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Stereoselective Synthesis of Spirocyclic Oxindoles *via* Prins Cyclizations

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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) reaction² to construct the *exo*-methylene pyran subunit of the macrocyclic core of (-)-zampanolide (**1**, Figure 1a).³ We envisioned use of this powerful methodology to access a variety of *exo*-methylene tetrahydropyrans (**3** and **4**, Figure 1b) using diverse ketals and acetals (**5** and **6**, Figure 1b) for diversity-oriented synthesis⁴ and chemical library development (Figure 1b). As part of our studies, we also considered preparation of pyran spirooxindole hybrid molecules⁵ (**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 alkaloids⁶ including the anticancer agent MI-63 (**2**, Figure 1a).⁷ In this communication, we report how our initial 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)-catalyzed⁸ ring-opening of chiral, non-racemic 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). 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 ether¹³ **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 CH₂Cl₂ was used as solvent,

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Supporting Information Available: Detailed experimental procedures and spectral data for all compounds. X-ray crystal structure coordinates and files in

spirooxindole **22** bearing an endocyclic alkene¹⁴ was isolated in moderate yield. A control experiment employing ketal **14** in the ISMS reaction with CH₂Cl₂ as a solvent afforded product **16** and its endocyclic olefin isomer (1:2 ratio).

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 cyclization¹⁵ 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 spirooxindole 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) in which the larger aryl substituent of the oxindole moiety adopts a *pseudo*-equatorial orientation¹⁷ (TS-1) leading to the observed diastereoisomer (*cf.* **27** and **28**; Scheme 3). 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; E = 8.25 Kcal/mol)¹¹ shows destabilizing 1,3-diaxial interactions in carbocation **30** which is derived from Prins cyclization through TS2.

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 catalyst¹⁹ 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).

Considering the well-documented racemization observed during Prins cyclization due to competitive oxonia-Cope rearrangement (Figure 3),²¹ we also measured the enantiomeric 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, 45²²) 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 stereoselective 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

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

Figure 2.
Proposed transition states.

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

Scheme 1.
Preparation of allyl silane 13

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.

Scheme 2.
 Spirooxindole pyrans *via* Prins cyclizations

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

Scheme 3.
Diastereoselective synthesis of spirooxindoles

yield (%) ^a	product	solvent	T[°C]
80		Et ₂ O	-78

16

T[°C]	solvent	product	yield (%) ^a
-78	Et ₂ O		84 dr>20:1

17

T[°C]	solvent	product	yield (%) ^a
-78	Et ₂ O		<2 ^b
-78 to rt	Et ₂ O		⁶³ dr= 1:1

T[°C]	solvent	product	yield (%) ^a
-78 to rt	CH ₂ Cl ₂		36

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) ₃]PF ₆	1 atm	CH ₂ Cl ₂	99	only 32

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

Table 3

Prins-type spiro-annulation

entry	alcohol	isatin
1	<chem>CC(=O)C[C@H](O)COPh</chem>

33

37

entry	alcohol	isatin
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2

3

38

37

entry

alcohol

isatin

4

36

entry

alcohol

isatin

5

24

^a Isolated yields.

^b Reaction conditions: TMSOTf (1.0 equiv), -40 °C to rt, 14 h, CH₂Cl₂.

^c TMSOTf (1.0 equiv), -40 °C to 0 °C, 3 h, CH₂Cl₂.

^d Isolated as an inseparable mixture of regioisomers. Hydrogenation was necessary to facilitate products separation.

*f*_{ir} = regioisomeric ratio; major isomer shown.

Table 4

Diastereoselective synthesis of spirooxindole oxepenes

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

46

≡

x-ray

^a Isolated yields

^b rr = regioisomeric ratio; major isomer shown. Reaction conditions: TMSOTf (1.0 equiv), -40 °C to rt, 3 h, CH₂Cl₂.