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Synthesis of Spirocyclic *C*-Arylribosides via Cyclotrimerization

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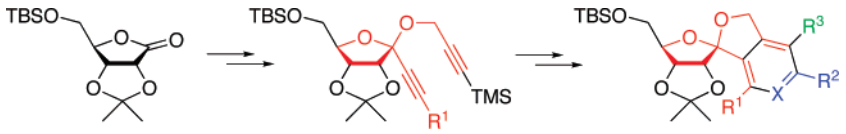
ABSTRACT



Spirocyclic *C*-arylribosides were synthesized from the known γ-ribonolactone derivative. Lithium acetylide addition followed by glycosylation with 3-(trimethylsilyl)propargyl alcohol converted the ribonolactone to silylated diynes. After desilylation or iodination, subsequent ruthenium-catalyzed cycloaddition of resultant diynes with alkynes or chloroacetonitrile gave spirocyclic *C*-arylribosides.

The synthesis of *C*-glycosides, in which the glycosidic oxygen is replaced by a carbon atom, has been an area of intense study in bioorganic and synthetic chemistry. This is because *C*-glycosides are stable toward enzymatic and chemical hydrolysis, and therefore, they are potent inhibitors for glycosidases and glycosyltransferases.[1] Frequently encountered *C*-glycoside motifs in nature are *C*-arylglycosides. Because of their significant biological activities, the total synthesis of natural products such as anthracyclinone *C*-glycosides, gilvocarcins, or kidamycins has been an important subject in synthetic organic chemistry.[2−5]

Papulacandins are also naturally occurring *C*-arylglycosides, some of which are active against *P. carinii pneumonia*, the common opportunistic infection in AIDS patients.[6] In contrast to other *C*-arylglycoside natural products, they have an interesting spirocyclic *C*-arylglycoside framework (Figure 1), which has been an attractive synthetic target.[7] On the other hand, furanose derivatives bearing a spiroacetal moiety have received less attention.[8] To the best of our knowledge, no spirocyclic *C*-arylribosides with structures related to the

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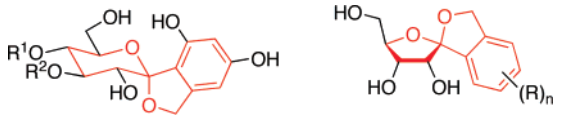


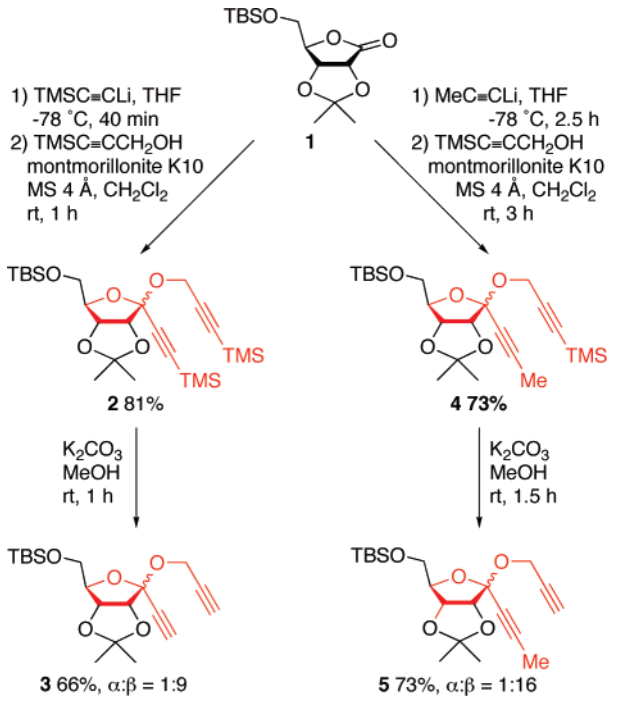
Figure 1. Spirocyclic *C*-arylglycoside framework of papulacandins (left) and unprecedented ribose analogues (right).

papulacandins have been reported to date, although *C*-arylnucleosides have received increasing attention as biologically important nucleoside mimetics.[9] Herein, we wish to report the diversity-oriented synthesis of the spirocyclic *C*-arylribosides using the Cp*RuCl-catalyzed [2 + 2 + 2] cycloaddition as a key step.[10]

C-Arylglycosides are generally obtained by the direct arylation of appropriate carbohydrate substrates, although the control of regio- and stereochemistry is a crucial problem.[11] In 1995, McDonald and co-workers reported a fascinating strategy to construct a spirocyclic *C*-arylglycoside framework closely related to the papulacandins.[12] Their method utilized the rhodium(I)-catalyzed [2 + 2 + 2] cycloaddition of a *C*-alkynyl-*O*-propargylglycoside with acetylene as a key step. The same strategy was applied to our synthesis of spirocyclic *C*-arylribosides, with significant improvements: (1) the short-step preparation of diyne substrates via highly stereoselective glycosylation using montmorillonite K10 clay reported by Tomooka, Nakai, and co-workers[13] and (2) the mild and efficient Cp*RuCl-catalyzed [2 + 2 + 2] cycloaddition developed by us.[14]

The crude hemiacetal obtained via addition of 2-(trimethylsilyl)ethynyllithium to the known γ-ribonolactone **1**[15] was directly submitted to the glycosylation with 3-(trimethylsilyl)-propargyl alcohol in the presence of montmorillonite K10 and 4 Å MS according to the literature[13a] to give silylated diyne **2** in 81% overall yield with high β-selectivity as reported (Scheme 1). After alkaline desilylation, diyne **3** was

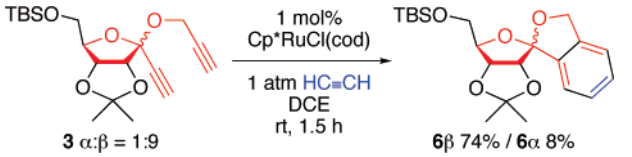
Scheme 1. Synthesis of Diynes **3** and **5** from γ-Ribonolactone **1**



obtained in 66% yield as an inseparable mixture with an α/β isomer ratio of 1:9.

With the ribose-derived diyne **3** in hand, the ruthenium-catalyzed cycloaddition with acetylene was carried out as shown in Scheme 2. Under an acetylene atmosphere, **3** was

Scheme 2. Cycloaddition of **3** with Acetylene



treated with 1 mol % of Cp*RuCl(cod) (Cp* = η^5-C_5Me_5, cod = 1,5-cyclooctadiene) in 1,2-dichloroethane (DCE) at room temperature for 1.5 h, resulting in the complete consumption of **3**. Purification by silica gel chromatography gave cycloadducts **6**β and **6**α in 74% and 8% yields, respectively.

To examine the cycloaddition regioselectivity, we next investigated the reaction of unsymmetrical diyne **5**, which was prepared from **1** in a manner to **3** as outlined in Scheme 1. Diyne **5** reacted with 4 equiv of 1-hexyne in the presence of 5 mol % of Cp*RuCl(cod) at ambient temperature to give corresponding cycloadducts **7**β and **7**α in 87% and 5%

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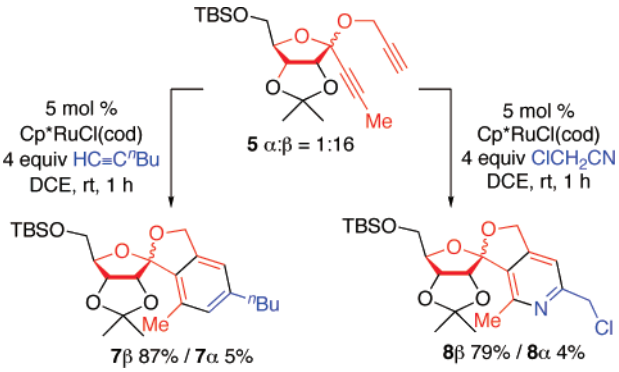
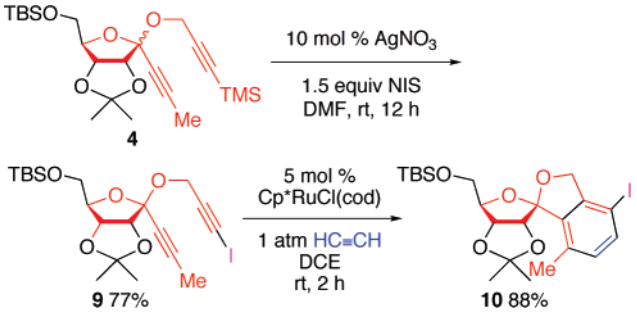
Scheme 3. Cycloadditions of **5** with 1-Hexyne and Chloroacetonitrile



yields, respectively (Scheme 3). Notably, both cycloadducts were formed as single regioisomers. Diyne **5** also successfully underwent cycloaddition with chloroacetonitrile (4 equiv) at room temperature to give the pyridine derivatives **8**β and **8**α in 79% and 4% yields, respectively.[16]

Recently, complexity generating, multicomponent coupling processes have become increasingly important in terms of the diversity-oriented synthesis toward the construction of small molecular libraries.[17] In this context, we recently developed the sequential silver-catalyzed Csp-H iodination/ruthenium-catalyzed cycloaddition/palladium-catalyzed coupling process, transforming 1,6-diynes into various highly conjugated aromatic molecules.[18] This novel strategy also significantly expands the product diversity in the present spirocyclic *C*-arylriboside synthesis. Toward this aim, we next attempted the synthesis of an iodinated spirocyclic *C*-arylriboside platform **10** (Scheme 4).[19] According to the

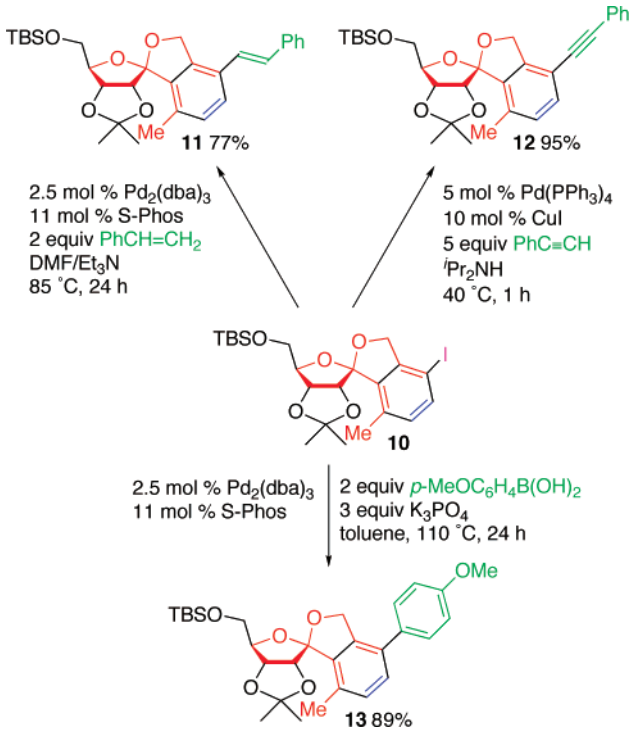
Scheme 4. Synthesis of **9** and Its Cycloaddition with Acetylene



report by Nishikawa, Isobe, and co-workers, trimethylsilyldiyne **4** was treated with 10 mol % of $AgNO_3$ and 1.5 equiv of *N*-iodosuccinimide (NIS) to afford iododiyne **9** in 77% yield without affecting the TBS ether moiety.[20] Iododiyne **9** was thereafter treated with 5 mol % of Cp*RuCl(cod) in DCE under an acetylene atmosphere at ambient temperature to deliver the desired **10** in 88% yield as a single stereoisomer.

The iodobenzene **10** was subsequently subjected to a range of palladium-catalyzed C−C bond-forming reactions (Scheme 5). The Mizoroki−Heck reaction with styrene was carried

Scheme 5. Cross-Coupling Reactions of *C*-Iodoarylriboside Platform **10**



out by using a catalyst system derived from 2.5 mol % of $Pd_2(dba)_3$ and 11 mol of % Buchwald's S−Phos,[21] affording *trans*-stilbene derivative **11** in 77% yield. The Sonogashira reaction with phenylacetylene under conventional conditions gave diphenylacetylene analogue **12** in 95% yield. Finally, the Suzuki−Miyaura coupling with *p*-methoxyphenylboronic acid proceeded successfully with the $Pd_2(dba)_3$/S-Phos catalyst system to furnish biphenyl derivative **13** in 89% yield.

In conclusion, we have successfully developed a convergent route to spirocyclic *C*-arylribosides with structures related to the papulacandins. The starting ribose-derived diynes were efficiently obtained from the known γ-ribonolactone derivative via acetylide addition/stereoselective glycosylation using montmorillonite K10 clay. The cycloadditions of the obtained diyne with acetylene, 1-hexyne, and

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chloroacetonitrile were carried out under the ruthenium catalysis to deliver the corresponding benzene and pyridine products in good yields and with excellent selectivity. Moreover, the ruthenium-catalyzed cycloaddition of the iododiyne derivative with acetylene gave the spirocyclic *C*-iodoarylriboside platform, which effectively underwent the Mizoroki−Heck reaction with styrene, the Sonogashira reaction with phenylacetylene, and the Suzuki−Miyaura coupling with *p*-methoxyphenylboronic acid.

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Supporting Information Available: Experimental procedures and analytical data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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