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Total Synthesis of (+)-Vicenin-2

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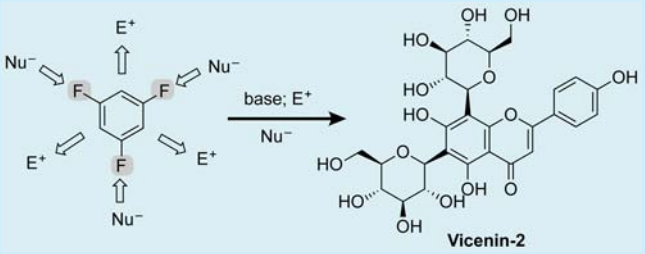
Supporting Information

ABSTRACT: The bis-*C*-glucosyl flavonoid vicenin-2 (**1**) has been synthesized by exploiting bis-*C*-glycosylation of 1,3,5-trifluorobenzene and aromatic nucleophilic substitution to transform fluorine atoms to oxygen functions in excellent yield.



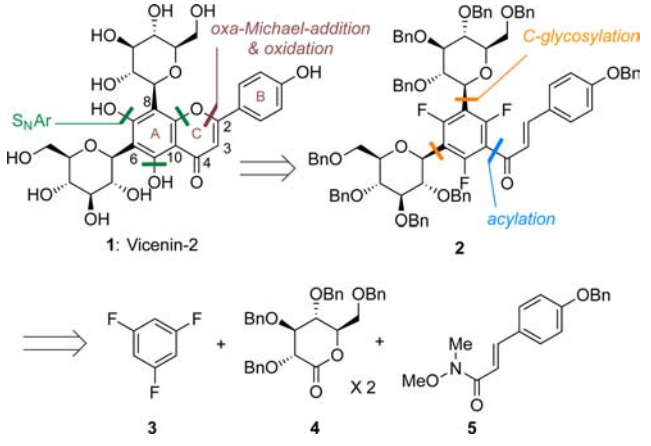
(+)-Vicenin-2 (**1**), a bis-*C*-glycosyl apigenin, was isolated from *Urtica circularis*[1] and other species[2] and has recently been reported to show various significant biological activities, including anti-inflammatory,[3a] anticancer,[3b] antidiabetic,[3c] and antioxidant effects.[3d]

Although the synthesis of **1** as well as other bis-*C*-glycosyl flavonoids has been limited in a few reports,[4] one approach exploited the $Sc(OTf)_3$-mediated bis-*C*-glycosylation of phloroacetophenone[4a,b] or (±)-naringenin[4c] with unprotected monosaccharides, directly giving the corresponding bis-*C*-glycosides, albeit in low yields after tedious purification. In addition, a later modification by Shie[4d] using tandem glycosylation of flavans requires many additional steps to complete the synthesis.

Herein we report an efficient synthesis of **1** that features the use of 1,3,5-trifluorobenzene as a starting material, exploiting two characteristic reactivities of fluorobenzenes: (1) ortho-lithiation,[5] and (2) nucleophilic aromatic substitution.[6]

Scheme 1 outlines the retrosynthetic analysis. The C ring in the flavone skeleton would be constructed via an intramolecular oxa-Michael addition of the A-ring phenolic chalcone followed by oxidation. The oxygen functions on the A ring would be installed by replacing the fluorine atoms by oxygen nucleophiles by means of the S_NAr reaction. Two sugar units and the cinnamoyl moiety would be introduced via the stepwise attack of aryl anions at the corresponding carbonyl derivatives **4** and **5**.

Scheme 1. Structure and Retrosynthetic Analysis of 1



Scheme 2 summarizes the assembly of the two sugar units and of the enone moiety onto 1,3,5-trifluorobenzene (**3**). Lithiation of **3** with *n*-BuLi (Et_2O, −78 °C, 1 h) followed by the reaction with lactone **4**[7] gave hemiketal **6** in quantitative yield. Reduction of lactol **6** with triethylsilane in the presence of $BF_3{\cdot}OEt_2$[8] gave mono-*β*-*C*-glycoside **7** in 83% yield. The *α* anomer, produced in 10% yield, was removed by column chromatography (silica gel, EtOAc/hexane 1:9 → 1:4). In the same manner, lithiation of *C*-glycosyl trifluorobenzene **7** with *n*-BuLi (Et_2O, −78 °C, 1 h) followed by the reaction with lactone **4** gave lactol **8** in only 18% yield with a sizable recovery of **7** (81%). However, **8** was obtained in 83% yield when *t*-BuLi (Et_2O, −78 °C, 1 h) was employed.

Reduction of lactol **8** gave C_2-symmetric bis-*β*-*C*-glycoside **9** in 82% yield. The anomeric protons at C(1′) in compounds **7** and **9** were assigned by extensive NMR studies (COSY, DEPT, HMBC, and HMQC), and the coupling constants $^3J_{H1'-H2'}$ of 9.4 Hz for **7** and 9.8 Hz for **9** clearly proved the *β*-stereochemistry of the anomeric centers.[8a]

Further deprotonation of **9** with *t*-BuLi (Et_2O, −78 °C, 1 h) followed by in situ trapping with *α*,*β*-unsaturated Weinreb amide **5**[9] afforded the key intermediate **2** in 80% yield with 15% recovery of **9**.[10] This reaction offers an effective approach for the construction of the chalcone skeleton, which has been mainly accessed via a Claisen−Schmidt condensation between benzaldehyde and acetophenone.[11]

With compound **2** in hand, we first attempted to replace all of the fluorine atoms by hydroxy or alkoxy groups (Scheme

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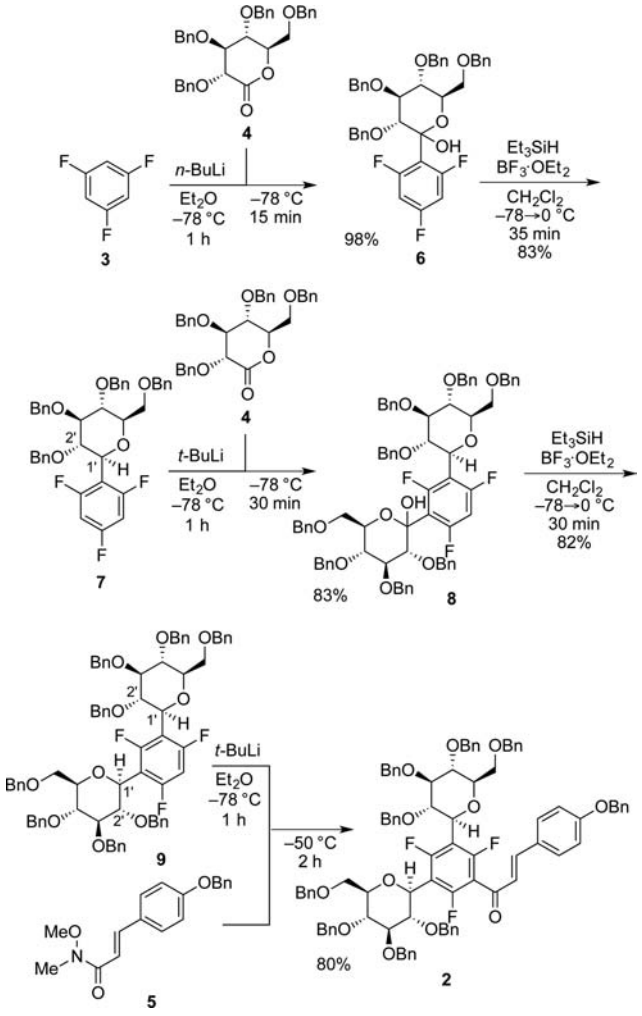
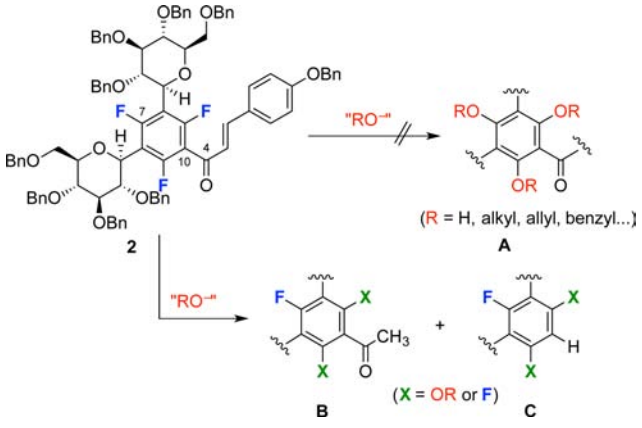
Scheme 2. Assembly of Building Blocks



3).[12] However, this proved unsuccessful, and no desired trisubstituted compound **A** was obtained. We identified that

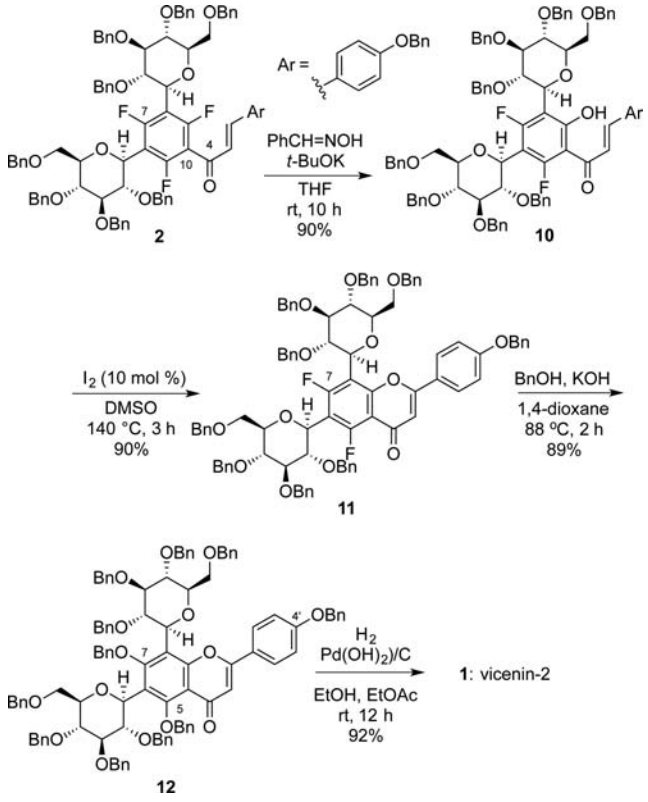
Scheme 3. Initial Approach for the Construction of Flavone



the harsh reaction conditions led to retro-aldol condensation and/or cleavage of the C(4)−C(10) bond in the mono- and disubstituted intermediates, giving compounds **B** and **C**, respectively. We further reasoned that the intermolecular oxa-Michael addition had probably preceded to the cleavage of the C(4)−C(10) bond, which would not occur had the benzopyrone ring been formed. In this way the free rotation around the C(4)−C(10) bond would be prevented, and the carbonyl group would adopt the coplanar conjugation to the benzene ring, rendering substitution of the fluorine atom at C(7) easier.

Following these guidelines, we proceeded to complete the total synthesis (Scheme 4). Regioselective substitution of a

Scheme 4. Endgame of the Synthesis



fluorine atom by a hydroxy group took place by the reaction of **2** with the anion of benzaldoxime in THF at room temperature, giving phenol **10** in 90% yield.[13] In the absence of benzaldoxime, the retro-aldol condensation of **2** occurred easily when KOH in THF was employed at room temperature.

The resulting compound **10** was converted to 4*H*-chromen-4-one derivative **11** (90% yield) using a catalytic amount of I_2 in DMSO at 140 °C.[14] Gratifyingly, the remaining two fluorine atoms in flavone **11** were successfully replaced with benzyl alkoxide. At this stage, the choice of solvent was crucial. Thus, treatment of **11** with a ground KOH pellet and benzyl alcohol in 1,4-dioxane at 88 °C for 2 h gave fully benzoxylated product **12** in 89% yield,[15] whereas in a dipolar aprotic solvent such as DMF, NMP, or DMSO the incorporated benzyloxy group(s) at C(4′), C(5), and C(7) unexpectedly suffered from ether cleavage by benzyl alkoxide, giving mono- and diphenolic products and dibenzyl ether.

In contrast to difluoro derivatives, dialkoxylated compound **12** did not allow rigorous NMR assignment even at elevated temperatures (295−373 K) because of the slow/hindered rotation around the *C*-glycosidic linkages on the NMR time scale (500 MHz).[16] Nonetheless, we were pleased to find that hydrogenolysis of **12** using ASCA-2 [$Pd(OH)_2/C$] (2.5 wt % Pd) as the catalyst in EtOH/EtOAc at room temperature for 12 h gave vicenin-2 (**1**) in 92% yield.[17] The spectroscopic and

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physical data ($[\alpha]_D$, ^{1}H and ^{13}C NMR, IR, and HRMS) were identical to those reported in literature.[18]

In summary, an efficient total synthesis of bis-*C*-glucosyl flavonoid vicenin-2 (**1**) has been achieved via bis-β-*C*-glucosylation of 1,3,5-trifluorobenzene and the transformation of all fluorine atoms to oxygen functions. This method paves the way to other bis-*C*-glycosyl natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02203.

Full experimental procedures, characterization data, and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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