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Iron-catalyzed enediene carbocyclizations. The total synthesis of (−)-gibboside

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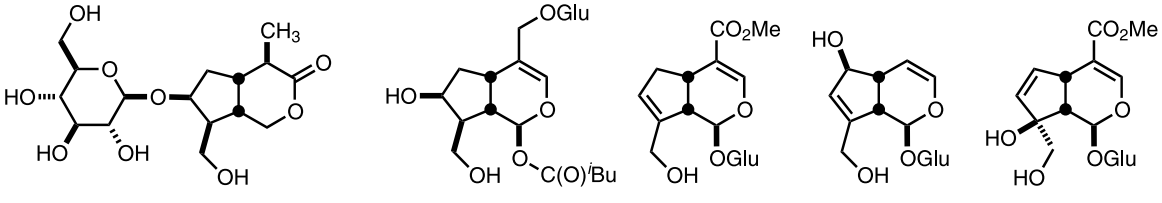
Abstract—The first total synthesis of (−)-gibboside is reported. The route features a novel iron-catalyzed carbocyclization as the key step for the construction of the *cis*,*trans*,*cis*-tetrasubstituted cyclopentane core.

The iridoid glucoside, (−)-gibboside (**1**), was isolated from the methanol extracts of *Patrinia gibbosa* roots, a plant indigenous to Sado Island in Japan.[1] The structure was assigned as depicted in **1** on the basis of spectroscopic analysis and the crystal structure determined of its pentaacetate derivative. While no biological data for this compound have been published, a variety of interesting activity has been seen in other iridoid glucosides.[2] Gibboside is structurally differentiated from other iridoid glucosides, some of which are shown in Scheme 1, by the presence of a hydroxymethyl group adjacent to the ring fusion, by the attachment of a β-D-glucose unit at the secondary alcohol, and by the presence of a lactone rather than dihydropyran ring. Biosynthetic studies defined a pathway for the formation of gibboside and the related natural product patrinoside, an iridoid glucoside also found in *P. gibbosa*,[3] and it is concluded from labeling studies that both the cyclopentane ring and the ring methyl substituent are oxidized after construction of the iridoid skeleton. The iridoids continue to attract significant synthetic interest,[4] but a total synthesis of gibboside has not previously been reported.

The iron-catalyzed carbocyclization of enedienes provides a novel method for the diastereoselective synthesis of substituted five- and six-membered ring systems[5] and has previously been applied to the enantioselective synthesis of a simple alkaloid analogue[6] as well as to the syntheses of iridoid monoterpenes (+)-isoiridomyrmecin and (−)-mitsugashiwalactone.[7] Herein, we report the total synthesis of (−)-gibboside (**1**) via the retrosynthetic plan outlined in Scheme 2. The plan features a diastereoselective iron-catalyzed carbocyclization to construct the *cis*,*trans*,*cis*-tetrasubstituted cyclopentane core of the molecule (i.e. the cyclization of **C** to **B**).

The synthesis of the functional version of enediene **C** (i.e. **7**) and its cyclization are shown in Scheme 3. We have previously described the deconjugative boron-mediated aldol reactions of the sorbic acid derived *N*-acyloxazolidine **2**.[8] This extension of Evans' chemistry[9] provides an efficient method to introduce 1,3-diene moieties with control of stereochemistry. Thus, condensation of **2** with 3-(triisopropylsilyloxy)propanal followed by reduction of the crude aldol product affords diol **3** (66–75% yield, >95% isomeric



(−)-Gibboside (**1**) Patrinoside Geniposide Aucubin Gardenoside

Scheme 1. The structures of (−)-gibboside and several related iridoid glucosides.

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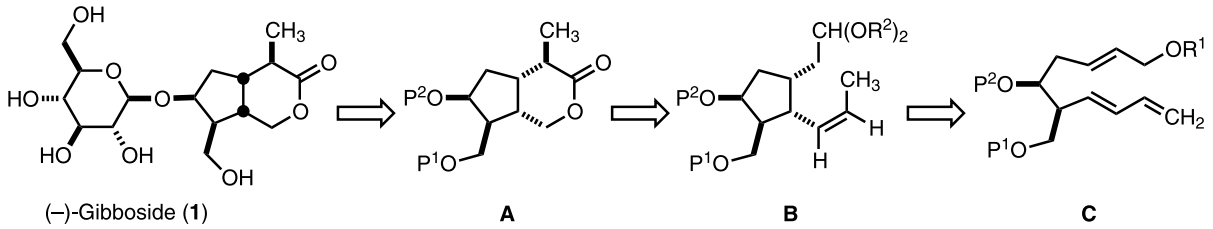
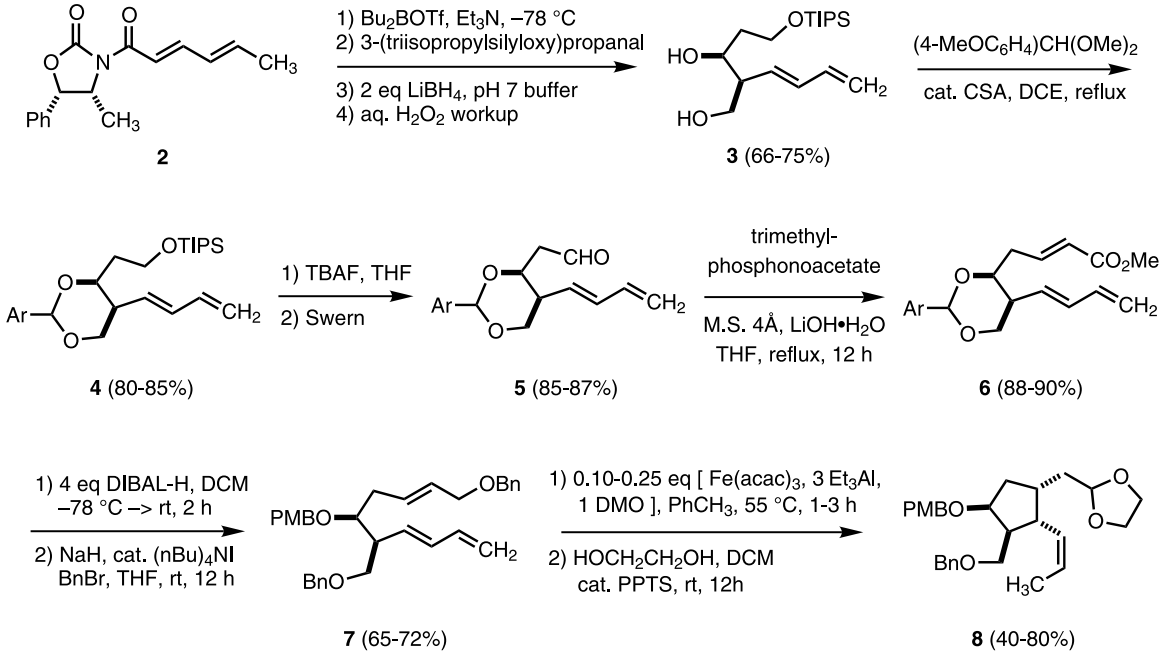


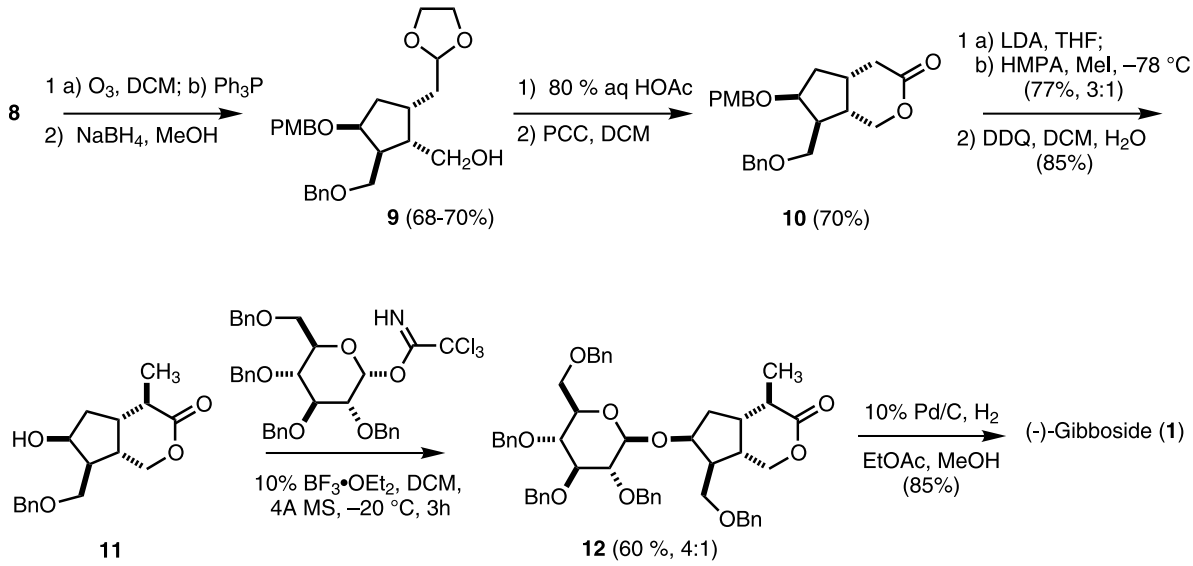
Scheme 2. Retrosynthesis of (–)-gibboside (**1**).



Scheme 3. The enantioselective preparation of enediene **7** and its iron-catalyzed cyclization.

purity). Initially, it was hoped that the boron-mediated aldol reaction could be used to couple **2** with a β,γ-unsaturated aldehyde, for example 5-benzyloxy-3-pentenal.[10] This approach would have significantly shortened the synthetic sequence required, but under the conditions employed for the reaction, the β,γ-unsaturated aldehyde apparently isomerizes to the more stable α,β-unsaturated isomer, 5-benzyloxy-2-pentenal, and only its condensation product is isolated. Nonetheless, the two chiral centers required for the enediene are efficiently set in the aldol reaction and elaboration of **3** is straightforward.

Protection of the 1,3-diol with *para*-anisaldehyde dimethyl acetal using catalytic camphor sulfonic acid in refluxing 1,2-dichloroethane (DCE) gives acetal **4** (4–12 h, 80–85%). When the reaction was run in refluxing dichloromethane (DCM), it was found to be quite sluggish and required significantly longer reaction time (2 days, 70%). Acetal **4** was formed as a 6:1 mixture of diastereomers at the acetal center. The mixture of epimers was treated with TBAF (1.0 M in THF) to remove the TIPS protecting group followed by Swern oxidation to the labile aldehyde **5** (85–87% for two steps). The aldehyde was subjected to olefination conditions using the Horner–Emmons procedure introduced by Bonadies,[11] conditions that have proven useful in our hands for the olefination of other labile aldehydes,[12] and the expected trienoate **6** was obtained in good yield (88–90%). The ester functionality in **6** can be selectively reduced upon treatment with DIBAL-H (2 equiv., –78°C in toluene) to give the corresponding allylic alcohol in good yield (90% yield). However, benzylidene acetals can also be cleaved regioselectively by DIBAL-H,[13] and the combined reductions of the ester and acetal are readily effected with good regiocontrol using excess DIBAL-H (4 equiv., DCM, –78°C to rt). Greater than 10:1 regioselectivity is observed in the acetal opening. The intermediate diol is benzylated to afford the desired enediene **7** (65–72% from **6**). The key iron-catalyzed carbocyclization of enediene **7** proved to be problematic. The iron catalyst is generated in situ via the reduction of iron(III) acetoacetonate with triethylaluminum in the presence of a bisoxazoline ligand (i.e. 2,2′-(1-methylethylidene)bis[4,5-dihydro-4,4-dimethyloxazole], DMO).[14] This cyclization provides a mixture of enol ethers, which is converted to the ethylene acetal upon treatment of the crude reaction mixture with ethylene glycol and catalytic PPTS. Compound **8** is obtained in high diastereomer purity (>95% one isomer). While we have a good deal of experience with this reaction, and have successfully used it for a variety of cyclization substrates, the yield obtained in this case



Scheme 4. The final stages of the synthesis of (–)-gibboside (**1**).

varied over a wide range (40–80%). We know from previous studies that the catalyst is quite sensitive to trace impurities in the reagents or starting material, and our attempts to fully understand and optimize the cyclization of **7** were hampered by its relatively limited availability.

The conversion of **8** to (–)-gibboside is straightforward (Scheme 4). Cleavage of the double bond by ozonolysis followed by reduction with $NaBH_4$ gives the hydroxyacetal **9** (68–70%). Hydrolysis by treatment with aqueous acetic acid (75°C) gives an intermediate lactol which upon PCC oxidation gives lactone **10** (70%). Diastereoselective alkylation of its derived enolate at low temperature (–78°C) by treatment with methyl iodide gives a 3:1 mixture of diastereomers (77%). Unfortunately, the diastereomer ratio could not be improved by further lowering the temperature to –100°C. The major isomer was treated with DDQ in DCM/H_2O to cleave the PMB group (85%).[15] $BF_3{\cdot}OEt_2$-catalyzed glycosidation with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate[16] (10% $BF_3{\cdot}OEt_2$, DCM, –20°C, 4 Å molecular sieves) gives a 4:1 mixture of diastereomers (60%), the major isomer being the expected β-glucoside **12**. Global benzyl group deprotection was effected by catalytic hydrogenation in the presence of Pd/C (85%). The analytical data for our synthetic (–)-gibboside[17] agree with that reported for the natural product.[1]

In summary, the first total synthesis of the unusual iridoid glycoside (–)-gibboside is reported. The route features a novel iron-catalyzed carbocyclization as the key step for the construction of the tetrasubstituted cyclopentane core.

Acknowledgements

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17. Synthetic (−)-gibboside (**1**): 4.9 mg obtained as a white amorphous solid: $[\alpha]_D$ −17.5° (*c* 0.1, MeOH) (lit. $[\alpha]_D$ −22.1° (*c* 1, MeOH). Note: Unfortunately, we were unable to measure the optical rotation under conditions identical to those reported in the literature); ^{1}H NMR (CD_3OD, 300 MHz) δ 4.42–4.31 (m, 3H), 4.10 (t, $J=11.2$ Hz, 1H), 3.88–3.81 (m, 2H), 3.70–3.60 (m, 2H), 3.36–3.22 (m, 3H), 3.14 (t, $J=8.4$ Hz, 1H), 2.55–2.43 (m, 2H), 2.41–2.20 (m, 2H), 1.93 (m, 1H), 1.54 (m, 1H), 1.14 (d, $J=6.5$, 3H); ^{13}C (CD_3OD 75 MHz) δ 179.2, 105.1, 84.7, 78.2, 77.9, 75.4, 71.1, 71.0, 62.7, 61.6, 51.4, 42.3, 41.2, 40.5, 39.9, 14.4; IR (NaCl plate) 3400, 2928, 1738, 1344, 1241, 1170, 1080, 1028 cm^{-1}; HRMS calcd for $C_{16}H_{26}NaO_9$ (M+ plus Na) 385.1467, found 385.1471 m/z.