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An Efficient Strategy for the Synthesis of Endocyclic Enol Ethers and Its Application to the Synthesis of Spiroacetals

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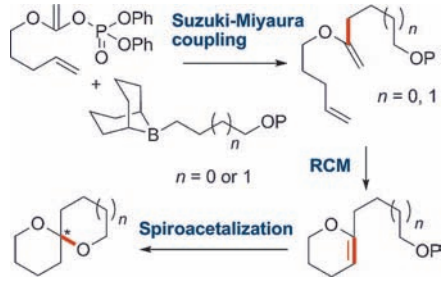
ABSTRACT

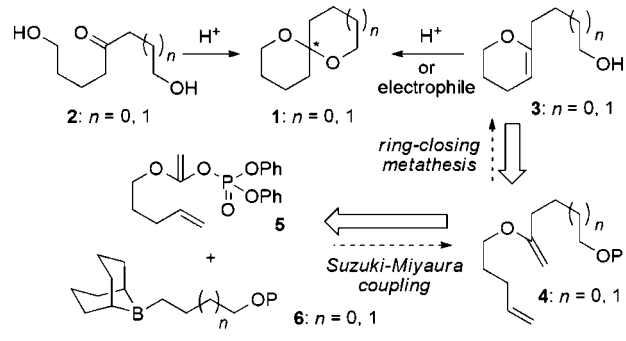


An efficient strategy for the synthesis of endocyclic enol ethers based on a Suzuki−Miyaura coupling/ring-closing metathesis sequence has been developed. The strategy has successfully been applied to the synthesis of spiroacetals, including cytotoxic marine metabolites attenols A and B.

Spiroacetal is a structural motif that is widely found in biologically active natural products such as insect pheromones, steroidal saponins, polyketide antibiotics, and marine metabolites.[1] Utilization of a spiroacetal substructure as a scaffold in the search for novel biologically functional molecules has also been investigated.[2] The most common approach to the synthesis of spiroacetals **1** is cyclization of keto-diols **2** under acidic conditions (Scheme 1). Meanwhile, spiroacetalization of endocyclic enol ethers **3** under thermodynamically equilibrating conditions also represents a powerful strategy for the construction of anomeric spiroacetals.[3]

A few methods for kinetic spiroacetalization of **3** that appear to be particularly effective for the synthesis of certain nonanomeric spiroacetals have also been reported.[4] Thus,

Scheme 1. General Plan for the Synthesis of Spiroacetals



(1) For reviews of the synthesis of spiroacetals: (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (b) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406.

(2) For examples: (a) Barun, O.; Kumar, K.; Sommer, S.; Langerak, A.; Mayer, T. U.; Müller, O.; Waldmann, H. *Eur. J. Org. Chem.* **2005**, 4773. (b) Zinzalla, G.; Milroy, L.-G.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 1977. (c) Milroy, L. G.; Zinzalla, G.; Prencipe, G.; Michel, P.; Ley, S. V.; Gunaratnam, M.; Beltran, M.; Neidle, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 2493.

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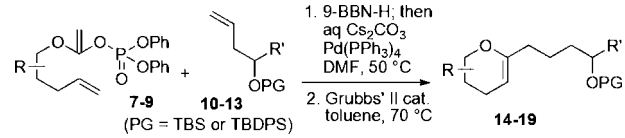
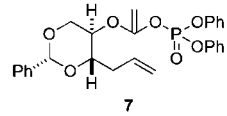
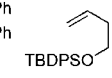
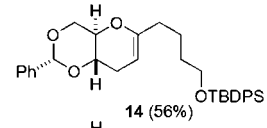
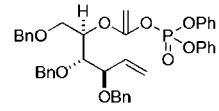
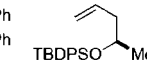
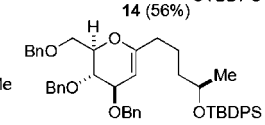
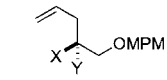
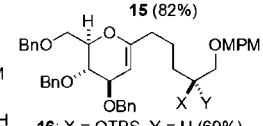
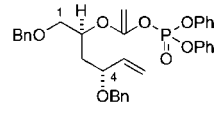
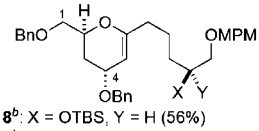
both thermodynamic and kinetic conditions are readily applicable to spiroacetalization of endocyclic enol ethers, making them versatile precursors for the synthesis of spiroacetals. However, limited methods are currently available for the synthesis of endocyclic enol ethers; the classical approaches usually involve electrophilic trapping of 2-lithio dihydropyrans, which often suffer from a narrow substrate scope due to the use of strong bases.[3,4] We describe herein an efficient strategy for the synthesis of endocyclic enol ethers based on a Suzuki−Miyaura coupling/ring-closing metathesis (RCM) sequence, and its application to the synthesis of a variety of spiroacetals, including cytotoxic marine metabolites attenols A and B.

We envisioned that endocyclic enol ether **3** could be synthesized from enol phosphate **5** and alkylborane **6** *via* **4** based on a Suzuki−Miyaura coupling/RCM sequence (Scheme 1).[5–8] In this way, spiroacetals can be rapidly elaborated from readily available acyclic precursors. This strategy is especially useful when the corresponding lactone-derived enol phosphate is not accessible or does not couple efficiently. A prerequisite for the success of our strategy was that the *inter*molecular Suzuki−Miyaura coupling of **5** and **6** must be more favored than the possible *intra*molecular Heck cyclization of **5**, although we previously showed that α-nitrogen-substituted alkenyl phosphates readily undergo an intramolecular Heck cyclization.[7c] We therefore examined the coupling of enol phosphates **7**−**9** with alkylboranes generated from the corresponding olefins **10**−**13** using $Pd(PPh_3)_4$ as a catalyst and aqueous Cs_2CO_3 as a base in DMF at 50 °C (Table 1). Subsequent RCM was accomplished by exposure of the resultant enol ethers to Grubbs' second-generation catalyst[9] in toluene (5 mM), affording a variety of endocyclic enol ethers **14**−**19** in good overall yields. These results clearly indicate that intermolecular Suzuki−Miyaura coupling predominated over the possible intramolecular Heck cyclization.

Table 1. Synthesis of Endocyclic Enol Ethers Based on a Suzuki−Miyaura Coupling/RCM Sequence[a]



enol phosphate	olefin	endocyclic enol ether
 **7**	 **10**	 **14** (56%)
 **8**	 **11**	 **15** (82%)
 **12**: X = OTBS, Y = H **13**: X = H, Y = OTBS		 **16**: X = OTBS, Y = H (69%) **17**: X = H, Y = OTBS (82%)
 **9**[b]	**12** **13**	 **18**[b]: X = OTBS, Y = H (56%) **19**[b]: X = H, Y = OTBS (64%)

[a] Cross-coupling: **10**−**13** (1.5 equiv), 9-BBN-H (2.6 equiv), THF, rt; then aq Cs_2CO_3 (3 equiv), $Pd(PPh_3)_4$ (0.1 equiv), **7**−**9** (prepared from 1 equiv of the corresponding acetate), DMF, 50 °C. RCM: Grubbs' second generation catalyst (0.1 equiv), toluene, 70 °C. The yields are overall from the respective acetates. [b] About 10:1 mixture of diastereomers at C4.

Spirocyclization of endocyclic enol ethers **14**−**19** under thermodynamic conditions was then examined (Table 2). After desilylation (TBAF, 81−100%), the resultant alcohol was exposed to CSA in CH_2Cl_2 at room temperature for 2 h. In the case of **14**−**16**, the doubly anomeric isomers **20**−**22** were exclusively formed in high yields.[10] The cyclization of **17** after desilylation produced a mixture of nonanomeric spiroacetals **23a**,**b** due to the presence of an unfavorable steric interaction within the corresponding doubly anomeric isomer.[10] In the case of **18** and **19**, the yields of the doubly anomeric spiroacetals **24** and **25** were poor because of the competitive Ferrier cyclization (see Supporting Information).[10] These results indicate that the stereochemistry of the C4 benzyloxy group strongly influences the course of cyclization.

We next examined kinetically controlled iodospirocyclization of **17**−**19**. Thus, treatment of **17**, after desilylation, with NIS in CH_2Cl_2 at −90 °C[4b] gave an inseparable 1:3 mixture of **26a** and **26b** in 98% yield. In contrast, iodo-spirocyclization of **18** was highly stereoselective and high-yielding; doubly anomeric spiroacetal **27** was isolated as a single stereoisomer in 83% yield.[10] In contrast, iodo-spirocycliza-

(3) For examples: (a) Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, *48*, 3865. (b) Ley, S. V.; Lygo, B. *Tetrahedron Lett.* **1984**, *25*, 113. (c) Kocienski, P.; Yeates, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1879. (d) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553. (e) Dubois, E.; Beau, J.-M. *Tetrahedron Lett.* **1990**, *31*, 5165. (f) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990**, *55*, 5808. (g) Crimmins, M. T.; O'Mahony, R. *J. Org. Chem.* **1990**, *55*, 5894. (h) Elsley, D. A.; MacLeod, D.; Miller, J. A.; Quayle, P.; Davies, G. M. *Tetrahedron Lett.* **1992**, *33*, 409.

(4) (a) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604. (b) Holson, E. B.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3719. (c) Potuzak, J. S.; Moilanen, S. B.; Tan, D. S. *J. Am. Chem. Soc.* **2005**, *127*, 13796. (d) Moilanen, S. B.; Potuzak, J. S.; Tan, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 1792.

(5) For a review of Suzuki-Miyaura coupling: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(6) For a review of olefin metathesis: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

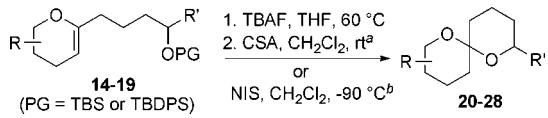
(7) For our successful application of palladium-catalyzed reactions of enol phosphates, see: (a) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075. (b) Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2007**, *5*, 1849. (c) Fuwa, H.; Sasaki, M. *Chem. Commun.* **2007**, 2876. (d) Fuwa, H.; Sasaki, M. *Org. Lett.* **2007**, *9*, 3347.

(8) Other examples of the synthesis of endocyclic enol ethers employing RCM: (a) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (b) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310. (c) Calimente, D.; Postema, M. H. D. *J. Org. Chem.* **1999**, *64*, 1770. (d) Clark, J. S.; Kimber, M. C.; Robertson, J.; McErlean, C. S. P.; Wilson, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 6157.

(9) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(10) For stereochemical assignments of the synthesized spiroacetals, see the Supporting Information.

Table 2. Synthesis of Spiroacetals under Acid-Catalyzed Thermodynamic or Electrophile-Driven Kinetic Conditions



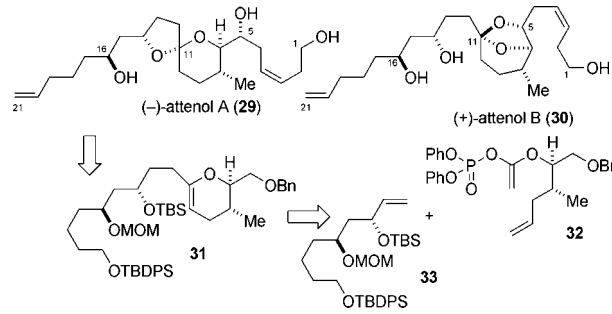
enol ether	spiroacetal(s)	enol ether	spiroacetal(s)
14[a]	**20** (100%[c]; 100%[d])	19[a]	**25** (89%[c]; 46%[d])
15[a]	**21** (100%[c]; 100%[d])	17[b]	**26a** + **26b** (100%[c]; 98% (**26a**:**26b** = 1:3)[d])
16[a]	**22** (100%[c]; 100%[d])		
17[a]	**23a** + **23b** (100%[c]; 88% (**23a**:**23b** = 2:3)[d])	18[b]	**27** (81%[c]; 83%[d])
18[a]	**24** (81%[c]; 22%[d])	19[b]	**28** (89%[c]; 90%[d])

[a] Acid-catalyzed spirocyclization: CSA (0.2 equiv), CH_2Cl_2, rt, 2 h. [b] Iodospirocyclization: NIS (1.5 equiv), CH_2Cl_2, −90 °C, 1.5 h. [c] Yields of desilylation step. [d] Yields of spirocyclization step.

tion of **19** delivered nonanomeric spiroacetal **28** in 90% yield as a single stereoisomer.[10] These results suggest that kinetically controlled spirocyclization of endocyclic enol ethers is a powerful method for the synthesis of both anomeric and nonanomeric spiroacetals. Additionally, these results indicate that the stereochemical outcome of iodo-spiroacetalization depends on the local structure of enol ethers, although it is known that activated glycals have a propensity for the axial addition of electrophiles.[4b]

We successfully applied our strategy to the total synthesis of attenols A and B (**29** and **30**, respectively), cytotoxic marine metabolites isolated from the Chinese bivalve *Pinna attenuata* by Uemura, Suenaga, and co-workers.[11] The absolute stereochemistry of these natural products was elucidated based on extensive NMR analysis coupled with the modified Mosher method and later unambiguously confirmed through total synthesis.[12,13] Our synthesis plan is summarized in Scheme 2. We envisaged that the spiroacetal

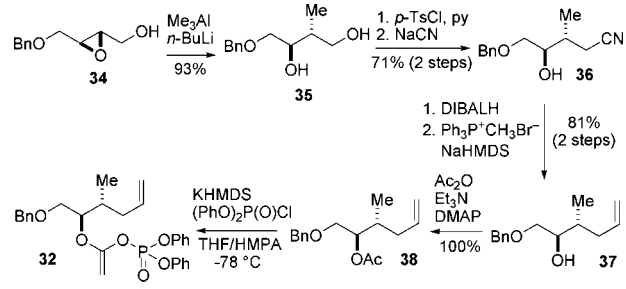
Scheme 2. Synthesis Plan for Attenols A and B



domain of **29** could be accessed by acid-catalyzed spirocyclization of endocyclic enol ether **31**, which in turn could be derived from enol phosphate **32** and an alkylborane generated from olefin **33** by the Suzuki−Miyaura coupling/RCM sequence.

The synthesis of enol phosphate **32** started with regio- and stereoselective epoxide opening[14] of **34** to give diol **35** (93% yield), which was converted to nitrile **36** in 71% yield in two steps (Scheme 3). Reduction of **36** followed by Wittig

Scheme 3. Synthesis of Enol Phosphate **32**



methylenation gave alcohol **37**, which was acylated to provide acetate **38** in good yield. Enolization of **38** with KHMDS in the presence of $(PhO)_2P(O)Cl$ afforded **32**.

The synthesis of olefin **33** commenced with protection of homoallylic alcohol **39**[15] to give MOM ether **40**, which was homologated to enoate **41** via olefin cross-metathesis (Scheme 4). Hydrogenation of **41** followed by reduction afforded

(11) Takeda, N.; Suenaga, K.; Yamada, K.; Zheng, S.-Z.; Chen, H.-S.; Uemura, D. *Chem. Lett.* **1999**, 1025.

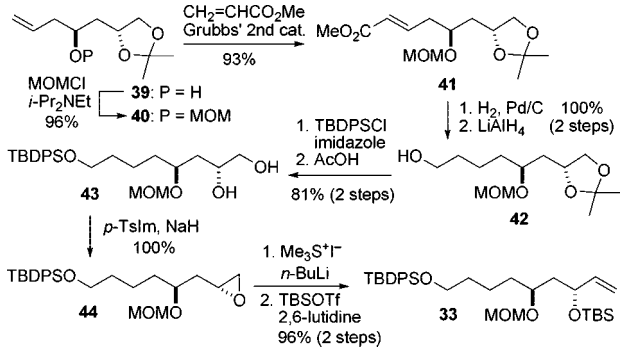
(12) (a) Suenaga, K.; Araki, K.; Sengoku, T.; Uemura, D. *Org. Lett.* **2001**, *3*, 527. (b) Araki, K.; Suenaga, K.; Sengoku, T.; Uemura, D. *Tetrahedron* **2002**, *58*, 1983.

(13) (a) Van de Weghe, P.; Aoun, D.; Boiteau, J.-G.; Eustache, J. *Org. Lett.* **2002**, *4*, 4105. (b) Enders, D.; Lenzen, A. *Synlett* **2003**, 2185. (c) La Cruz, T. E.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 2602.

(14) Sasaki, M.; Tanino, K.; Miyashita, M. *Org. Lett.* **2001**, *3*, 1765.

(15) Kocienski, P. J.; Yeates, C.; Steet, S. D. A.; Campbell, S. F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2183.

Scheme 4. Synthesis of Olefin **33**



alcohol **42**. Routine protective group manipulations gave diol **43**, which was directly converted to epoxide **44** by 1-(*p*-toluenesulfonyl)imidazole/NaH[16] in 100% yield. Exposure of **44** to dimethylsulfonium ylide[17] followed by silylation furnished **33** in 96% yield (two steps).

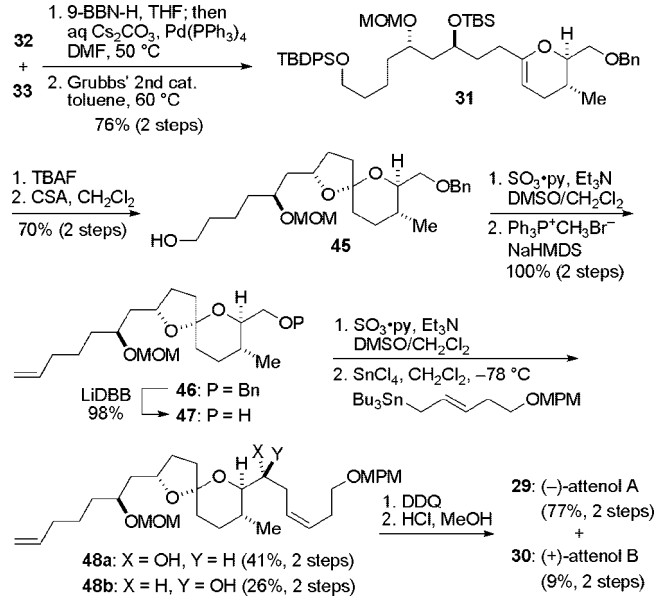
With requisite fragments **32** and **33** in hand, our attention turned to the fragment assembly process and the completion of the synthesis (Scheme 5). Hydroboration of **33** with 9-BBN-H generated an alkylborane, which was in situ coupled with **32** [$Pd(PPh_3)_4$, aqueous Cs_2CO_3, DMF, 50 °C]. Subsequent RCM delivered endocyclic enol ether **31** in 76% yield from **33**.[18] Desilylation followed by acid treatment furnished spiroacetal **45** as a single stereoisomer in 70% yield.[10] Oxidation of the remaining hydroxy group and subsequent methylenation gave olefin **46** in 100% yield. Debenzylation provided alcohol **47**, which was oxidized and then allylated[13a] to give a separable mixture of alcohols **48a**,**b**. Finally, removal of the protective groups furnished (−)-attenol A (**29**) along with (+)-attenol B (**30**). The spectroscopic data of synthetic **29** and **30** were in full accordance with those of natural **29** and **30**, respectively.

(16) Hong, C. H.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693.

(17) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Flack, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449.

(18) We have also examined the synthesis of enol ether **31** by a Suzuki−Miyaura coupling of an alkylborane generated from **33** and a lactone-derived enol phosphate under the identical conditions, albeit in moderate yield (53% from **33**). Moreover, we recently experienced difficulties in preparing enol phosphates or triflates from certain β-alkoxy lactones. These problems can be circumvented by using the Suzuki−Miyaura coupling/RCM strategy.

Scheme 5. Completion of the Total Synthesis



In conclusion, we have developed an efficient strategy for the synthesis of endocyclic enol ethers based on the Suzuki−Miyaura coupling/RCM sequence. Coupled with thermodynamic and kinetic spiroacetalizations, the present strategy allows for rapid access to structurally diverse spiroacetals from a small set of readily available acyclic precursors. Furthermore, the present strategy has been successfully applied to the synthesis of cytotoxic marine metabolites attenols A and B.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds, and stereochemical assignment of synthesized spiroacetals. This material is available free of charge via the Internet at http://pubs.acs.org.

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