A Convergent Synthesis of the Tetrasaccharide Fragment of the Purported Structure of Durantanin I

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A convergent synthesis of the tetrasaccharide subunit in the proposed structure of durantanin I is reported. The signature step is represented by the unique assembly of apiofuranoside ring by the sequential Pd—Ru metal catalysis. Per-dihydroxylation at the late stage delivered the target compound in a highly efficient manner. In addition, a tetrasaccharide derivative possessing unnatural apiose unit was also synthesized with comparable efficiency to that for the natural form.

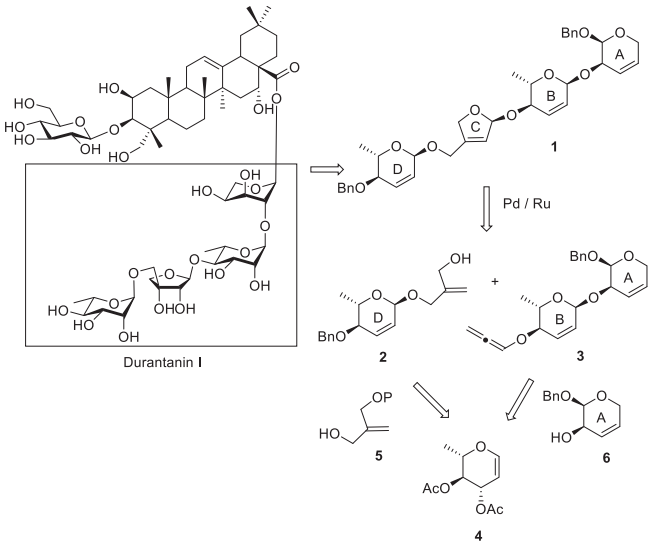
Keywords: Durantanin, Oligosaccharide, Apiose, Total synthesis, Hydroalkoxylation

Triterpenoid saponins are found in a wide variety of dicotyledonous plants as a constituents of the cell membrane. Their diverse structures and unique biological/pharmacological activities have drawn considerable attention not only from the field of natural product chemistry but also from that of synthetic organic chemistry.[1] Durantanin I, a member of triterpenoid-type saponin, was isolated from the leaves of *Duranta repens* by Hiradate and co-workers.[2,3] This compound exhibits significant plant growth inhibitory activities. Its structure was elucidated as polygalacic acid-3-*O*-β-D-glucopyranoside combined with unique tetrasaccharide subunit consisting of 28-*O*-[α-L-rhamnopyranosyl-(1 → 3′)-β-D-apiofuranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranoside] (Scheme 1). This tetrasaccharide moiety bearing an apiofuranose residue poses a great synthetic challenge. However, access to this fragment has remained unknown, despite previous studies on the preparation of various apiofuranose glycosides.[4] Here, we wish to report a first synthesis of the proposed structure for this tetrasaccharide moiety. A key event involves palladium-catalyzed asymmetric intermolecular hydroalkoxylation of alcohol nucleophile in combination with the ring-closing-metathesis that assembles the apiofuranose unit in a highly efficient manner. [5–7]

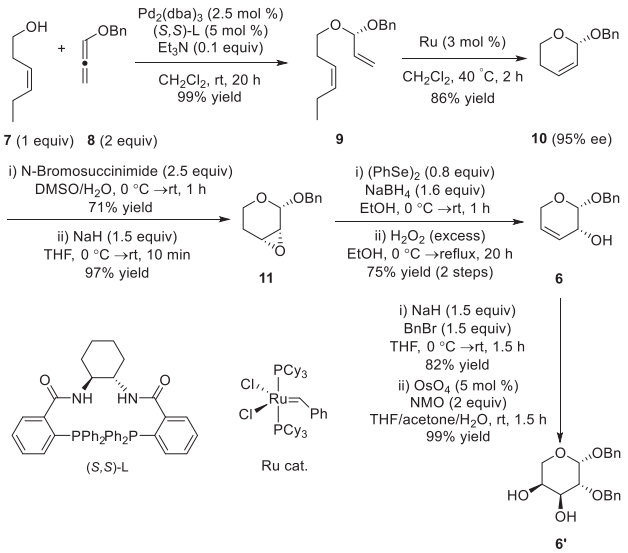
On the basis of our own experience in the *de novo* β-apiofuranoside synthesis,[6] we envisaged that the tetrasaccharide unit can be constructed from the tetraene precursor **1** by the late-stage per-dihydroxylation.[8] The proposed substrate-driven stereoselectivity of the dihydroxylation of BCD ring is verified by the related studies.[6,8] In addition, we were confident that the stereoselectivity of the unprecedented dihydroxylation of the ring A may be effectively controlled by the *cis*-1,2-bis-alkoxy groups installed in the ring A. The intermediate **1** can be prepared in a convergent manner from the allylic alcohol **2** and alkoxyallene **3** by way of the Pd—Ru sequential metal catalysis discussed above.[6] Notably, a skeleton of the β-D-apiofuranoside (ring C) is welded by this transformation. Both of these intermediates can be readily derived from commercially available 3,4-di-*O*-acetyl-6-deoxy-L-glucal **4** by Lewis acid-mediated coupling reaction (Ferrier reaction).[9] Of the two reactions, construction of the AB ring seemed to be more challenging because it generates a disaccharide component. Thus, we decided to explore first the assembly of **3**.

The initial stage of the work commenced with the asymmetric synthesis of the cyclic benzylic acetal intermediate **10** (Scheme 2). For example, commercially available alcohol **7** (1 equiv) was combined with benzyloxyallene **8** (2 equiv) in the presence of $Pd_2(dba)_3$ (2.5 mol %), ligand (*S*,*S*)-L (5 mol %) and catalytic amount of Et_3N (0.1 equiv) in CH_2Cl_2 at 20 °C. As depicted in Scheme 1, this reaction successfully produced acyclic acetal **9** in ~99% yield. Subsequent ring-closing-metathesis (RCM) reaction employing first generation Grubbs catalyst at 40 °C gave cyclic acetal **10** in 86% yield and 95% ee (for the determination of ee and absolute configuration, see the SI). At this point, we reasoned that compound **6** could be obtained from **10** by way of *syn*-epoxide formation (compound **11**) and the ensuing base-mediated opening reaction. As anticipated, initial efforts toward direct epoxidation (such as *m*-chloroperbenzoic acid or dimethyldioxirane) provided the isomeric *anti*-product as the major product. This unsuccessful preliminary result led us to consider a well-known protocol mediated by the bromohydrin formation.[10] Indeed, reaction of **10** with *N*-bromosuccinimide (2.5 equiv) in dimethylsulfoxide/H_2O and the subsequent addition of NaH (1.5 equiv) generated the desired *syn*-epoxide **11** in 69% (over two steps). Treatment of this compound with strong base (such as *t*-BuLi) failed to produce **6** in a reproducible manner. Thus, we decided to rely on an indirect method

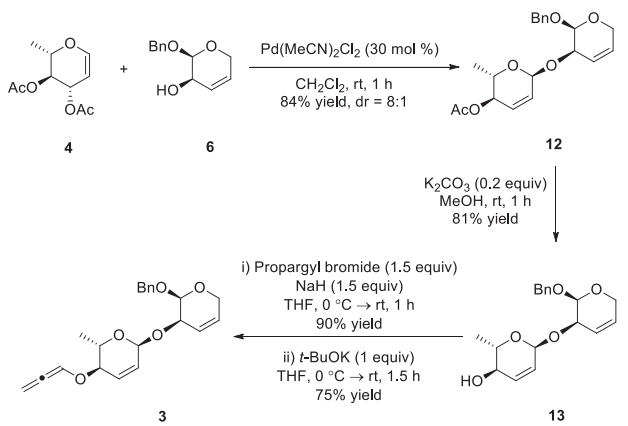
†These authors contributed equally to this work.



Scheme 1. Retrosynthetic analysis of durantanin I.



Scheme 2. Synthesis of intermediate 6.



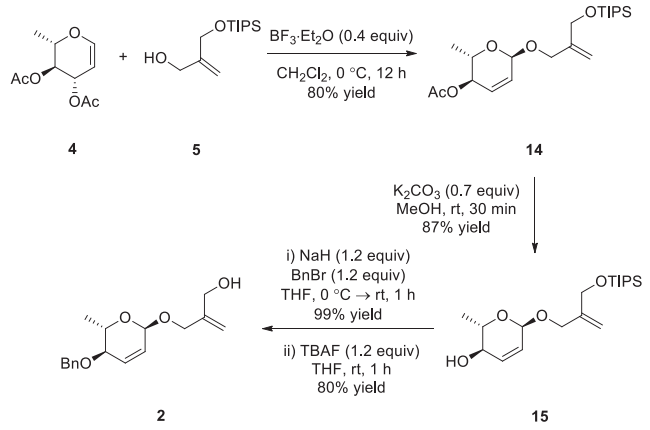
Scheme 3. Preparation of the alkoxyallene 3.

producing allylic alcohol from the epoxide precursor.[11] Following a related protocol, epoxide **11** was first treated with $(PhSe)_2$ (0.8 equiv) and $NaBH_4$ (1.6 equiv) in EtOH. Subsequent oxidation with H_2O_2 under reflux successfully gave allylic alcohol **6** in 75% yield (over two steps).[12] Conversion of the alcohol into the benzyl ether and the subsequent Os-catalyzed dihydroxylation reaction produced *cis*-1,-2-arabinopyranoside **6′** in 81% yield (over two steps) as a single diastereomer, as anticipated. The relative and absolute stereochemistry of this compound were rigorously established by the comparison of the spectral data with the literature values (see the SI).[13]

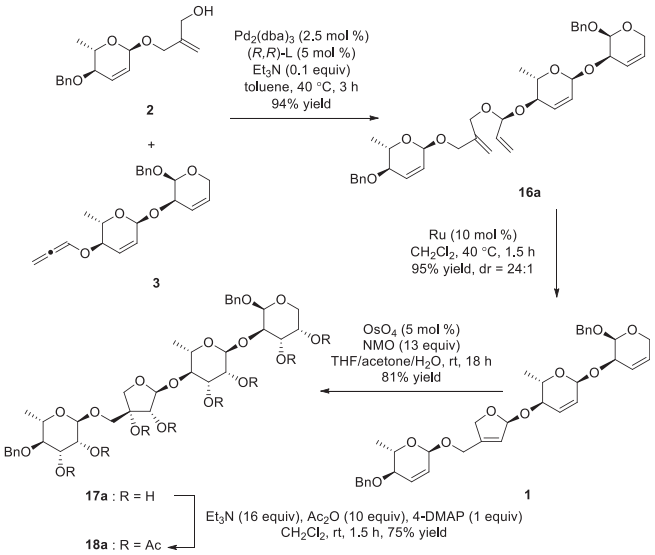
With allylic alcohol **6** in hand, preparation of disaccharide (AB ring) was then investigated. Initial efforts using strong Lewis acid-mediated Ferrier-type glycosylation showed only formation of untractable mixture of compounds, presumably due to the instability of the anomeric centers in **12** (Scheme 3). Notably, employing $Pd(MeCN)_2Cl_2$ (10 mol %) catalyst based upon Galan's work[14] generated **12**, albeit in low ~20% yield. Increasing the catalyst loading (30 mol %) under diluted condition in CH_2Cl_2 delivered **12** in significantly higher 84% yield as an inseparable mixture of two anomers (α:β = 8:1).[15] Subsequent deacetylation using catalytic K_2CO_3 (0.2 equiv) proceeded uneventfully to produce **13** in diastereomerically pure form in 81% yield after column chromatography. From this allylic alcohol, alkoxyallene **3** was prepared via a two-step event combining propargylation and base-catalyzed isomerization[16] in 68% yield (over two steps).

Unlike **6**, achiral allylic alcohol **5** was smoothly converted to the corresponding acetal **14** in 80% yield by the Ferrier-type glycosylation using sub-stoichiometric amount of $BF_3{\cdot}Et_2O$ (0.4 equiv). Deacetylation of this compound provided alcohol **15** in 87% yield. Introduction of *O*-benzyl group using NaH (1.2 equiv) and BnBr (1.2 equiv) followed by desilylation reaction employing TBAF (1.2 equiv) generated alcohol substrate **2** in 80% yield (over two steps, Scheme 4)

Having secured the coupling partners **2** and **3**, we examined the key sequential catalysis that assembles furanoglycoside (ring C). As depicted in Scheme 5, acyclic acetal **16a** was obtained from **2** and **3** in 94% yield by employing $Pd_2(dba)_3$ (2.5 mol %) and (*R*,*R*)-L (5 mol%) at 40 °C. The subsequent RCM reaction employing first generation Grubbs catalyst (10 mol %) at 40 °C gave the desired tetrasaccharide **1** as the exclusive diastereomer in 95% yield (dr = 24:1).[17] Final per-dihydroxylation reaction of this compound using OsO_4 (5 mol %) and N-methylmorpholine oxide (NMO) (13 equiv) produced octa-ol **17a** in 81% yield as a single diastereomer. Due to the troublesome separation from residual NMO, this compound was converted into the peracetyl derivative **18a**. This task was accomplished in 75% yield by the treatment of **17a** with Et_3N (16 equiv), Ac_2O (10 equiv) in the presence of N,N-dimethylaminopyridine (1 equiv). Thus, the target compound **18a** was obtained from benzyloxyallene **2** in 14 (longest linear) steps. Remarkably,



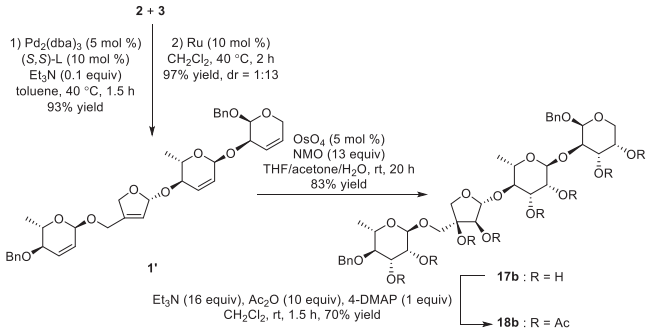
Scheme 4. Preparation of the allylic alcohol 2.



Scheme 5. Convergent synthesis of the tetrasaccharide.

the chemoselective metal catalysis allowed for the facile synthesis of potentially labile tetraene **1**, which was per-dihydroxylated at the late stage to deliver the desired target octa-ol **17a** in a highly efficient manner.

In addition to the natural form **17a**, its unnatural analog **17b** possessing β-L-apiofuranoglycoside was also easily synthesized by simply changing the ligand to the enantiomeric (*S*,*S*)-L form for the palladium-catalyzed hydroalkoxylation reaction (Scheme 6). This reaction required somewhat higher catalyst loading (10 mol %) for the complete conversion. Nevertheless, the desired compound **1′** was obtained in pure form after RCM reaction in 90% yield over two steps (dr = 1:13).[17] The subsequent per-dihydroxylation with OsO_4 (5 mol %) and NMO (13 equiv) gave octa-ol **17b** in 83% yield, which was also converted into the per-acetyl derivative **18b** in 70% yield. This facile synthesis of the diastereomeric form illustrates another beneficial feature of the proposed synthesis, which should find further use for the derivatization of the natural products.



Scheme 6. Convergent synthesis of diastereomeric tetrasaccharide.

In summary, the first synthetic route to the tetrasaccharide subunit of durantanin I and its diastereomer was devised. The key reaction utilizes the Pd-catalyzed hydroalkoxylation of alcohol followed by Ru-catalyzed ring-closing-metathesis reaction. Currently, we are working on the total synthesis of durantanin I as well as expanding the utility of the sequential metal catalysis for the synthesis of other saponin oligosaccharides.

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Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

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