Organic LETTERS

Letter

pubs.acs.org/OrgLett

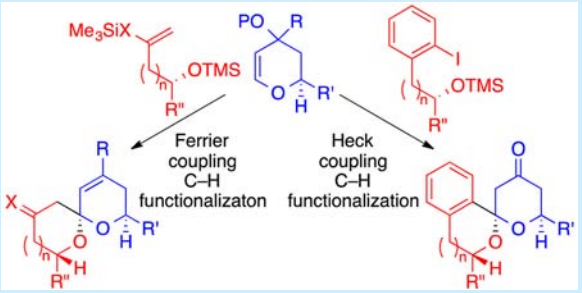
# Convergent One-Pot Oxidative [*n* + 1] Approaches to Spiroacetal Synthesis

GuangRong Peh and Paul E. Floreancig*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

Supporting Information

**ABSTRACT:** Two one-pot oxidative annulative approaches to spiroacetal synthesis are described. One approach uses a Lewis acid mediated Ferrier reaction in the fragment-coupling stage followed by DDQ-promoted oxidative carbon–hydrogen bond cleavage and cyclization. An alternative approach employs a Heck reaction for fragment coupling followed by DDQ-mediated enone formation and cyclization. These strategies provide convergent routes to common subunits in natural products, medicinal agents, and chemical libraries under mild reaction conditions.




Spiroacetals are integral components in numerous biologically active natural products of marine origin[1] as represented by alotaketal A (**1**, Figure 1),[2] a potent activator of the cAMP cell-signaling pathway. Spiroacetal subunits are also present in non-natural biologically active compounds such as the selective sodium glucose cotransporter 2 inhibitor tofogliflozin (**2**),[3] which has recently been approved for the treatment of type 2 diabetes. The structural rigidity and capacity to orient functional groups in defined spatial arrangements has resulted in spiroacetals serving as scaffolds for chemical libraries[4] that have delivered hits for B-cell chronic lymphocytic leukemia treatment,[5] apoptosis induction,[6] and microtubule disruption.[7]

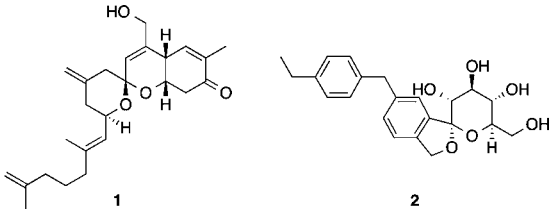
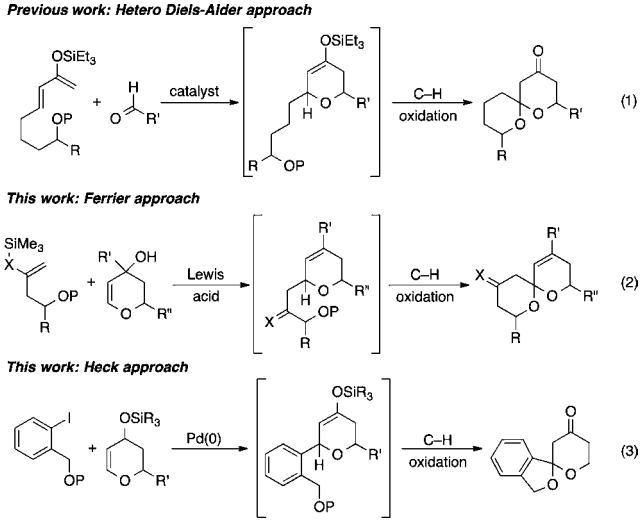



**Figure 1.** Representative biologically active spiroacetals.

Protocols to prepare spiroacetals generally proceed through the formation of a diol that contains a ketone, or a suitable surrogate, followed by a cyclization step.[8] These routes have proven to be remarkably versatile for complex molecule construction. One-pot, convergent approaches to spiroacetal synthesis, however, would mitigate functional and protecting group manipulations, thereby increasing step economy[9] in the formation of these structures. We have been exploring convergent, one-pot approaches to spiroacetal synthesis through telescoping fragment-coupling processes with oxidative carbon–hydrogen cleavage. The oxidations generate electrophiles that cyclize with appended alcohols. We recently reported the realization of this approach through the use of hetero-Diels–Alder reactions for fragment coupling (Scheme 1).[10] The intermediate silyloxy dihydropyrans are excellent substrates for DDQ-mediated carbon–hydrogen bond cleavage to yield enone substrates that cyclize under acidic conditions. This manuscript describes two new formal [*n* + 1], one-pot oxidative annulation approaches to form spiroacetals from dihydropyrans. These processes utilize Ferrier[11] and Heck[12] reactions in the fragment-coupling phase. The intermediate allylic ethers that form through these processes are excellent substrates for oxidative carbon–hydrogen bond cleavage,[13] leading to the cyclization phase that delivers the desired targets.[14] The mild reaction conditions, wide

**Scheme 1. Convergent, Oxidative Approaches to Spiroacetals**




**Received:** June 15, 2015
**Published:** July 21, 2015



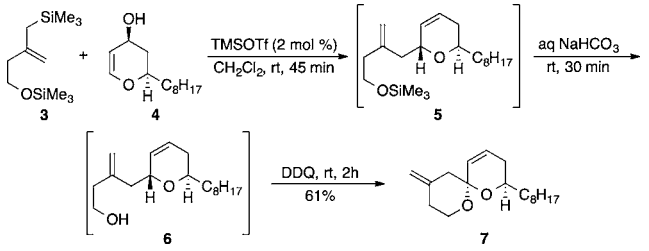


DOI: 10.1021/acs.orglett.5b01736
*Org. Lett.* 2015, 17, 3750–3753

substrate scope, and significant increases in molecular complexity make these processes extremely attractive for synthesizing these important structures.

The development of the Ferrier reaction-based annulation protocol[15] is shown in Scheme 2. Allylsilane **3**, prepared through

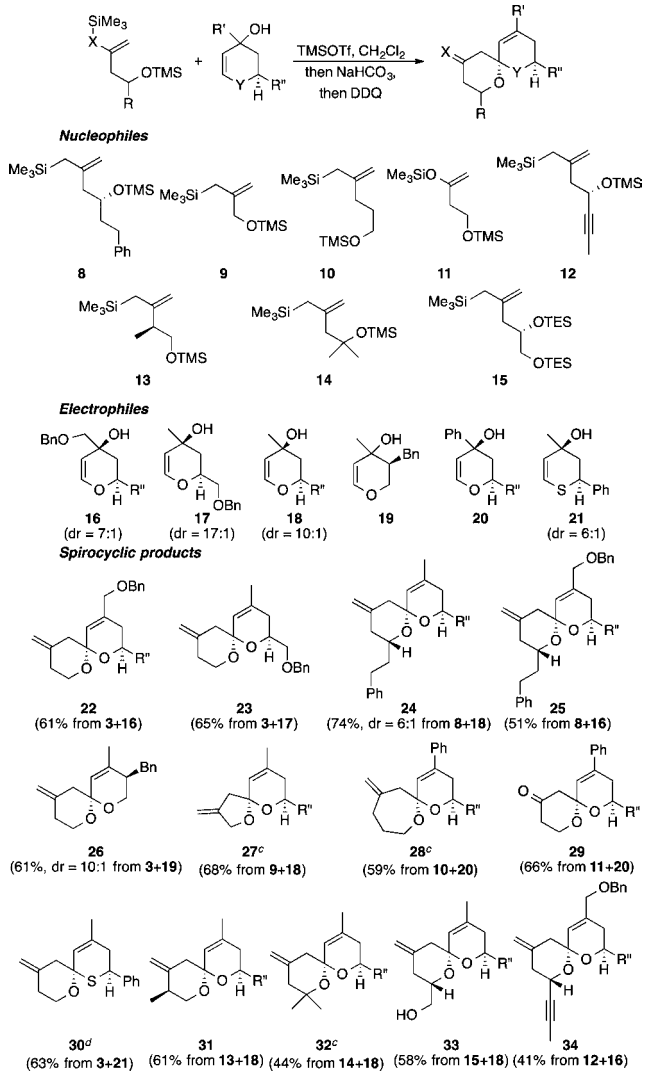
**Scheme 2. Ferrier Reaction-Based Approach to Oxidative Annulation**




allylic lithiation of the corresponding alkenol followed by trapping with $Me_3SiCl$,[16] reacts stereoselectively with dihydropyran **4**, readily accessed through a hetero-Diels–Alder reaction between Danishefsky's diene[17] and nonanal followed by a Luche reduction,[18] in the presence of TMSOTf (2 mol %)[19] whereby stereocontrol is dictated by the stereoelectronically favored axial approach to the intermediate oxocarbenium ion (see the Supporting Information for structure determination).[20] The resulting allylic ether **5**, although containing the unsaturation and the cation-stabilizing group that we have shown to be essential for DDQ-mediated carbon–hydrogen bond cleavage,[21] proved to be inert to oxidation. Cleaving the silyl ether with a minimal amount of aqueous $NaHCO_3$ to yield alcohol **6** followed by the addition of molecular sieves and DDQ, however, provided spirocycle **7** in 61% yield as a single stereoisomer for the one-pot procedure. The stereochemical outcome is consistent with kinetic control, through addition into the oxocarbenium ion, and thermodynamic control due to the anomerically favorable orientation of the spiroacetal. This example illustrates a convergent approach that employs mild reaction conditions to generate spiroacetals from readily accessible precursors. The smooth reactivity of alcohol **6** in contrast to the lack of reactivity of silyl ether **5** also provides evidence that the DDQ-mediated carbon–hydrogen bond cleavage requires a rapid and thermodynamically favorable termination step for starting material to be consumed, indicating that the oxidation is reversible.

The scope of the process is illustrated in Scheme 3, where the nucleophilic and dihydropyran building blocks are shown in addition to the spiroacetal products. Enantiomerically enriched dihydropyrans were accessed by using Jacobsen's protocol[22] for the cycloaddition step, and allylsilanes were prepared through lithiation/silylation or through the Bunnelle process[23] on the corresponding esters.[24] These examples show that dihydropyrans containing tertiary allylic alcohols, prepared through the addition of the appropriate organometallic reagent into the hetero-Diels–Alder reaction product and used as inconsequential mixtures of diastereomers (major diastereomer shown), are excellent substrates for the procedure. Substrate **16**, in which the tertiary alcohol contains a benzyloxymethyl group, reacts somewhat less efficiently than substrate **17**, in which the tertiary alcohol contains a methyl group. This can be attributed to the benzyloxy group's inductive destabilization of the intermediate oxocarbenium ion in the oxidative cyclization step. However, the increased functional group content in the product can be useful

**Scheme 3. Annulation Scope**[a,b]




[a]Reactions were conducted at rt in accord with Scheme 2 unless otherwise noted. [b]R″ = *n*-$C_8H_{17}$ unless otherwise noted. [c]Cyclization proceeded at 0 °C. [d]Cyclization was complete within 15 min.

in the synthesis of compounds such as **1**. This inductive destabilization is not a significant impediment in the cyclization when the benzyloxymethyl group is at the 6-position of the dihydropyran, making compounds with higher functional group content at that site, such as **23**, accessible. Dihydropyrans that contain a substituent at the 5-position, as required for the synthesis of **1**, could undergo cyclization more slowly than substrates that are substituted at the 6-position due to the presence of allylic-1,2 strain[25] in the oxocarbenium ion intermediate. However, spirocycle **26** was accessed in acceptable yield through the union of **3** and **19**. The stereochemical outcome of this reaction was dictated by allylic strain, with the benzyl group occupying an axial orientation in the product. The formation of a minor diastereomer indicates that substituents at the 5-position of the dihydropyran exert a slightly lower influence on the stereochemical outcome of the reactions than substituents at the 6-position.

Allylsilanes that contain secondary alcohols are suitable nucleophiles for these transformations, as illustrated by the formation of **24**, **25**, **33**, and **34**. This indicates that the method

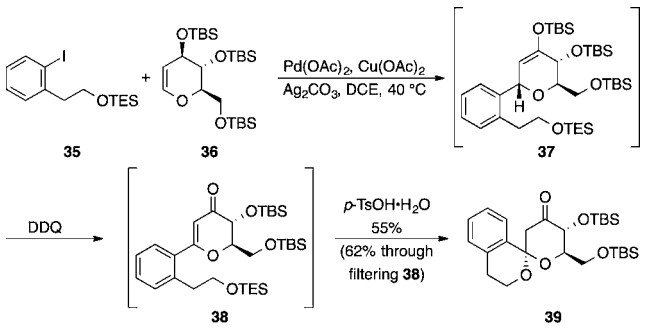


DOI: 10.1021/acs.orglett.5b01736
*Org. Lett.* 2015, 17, 3750–3753

will be useful for the union of complex fragments for the construction of functionally dense spiroacetals. Spirocycle **24** was isolated as a 6:1 mixture of diastereomers as a result of allylsilane **8** being prepared in 74% ee. The formation of the minor product illustrates that the spirocyclization is applicable to the preparation of compounds that contain an axially oriented substituent. Tetrahydrofurans and oxepanes can be fused to tetrahydropyrans as shown in the preparation of **27** and **28**. The formation of **27** is remarkable because the cyclization occurs in preference to allylic alcohol oxidation.[26] The construction of **28** and **29** shows that dihydropyrans containing tertiary benzylic alcohols are excellent substrates, illustrating the promise of this protocol to deliver structurally diverse products. Enolsilanes are competent nucleophiles that yield ketone-containing products, as shown in the formation of **29**, despite the enhanced inductive effect from the intermediate ketone in comparison to the alkene from previous examples. Dihydrothiopyrans can be used to generate sulfur-containing spirocycles, as shown by the formation of **30**. This result is consistent with our previous studies[27] showing that sulfides react with comparable efficiency to ethers. Various substitution patterns are tolerated in the nucleophilic fragment, shown by the formation of **31** with a branch at the allylic position, **32** with a tertiary ether, and **33** with a functionalized secondary ether. The alkynyl group in **34** can serve as an oxidatively stable precursor to alkenyl-substituted spirocycles such as **1**.

The scope of this process can be expanded through the use of a broader range of nucleophiles and by retention of oxygenation during the fragment-coupling stage. These objectives can be achieved through the use of a Heck reaction to join the subunits. Telescoping a Heck reaction with oxidative cyclization required the identification of coupling conditions that proceed in 1,2-dichloroethane, the optimal solvent for the oxidation step. As shown in Scheme 4, aryl iodide **35** reacts with glucal derivative **36**

**Scheme 4. Heck Reaction-Based Spirocycle Formation**

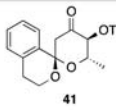
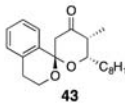
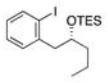
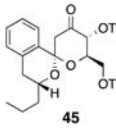
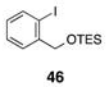
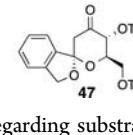



under Ye's conditions[28] to yield intermediate enolsilane **37**. These conditions proved to be optimal for this transformation though they were originally developed for oxidative Heck reactions and our reactions are not oxidative processes. The Pd(0) that is required to initiate the coupling most likely forms through glycal oxidation. The stereochemical outcome of the Heck reaction was determined through independent synthesis (see the Supporting Information) and is consistent with the classical mechanism of *syn*-carbopalladation followed by *syn*-$\beta$-hydride elimination.[12]

Adding DDQ provided enone **38**, which was converted to spirocycle **39** by the addition of *p*-TsOH. This transformation proceeded in 55% yield for the one-pot protocol. The sluggish rate of the oxidation in comparison to earlier studies on electron-rich alkene oxidation[29] suggested that the metals from the Heck coupling inhibit this step. Therefore, the reaction mixture was filtered through a short pad of silica gel and the filtrate was subjected to DDQ-mediated oxidation and acid-promoted cyclization. This process increased the oxidation rate and improved the reaction yield to 62%.

Other examples of this transformation are shown in Table 1. Rhamnal derivative **40** (Table 1, entry 1) reacts with

**Table 1. Further Examples of Telescoped Heck Coupling and Oxidative Cyclization**

| entry[a] | iodoarene | dihydropyran | product | yield (%) |
|---|---|---|---|---|
| 1 | 35 |  40 |  41 | 58[b] (61)[c] |
| 2 | 35 |  42 |  43 | 53[b] (58)[c] |
| 3 |  44 | 36 |  45 | 61[b] (70)[c] |
| 4 |  46 | 36 |  47 | 32[b] (47)[d] |

[a]See Supporting Information for details regarding substrate synthesis, reaction conditions, and product characterization. [b]Yields refer to isolated, purified materials of the one-pot protocol. [c]Parenthetical yields refer to reactions that were filtered following the Heck reaction. [d]Parenthetical yield refers to a protocol in which the product from the Heck reaction was purified by flash chromatography.

approximately the same efficiency as **36** to yield **41**. Compounds such as **42** (Table 1, entry 2) with alkyl, rather than silyloxy, groups at the 5-position are also suitable substrates. Iodoarenes that contain secondary silyl ethers, such as **44** (Table 1, entry 3), react smoothly to form spirocycles. The capacity to use secondary alcohols as nucleophiles significantly expands the complexity of accessible structures through this route. Dihydroisobenzofuran structures of the type that are present in **2** can be prepared by shortening the tether between the arene and the silyl ether. Coupling **36** with iodoarene **46** provided spirocycle **47**, albeit in a modest 32% yield (Table 1, entry 4). A significant quantity of the dihydropyran starting material was recovered, indicating that the Heck coupling was not efficient. When the reactions were conducted separately the Heck reaction proceeded in 63% yield and the oxidative cyclization proceeded in 75% yield for an overall yield of 47%. Benzylic alcohol oxidation was not observed to be competitive with oxidative cyclization. Despite the modest yield of the transformation, the facile access to the substrates and the potential for the products to act as glucose cotransporter 2 inhibitors make the approach very attractive for developing structure−activity relationships.

Short, efficient syntheses of large, functional group-rich structures from simple materials require reactions that lead to significant increases in molecular complexity. Whitlock defines molecular complexity by the number of rings, stereocenters,



DOI: 10.1021/acs.orglett.5b01736
*Org. Lett.* 2015, 17, 3750−3753

unsaturations, and heteroatoms in a molecule, and by size, as defined by bond number or molecular weight.[30] Therefore, bimolecular annulation reactions are inherently beneficial processes for increasing molecular complexity and, therefore, expediting complex molecule synthesis. We have described telescoped [$n$ + 1]-annulation processes that couple Ferrier or Heck fragment-coupling reactions with oxidative carbon−hydrogen bond cleavage to deliver spiroacetals. The precursors for these reactions are readily prepared, and the experimental protocols are facile with no exceptional efforts being required to eliminate oxygen or water. These factors, coupled with the broad scope, abundant options for product functionalization, and wide range of biological activities that spiroacetals exhibit, make this based approach highly attractive for numerous applications.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details and spectral data for all new compounds, and synthetic schemes for all substrates. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01736.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: florean@pitt.edu.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the National Institutes of Health (P50-GM067082) and the National Science Foundation (CHE-1151979) for generous support of this work.

## ■ REFERENCES


(1) (a) Francke, W.; Kitching, W. *Curr. Org. Chem.* **2001**, *5*, 233. (b) Jacobs, M. F.; Kitching, W. *Curr. Org. Chem.* **1998**, *2*, 395.

(2) Isolation: (a) Forestieri, R.; Merchant, C. E.; de Voogd, N. J.; Matainaho, T.; Kieffer, T. J.; Andersen, R. J. *Org. Lett.* **2009**, *11*, 5166. Synthesis: (b) Huang, J.; Yang, J. R.; Zhang, J.; Yang, J. *J. Am. Chem. Soc.* **2012**, *134*, 8806. (c) Xuan, M.; Paterson, I.; Dalby, S. M. *Org. Lett.* **2012**, *14*, 5492. (d) Huang, J.; Yang, J. R.; Zhang, J.; Yang, J. *Org. Biomol. Chem.* **2013**, *11*, 3212.

(3) Ohtake, Y.; Sato, T.; Kobayashi, T.; Nishimoto, M.; Taka, N.; Takano, K.; Yamamoto, K.; Ohmori, M.; Yamaguchi, M.; Takami, K.; Yeu, S.-Y.; Ahn, K.-H.; Matsuoka, H.; Morikawa, K.; Suzuki, M.; Hagita, H.; Ozawa, K.; Yamaguchi, K.; Kato, M.; Ikeda, S. *J. Med. Chem.* **2012**, *55*, 7828.

(4) (a) Kulkarni, B. A.; Roth, G. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Comb. Chem.* **2002**, *4*, 56. (b) Barun, O.; Kumar, K.; Sommer, S.; Langerak, A.; Mayer, T. U.; Müller, O.; Waldmann, H. *Eur. J. Org. Chem.* **2005**, *2005*, 4773. (c) Zinzalla, G.; Milroy, L.-G.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 1977. (d) Moilanen, S. B.; Potuzak, J. S.; Tan, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 1792. (e) Choi, K. W.; Brimble, M. A. *Org. Biomol. Chem.* **2009**, *7*, 1424.

(5) Milroy, L.-G.; Zinzalla, G.; Loiseau, F.; Qian, Z.; Prencipe, G.; Pepper, C.; Fegan, C.; Ley, S. V. *ChemMedChem* **2008**, *3*, 1922.

(6) Mitsuhashi, S.; Shima, H.; Kawamura, T.; Kikuchi, K.; Oikawa, M.; Ichihara, A.; Oikawa, H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2007.

(7) Uckun, F. M.; Mao, C.; Vassilev, A. O.; Huang, H.; Jan, S. T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 541.

(8) (a) Palmes, J. A.; Aponick, A. *Synthesis* **2012**, *44*, 3699. (b) Raju, B. R.; Saikia, A. K. *Molecules* **2008**, *13*, 1942. (c) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406. (d) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227.

(9) For one-pot spiroannulation processes, see: (a) Markó, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211. (b) Siau, W.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2014**, *136*, 17726.

(10) Han, X.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2014**, *53*, 11075.

(11) For a recent review, see: Gómez, A. M.; Lobo, F.; Uriel, C.; López, J. C. *Eur. J. Org. Chem.* **2013**, *2013*, 7221.

(12) For a review, see: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(13) (a) Peh, G. R.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 5614. (b) Han, X.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 3808. (c) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5894. (d) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 3069. (e) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567. (f) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184.

(14) For a review on C−H functionalization routes to spiroacetals, see: Sperry, J.; Liu, Y.-C.; Brimble, M. A. *Org. Biomol. Chem.* **2010**, *8*, 29. For a recently reported unique approach, see: Donohoe, T. J.; Lipiński, R. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2491.

(15) The Brimble group recently reported a variant on this protocol. See: Hubert, J. G.; Furkert, D. P.; Brimble, M. A. *J. Org. Chem.* **2015**, *80*, 2715.

(16) Carlson, R. M. *Tetrahedron Lett.* **1978**, *19*, 111.

(17) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

(18) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(19) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Tetrahedron Lett.* **1994**, *35*, 5673.

(20) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3803.

(21) For a mechanistic analysis of this type of reaction, see: Jung, H. H.; Floreancig, P. E. *Tetrahedron* **2009**, *65*, 10830.

(22) (a) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403. (b) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398.

(23) Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261.

(24) Please see the Supporting Information for the preparation of the subunits and detailed procedures for the spiroannulation reactions.

(25) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(26) Peng, K.; Chen, F.; She, X.; Yang, C.; Cui, Y.; Pan, X. *Tetrahedron Lett.* **2005**, *46*, 1217.

(27) Cui, Y.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 1720.

(28) Xiong, D.-C.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2009**, *11*, 1709.

(29) (a) Brizgys, G. J.; Jung, H. H.; Floreancig, P. E. *Chem. Sci.* **2012**, *3*, 438. (b) Liu, L.; Floreancig, P. E. *Org. Lett.* **2009**, *11*, 3152.

(30) Whitlock, H. W. *J. Org. Chem.* **1998**, *63*, 7982.




DOI: 10.1021/acs.orglett.5b01736
*Org. Lett.* 2015, 17, 3750−3753