis of the corresponding γ-hydroxybutenolide derivatives. The 2-TBDMS-furanmethylid **c** is recommended for the synthesis of the corresponding α-silylfuran derivatives conjugated at the 3-position, because **c** is easily prepared from 3-furanmethanol and provided the coupling products in high yields with any of the aldehydes examined herein. On the other hand, the synthesis of the α-silylfuran derivatives conjugated at the 4-position such as **5**, **9d**, and **12** can be efficiently achieved by utilizing 5-TMS-furanmethylid **d**. Notably, 5-TBDMS-furanmethylid **e** exhibited excellent reactivity even toward the notorious aldehyde **10**, though its preparation from 3-furaldehyde is somewhat troublesome.

3. Experimental

3.1. General

All commercially available reagents were used without further purification. All solvents were used after distillation. Tetrahydrofuran and diethylether were refluxed over and distilled from sodium. Dichloromethane was refluxed over and distilled from P_2O_5. Preparative separation was usually performed by column chromatography on silica gel (FUJI silysia LTD, BW-200 and BW-300) and on aluminum oxide (Merck, Aluminum oxide 90, standardized, activity II-III) deactivated with 5 w/% of H_2O, and by thin layer chromatography on silica gel (Merck, 20×20 cm, Silica gel 60 F_{254}, 1 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL α-400 spectrometer and chemical shifts were represented as δ-values relative to the internal standard TMS. IR spectra were recorded on a JAS.CO FT/IR-8000 Fourier Transform Infrared Spectrometer. High resolution mass spectra (HRMS) were measured on a Hitachi M-4100 Tandem Mass Spectrometer. Melting points were uncorrected.

3.1.1. 3-(2-Trimethylsilylfuryl)methyltriphenylphosphonium bromide (B). To an ether (30 mL) solution of 3-(2-trimethylsilyl)furylmethanol[4,8] (500 mg, 2.94 mmol) and pyridine (0.04 mL, 0.49 mmol) was added phosphorus tribromide (0.34 mL, 3.53 mmol) at 0°C. After the reaction mixture was stirred at room temperature for 80 min, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the corresponding crude bromide, which was used without further purification.

To a benzene (30 mL) solution of the crude bromide obtained above was added triphenylphosphine (1.16 g, 4.41 mmol) at room temperature. After stirring for 4 h under the reflux condition, the reaction mixture was filtered to give the corresponding phosphonium salt **B** (691 mg, 47%) as a white solid: mp 159–160°C; IR (KBr disk, cm^{-1}) 3063, 2855, 2787, 1441, 1250, 1167, 1113, 839; ^{1}H NMR (400 MHz, CD_3OD) δ 0.01 (s, 9H), 4.66 (d, 2H, *J*=13.6 Hz), 5.81 (brs, 1H), 7.60–7.66 (m, 6H), 7.69 (d, 1H, *J*=1.6 Hz), 7.74–7.79 (m, 6H), 7.91–7.96 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ-2.9, 21.7 (d, *J*=51.0 Hz), 110.6, 117.4 (d, *J*=85.6 Hz), 120.2 (d, *J*=8.3 Hz), 130.1 (d, *J*=12.3 Hz), 133.8 (d, *J*=9.0 Hz), 135.3 (d, *J*=3.3 Hz), 148.0; FAB HRMS *m*/*z* calcd for $C_{26}H_{28}OSiP$ $(M-Br)^+$ 415.1647, found 415.1638.

3.1.2. 3-(2-*tert*-Butyldimethylsilylfuryl)methyltriphenylphosphonium bromide (C). To a dichloromethane (35 mL) solution of 3-(2-*tert*-butyldimethylsilyl)furylmethanol (2.51 g, 11.8 mmol) was added carbon tetrabromide (5.26 g, 20.1 mmol) at 0°C. The reaction mixture was stirred at 0°C for 10 min, and triphenylphosphine (6.65 g, 20.1 mmol) was added at the same temperature. After the mixture was stirred for 15 min, the bulk of dichloromethane was removed in vacuo, and ether was added. The precipitate formed was removed by decantation for several times, and the resulting solution was concentrated in vacuo to provide the corresponding crude bromide, which was immediately used for the next reaction.

To a benzene (50 mL) solution of the crude bromide obtained above was added triphenylphosphine (6.65 g, 20.1 mmol) at room temperature. After stirring for 8 h at 50°C, the reaction mixture was filtered to give the corresponding triphenylphosphonium salt **C** (4.93 g, 78%) as a white solid: mp 232–233°C; IR (KBr disk, cm^{-1}) 2953, 2849, 1562, 1476, 1437, 1248, 1169, 1113, 843; ^{1}H NMR (400 MHz, CD_3OD) δ −0.08 (s, 6H), 0.83 (s, 9H), 4.63 (d, 2H, *J*=13.6 Hz), 5.81 (dd, 1H, *J*=1.7, 1.0 Hz), 7.58–7.64 (m, 6H), 7.72 (d, 1H, *J*=1.6 Hz), 7.74–7.79 (m, 6H), 7.91–7.96 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ −7.3, 16.8, 21.9 (*J*=51.0 Hz), 25.2, 110.5, 117.3 (*J*=85.6 Hz), 121.4 (*J*=8.2 Hz), 127.8, 130.1 (*J*=12.3 Hz), 133.8 (*J*=9.1 Hz), 135.3 (*J*=3.3 Hz), 148.1; FAB HRMS *m*/*z* calcd for $C_{29}H_{34}OSiP$ $(M-Br)^+$ 457.2117, found 457.2116.

3.1.3. 3-(5-Trimethylsilylfuryl)methyltriphenylphosphonium bromide (D). To an ether (50 mL) solution of 3-(5-trimethylsilyl)furylmethanol (2.23 g, 13.4 mmol) and pyridine (0.87 mL, 10.7 mmol) was added phosphorus tribromide (1.52 mL, 16.1 mmol) at 0°C and stirred for 15 min at this temperature. After the reaction mixture was stirred at room temperature for an additional 1 h, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the corresponding crude bromide, which was used without further purification.

To a benzene (130 mL) solution of the crude bromide obtained above was added triphenylphosphine (5.26 g, 20.1 mmol) at room temperature. After stirring for 2 h at 60°C, the reaction mixture was filtered to give the

corresponding triphenylphosphonium salt **D** (4.45 g, 67%) as a white solid: mp 166–167°C (recrystallization from MeOH–hexane); IR (KBr disk, cm^{-1}) 3070, 2880, 1595, 1442, 1242, 1114, 848; ^1H NMR (400 MHz, CD_3OD) δ 0.15 (s, 9H), 4.77 (d, 2H, J=14.0 Hz), 6.05 (s, 1H), 7.47 (d, 1H, J=4.4 Hz), 7.70–7.76 (m, 12H), 7.88–7.92 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ-1.9, 21.2 (d, J=51.0 Hz), 112.6, 119.5 (d, J=85.0 Hz), 122.6, 131.4 (d, J=12.0 Hz), 135.2 (d, J=9.0 Hz), 136.5, 148.5 (d, J=9.0 Hz); FAB HRMS m/z calcd for $C_{26}H_{28}OSiP$ $(M-Br)^+$ 415.1647, found 415.1641.

3.1.4. 3-(5-*tert*-Butyldimethylsilyl)furylmethanol. To a solution of morpholine (2.6 mL, 30.0 mmol) in THF (240 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 18.8 mL, 30.0 mmol) at −78°C. The reaction mixture was stirred at −78°C for 20 min and 3-furaldehyde (2.0 mL, 23.1 mmol) was added dropwise at the same temperature. After the mixture was stirred at −78°C for an additional 20 min, *sec*-butyllithium (1.0 M solution in cyclohexane, 27.7 mL, 27.7 mmol) was added at this temperature. The resulting mixture was stirred for 7.5 h at −78°C, and *tert*-butyldimethylsilylchloride (7.00 g, 46.4 mmol) was added at the same temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 12 h, 1N HCl solution was rapidly added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with 1N HCl solution, saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Rough column chromatography on silica gel (5% ethyl acetate in hexane) gave the corresponding 3-(5-*tert*-butyldimethylsilyl)furaldehyde, which was reduced without further purification.

To a solution of the crude aldehyde obtained above in methanol (100 mL) was added sodium borohydride (437 mg, 11.6 mmol) at 0°C. After the reaction mixture was stirred at this temperature for 10 min, 1N HCl solution was slowly added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with 1N HCl solution, saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Column chromatography on silica gel (gradually from 2 to 17% ethyl acetate in hexane) gave the corresponding alcohol (894 mg, 18%) as a yellow oil: IR (neat, cm^{-1}) 3337, 1470, 1252, 1076, 1020; ^1H NMR (400 MHz, $CDCl_3$) δ 0.22 (s, 6H), 0.92 (s, 9H), 4.57 (d, 2H, J=0.5 Hz), 6.68 (s, 1H), 7.62 (d, 1H, J=0.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −6.4, 16.7, 26.3 56.6, 120.9, 124.9, 144.2, 160.2; EI HRMS m/e calcd for $C_{11}H_{20}O_2Si$ (M^+) 212.1231, found 212.1250.

3.1.5. 3-(5-*tert*-Butyldimethylsilylfuryl)methyltriphenylphosphonium bromide (E). To an ether (30 mL) solution of 3-(5-*tert*-butyldimethylsilyl)furylmethanol (784 mg, 3.69 mmol) and pyridine (0.24 mL, 2.96 mmol) was added phosphorus tribromide (0.84 mL, 8.86 mmol) at 0°C, and the mixture was stirred for 10 min at this temperature. After the reaction mixture was stirred at room temperature for 105 min, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the corresponding crude bromide, which was used without further purification.

To a benzene (20 mL) solution of the crude bromide obtained above was added triphenylphosphine (1.45 g, 5.54 mmol) at room temperature. After stirring for 3 h under the reflux condition, the reaction mixture was concentrated in vacuo. Recrystallization of the obtained crude solids from ether provided the corresponding triphenylphosphonium salt **E** (1.44 g, 72%) as a white solid: mp 232–233°C; IR (KBr disk, cm^{-1}) 1437, 1252, 1080, 839; ^1H NMR (400 MHz, CD_3OD) δ 0.12 (s, 6H), 0.84 (s, 9H), 4.82 (d, 2H, J=14.2 Hz), 6.12 (d, 1H, J=1.2 Hz), 7.51–7.53 (m, 1H), 7.70–7.78 (m, 12H), 7.88–7.93 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ −7.9, 16.0, 19.8 (d, J=51.8 Hz), 25.1, 111.0 (d, J=9.0 Hz), 117.9 (d, J=85.6 Hz), 122.3, 129.9 (d, J=12.3 Hz), 133.7 (d, J=9.9 Hz), 135.0 (d, J=2.4 Hz), 147.2 (d, J=9.1 Hz), 160.2; FAB HRMS m/z calcd for $C_{29}H_{34}OSiP$ $(M-Br)^+$ 457.2117, found 457.2116.

3.1.6. (*E*)- and (*Z*)-3-(β-Styryl)furan (9a). To a solution of 3-furylmethyltriphenylphosphonium bromide **A** (598 mg, 1.41 mmol) in ether (7 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 0.88 mL, 1.41 mmol) at 0°C. The reaction mixture was stirred at 0°C for 15 min, and an ether (1 mL) solution of benzaldehyde (100 mg, 0.942 mmol) was added at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 20 min, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Column chromatography on silica gel (1% ethyl acetate in hexane) gave a 4:5 mixture of (*E*)- and (*Z*)-stereoisomers (131 mg, 82%). These stereoisomers were successfully separated by preparative TLC on silica gel (9% ethyl acetate in hexane): Data for (*E*)-stereoisomer (white solid): IR (KBr disk, cm^{-1}); 1155, 1073, 1020, 963, 870, 783; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66–6.67 (m, 1H), 6.82 (d, 1H, J=16.0 Hz), 6.97 (d, 1H, J=16.4 Hz), 7.32–7.36 (m, 3H), 7.41–7.46 (m, 3H), 7.532–7.534 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.4 118.4 124.5, 126.1, 127.3, 128.4, 128.6, 137.3, 140.9, 143.7; EI HRMS m/e calcd for $C_{12}H_{10}O$ (M^+) 170.0731, found 170.0732. Data for (*Z*)-stereoisomer (colorless liquid): IR (neat, cm^{-1}); 1505, 1491, 1159, 1074, 1022; ^1H NMR (400 MHz, $CDCl_3$) δ 6.115–6.119 (m, 1H), 6.38 (d, 1H, J=12.0 Hz), 6.55 (d, 1H, J=12.0 Hz), 7.22–7.36 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.2, 120.1, 122.3 127.1, 128.2, 128.7, 129.4, 137.9, 142.0, 142.5; EI HRMS m/e calcd for $C_{12}H_{10}O$ (M^+) 170.0731, found 170.0735.

3.1.7. (*E*)- and (*Z*)-3-(β-Styryl)-2-trimethylsilylfuran (9b). To a solution of 3-(2-trimethylsilylfuryl)methyltriphenylphosphonium bromide **B** (518 mg, 1.05 mmol) in ether (7 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 0.65 mL, 1.05 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min, and an ether (1 mL) solution of benzaldehyde (74 mg, 0.697 mmol) was added at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 30 min, H_2O was added, and the resulting

mixture was extracted with ether. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Column chromatography on silica gel (2% ethyl acetate in hexane) gave a 10:7 mixture of (*E*)- and (*Z*)-stereoisomers (168 mg, 99%). These compounds were separated by column chromatography on silica gel (hexane): data for (*E*)-stereoisomer (white solid): IR (KBr disk, cm^{-1}); 1250, 1144, 1092, 1053, 957; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9H), 6.33 (d, 1H, J=1.7 Hz), 6.46 (d, 1H, J=16.1 Hz), 6.78 (d, 1H, J=16.1 Hz), 6.86–6.90 (m, 1H), 6.99 (dd, 2H, J=7.3, 7.3 Hz), 7.09 (d, 2H, J=7.6 Hz), 7.22 (d, 1H, J=1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.0, 108.1, 120.7, 127.0, 128.1, 129.2, 129.6, 134.9, 138.5, 147.6, 159.1; EI HRMS *m/e* calcd for $C_{15}H_{18}OSi$ (M^+) 242.1126, found 242.1140. Data for (*Z*)-stereoisomer (colorless liquid): IR (neat, cm^{-1}); 1252, 1101, 1051; ^1H NMR (400 MHz, $CDCl_3$) δ 0.31 (s, 9H), 6.06 (d, 1H, J=1.7 Hz), 6.52–6.53 (m, 2H), 7.19–7.33 (m, 5H), 7.40 (d 1H, J=1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.2, 110.3, 121.5, 127.0, 128.1, 129.0, 129.7, 132.1, 137.7, 145.7, 158.4; EI HRMS *m/e* calcd for $C_{15}H_{18}OSi$ (M^+) 242.1126, found 242.1129.

3.1.8. (*E*)- and (*Z*)-3-(β-Styryl)-2-*tert*-butyldimethylsilylfuran (9c). To a solution of 3-(2-*tert*-butyldimethylsilylfuryl)methyltriphenylphosphonium bromide **C** (2.21 g, 4.24 mmol) in ether (30 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 2.65 mL, 4.24 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min, and an ether (2 mL) solution of benzaldehyde (300 mg, 2.83 mmol) was added at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 30 min, H_2O was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Column chromatography on silica gel (hexane) gave a 10:7 mixture of (*E*)- and (*Z*)-stereoisomers (746 mg, 93%). These stereoisomers were separated by column chromatography on silica gel (hexane): Data for (*E*)-stereoisomer (white solid): IR (KBr disk, cm^{-1}); 1250, 1142, 1092, 957; ^1H NMR (400 MHz, $CDCl_3$) δ 0.37 (s, 6H), 0.94 (s, 9H), 6.70 (dd, 1H, J=1.7, 0.5 Hz), 6.81 (d, 1H, J=16.1 Hz), 7.14 (d, 1H, J=16.1 Hz), 7.23 (dddd, 1H, J=7.3, 7.3, 2.0, 2.0 Hz), 7.34 (dd, 2H, J=8.1, 8.1 Hz), 7.42–7.44 (m, 2H), 7.59 (dd, 1H, J=2.0, 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 17.6, 26.4, 107.1, 120.3, 126.1, 127.2, 128.2, 128.7, 135.0, 137.7, 146.9, 157.0; EI HRMS *m/e* calcd for $C_{18}H_{24}OSi$ (M^+) 284.1595, found 284.1586. Data for (*Z*)-stereoisomer (colorless liquid): IR (neat, cm^{-1}); 1470, 1395, 1252, 1096; ^1H NMR (400 MHz, $CDCl_3$) δ 0.31 (s, 6H), 0.94 (s, 9H), 6.05 (dd, 1H, J=1.7, 0.5 Hz), 6.51 (d, 1H, J=12.2 Hz), 6.55 (d, 1H, J=12.2 Hz), 7.19–7.31 (m, 5H), 7.40–7.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.7, 17.8, 26.4, 110.3, 121.9, 127.0, 128.0, 129.0, 129.5, 133.2, 137.7, 145.8, 157.3; EI HRMS *m/e* calcd for $C_{18}H_{24}OSi$ (M^+) 284.1595, found 284.1592.

3.1.9. (*E*)- and (*Z*)-4-(β-Styryl)-2-trimethylsilylfuran (9d). To a solution of 3-(5-trimethylsilylfuryl)methyltriphenylphosphonium bromide **D** (525 mg, 1.06 mmol) in ether (7 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 0.66 mL, 1.06 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min, and an ether (1 mL) solution of benzaldehyde (75 mg, 0.707 mmol) was added at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 20 min, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Column chromatography on silica gel (3% ethyl acetate in hexane) gave a 1:1 mixture of (*E*)- and (*Z*)-stereoisomers (151 mg, 88%). These stereoisomers were separated by preparative TLC on silica gel (2% ethyl acetate in hexane): Data for (*E*)-stereoisomer (white solid): IR (KBr disk, cm^{-1}); 1248, 1119, 1076, 961; ^1H NMR (400 MHz, $CDCl_3$) δ 0.29 (s, 9H), 6.82 (d, 1H, J=16.4 Hz), 6.88 (d, 1H, J=0.5 Hz), 6.99 (d, 1H, J=16.1 Hz), 7.20–7.24 (m, 1H), 7.33 (dd, 2H, J=7.6, 7.6 Hz), 7.44 (d, 2H, J=7.8 Hz), 7.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.7, 117.0, 118.4, 124.5, 126.1, 127.2, 128.0, 128.6, 137.6, 145.1, 161.9; EI HRMS *m/e* calcd for $C_{15}H_{18}OSi$ (M^+) 242.1126, found 242.1141. Data for (*Z*)-stereoisomer (colorless liquid): IR (neat, cm^{-1}); 1252, 1125, 1074, 910; ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H), 6.35 (s, 1H), 6.37 (d, 1H, J=13.1 Hz), 6.51 (d, 1H, J=12.0 Hz), 7.23–7.36 (m, 5H), 7.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.8, 120.1, 120.3, 122.2, 127.1, 128.2, 128.6, 129.0, 138.1, 146.1, 160.3; EI HRMS *m/e* calcd for $C_{15}H_{18}OSi$ (M^+) 242.1126, found 242.1135.

3.1.10. (*E*)- and (*Z*)-4-(β-Styryl)-2-*tert*-butyldimethylsilylfuran (9e). To a solution of 3-(5-*tert*-butyldimethylsilylfuryl)-methyltriphenylphosphonium bromide **E** (570 mg, 1.06 mmol) in ether (7 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 0.66 mL, 1.06 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min, and an ether (1 mL) solution of benzaldehyde (75 mg, 0.707 mmol) was added at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 10 min, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Column chromatography on silica gel (2% ethyl acetate in hexane) gave a 1:1 mixture of (*E*)- and (*Z*)-stereoisomers (200 mg, 100%). These compounds were separated by column chromatography on silica gel (gradually 0–2% ethyl acetate in hexane): Data for (*E*)-stereoisomer (white solid): IR (KBr disk, cm^{-1}); 1470, 1252, 1113, 1076, 953; ^1H NMR (400 MHz, $CDCl_3$) δ 0.26 (s, 6H), 0.95 (s, 9H), 6.83 (d, 1H, J=16.4 Hz), 6.896–6.899 (m, 1H), 6.99 (d, 1H, J=16.1 Hz), 7.21–7.26 (m, 1H), 7.34 (dd, 2H, J=7.3, 7.3 Hz), 7.45 (dm, 2H, J=7.8 Hz), 7.73 (d, 1H, J=0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −6.3, 16.8, 26.3, 118.2, 118.5, 124.4, 126.0, 127.2, 127.9, 128.6, 137.6, 145.3, 160.4; EI HRMS *m/e* calcd for $C_{18}H_{24}OSi$ (M^+) 284.1595, found 284.1602. Data for (*Z*)-stereoisomer (colorless oil): IR (neat, cm^{-1}); 1470, 1252, 1125, 1074; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 6H), 0.89 (s, 9H), 6.380–6.383 (m, 1H), 6.40 (d, 1H, J=12.0 Hz), 6.53 (d, 1H, J=12.0 Hz), 7.25–7.37 (m, 5H), 7.55 (d, 1H, J=0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −6.5, 16.7, 26.2, 120.3,

121.4, 122.1, 127.1, 128.1, 128.7, 129.0, 138.0, 146.1, 158.7; EI HRMS *m/e* calcd for $C_{18}H_{24}OSi$ (M^+) 284.1595, found 284.1593.

3.1.11. (*E*)-3-[2-(1,2-Epoxy-2,6,6-trimethylcyclohexyl)-vinyl] furan (10a). To a solution of 3-furylmethyltriphenylphosphonium bromide **A** (566 mg, 1.34 mmol) in ether (9 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 0.84 mL, 1.34 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min, and an ether (1 mL) solution of the epoxyaldehyde **10** (150 mg, 0.892 mmol) was added at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 2.5 h, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Column chromatography on aluminum oxide (2% ethyl acetate in hexane) gave the conjugated furan derivative **10a** (96 mg, 46%) as a colorless oil: IR (neat, cm^{-1}); 1460, 1379, 1260, 1161, 1073, 1024; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.04–1.10 (m, 1H), 1.12 (s, 3H), 1.18 (s, 3H), 1.39–1.52 (m, 3H), 1.72–1.79 (m, 1H), 1.87–1.95 (m, 1H), 6.12 (d, 1H, J=15.6 Hz), 6.40 (d, 1H, J=15.9 Hz), 6.53 (d, 1H, J=2.0 Hz), 7.36–7.37 (m, 1H), 7.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 21.0, 25.9, 30.1, 33.7, 35.7, 65.5, 71.0, 107.5, 122.3, 123.8, 124.8, 140.4, 143.4; EI HRMS *m/e* calcd for $C_{15}H_{20}O_2$ (M^+) 232.1462, found 232.1450.

3.1.12. (*E*)-3-[2-(1,2-Epoxy-2,6,6-trimethylcyclohexyl)-vinyl]-2-trimethylsilylfuran (10b). To a solution of 3-(2-trimethylsilylfuryl)methyltriphenylphosphonium bromide **B** (230 mg, 0.464 mmol) in ether (3.6 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 0.29 mL, 0.464 mmol) at 0°C. The reaction mixture was stirred at 0°C for 10 min, and an ether (1 mL) solution of the epoxyaldehyde **10** (52 mg, 0.309 mmol) was added at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 30 min, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Column chromatography on aluminum oxide (2% ethyl acetate in hexane) gave the corresponding conjugated furan derivative **10b** (57 mg, 53%) as a colorless oil: IR (neat, cm^{-1}); 1460, 1381, 1252, 1098; ^1H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 9H), 0.97 (s, 3H), 1.12 (s, 3H), 1.19 (s, 3H), 1.40–1.56 (m, 4H), 1.73–1.80 (m, 1H), 1.88–1.95 (m, 1H), 6.10 (d, 1H, J=15.9 Hz), 6.53 (d, 1H, J=1.7 Hz), 6.57 (d, 1H, J=15.9 Hz), 7.53 (d, 1H, J=1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.0, 17.1, 21.0, 25.9, 30.1, 33.7, 35.8, 65.6, 71.2, 107.5, 123.7, 124.9, 133.8, 146.4, 158.4; EI HRMS *m/e* calcd for $C_{18}H_{28}O_2Si$ (M^+) 304.1857, found 304.1867.

3.1.13. (*E*)-3-[2-(1,2-Epoxy-2,6,6-trimethylcyclohexyl)-vinyl]-2-*tert*-butyldimethylsilylfuran (10c). To a solution of 3-(2-*tert*-butyldimethylsilylfuryl)methyltriphenylphosphonium bromide **C** (1.26 g, 2.41 mmol) in ether (12 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 1.70 mL, 2.66 mmol) at 0°C. The reaction mixture was stirred at 0°C for 10 min, and an ether (2 mL) solution of the epoxyaldehyde **10** (203 mg, 1.21 mmol) was added at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 30 min, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Column chromatography on aluminum oxide (2% ethyl acetate in hexane) gave the corresponding conjugated furan derivative **10c** (305 mg, 73%) as a colorless oil: IR (neat, cm^{-1}); 1464, 1389, 1362, 1252, 1094; ^1H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 6H), 0.89 (s, 9H), 0.96 (s, 3H), 1.12 (s, 3H), 1.18 (s, 3H), 1.41–1.49 (m, 4H), 1.73–1.78 (m, 1H), 1.89–1.93 (m, 1H), 6.11 (d, 1H, J=15.6 Hz), 6.55 (d, 1H, J=1.7 Hz), 6.58 (d, 1H, J=15.6 Hz), 7.50 (d, 1H, J=1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, 17.1, 17.5, 21.0, 25.8, 25.9, 26.4, 30.1, 33.7, 35.8, 65.6, 71.2, 107.3, 124.2, 124.7, 134.3, 146.6, 156.1; EI HRMS *m/e* calcd for $C_{21}H_{34}O_2Si$ (M^+) 346.2326, found 346.2319.

3.1.14. (*E*)-4-[2-(1,2-Epoxy-2,6,6-trimethylcyclohexyl)-vinyl]-2-trimethylsilylfuran (10d). To a solution of 3-(5-trimethylsilylfuryl)methyltriphenylphosphonium bromide **D** (442 mg, 0.892 mmol) in ether (6 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 0.56 mL, 0.892 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min, and an ether (1 mL) solution of the epoxyaldehyde **10** (100 mg, 0.594 mmol) was added at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 1 h, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Unfortunately, the conjugated furan derivative **10d** could not be completely purified by column chromatography, and its presence in the crude mixture was only detected by the observation of the characteristic signals of its ^1H NMR and MS (yield was less than 20%): ^1H NMR (400 MHz, $CDCl_3$) (characteristic signals of **10d**) δ 6.12 (d, 1H, J=15.9 Hz), 6.42 (d, 1H, J=15.6 Hz), 6.75 (s, 1H), 7.60 (s, 1H); EI HRMS *m/e* calcd for $C_{18}H_{28}O_2Si$ (M^+) 304.1857, found 304.1855.

3.1.15. (*E*)-4-[2-(1,2-Epoxy-2,6,6-trimethylcyclohexyl)-vinyl]-2-*tert*-butyldimethylsilylfuran (10e). To a solution of 3-(5-*tert*-butyldimethylsilylfuryl)methyltriphenylphosphonium bromide **E** (479 mg, 0.892 mmol) in ether (5 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 0.56 mL, 0.892 mmol) at 0°C. The reaction mixture was stirred at 0°C for 40 min, and an ether (1 mL) solution of the epoxyaldehyde **10** (100 mg, 0.594 mmol) was added at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 10 min, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Rapid column chromatography on aluminum oxide (2% ethyl acetate in hexane) gave the corresponding conjugated furan derivative **10e** (196 mg, 95%) which was analyzed by the observation of the characteristic signals of its ^1H NMR and MS: ^1H NMR (400 MHz, $CDCl_3$) (characteristic signals of **10e**) δ 6.11 (d, 1H, J=15.9 Hz),

6.41 (d, 1H, J=15.6 Hz), 6.74 (s, 1H), 7.60 (s, 1H); EI HRMS *m/e* calcd for $C_{21}H_{34}O_2Si$ (M^+) 346.2326, found 346.2330.

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