Synthesis of Spiro *C*-Arylglycoriboside via Pd(II)-Catalyzed Spirocyclization

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Abstract: Spiro *C*-arylglycoriboside was synthesized in 21 steps via Pd(II)-catalyzed spirocyclization as a key reaction. Hemiketal was obtained in 47% overall yield from *cis*-2-butene-1,4-diol and spirocyclized with $PdCl_2(PhCN)_2$ in dilute THF solution (0.01 M) to afford the 1,6-dioxaspiro[4.4]nonane skeleton in high yield. The spirocyclo adduct was transformed into spiro *C*-arylglycoriboside in five steps.

Key words: spiro compound, palladium, heterocycles, stereoselectivity, cyclization

Spiroketals such as 1,6-dioxaspiro[4.5]decane, 1,7-dioxaspiro[5.5]undecane and 1,6-dioxaspiro[4.4]nonane occur widely as substructures of natural products from many sources, including insects, microbes, plants, fungi and marine organisms.[1] Papulacandin D is also a naturally occurring spiroketal compound which contains a 1,6-dioxaspiro[4.5]decane skeleton with an aryl-β-D-*C*-glycopyranoside.[2] Its pharmacological activities, along with the structural complexity of spiro *C*-arylglycopyranosides, have triggered intense interest in the synthesis and chemical reactivity of these compounds.[3] On the other hand, spiro *C*-arylglycofuranoside does not occur naturally and has received less attention (Figure 1), although *C*-arylnucleosides are biologically important nucleoside mimetics.[4] Recently, Yamamoto and co-workers have reported a synthesis of acetonide-protected spiro *C*-arylglycoriboside using Cp*RuCl-catalyzed [2+2+2]-cycloaddition.[5] We report here a synthesis of spiro *C*-arylglycoriboside via palladium(II)-catalyzed spirocyclization, in order to examine its pharmacological activities.

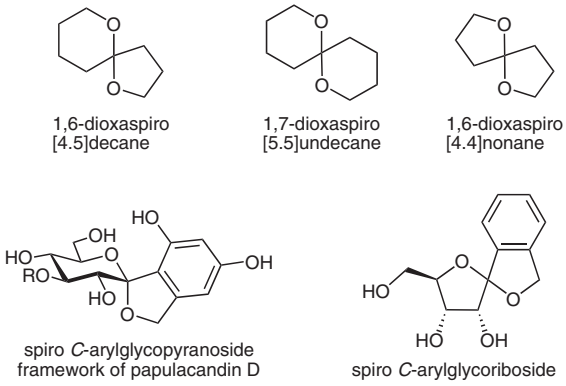
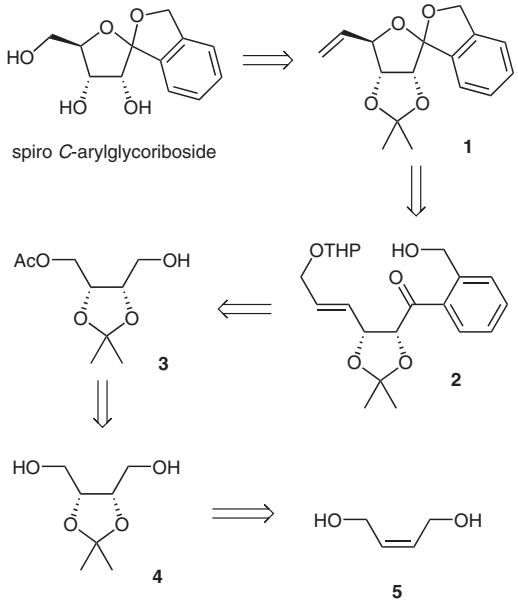


Figure 1 Spirocyclic compounds



Scheme 1 Retrosynthesis of spiro *C*-arylglycoriboside

Our retrosynthetic analysis is illustrated in Scheme 1. We envisioned that spiro *C*-arylglycoriboside would be obtained by transformation of the spiro compound 1, and its spiroketal moiety would be constructed by palladium(II)-catalyzed cyclization of the keto alcohol **2**. The keto alcohol **2** would be readily prepared by side chain elongation of the acetate **3**.[6] Optically active acetate **3** would be synthesized by asymmetric acetylation of the *meso*-diol **4** using lipase. Finally, the *meso*-diol **4** would be readily available from *cis*-2-butene-1,4-diol (**5**).

Our synthesis commenced with benzoylation of the diol **5** followed by dihydroxylation with a catalytic amount of OsO_4, using NMO as a reoxidant, to afford the diol **6**. Protection of **6** as its acetonide, followed by methanolysis, gave the *meso*-diol **4** as a key intermediate. Then, the *meso*-diol **4** was subjected to asymmetric acetylation with lipase AK Amano 20 in vinyl acetate to give almost opti-

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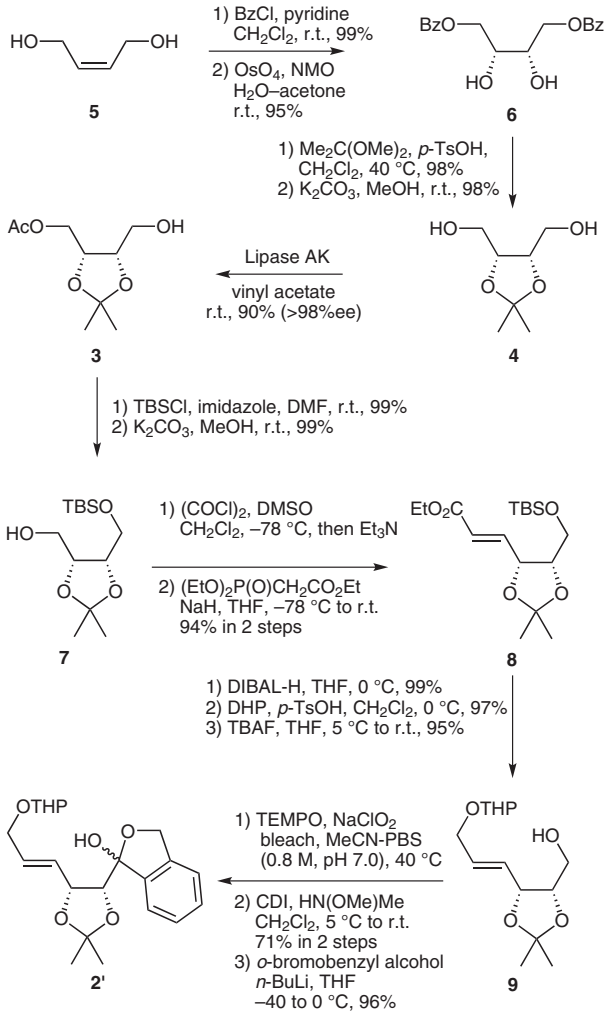
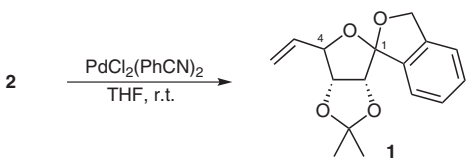
cally pure acetate **3**. The enantiopurity of **3** was confirmed by NMR analysis of both MPA esters of **3** and was determined to be >98%. Protection of the hydroxy group of **3** as its TBS ether, followed by methanolysis, afforded the alcohol **7**. Swern oxidation of the alcohol **7** followed by Horner–Wadsworth–Emmons reaction of the resulting aldehyde afforded the α,β-unsaturated ester **8**. Reduction of the ester **8** with DIBAL-H followed by protection of the resulting alcohol as its THP ether and deprotection of the TBS group with TBAF afforded the alcohol **9**. Oxidation of the alcohol **9** in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), $NaClO_2$ and bleach,[7] followed by condensation of the resulting carboxylic acid and *N*,*O*-dimethylhydroxylamine with carbonyldiimidazole (CDI), provided Weinreb's amide, which was treated with *o*-bromobenzyl alcohol and *n*-BuLi to afford not keto alcohol **2**, but hemiketal **2′** in 47% overall (Scheme 2) yield from *cis*-2-butene-1,4-diol (**5**). The presence of the hydroxy group in the hemiketal **2′** was confirmed by the presence of a strong absorption band in the region of 3384 cm^{-1} in the IR spectrum.



Scheme 2

With the requisite hemiketal **2′** in hand, we next focused on Pd(II)-catalyzed spirocyclization (Table 1). On the basis of our previous work, the cyclization was conducted in THF and $PdCl_2(PhCN)_2$ was used as a Pd(II) catalyst.[8] When the hemiketal **2′** was treated with 10 mol% of the Pd(II) catalyst in THF (0.1 M) at room temperature, the spirocyclization proceeded smoothly and the spiro compound **1** was isolated as a diastereomeric mixture (**1a**:**1b**:**1c** = 7.7:2.2:1) in 60% yield (entry 1). The diastereomeric ratio was determined from 600-MHz ^{1}H NMR spectra, and the stereochemistry at C1 and C4 was confirmed by single-crystal X-ray diffraction analysis after transformation of **1** into the corresponding crystalline compound. Then, we investigated the effect of concentration on the reaction. When the spirocyclization was conducted in more dilute THF solution (0.05 M or 0.01 M), the yield was improved and **1** was obtained in 77% and 83% yield, respectively (entries 2 and 3). We next investigated the effect of the amount of the Pd(II) catalyst. When the hemiketal **2′** was treated with 2 mol% of the Pd(II) catalyst, the spirocyclization did not proceed completely and the yield was much lower than that in the case of entry 3 (entry 4). This was because the Pd(II) catalyst was deactivated and precipitated as palladium black before the substrate **2′** was completely consumed. In contrast, when the spirocyclization was conducted in the presence of 20 mol% of Pd(II) catalyst, the reaction proceeded smoothly and **1** was obtained in 91% yield (entry 5).

Table 1 Pd(II)-Catalyzed Spirocyclization[a]



Entry	Pd(II) (mol%)	Concn (mol/L)	Time (min)	Yield (%)	Ratio[b] **1a/1b/1c** 1*R*,4*R*/1*R*,4*S*/1*S*,4*R*[c]
1	10	0.1	60	60	7.7:2.2:1
2	10	0.05	60	77	13.2:4.4:1
3	10	0.01	60	83	11.5:3.4:1
4	2	0.01	60	51	16.8:1.8:1
5	20	0.01	15	91	12.6:4.6:1

[a] All reactions were conducted under an argon atmosphere.
[b] The ratio was determined from 600-MHz ^{1}H NMR spectra.
[c] The stereochemistry at C1 and C4 was confirmed by single-crystal X-ray diffraction analysis after transformation of **1** into a crystalline compound.

We then focused on the further transformation of **1a** into diol **12** (Scheme 3). Oxidative cleavage of the olefin in spirocyclo adduct **1a** with OsO_4–$NaIO_4$[9] followed by reduction of the resulting aldehyde gave the alcohol **10a**[10] in 76% yield over two steps. Protection of the hydroxy group of **10a** with benzoyl chloride and pyridine provided the benzoate **11a** in 99% yield. Removal of the acetonide group with 70% aqueous trifluoroacetic acid gave **12a** and

12c as an epimeric mixture (*R*:*S* = 1:10) in 98% yield. The two epimers were separated and purified by silica gel column chromatography. The stereochemistry of **12a** was confirmed unequivocally by single-crystal X-ray diffraction analysis (Figure 2).

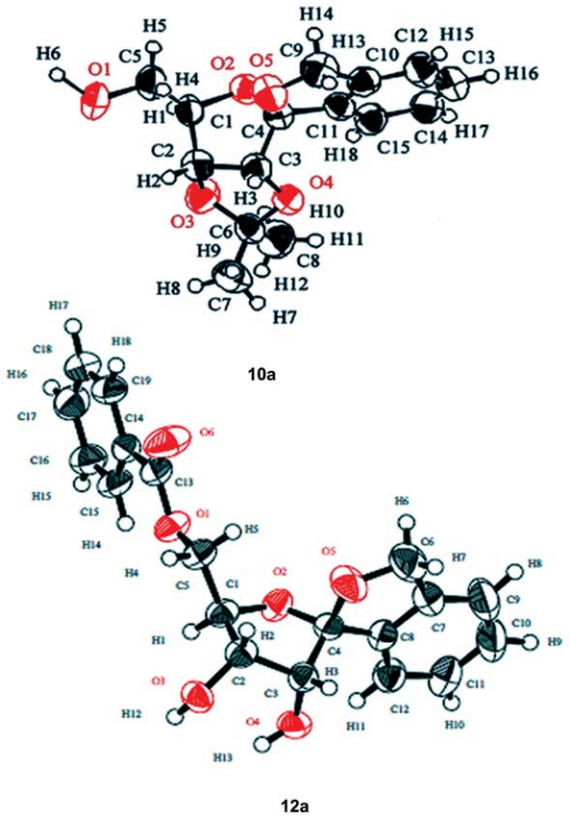
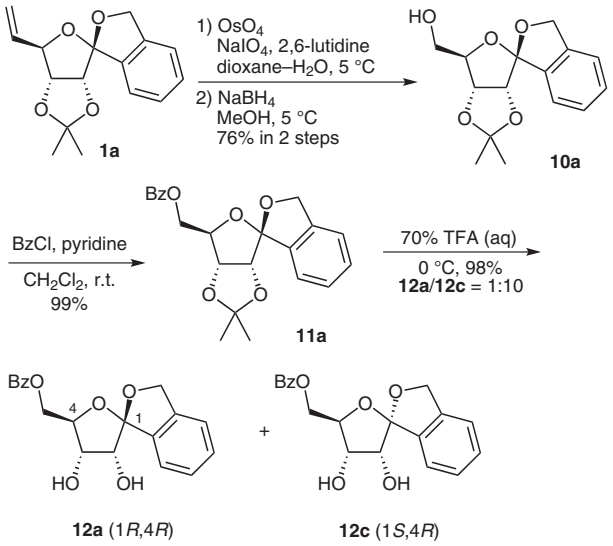
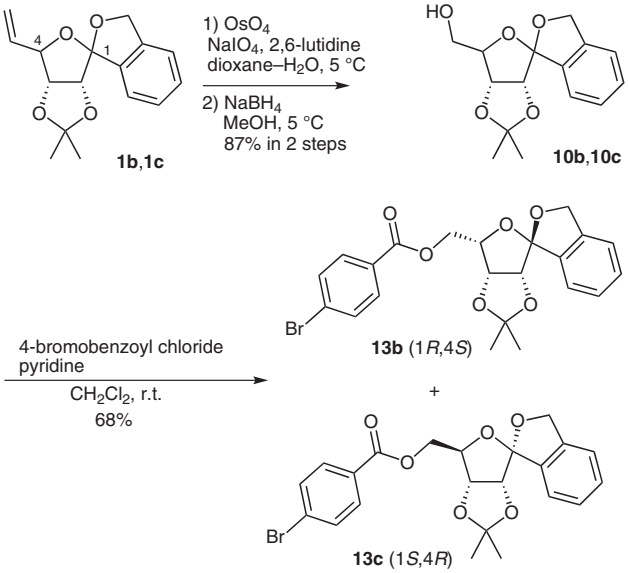


Figure 2 ORTEP diagram of **10a** and **12a**



Scheme 3

The stereochemistry at C1 and C4 in the cycloadducts **1b** and **1c** was also confirmed by single-crystal X-ray diffraction analysis after transformation of the olefin **1** into the 4-bromobenzoate **13** (Scheme 4). The inseparable cycloadducts were transformed into the alcohol **10** in the same manner as described for **1a** in 87% yield over two steps. The inseparable alcohol **10** was treated with 4-bromobenzoyl chloride and pyridine to afford the benzoate **13**. The diastereomers could be separated and purified by silica gel column chromatography at this stage.



Scheme 4

The stereochemistry of **13b** and **13c** was confirmed unequivocally by single-crystal X-ray diffraction (Figure 3).

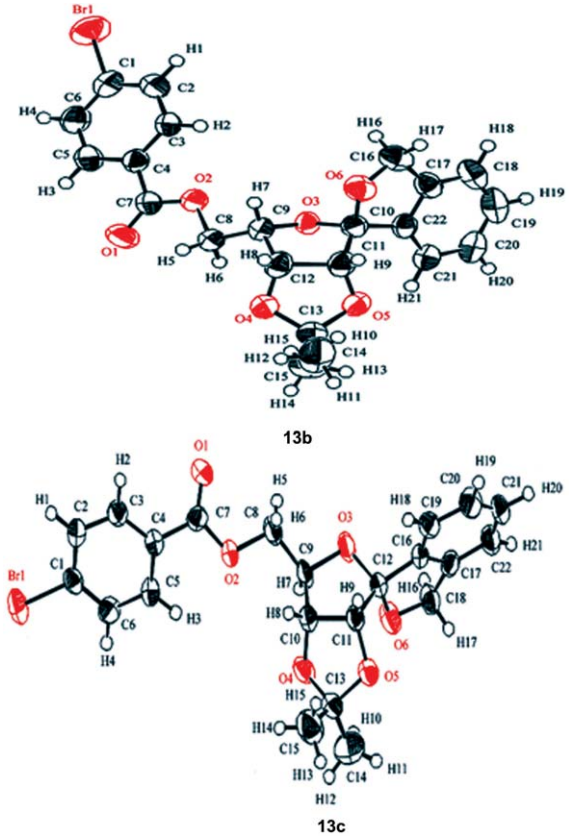
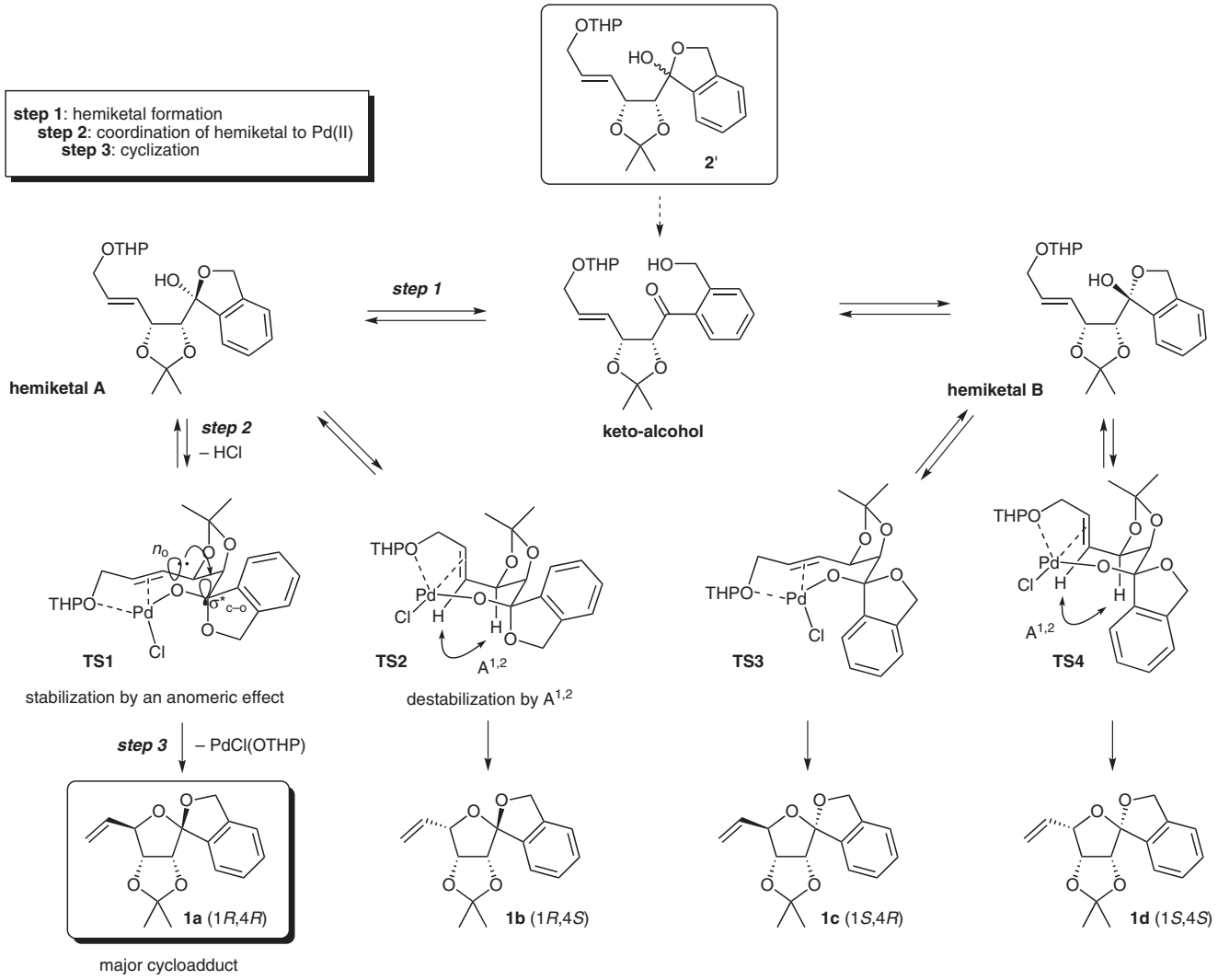


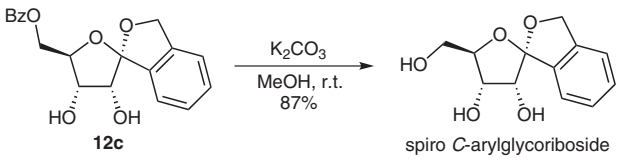
Figure 3 ORTEP diagram of **13b** and **13c**



Scheme 5 Plausible mechanism of Pd(II)-catalyzed spirocyclization

A plausible mechanism of Pd(II)-catalyzed spirocyclization is illustrated in Scheme 5.[11] The hemiketal **2′** exists in equilibrium with hemiketal A, B and keto alcohol. Pd-π complex is formed by coordination of $PdCl_2$ with allylic ether at one π-face of the olefin with the assistance of the adjacent hydroxy group. This complex may be present as an equilibrium mixture of four structures (**TS1**, **TS2**, **TS3** and **TS4**) through the formation of hemiketal having alternative stereochemistry and coordination of $PdCl_2$ with the other π-face of the olefin. Although the conformations **TS1** and **TS2** are stabilized by anomeric effect (n_o-σ^*_{c-o}), the conformations **TS3** and **TS4** are not. In addition, although the conformations **TS2** and **TS4** are destabilized by $A^{1,2}$ strain, the conformations **TS1** and **TS3** are not. Therefore, spirocyclization of hemiketal **2′** should proceed preferentially through the most likely conformation **TS1**. A *syn*-attack of the hydroxy group in the hemiketal on the electrophilic sp^2 carbon in **TS1** occurs intramolecularly from the same side of the Pd-complex in a 5-*exo*-trigonal fashion to give a σ-Pd complex followed by *syn*-elimination of PdCl(OTHP), affording spiro compound **1a** with (1*R*,4*R*) configuration. In the catalytic cycle, PdCl(OTHP) may catalyze the reaction by itself or regenerate $PdCl_2$ with chloride ion. For this reason, this Pd(II)-catalyzed spirocyclization proceeds smoothly in the absence of any reoxidant.

Finally, methanolysis of **12c** provided spiro *C*-arylglycoriboside in 87% yield (Scheme 6).



Scheme 6 Synthesis of spiro *C*-arylglycoriboside

In conclusion, spiro *C*-arylglycoriboside has been synthesized from *cis*-2-butene-1,4-diol in 21 steps by using Pd(II)-catalyzed spirocyclization as a key reaction. Further application of this synthetic strategy to the synthesis of spiro *C*-arylglycofuranoside analogues for evaluation of their pharmacological activity is in progress.

Acknowledgment

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