ORGANIC LETTERS

2009
Vol. 11, No. 15
3362−3365

Stereoselective Synthesis of Spirocyclic Oxindoles via Prins Cyclizations

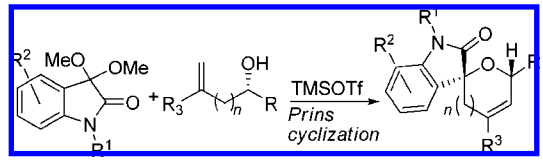
M. Paola Castaldi, Dawn M. Troast, and John A. Porco, Jr.*

Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

porco@bu.edu

Received May 28, 2009

ABSTRACT



The synthesis of spirocyclic oxindole pyran and oxepene frameworks using highly stereoselective Prins cyclizations of homoallylic and *bis*-homoallylic alcohols and isatin ketals is described.

Exo-methylene pyrans are present in a variety of biologically active natural products.[1] We recently employed the intramolecular silyl-modified Sakurai (ISMS) reaction[2] to construct the exomethylene pyran subunit of the macrocyclic core of (−)-zampanolide (**1**, Figure 1a).[3] We envisioned use of this powerful methodology to access a variety of exomethylene tetrahydropyrans (**3** and **4**, Figure 1b) using diverse ketals and acetals (**5** and **6**, Figure 1b) for diversity-oriented synthesis[4] and chemical library development (Figure 1b). As part of our studies, we also considered preparation of pyran

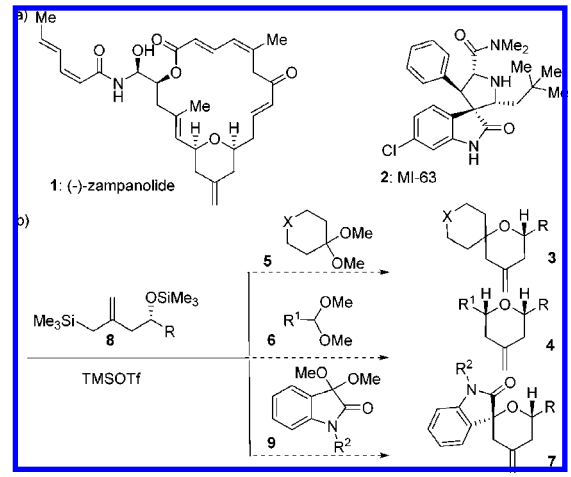


Figure 1. (a) Representative *exo*-methylene pyran spirooxindole molecules. (b) Initial synthesis plan.

spirooxindole hybrid molecules[5] (**7**, Figure 1b) from allylsilanes **8** and isatin ketals **9** in order to merge fragments of two biologically interesting motifs. The spirooxindole core structure is represented in numerous pharmacological agents and alkaloids[6] including the anticancer agent MI-63 (**2**, Figure 1a).[7] In this communication, we report how our initial

(1) (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126. (b) Tanaka, J.-i.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535. (c) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.* **2001**, 775. (d) Takahashi, S.; Okada, A.; Nishiwaki, M.; Nakata, T. *Heterocycles* **2006**, *69*, 487.

(2) (a) Marko, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211. (b) Marko, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595.

(3) (a) Hoye, T. R.; Hu, M. *J. Am. Chem. Soc.* **2003**, *125*, 9576. (b) Sanchez, C. C; Keck, G. E. *Org. Lett.* **2005**, *7*, 3053. (c) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485. (d) Troast, D. M.; Yuan, J.; Porco, J. A., Jr. *Adv. Synth. Catal.* **2008**, *350*, 1701.

(4) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (c) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74. (d) Spring, D. R. *Chem. Soc. Rev.* **2005**, *34*, 472.

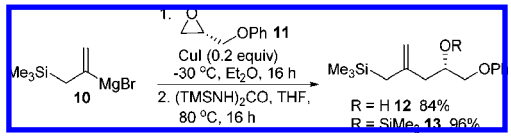
(5) (a) Tietze, L. F.; Bell, H. P.; Chandrasekhar, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3996. (b) Su, S.; Acquilano, D. E.; Arumugasamy, J.; Beeler, A. B.; Eastwood, E. L.; Giguere, J. R.; Lan, P.; Lei, X.; Min, G. K.; Yeager, A. R.; Zhou, Y.; Panek, J. S.; Snyder, J. K.; Schaus, S. E.; Porco, J. A., Jr. *Org. Lett.* **2005**, *7*, 2751. (c) Banerjee, A.; Sergienko, E.; Vasile, S.; Gupta, V.; Vuori, K.; Wipf, P. *Org. Lett.* **2009**, *11*, 65.

10.1021/ol901201k CCC: $40.75
Published on Web 07/14/2009

synthesis plan evolved to identify stereoselective, Lewis acid-mediated Prins cyclizations to access both enantioenriched spirocyclic oxindole pyrans and oxepenes.

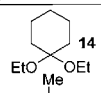
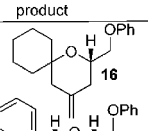
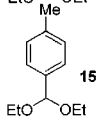
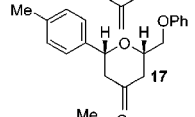
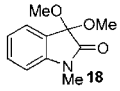
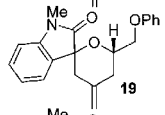
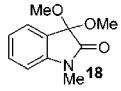
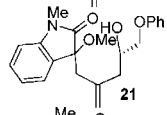
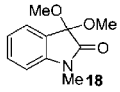
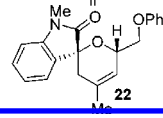
In initial studies, allyl silane **12** and derived silyl ether **13** (Scheme 1) were prepared employing Cu(I)-catalyzed[8]

Scheme 1. Preparation of Allylsilane **13**



ring-opening of chiral, nonracemic epoxide **11** with vinyl Grignard **10**.[9] After optimization of ISMS reaction conditions, ketals **14** and acetal **15**[10] were successfully employed in the synthesis of spirocyclic *exo*-methylene pyran **16** and 2,6-*syn*-disubstituted pyran **17**[11] (Table 1, entries 1 and 2).

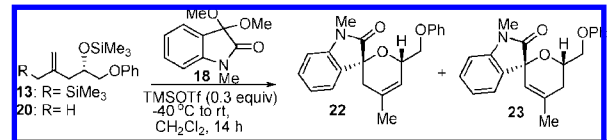
Table 1. Use of Allylsilane **13** in ISMS Reactions*

entry	acetal/ketal	T [°C]	solvent	product	yield (%)[a]
1	 14	-78	Et_2O	 16	80
2	 15	-78	Et_2O	 17	84 dr > 20:1
3	 18	-78	Et_2O	 19	<2[b]
4	 18	-78 to rt	Et_2O	 21	63 dr = 1:1
5	 18	-78 to rt	CH_2Cl_2	 22	36

* Reaction conditions: allylsilane **13** (1.1 equiv), TMSOTf (0.3 equiv), 2,6-*t*-Bu-4-Me-pyridine (DBMP) (0.05 equiv), 4 Å MS, 14 h. [a] Isolated yields. [b] Not observed, *N*-methylisatin and desilylated allylsilane **20** recovered.

Subjection of *N*-methyl isatin dimethylketal **18**[12] (Table 1) and allyl silane **13** to optimized ISMS reaction conditions (Table 1, entry 3) did not afford the desired spiroannulated product **19** and led only to recovery of silyl ether[13] **20** (Scheme 2) and *N*-methyl isatin. Warming of the reaction to room temperature afforded product **21**, presumably from direct allylation of the derived isatin oxonium ion with allylsilane **13** (Table 1, entry 4). Attempts to convert compound **21** into the desired spiroannulated product under acidic conditions afforded a complex mixture of products. When CH_2Cl_2 was used as solvent, spirooxindole **22** bearing

Scheme 2. Spirooxindole Pyrans via Prins Cyclizations

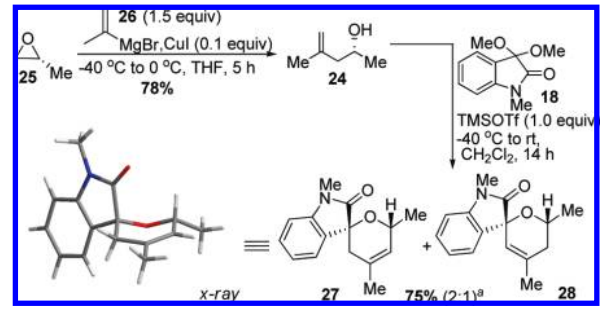


entry	R	additive	result [a]
1	$SiMe_3$	DBMP (0.1 equiv)	**22** = 38% **23** = 19%
2	H	DBMP (0.1 equiv)	**22** = 46% **23** = 20%
3	H	None	**22** = 58% **23** = 24%

[a] Isolated yield.

an endocyclic alkene[14] was isolated in moderate yield. A control experiment employing ketal **14** in the ISMS reaction with CH_2Cl_2 as a solvent afforded product **16** and its endocyclic olefin isomer (1:2 ratio).

Scheme 3. Diastereoselective Synthesis of Spirooxindoles



[a] Ratio of **27**:**28** determined by ^{1}H NMR analysis of a crude sample.

Based on these observations and given that spiroannulation did not occur at low temperature (−78 °C), we performed the reaction at higher temperatures which afforded spirooxindoles **22** and **23** in good overall yield (Scheme 2, entry 1). The apparent isomerization of the double bond (endocyclic vs exocyclic olefin) suggested the possibility of a mechanistic pathway which was different than the expected ISMS reaction. Intramolecular Prins-type cyclization[15] of homoallylic silyl ether **20** derived from desilylation of **13** could account for such an outcome. To support this hypothesis, homoallylic silyl ether **20** was synthesized and employed in the reaction to afford products **22** and **23** in good overall yield (Scheme 2, entries 2 and 3). An additional spirooxin-

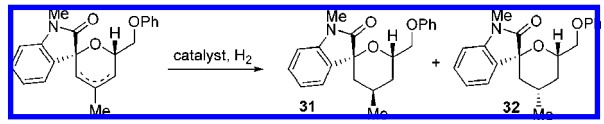
(6) (a) Kang, T.-H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharamacol.* **2002**, *444*, 39. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (c) Kumar, R. R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. *J. Med. Chem.* **2008**, *51*, 5731.

(7) (a) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432. (b) Shangary, S.; Wang, S. *Annu. Rev. Pharmacol. Toxicol.* **2009**, *49*, 223.

(8) Nishiyama, H.; Yokoyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1982**, *23*, 1267.

(9) Takano, S.; Kamikubo, T.; Sugihara, T.; Suzuki, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1993**, *4*, 201.

Table 2. Amide-Directed Hydrogenation



spirooxindole	catalyst	H_2	solvent	conversion[a] (%)	ratio[a]
22	Pd/C	50 psi	MeOH	96	2:1
23	Pd/C	50 psi	MeOH	99	7:1
22	Wilkinson's catalyst $RhCl(PPh_3)_3$	50 psi	EtOH/benzene		
22 + **23**	Crabtree's catalyst $[Ir(cod)py(PCy_3]PF_6$	1 atm	CH_2Cl_2	99	only **32**

[a] Conversion and ratios of **31**:**32** determined by ^1H NMR analysis of crude samples.

dole pyran synthesis sequence is shown in Scheme 3. Preparation of homoallylic alcohol **24**[16] by epoxide ring-opening, followed by treatment with isatin ketal **18** and TMSOTf, afforded spirooxindoles **27** and **28** (Scheme 3). The relative stereochemistry and alkene position of major stereoisomer **27** were confirmed by X-ray crystallographic analysis.[11]

In order to explain the stereochemical outcome of the Prins cyclizations, we propose a chair transition state (Figure 2)

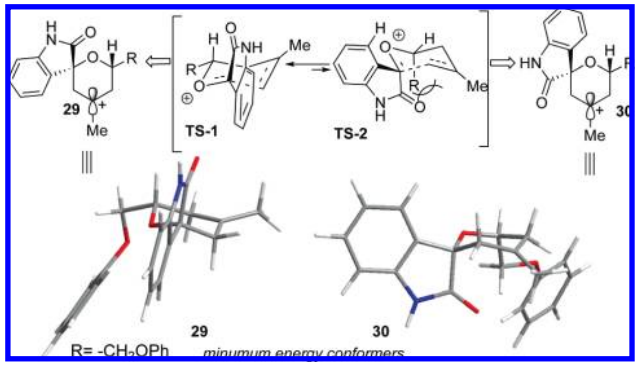


Figure 2. Proposed transition states.

in which the larger aryl substituent of the oxindole moiety adopts a *pseudo*-equatorial orientation[17] (TS-1) leading to the observed diastereoisomer (cf. **22** and **23**, Scheme 2). An alternative chair (TS-2) leading to the disfavored diastereoisomer has significant steric interactions between the isatin carbonyl oxygen and the R substituent on the chiral center. Examination of molecular models of the proposed intermediate tertiary carbocations **29** and **30** obtained using Spartan conformational searches (AM1) followed by DFT minimization (performed using a 6-31G* basis set; $\Delta E = 8.25$ kcal/mol)[11] shows destabilizing 1,3-diaxial interactions in carbocation **30** which is derived from Prins cyclization through TS-2.

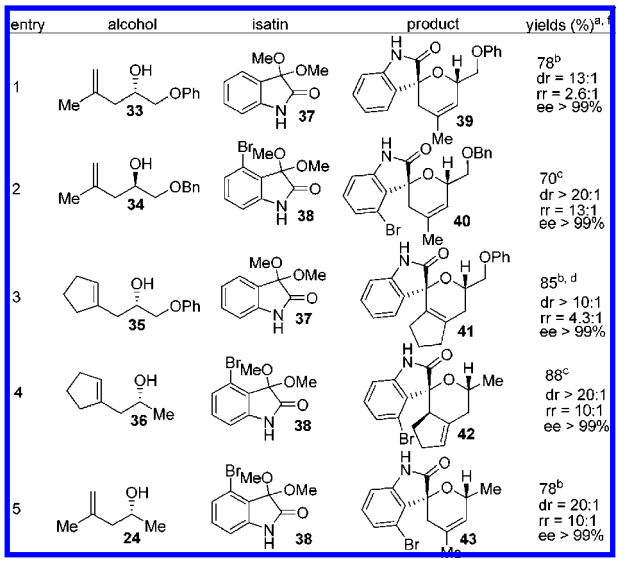
In order to confirm the relative stereochemistry at the spiro center of minor regioisomer **23** generated during the Prins cyclization, we subjected both regioisomers **22** and **23** to metal-catalyzed hydrogenation. Interestingly, using catalytic amounts of Pd/C, a mixture of chromatographically separable diastereoisomers **31** and **32** were observed by ^1H NMR analysis of crude samples, indicating that regioisomers **22** and **23** had the same relative stereochemistry at the spiro center (Table 2).

In light of the poor diastereoselectivity observed using standard hydrogenation conditions, we next evaluated the possibility of amide-directed hydrogenation.[18] While use of Wilkinson's catalyst did not generate the desired hydrogenated product, use of Crabtree's catalyst[19] led to the production of **32** in excellent diastereoselectivity (dr >30:1) indicating complete substrate control in the amide-directed hydrogenation (Table 2).

In order to broaden the scope of the methodology to access spirocyclic oxindoles, we prepared a series of homoallylic alcohols (**24**, **33**-**36**) and isatin ketals (**18**, **37**,[20] **38**) for examination in the Prins cyclization (Table 3). Cyclizations were found to be successful with isatin ketals bearing NH functionality to afford spirooxindole products **39**-**43**. Introduction of a bulky bromine substituent on the 4-position of the isatin ketal (Table 3, entries 2, 4 and 5) resulted in improved diastereoselectivity and noticeably influenced the product olefin regiochemistry (*cf.* entries 3 and 4), which may be explained by highly regioselective elimination of a carbocation intermediate distal from the bromo-oxindole moiety (cf. **29**, Figure 2).

(10) Karimi, B.; Ebrahimian, G. R.; Seradj, H. *Synlett* **1999**, *9*, 1456.
(11) See the Supporting Information for complete experimental details.
(12) Muschalek, B.; Weidner, I.; Butenschon, H. *J. Organomet. Chem.* **2007**, *692*, 2415.
(13) For protodesilylation of allylsilanes, see: (a) Fleming, I.; Langley, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1421. (b) Leroy, B.; Markó, I. E. *Tetrahedron Lett.* **2001**, *42*, 8685.
(14) For solvent effects in ISMS reactions, see: (a) Keck, G. E.; Covel, J. A.; Shiff, T.; Yu, T. *Org. Lett.* **2002**, *4*, 1189. For alternative syntheses of spirocyclic oxindole pyrans, see: (b) Smet, M.; Oosterwijck, C. V.; Hecke, K. V.; Meervelt, L. V.; Vandendriessche, A.; Dehaen, W. *Synlett* **2004**, 2388. (c) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2006**, *71*, 2346.
(15) (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505. (b) Abdelaziz, M.; Marko, I. E.; Adams, H. *Tetrahedron Lett.* **1991**, *32*, 4783. (c) Ghosh, A. K.; Shin, D.; Schiltz, G. *Heterocycles* **2002**, *58*, 659.
(16) (a) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *17*, 1503. (b) Alcaraz, L.; Cridland, A.; Kinchin, E. *Org. Lett.* **2001**, *3*, 4051.

Table 3. Prins-Type Spiro-annulation



[a] Isolated yields [b] Reaction conditions: TMSOTf (1.0 equiv), −40 °C to rt, 14 h, CH_2Cl_2. [c] TMSOTf (1.0 equiv), −40 to 0 °C, 3 h, CH_2Cl_2. [d] Isolated as an inseparable mixture of regioisomers. Hydrogenation was necessary to facilitate products separation. [f] rr = regioisomeric ratio; major isomer shown.

Considering the well-documented racemization observed during Prins cyclization due to competitive oxonia-Cope rearrangement (Figure 3),[21] we also measured the enantio-

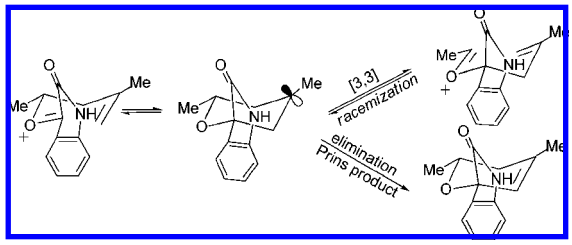


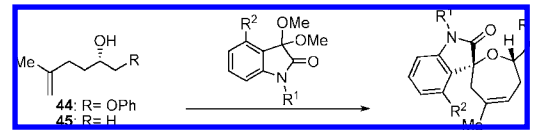
Figure 3. Possible racemization of Prins cyclization products via 2-oxonia-Cope rearrangement.

meric excess of the spirocyclic products. In all cases, we did not observed erosion in enantiopurity (Tables 3 and 4). These findings are consistent with the observations that stabilization of the intermediate tetrahydropyranyl cation raises the transition states energy for ring-opening and effectively eliminates the oxonia-Cope rearrangement.[21a,b]

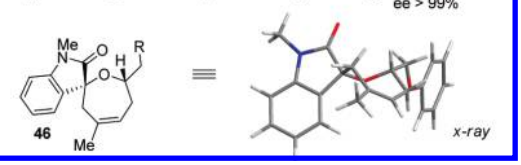
Finally, we extended the methodology to intramolecular Prins cyclization of *bis*-homoallylic alcohols (Table 4, **44**, **45**[22]) and isatin ketals (Table 4, **18**, **37**, **38**) to generate spirocyclic oxindole oxepenes[14b,23] **46-50** in high diastereo- and regioselectivity (Table 4). The relative stereochemistry of spirooxindole **46** was confirmed *via* X-ray crystallographic analysis.[11]

In conclusion, enantiopure spirocyclic oxindole pyrans and oxepenes have been efficiently synthesized by highly ste-

Table 4. Diastereoselective Synthesis of Spirooxindole Oxepenes



entry	R	R^1	R^2	product	yields (%)[a,b]
1	OPh	H	Me	**46**	51 dr > 20:1 rr = 10:1 ee > 99%
2	OPh	H	H	**47**	41 dr > 20:1 rr = 10:1 ee > 99%
3	OPh	Br	H	**48**	43 dr > 20:1 rr = 13:1 ee > 99%
4	H	H	H	**49**	56 dr > 20:1 rr = 16:1 ee > 99%
5	H	Br	H	**50**	57 dr > 20:1 rr = 20:1 ee > 99%



[a] Isolated yields. [b] rr = regioisomeric ratio; major isomer shown. Reaction conditions: TMSOTf (1.0 equiv), −40 °C to rt, 3 h, CH_2Cl_2.

reoselective Prins-type cyclizations of both homoallylic and *bis*-homoallylic alcohols and isatin ketals. The protocol is highly complementary to related annulations involving chiral organosilanes.[24] Further studies involving related annulations and library synthesis applications are in progress and will be reported in due course.

Acknowledgment. Financial support from the NIGMS (P41 GM076263 and P50 GM067041) is gratefully acknowledged. We thank Ms. Jiayi Yuan (Boston University) for preliminary studies, Professors James Panek, Aaron Beeler, Ramesh Jasti, and Ms. Yun Zhang (Boston University) for helpful discussions, and Dr. Emil Lobkovsky (Cornell University) for X-ray crystallographic analysis.

Supporting Information Available: Detailed experimental procedures and spectral data for all compounds. X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901201K

(17) (a) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960. (b) Overman, L. E.; Watson, D. A. *J. Org. Chem.* **2006**, *71*, 2587.

(18) For a review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(19) (a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205. (b) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

(20) Pinder, L. J.; Weinreb, S. M. *Tetrahedron Lett.* **2003**, *44*, 4141.

(21) (a) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939–9945. (b) Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005**, 3727. (c) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640.

(22) Mothes, E.; Sentets, S.; Luquin, M. A.; Mathieu, R.; Lugan, N.; Lavigne, G. *Organometallics* **2008**, *27*, 1193.

(23) For an alternative synthesis of spirooxepenes, see: Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044.

(24) Zhang, Y.; Panek, J. *Org. Lett.* **2009**, *11*, (DOI 10.1021/ol901202t).