Organic LETTERS

Letter

pubs.acs.org/OrgLett

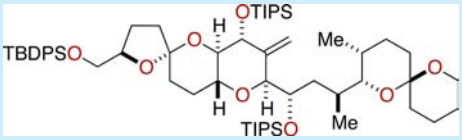
Concise Synthesis of the C15−C38 Fragment of Okadaic Acid: Application of the Suzuki−Miyaura Reaction to Spiroacetal Synthesis

Haruhiko Fuwa,* Keita Sakamoto, Takashi Muto, and Makoto Sasaki

Graduate School of Life Sciences, Tohoku University, 2-1-1 Katahira, Aoba-ku, Sendai 980-8577, Japan

Supporting Information

ABSTRACT: A concise synthetic entry to the C15−C38 fragment of okadaic acid by exploiting a Suzuki−Miyaura reaction for the rapid assembly of the spiroacetal substructures has been developed. The present synthesis was completed in 19 linear steps from a commercially available material, showcasing the efficiency of our synthetic strategy.



Okadaic acid (**1**, Figure 1), a diarrhetic shellfish poison, was originally isolated from the marine sponges

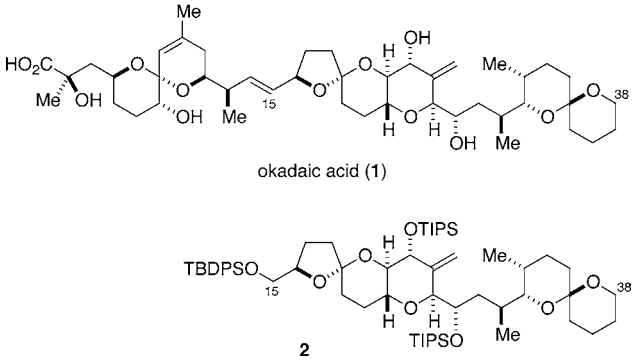


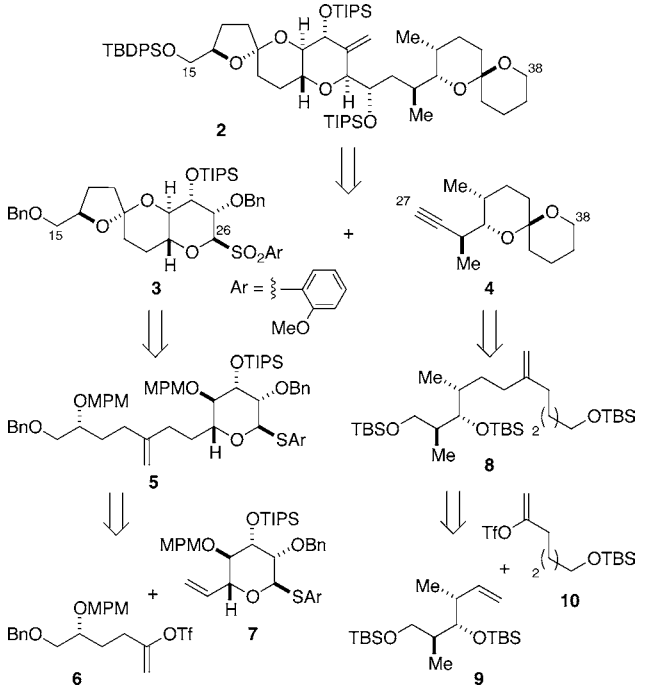
Figure 1. Structures of okadaic acid (**1**) and the C15−C38 fragment **2**.

Halichondria okadai and *Halichondria melanodocia*[1] and subsequently identified from the marine dinoflagellates *Prorocentrum lima* and *Dinophysis fortii*.[2] Okadaic acid is known to inhibit protein phosphatases 1 and 2A (PP1 and PP2A, respectively) and show a range of biological activities, including tumor-promoting activity and apoptosis-inducing ability.[3] X-ray crystallographic studies have successfully elucidated how this natural product binds to PP1 and PP2A at the atomic level.[4] Recent studies have identified another class of specific targets, okadaic acid-binding proteins (OABPs), from *H. okadai*.[5] However, the exact physiological role of OABPs remains to be elucidated. Moreover, Uesugi et al. have quite recently reported that a synthetic derivative of **1** shows selective cytotoxicity against human pluripotent stem cells.[6]

The complex structure of **1**, established by X-ray crystallographic analysis,[1] poses significant challenges to the synthetic community. The Isobe,[7] Forsyth,[8] and Ley[9] groups have independently achieved the total synthesis of **1**. However, the structure−activity relationship (SAR) of **1** has not been fully resolved,[10] and a concise and modular synthetic approach toward **1** and its analogues is required for elucidating the SAR and unique biological activity in greater detail. Toward this end, we describe herein a concise synthetic entry to the C15−C38 fragment **2** of okadaic acid.

Our synthesis plan toward **2** is summarized in Scheme 1. We envisaged that **2** could be obtained from the sulfone **3** and the

Scheme 1. Synthesis Plan toward 2



alkyne **4**, according to the previous work by Ley and coworkers.[9] We planned to exploit the Suzuki−Miyaura reaction[11,12] for rapid assembly of the spirocyclic skeletons of **3** and **4**. Since the spiroacetal substructures embedded within **3** and **4** are thermodynamically favored by the virtue of anomeric effect, these intermediates would be easily available from the

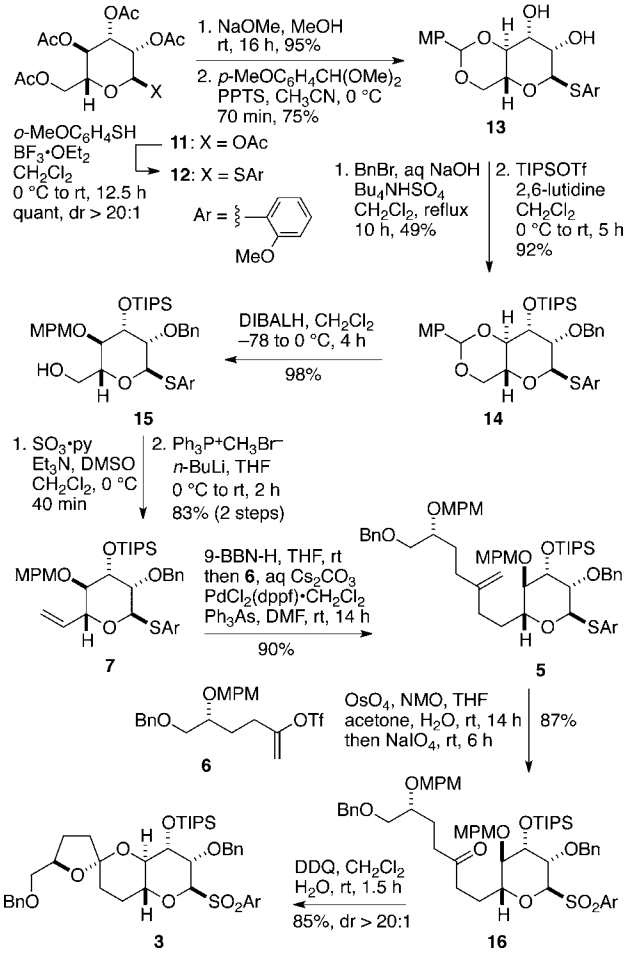
Received: December 3, 2014
Published: December 26, 2014

DOI: 10.1021/ol503491t
Org. Lett. 2015, 17, 366−369

respective keto diol counterparts.[13] Thus, the sulfone **3** representing the C15−C26 fragment was traced back to the *exo*-olefin **5** as a synthetic equivalent of the corresponding keto diol, and **5** in turn could be derived from the enol triflate **6** and the olefin **7** via a Suzuki−Miyaura reaction.[11] In a similar manner, we envisioned that the alkyne **4** that corresponds to the C27−C38 fragment would be obtainable from the *exo*-olefin **8**, which could be prepared from the olefin **9** and the enol triflate **10** via a Suzuki−Miyaura reaction[11] and a spiroacetalization.

The synthesis of the sulfone **3**, depicted in Scheme 2, started with thioglycosylation of commercially available α-D-mannose

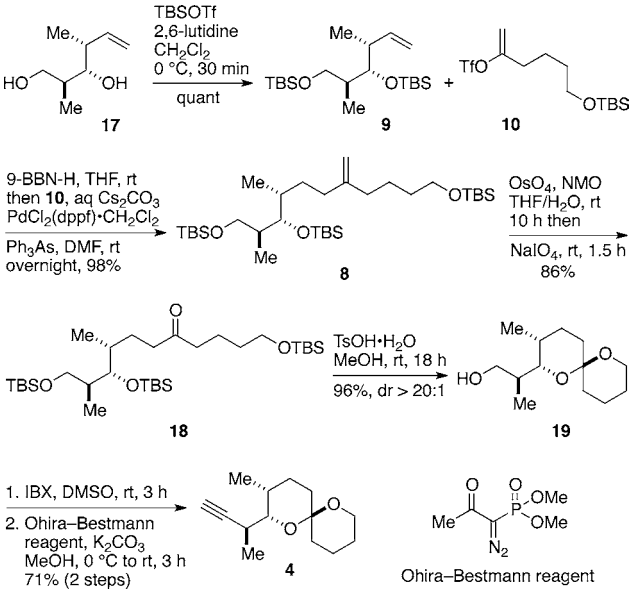
Scheme 2. Synthesis of Sulfone 3



pentaacetate (**11**) with *o*-methoxybenzenethiol (quant, dr >20:1). Deacetylation of the thioglycoside **12** (95%) followed by selective protection of the resultant tetraol with *p*-methoxybenzylidene acetal provided the diol **13** (75%). Selective benzylation of the axial hydroxy group (BnBr, aq NaOH, Bu_4NHSO_4, CH_2Cl_2, reflux, 49%)[14] and subsequent silylation of the remaining alcohol with TIPSOTf/2,6-lutidine gave the silyl ether **14** (92%). Regioselective reduction of the *p*-methoxybenzylidene acetal using DIBALH[15] delivered the alcohol **15** (98%), which was oxidized[16] and then methylenated to afford the olefin **7** (83%, two steps). Hydroboration of **7** with 9-BBN-H followed by in situ coupling[11] with the enol triflate **6**[17] (aq Cs_2CO_3, $PdCl_2(dppf)\cdot CH_2Cl_2$, Ph_3As, DMF)[18] provided the *exo*-olefin **5** in 90% yield. Oxidative cleavage of the double bond with spontaneous oxidation of the sulfide (OsO_4, NMO; then $NaIO_4$, 87%) gave the ketone **16**. Removal of the MPM group and concomitant spiroacetalization furnished the sulfone **3** in 85% yield (dr >20:1). The relative configuration of **3** was established on the basis of NOE experiments.[19]

The synthesis of the alkyne **4** commenced with known diol **17**,[8a] prepared in four steps from the (*S*)-Roche ester (Scheme 3). Silylation of **17** gave the olefin **9** (quant), which was

Scheme 3. Synthesis of Alkyne 4

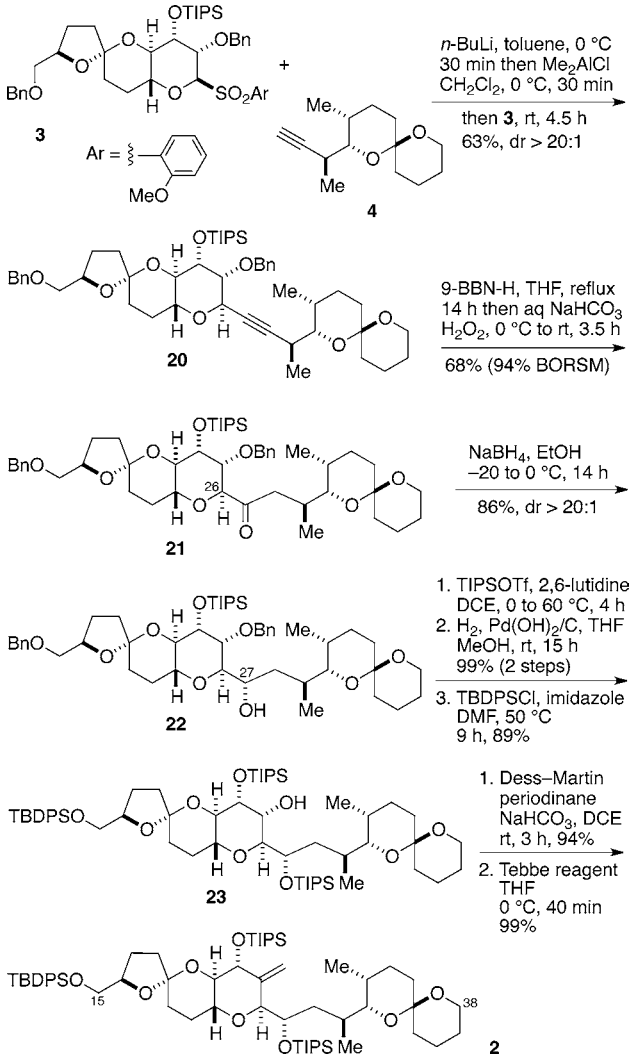


hydroborated with 9-BBN-H and then coupled[11] with the enol triflate **10**[20] (aq Cs_2CO_3, $PdCl_2(dppf)\cdot CH_2Cl_2$, Ph_3As, DMF)[18] to afford the *exo*-olefin **8** in 98% yield. After cleavage of the double bond (OsO_4, NMO; then $NaIO_4$, 86%), the resultant ketone **18** was exposed to acidic methanol to induce desilylation and spontaneous spiroacetalization, leading to the thermodynamically favored spiroacetal **19**[8a] in 96% yield (dr >20:1). Oxidation[21] of **19** followed by alkynylation with the Ohira−Bestmann reagent[22] (K_2CO_3, MeOH) afforded the alkyne **4** (71%, two steps).[9]

With the sulfone **3** and alkyne **4** available, we coupled these subunits under the conditions reported by Ley and co-workers[9] (Scheme 4). Deprotonation of **4** with *n*-BuLi followed by addition of Me_2AlCl generated the corresponding alkynylaluminum species, which was reacted in situ with **3** to furnish the coupling product **20** in 63% yield (dr >20:1). In contrast, our initial attempt to use the corresponding benzenesulfonyl counterpart of **3** was completely unsuccessful because of its low reactivity toward the alkynylaluminum prepared from **4**.[23] Hydroboration of **20** with 9-BBN-H followed by oxidative workup provided the ketone **21** (68%, 94% based on recovered starting material (BORSM)). At this stage, the configuration of the C26 stereogenic center was determined on the basis of ROE experiments and $^3J_{H,H}$ analysis.[19] The ketone **21** was reduced with $NaBH_4$ to give the alcohol **22** in 86% yield (dr >20:1). The absolute configuration of the newly generated C27 stereogenic center was established by a modified Mosher analysis.[24] The stereoselectivity of this reduction could be explained by considering a polar Felkin−Anh model.[7d,25] Silylation of **22** with TIPSOTf/2,6-lutidine, hydrogenolysis of the benzyl ethers (99%, two steps), and subsequent selective silylation of the liberated primary alcohol with TBDPSCl/

DOI: 10.1021/ol503491t
Org. Lett. 2015, 17, 366−369

Scheme 4. Synthesis of the C15−C38 Fragment 2



imidazole provided the alcohol **23** (89%). Dess−Martin oxidation[26] (94%) followed by methylenation with Tebbe reagent[27] afforded the C15−C38 fragment **2** (99%).

In conclusion, we have developed a concise synthetic entry to the C15−C38 fragment **2** of okadaic acid by exploiting Suzuki−Miyaura reaction for the synthesis of the spiroacetal substructures. Our synthetic strategy allows for rapid assembly of complex spiroacetals in high yield. The present synthesis of **2** requires just 19 linear steps from a commercially available material and thus compares favorably with the previous work by other groups. This work sets the stage for the development of elaborated synthetic analogues of okadaic acid to elucidate the SAR and biological activity in detail. Work along this line is currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hfuwa@m.tohoku.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Professor Keiichi Konoki (Graduate School of Agricultural Science, Tohoku University) for his fruitful discussions and encouragement. This work was supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas "Chemical Biology of Natural Products" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.[28]

■ REFERENCES

(1) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Engen, D. V.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469−2471.

(2) (a) Murakami, Y.; Oshima, Y.; Yasumoto, T. *Bull. Jpn. Soc. Sci. Fish.* **1982**, *48*, 69−72. (b) Yasumoto, T.; Seino, N.; Murakami, Y.; Murata, M. *Biol. Bull.* **1987**, *172*, 128−131.

(3) (a) Murata, M.; Shimatani, M.; Sugitani, H.; Oshima, Y.; Yasumoto, T. *Bull. Jpn. Soc. Sci. Fish.* **1982**, *48*, 549−552. (b) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019−1025. (c) Suganuma, M.; Fujiki, H.; Suguri, H.; Yoshizawa, S.; Hirota, M.; Nakayasu, M.; Ojika, M.; Wakamatsu, K.; Yamada, K.; Sugimura, T. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 1768−1771. (d) Bialojan, C.; Takai, A. *Biochem. J.* **1988**, *256*, 283−290. (e) Davis, M. A.; Chang, S. H.; Trump, B. F. *Toxicol. Appl. Pharmacol.* **1996**, *141*, 93−101. (f) Yan, Y.; Shay, J. W.; Wright, W. E.; Mumby, M. C. *J. Biol. Chem.* **1997**, *272*, 15220−15226. (g) von Zezschwitz, C.; Vorwerk, H.; Tergau, F.; Steinfelder, H. J. *FEBS Lett.* **1997**, *41*, 147−151. (h) Morimoto, Y.; Ohba, T.; Kobayashi, S.; Haneji, T. *Exp. Cell Res.* **1997**, *230*, 181−186. (i) Kawamura, K.-i.; Grabowski, D.; Weizer, K.; Bukowski, R.; Ganapathi, R. *Br. J. Cancer* **1996**, *73*, 183−188.

(4) (a) Maynes, J. T.; Bateman, K. S.; Cherney, M. M.; Das, A. K.; Luu, H. A.; Holmes, C. F. B.; James, M. N. G. *J. Biol. Chem.* **2001**, *276*, 44078−44882. (b) Xing, Y.; Xu, Y.; Chen, Y.; Jeffrey, P. D.; Chao, Y.; Lin, Z.; Li, Z.; Strack, S.; Stock, J. B.; Shi, Y. *Cell* **2006**, *127*, 341−353.

(5) (a) Sugiyama, N.; Konoki, K.; Tachibana, K. *Biochemistry* **2007**, *46*, 11410−11420. (b) Konoki, K.; Saito, K.; Matsuura, H.; Sugiyama, N.; Cho, Y.; Yotsu-Yamashita, M.; Tachibana, K. *Bioorg. Med. Chem.* **2010**, *18*, 7607−7610. (c) Konoki, K.; Onoda, T.; Furumochi, S.; Cho, Y.; Yotsu-Yamashita, M.; Yasumoto, T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5833−5835.

(6) Kuo, T.-F.; Mao, D.; Hirata, N.; Khambu, B.; Kimura, Y.; Kawase, E.; Shimogawa, H.; Ojika, M.; Nakatsuji, N.; Ueda, K.; Uesugi, M. *J. Am. Chem. Soc.* **2014**, *136*, 9798−9801.

(7) (a) Ichikawa, Y.; Isobe, M.; Bai, D.-L.; Goto, T. *Tetrahedron* **1987**, *43*, 4737−4748. (b) Ichikawa, Y.; Isobe, M.; Goto, T. *Tetrahedron* **1987**, *43*, 4749−4758. (c) Ichikawa, Y.; Isobe, M.; Masaki, H.; Kawai, T.; Goto, T. *Tetrahedron* **1987**, *43*, 4759−4766. (d) Isobe, M.; Ichikawa, Y.; Bai, D.-L.; Masaki, H.; Goto, T. *Tetrahedron* **1987**, *43*, 4767−4776.

(8) (a) Urbanek, R. A.; Sabes, S. F.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2523−2533. (b) Sabes, S. F.; Urbanek, R. A.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2534−2542. For related work from the Forsyth group, see: (c) Dounay, A. B.; Urbanek, R. A.; Sabes, S. F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2258−2262. (d) Dounay, A. B.; Urbanek, R. A.; Frydrychowski, V. A.; Forsyth, C. J. *J. Org. Chem.* **2001**, *66*, 925−938. (e) Fang, C.; Pang, Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528−4531. (f) Pang, Y.; Fang, C.; Twiner, M. J.; Miles, C. O.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7631−7635 and references cited therein.

(9) Ley, S. V.; Humphries, A. C.; Eick, H.; Downham, R.; Ross, A. R.; Boyce, R. J.; Pavey, J. B. J.; Pietruszka, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3907−3911.

DOI: 10.1021/ol503491t
Org. Lett. 2015, 17, 366−369

(10) (a) Nishiwaki, S.; Fujiki, H.; Suganuma, M.; Furuya−Suguri, H.; Matsushima, R.; Iida, Y.; Ojika, M.; Yamada, K.; Uemura, D.; Yasumoto, T.; Schmitz, F. J.; Sugimura, T. *Carcinogenesis* **1990**, *11*, 1837−1841. (b) Takai, A.; Murata, M.; Torigoe, K.; Isobe, M.; Mieskes, G.; Yasumoto, T. *Biochem. J.* **1992**, *284*, 539−544. (c) Frydrychowski, V. A.; Urbanek, R. A.; Dounay, A. B.; Forsyth, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 647−649. (d) Kita, M.; Kuramoto, M.; Chiba, T.; Yamada, A.; Yamada, N.; Ishida, T.; Haino, T.; Yamada, K.; Ijuin, Y.; Ohno, O.; Uemura, D. *Heterocycles* **2008**, *76*, 1033−1042. (e) Huhn, J.; Jeffrey, P. D.; Larsen, K.; Rundberget, T.; Rise, F.; Cox, N. R.; Arcus, V.; Shi, Y.; Miles, C. O. *Chem. Res. Toxicol.* **2009**, *22*, 1782−1786.

(11) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722−6737.

(12) We have previously reported the synthesis of endocyclic enol ethers via Suzuki−Miyaura reaction and its application to spiroacetal synthesis. See: (a) Fuwa, H.; Sasaki, M. *Org. Lett.* **2008**, *10*, 2549−2552. (b) Fuwa, H.; Noji, S.; Sasaki, M. *Org. Lett.* **2010**, *12*, 5354−5357. (c) Fuwa, H.; Sekine, K.; Sasaki, M. *Org. Lett.* **2013**, *15*, 3970−3973. (d) Fuwa, H.; Muto, T.; Sekine, K.; Sasaki, M. *Chem.—Eur. J.* **2014**, *20*, 1848−1860 However, this strategy was found to be less effective for the synthesis of the spiroacetal substructures of okadaic acid. Details will be reported in a full account..

(13) (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661. (b) Raju, B. R.; Saikia, A. K. *Molecules* **2008**, *13*, 1942−2038.

(14) Garegg, J.; Iversen, T.; Oscarson, S. *Carbohydr. Res.* **1976**, *50*, C12−C14.

(15) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1984**, 201−202.

(16) Parikh, J. R.; Doering, W.; von, E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(17) For the preparation of **6**, see the Supporting Information.

(18) (a) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014−11015. (b) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027−9031.

(19) See the Supporting Information for details.

(20) For the preparation of **10**, see the Supporting Information.

(21) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019−8022.

(22) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522.

(23) Ley and co-workers proposed that the *o*-methoxy group on the phenylsulfonyl group would enhance the coordinating ability of the sulfonyl group to the alkynylaluminum species.[9] For a related discussion, see: Fried, J.; Sih, J. C.; Lin, C. H.; Dalven, P. *J. Am. Chem. Soc.* **1972**, *94*, 4343−4345.

(24) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(25) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70.

(26) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

(27) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613.

(28) Ueda, M. *Chem. Lett.* **2012**, *41*, 658−666.

DOI: 10.1021/ol503491t
Org. Lett. 2015, 17, 366−369