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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

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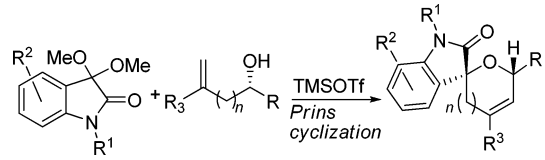
ABSTRACT



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

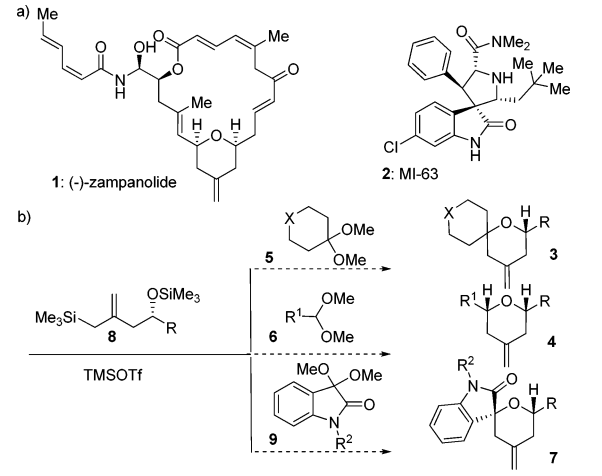


Figure 1. (a) Representative *exo*-methylene pyran spirooxindole molecules. (b) Initial synthesis plan.

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

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(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.

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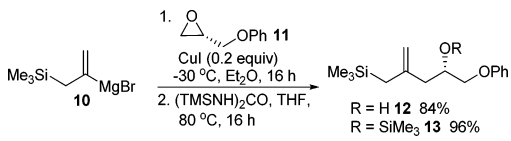
synthesis plan evolved to identify stereoselective, Lewis acid-mediated Prins cyclizations to access both enantioenriched spirocyclic oxindole pyrans and oxepenes.

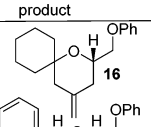
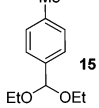
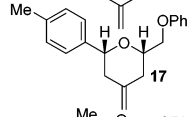
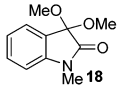
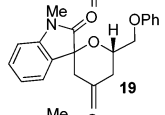
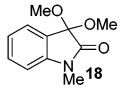
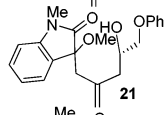
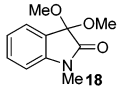
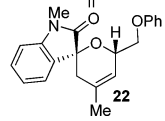
In initial studies, allyl silane **12** and derived silyl ether **13** (Scheme 1) were prepared employing Cu(I)-catalyzed[8]

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).

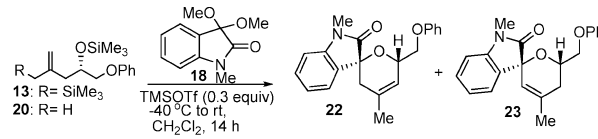
Table 1. Use of Allylsilane **13** in ISMS Reactions*

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

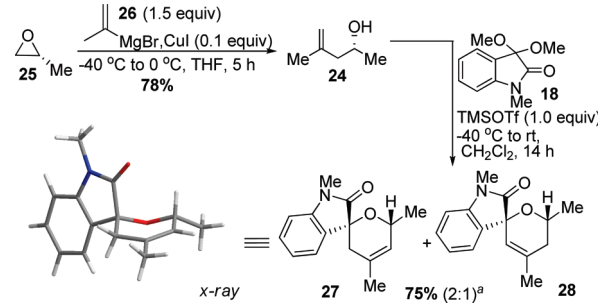


entry	R	additive	result [a]
1	$SiMe_3$	DBMP (0.1 equiv)	**22** = 38% **23** = 19%
2	H	DBMP (0.1 equiv)	**22** = 46% **23** = 20%
3	H	None	**22** = 58% **23** = 24%

[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-

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(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.

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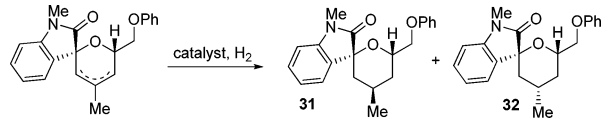
(9) Takano, S.; Kamikubo, T.; Sugihara, T.; Suzuki, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1993**, *4*, 201.

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)

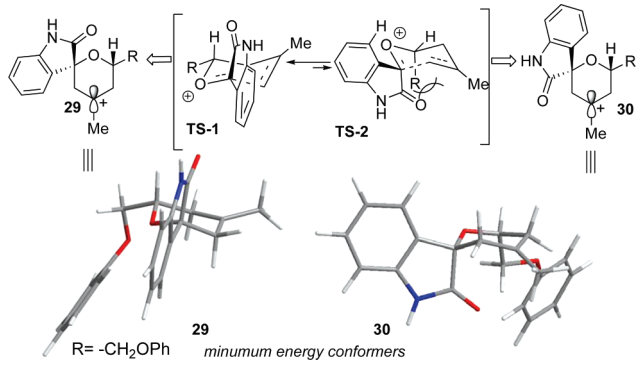


Figure 2. Proposed transition states.

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.

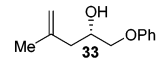
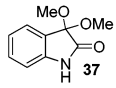
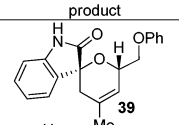
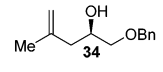
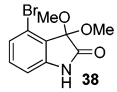
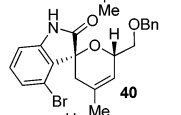
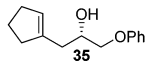
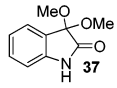
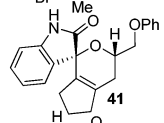
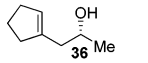
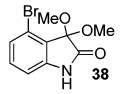
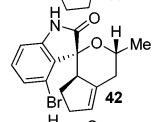
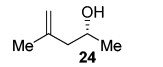
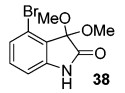
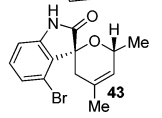
In order to confirm the relative stereochemistry at the spiro center of minor regioisomer **23** generated during the Prins cyclization, we subjected both regioisomers **22** and **23** to metal-catalyzed hydrogenation. Interestingly, using catalytic amounts of Pd/C, a mixture of chromatographically 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

entry	alcohol	isatin	product	yields (%)[a, f]
1	 **33**	 **37**	 **39**	78[b] dr = 13:1 rr = 2.6:1 ee > 99%
2	 **34**	 **38**	 **40**	70[c] dr > 20:1 rr = 13:1 ee > 99%
3	 **35**	 **37**	 **41**	85[b, d] dr > 10:1 rr = 4.3:1 ee > 99%
4	 **36**	 **38**	 **42**	88[c] dr > 20:1 rr = 10:1 ee > 99%
5	 **24**	 **38**	 **43**	78[b] dr = 20:1 rr = 10:1 ee > 99%

[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-

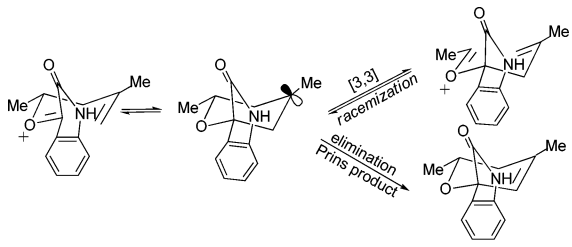


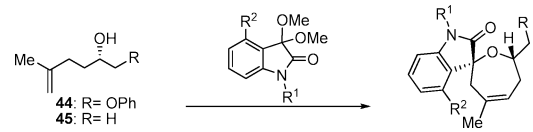
Figure 3. Possible racemization of Prins cyclization products via 2-oxonia-Cope rearrangement.

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]

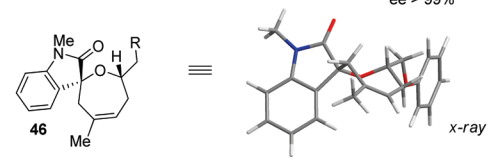
In conclusion, enantiopure spirocyclic oxindole pyrans and oxepenes have been efficiently synthesized by highly ste-

Table 4. Diastereoselective Synthesis of Spirooxindole Oxepenes



44: R= OPh
45: R= H

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.

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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.

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