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Synthesis of the C(1)–C(18) Segment of Lophotoxin and Pukalide. Control of 2-Alkenylfuran (*E*/*Z*)-Configuration

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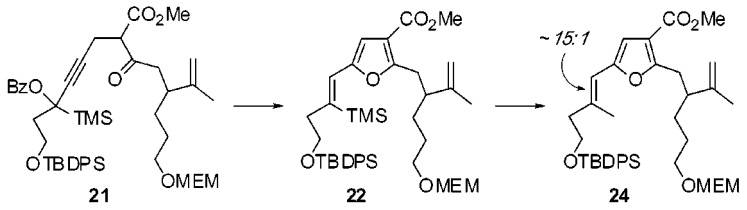
ABSTRACT



The convergent synthesis of the fully functionalized C(1)–C(18) segment 24 of the furanocembranes lophotoxin and pukalide was accomplished in 11 steps and 10% overall yield. The key step was a stereoselective conversion of alkynoate 21 to trimethylsilyl 2-alkenylfuran 22.

The major biomedical interest in lophotoxin, pukalide, and the closely related bipinnatins results from their selective irreversible binding to nicotinic acetylcholine receptors.[1] Lophotoxin is a member of the family of furanocembrane natural products (Figure 1), and no total synthesis has been reported to date.[2] In related work, Paquette and co-workers reported the synthesis of gorgiacerone and acerosolide, using as the key cyclization step in both syntheses an allylchromium attack on an aldehyde.[3] Marshall and co-workers have synthesized (−)-kallolide B by a diastereoselective [2,3] Wittig rearrangement and, most recently, (−)-deoxypukalide using as a key step an intraannular SiO_2-mediated cyclization of a 4-oxopropargylic β-keto ester.[4]

We recently reported a new method for synthesizing 2-alkenylfurans.[5] In our approach, α-propargyl β-keto esters are cyclized to the desired 2-alkenylfurans, under either palladium or mild base catalysis. A major advantage of this approach is that the entire 2-alkenylfuran segment is assembled in one step from readily available precursors; in

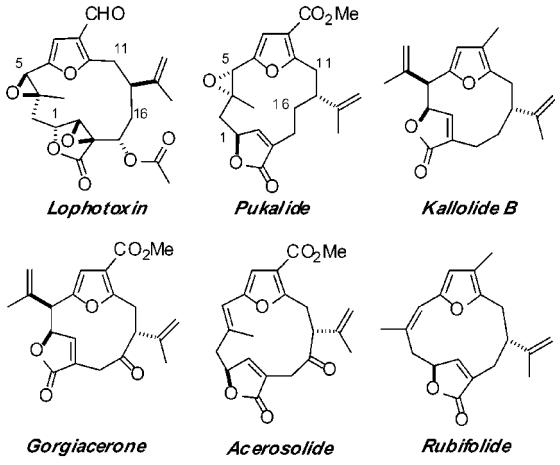


Figure 1. Structures of common furanocembranes.

(1) Abramson, S. N.; Fenical, W.; Taylor, P. *Drug Dev. Res.* **1991**, *24*, 297.

(2) For relevant synthetic approaches, see: (a) Cases, M.; Gonzalez-Lopez de Turiso, F.; Pattenden, G. *Synlett* **2001**, 1869. (b) Marshall, J. A.; McNulty, L. M.; Zou, D. *J. Org. Chem.* **1999**, *64*, 5193. (c) Paterson, I.; Brown, R. E.; Urch, C. J. *Tetrahedron Lett.* **1999**, *40*, 5807. (d) Astley, M. P.; Pattenden, G. *Synthesis* **1992**, 101. (e) Tius, M. A.; Trehan, S. *J. Org. Chem.* **1986**, *51*, 765. (f) Paterson, I.; Gardner, M.; Banks, B. J. *Tetrahedron* **1989**, *45*, 5283.

(3) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926.

(4) (a) Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729. (b) Marshall, J. A.; Liao, J. *J. Org. Chem.* **1998**, *63*, 5962. (c) Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037.

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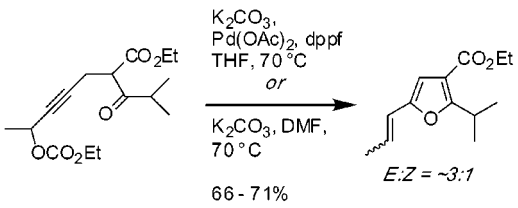
addition, the cyclization conditions should be compatible with a variety of functional groups. However, this approach suffered in that the cyclization reaction showed poor (*E*/*Z*)-selectivity with regard to the alkene portion of the 2-alkenylfuran. In a relevant example in our original report, we observed a 3:1 isomeric ratio for a 1,2-disubstituted alkene (Scheme 1). It seems likely that the ratio would be worse

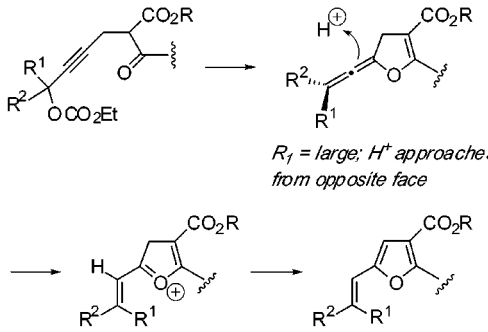
Scheme 1[5]



for the trisubstituted alkene products required for furanocembrane syntheses.

A possible solution to this problem arose from consideration of the probable mechanism for 2-alkenylfuran formation (Scheme 2). Both the palladium- and base-catalyzed reactions

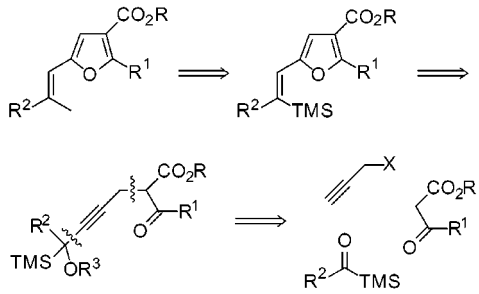
Scheme 2



likely afford an initial allene product, which then isomerizes to a 2-alkenylfuran via a protonation−deprotonation sequence. The (*E*/*Z*)-ratio would accordingly depend on the facial selectivity of the allene protonation step. It follows that if one face of the allene was blocked by a bulky group (R^1 in Scheme 2), then one alkene isomer should dominate.[6] This model predicts that the large group (R^1) should end up *cis* to the furan.

Unfortunately, in the furanocembrane targets of interest, there is no sterically large group that could have the desired directing effect; the two relevant substituents are similar in size. We reasoned that this issue could be resolved by retrosynthetically substituting a trimethylsilyl group for one of the substituents (Scheme 3). The bulky TMS group was

Scheme 3



expected to provide the desired selectivity in the 2-alkenylfuran-forming reaction and could subsequently be transformed to the desired (methyl) group. Realization of this strategy required an extension of our furan synthesis protocol[5] to acylsilanes.

β-Keto ester **2** was easily obtained in one step from known propargylic ester **1**[7] by reaction with the anion of *syn*-benzaldehyde oxime in a procedure slightly modified from a report by Gómez et al. (Scheme 4).[8−10] Commercially available acetyltrimethylsilane was reacted with the anion of propargyl chloride, affording propargyl alcohol **3**.[11] Propargylic alcohol **3** was benzoylated using Vedej's protocol,[12] and the resulting benzoate **4** was used for alkylation of the anion of *β*-keto ester **2**, affording coupling product **5**. In this alkylation, it was important to first transform the propargylic chloride to the corresponding iodide; attempts to form the iodide in situ resulted in low yields.

After much experimentation, we were able to efficiently cyclize 2-alkenylfuran precursor **5** under palladium catalysis in a heated acetonitrile/water solvent mixture.[13] The silyl 2-alkenylfuran product **6** was formed as one predominant alkene isomer (ca. 14:1). Furthermore, this isomer could be almost completely isomerized to the alternative isomer (**7**, >30:1) by reaction with a catalytic amount of diphenyl

(5) Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132.

(6) For related examples that exploit the axial asymmetry of allenes as a stereocontrolling element, see: (a) Aso, M.; Ikeda, I.; Kawabe, T.; Shiro, M.; Kanematsu, K. *Tetrahedron Lett.* **1992**, *33*, 5787. (b) Ikeda, I.; Gondo, A.; Shiro, M.; Kanematsu, K. *Heterocycles* **1993**, *36*, 2669. (c) Ikeda, I.; Honda, K.; Osawa, E.; Shiro, M.; Aso, M.; Kanematsu, K. *J. Org. Chem.* **1996**, *61*, 2031. (d) De Schrijver, J.; De Clercq, P. J. *Tetrahedron Lett.* **1993**, *34*, 4369. (e) Yang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2001**, *123*, 761. (f) Trost, B. M.; Oi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1230. (g) Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307. For reviews on allenes, see: (h) Smadja, W. *Chem. Rev.* **1983**, *83*, 263. (i) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805.

(7) Baxter, J.; Mata, E. G.; Thomas, E. J. *Tetrahedron* **1998**, *54*, 14359.

(8) Gómez, V.; Pérez-Medrano, A.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 1219.

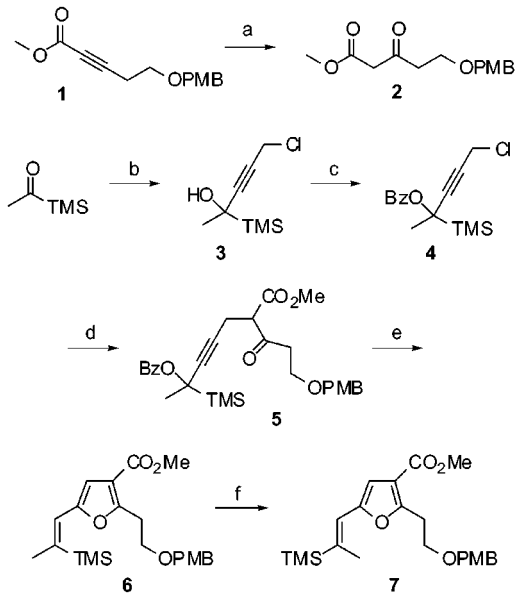
(9) *β*-Keto ester **2** has been reported,[10] but the details on its preparation are lacking. Reference 10b reports in a footnote that **2** can be prepared by reaction of the dianion of methyl acetoacetate with [(*p*-methoxybenzyl)-oxy]methyl chloride.

(10) (a) Jones, A. B.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17. (b) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.

(11) We did not encounter significant problems with rearrangements in our preparation of **3**. However, both a Brook rearrangement and a [1,2] TMS group shift have been reported for this same coupling under different conditions. See: (a) Cunico, R. F.; Nair, S. K. *Synth. Commun.* **1996**, *26*, 803. For related studies, see: (b) Kuwajima, I.; Kato, M. *Tetrahedron Lett.* **1980**, *21*, 623. (c) Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7791. (d) Bienz, S.; Enev, V.; Huber, P. *Tetrahedron Lett.* **1994**, *35*, 1161.

(12) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702.

Scheme 4[a]

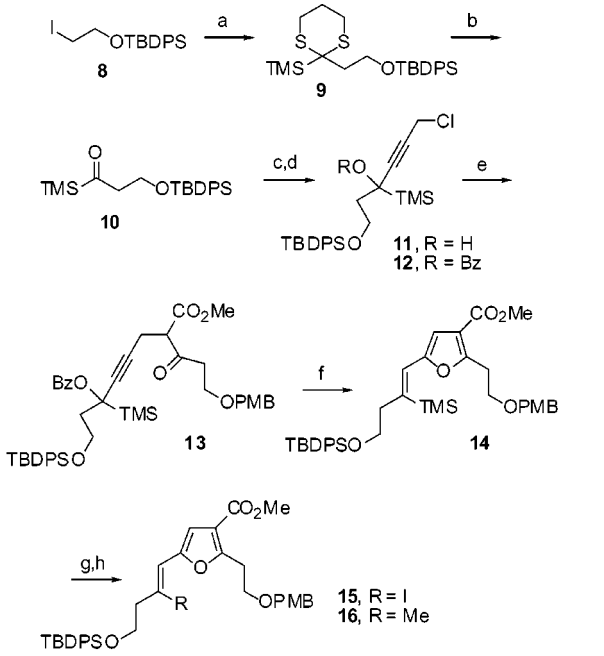


[a] (a) *syn*-Benzaldehyde oxime, NaH, THF/HMPA; then **1** (75%); (b) propargyl chloride, *n*-BuLi, Et_2O, −78 °C, then $TMSCOCH_3$ (94%); (c) Bz_2O, TEA, $MgBr_2$, CH_2Cl_2 (90%); (d) (i) NaI, acetone, Δ, (ii) **2**/NaH, THF (79%, two steps); (e) K_2CO_3, $Pd(OAc)_2$, dppf, 10:1 CH_3CN/H_2O, 80 °C (73%); (f) PhSeSePh, THF, Δ (96%).

diselenide in refluxing THF.[14] The two isomers could be unequivocally assigned as (*Z*)-**6** and (*E*)-**7** by ^1H and ^{13}C NMR chemical shift values[15] and ^1H NMR NOE spectroscopic studies. The highly stereoselective formations of **6** and **7** provide a solid proof of concept for our mechanistic hypothesis outlined in Scheme 2.

We next turned to a more complex acylsilane precursor containing a side chain relevant to our planned furanocembrane syntheses (Scheme 5). Trimethylsilyl dithiane was alkylated with iodide **8**.[16] The hydrolysis of the resulting silyl dithiane **9** to afford acylsilane **10** proved to be problematic. Of the variety of known methods attempted for this transformation,[17,18] only the use of mercuric salt ($HgClO_4$, $CaCO_3$, THF/H_2O; 72% from iodide **8**)[17b] worked well, but we were reluctant to use this method on a large scale, as it is both costly and leads to toxic side products. Finally, we investigated the use of supported iron(III) nitrate, a reagent

Scheme 5[a]



[a] (a) (i) TMS-dithiane, *n*-BuLi, THF, −20 °C, then **8**, −20 °C; (b) $Fe(NO_3)_3 \cdot 9H_2O$, basic alumina, hexane, 43 °C (70%, two steps); (c) propargyl chloride, *n*-BuLi, Et_2O, −78 °C, then **10** (71%); (d) Bz_2O, TEA, $MgBr_2$, CH_2Cl_2 (80%); (e) (i) NaI, acetone, Δ, (ii) **2**/NaH, THF (87%, two steps); (f) K_2CO_3, $Pd(OAc)_2$, dppf, 10:1 CH_3CN/H_2O, 84 °C (72%); (g) I_2, $AgClO_4$, pyridine, THF (88%); (h) Me_2Zn, $Pd(PPh_3)_4$, THF (98%).

that has previously been used for dithiane but not for silyl dithiane hydrolysis.[19] Initial attempts using silica gel as the support resulted in multiple products; however, a switch to basic alumina as the support provided **10** in 70% overall yield from **8**. Acylsilane **10** was then converted to silyl 2-alkenylfuran **14** according to the reaction sequence used for the preparation of furan **6**. Reaction with lithiated propargyl chloride afforded alcohol **11**, which was benzoylated to afford **12**. This benzoate was used to alkylate the anion of β-keto ester **2**, and the resulting product **13** was cyclized to give (*Z*)-2-alkenylfuran **14** in excellent selectivity (ca. 15:1).[20]

For the conversion of the TMS group to the desired methyl substituent, **14** was subjected to silane−iodine exchange.[21] The resulting vinyl iodide **15** was reacted with dimethylzinc under palladium catalysis to afford 2-alkenylfuran **16**.[22] NOE

(13) These conditions were first developed with ethyl acetoacetate as the β-keto ester component. The corresponding 2-alkenylfuran product was difficult to purify, however. Importantly, our originally reported conditions employing THF as a solvent were completely unsuccessful, resulting in no reaction. Use of ethanol at reflux led to product, but in low yields; reaction in dimethylformamide (starting at room temperature and warming to ca. 85 °C) was successful (55%) but not always reproducible. Reaction in acetonitrile at reflux was slow; but use of a hot 10:1 acetonitrile/water mixture resulted in reproducible yields of ca. 55%.

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(15) (a) Dorman, D. E.; Jautelat, M.; Roberts, J. D. *J. Org. Chem.* **1971**, *36*, 2757. (b) Chan, T. H.; Mychajlowskij, W.; Amouroux, R. *Tetrahedron Lett.* **1977**, *18*, 1605.

(16) For a preparation of iodide **8**, see: Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 3910.

(17) (a) Plantier-Royon, R.; Portella, C. *Tetrahedron Lett.* **1996**, *37*, 6113. (b) Bouillon, J.; Portella, C. *Eur. J. Org. Chem.* **1999**, 1571. (c) Saleur, D.; Bouillon, J.; Portella, C. *Tetrahedron Lett.* **2000**, *41*, 321.

(18) For alternative protocols for silyl dithiane hydrolysis, see: (a) Corey, E. J.; Seebach, D.; Freedman, R. *J. Am. Chem. Soc.* **1967**, *89*, 434. (b) Suda, K.; Watanabe, J.; Takanami, T. *Tetrahedron Lett.* **1992**, *33*, 1355. (c) Chuang, T.-H.; Fang, J.-M.; Jiaang, W.-T.; Tsai, Y.-M. *J. Org. Chem.* **1996**, *61*, 1794. (d) Patrocínio, A. F.; Moran, P. J. S. *J. Organomet. Chem.* **2000**, *603*, 220.

(19) (a) Cornelis, A.; Laszlo, P. *Synthesis* **1985**, *909*. (b) Hirano, M.; Ukawa, K.; Yakabe, S.; Morimoto, T. *Synth. Commun.* **1997**, *1527*. (c) Hirano, M.; Ukawa, K.; Yakabe, S.; Clark, J. H.; Morimoto, T. *Synthesis* **1997**, 858.

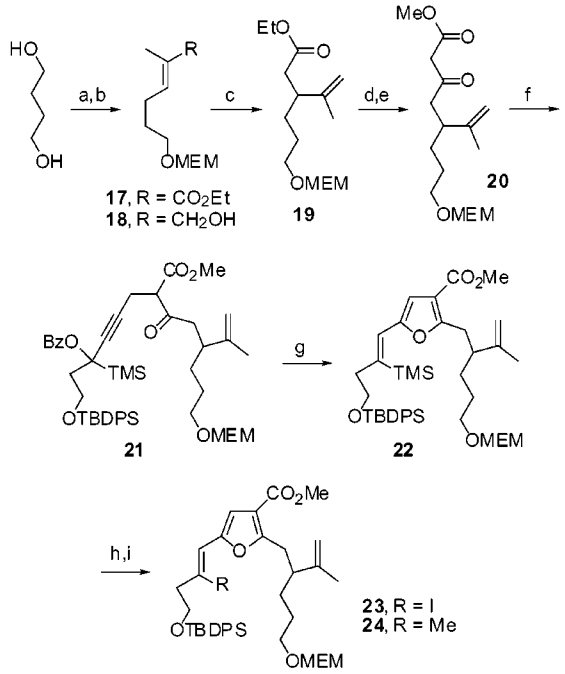
(20) (*Z*)-**14** can be isomerized to the corresponding (*E*)-isomer, but this process is much slower than the isomerization of (*Z*)-**6**. Treatment of (*Z*)-**14** with 10 equiv of diphenyl diselenide in tetrahydrofuran at reflux affords, after 8 d, a 4.4:1 (*E*):(*Z*) ratio of alkenes.

studies confirmed that **16** was the expected (*E*)-isomer; however, a minor alkene isomerization during the silane−iodine exchange step reduced the (*E*):(*Z*)-ratio to ca. 12:1.[23]

The preparation of the advanced C(1)−C(18) segment of lophotoxin and pukalide was accomplished in 10% overall yield by this strategy (Scheme 6). *β*-Keto ester **20** was prepared from 1,4-butanediol, which was monoprotected and then subjected to a combination Swern−Wittig reaction[24] to afford α,*β*-unsaturated ester **17** (Scheme 6). Reduction with diisobutylaluminum hydride afforded alcohol **18**, which was subjected to a Johnson ortho ester−Claisen rearrangement[25] to yield ester **19**. After hydrolysis of **19**, the resulting acid was converted to *β*-keto ester **20** according to the method of Li and Franck.[26] Alkylation of the sodium enolate of **20** with the iodide of benzoate **12**, and cyclization of *β*-keto ester **21** to silyl 2-alkenylfuran **22**, was followed by silane−iodine exchange to afford vinyl iodide **23**. Finally, reaction of **23** with dimethylzinc under palladium catalysis afforded (*E*)-**24** in excellent yield and stereoselectivity (ca. 15:1).

In conclusion, we have accomplished an extension of our 2-alkenylfuran synthesis that employs allene stereochemistry for control of alkene configuration. The face-selective protonation of a silyl allene intermediate provides trisubstituted 2-alkenylfurans in good overall yield. Other noteworthy features of our approach include the use of Al_2O_3-supported iron(III) nitrate for hydrolysis of silyl dithioketals and the stereoselective isomerization of vinylsilane (*Z*)-**6** to (*E*)-**7** in the presence of catalytic diphenyl diselenide. The C(1)−C(18) segment of lophotoxin and pukalide was thus prepared in 11 steps and 10% yield.

Scheme 6[a]



[a] (a) (i) MEMCl, DIEA, CH_2Cl_2, (ii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; TEA, 0 °C; (carbethoxyethylidene)triphenylphosphorane, rt (67%, two steps); (b) DIBALH, CH_2Cl_2, −78 °C (83%); (c) triethylorthoacetate, $EtCO_2H$, Δ (81%); (d) LiOH·H_2O, 3:1 EtOH:H_2O; (e) (i) Meldrum's acid, DCC, DMAP, CH_2Cl_2, (ii) MeOH, Δ (58%, three steps); (f) NaH, THF, 0 °C, then add the iodide of **12**; (g) K_2CO_3, $Pd(OAc)_2$, dppf, 10:1 CH_3CN:H_2O, 84 °C; (h) I_2, $AgClO_4$, pyridine, THF (39%, three steps); (i) Me_2Zn, $Pd(PPh_3)_4$, THF (98%).

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, including copies of ^1H and ^{13}C NMR for **5**, **6**, **7**, **13**, **14**, **15**, **16**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For methods for iododesilylation of vinylsilanes, see: (a) Chan, T. H.; Lau, P. W. K.; Mychajlowskij, W. *Tetrahedron Lett.* **1977**, *18*, 3317. (b) Chan, T. H.; Koumaglo, K. *Tetrahedron Lett.* **1986**, *27*, 883. (c) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647. (d) Alimardanov, A.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 3839.

(22) Marshall, J. A.; Zou, D. *Tetrahedron Lett.* **2000**, *41*, 1347.

(23) Silyl 2-alkenylfurans **6** and **7** were also subjected to the same silane−iodine exchange conditions used to prepare **15**; these reactions proceeded with retention of alkene configuration as determined by ^1H and ^{13}C chemical shift and ^1H NMR NOE spectroscopic studies on the vinyl iodide products. In the case of (*Z*)-**6**, a significant amount of alkene isomerization was noted, and the vinyl iodide product was isolated as a ca. 1:6 (*E*):(*Z*) mixture. In the case of (*E*)-**7**, little to no isomerization occurred.

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(25) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5; pp 827−874.

(26) (a) Li, B. Q.; Franck, R. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2629. For a similar approach using an acid chloride, see: (b) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087.