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Asymmetric Total Synthesis of the Iridoid β-Glucoside (+)-Geniposide via Phosphine Organocatalysis

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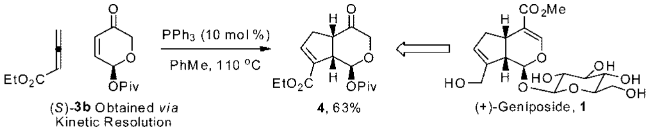
ABSTRACT



Phosphine-catalyzed [3 + 2] cycloaddition of ethyl-2,3-butadienoate with enone (*S*)-3b occurs with high levels of regio- and stereocontrol to deliver the *cis*-fused cyclopenta[c]pyran 4 characteristic of the iridoid family of natural products. Cycloadduct 4 was converted to the iridoid glycoside (+)-geniposide in 10 steps.

The iridoids are a large family of monoterpenoid natural products structurally characterized by a highly oxygenated *cis*-fused cyclopenta[c]pyran ring system.[1] Members of this class embody a diverse range of biological activities,[1d,2] which has made them popular synthetic targets.[3] Despite enormous progress, synthetic approaches to iridoid natural products that incorporate their natural β-glycosides remain rare due to difficulties associated with the glycosidation.[4]

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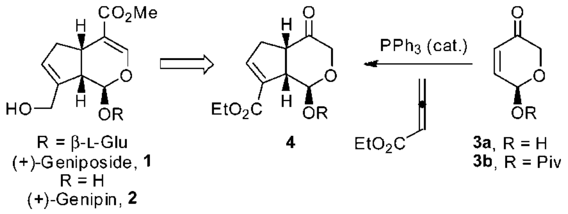
In the course of our studies in the area of phosphine organocatalysis,[5−9] we explored intramolecular variants of Lu's phosphine-catalyzed [3 + 2] cycloaddition reported in 1995.[5a,10−12] Whereas the intermolecular cycloaddition generally provides mixtures of regio- and stereoisomeric adducts, the intramolecular cycloaddition delivers diquinanes in structurally homogeneous form. As a regio- and stereocontrolled intermolecular cycloaddition of this type would be of great utility, we explored dipolarophiles possessing γ-heteroatom substitution, as in the case of enones **3**, which are prepared conveniently through the Achmatowicz reaction of furfuryl alcohol.[13] It was postulated that such γ-heteroatom substitution should (a) activate the dipolarophile toward cycloaddition, (b) reinforce the inherent regiochemical bias, and (c) direct the diastereofacial selectivity of cycloaddition.

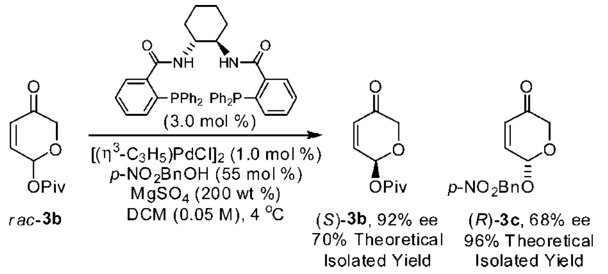
Here, we report that "Achmatowicz enones" **3** engage in regio- and stereocontrolled intermolecular [3 + 2] cycloaddition, thus providing direct access to the iridoid ring system **4**. This methodology was applied to the synthesis of the iridoid glycoside (+)-geniposide **1**,[14] which displays antitumor[15] and anti-inflammatory[16] activity. The total asymmetric synthesis of (+)-geniposide **1** constitutes a formal synthesis of its aglycone (+)-genipin **2**,[17,18] which recently has garnered attention as an effective treatment for type II diabetes (Scheme 1).[19]

Scheme 1. Retrosynthetic Analysis of (+)-Geniposide **1** and (+)-Genipin **2**



Exposure of commercially available furfuryl alcohol to *m*-CPBA in dichloromethane delivered lactol *rac*-**3a** in 78% yield,[13] which was converted to the pivalate *rac*-**3b** in 80% yield. Kinetic resolution of *rac*-**3b** was attempted under the conditions of palladium-catalyzed allylic substitution employing *p*-nitrobenzyl alcohol as the nucleophile.[20] After careful optimization, it was found that chirally modified palladium catalysts arising from the combination of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (1.0 mol %) and the parent Trost ligand (3 mol %) enable recovery of the allylic pivalate (*S*)-**3b** in 92% ee in a satisfactory 70% theoretical isolated yield (Scheme 2). Optically pure (*S*)-**3b** is readily obtained upon recrystallization from pentane. The byproduct (*R*)-**3c** was isolated in 96% theoretical isolated yield in 68% ee. Absolute stereochemistry was determined by single-crystal X-ray diffraction analysis of the 4,5-dichlorophthalimide adduct of (*S*)-**3b** using the anomalous dispersion method and is consistent with the stereochemical models developed by Trost for related kinetic resolutions.[21]

Scheme 2. Kinetic Resolution of *rac*-**3b** Using Palladium-Catalyzed Allylic Substitution



[a] Theoretical yields are based on a maximum 50% isolated yield.

With (*S*)-**3b** in hand, the phosphine-catalyzed [3 + 2] cycloaddition was attempted using ethyl-2,3-butadienoate. Gratifyingly, using triphenylphosphine as catalyst (10 mol %) in toluene (0.2 M) at 110 °C, the desired cycloadduct **4** was obtained in 63% isolated yield after 30 min as a single regio- and stereoisomer, as confirmed by single-crystal X-ray diffraction analysis. Note that while 2 equiv of (*S*)-**3b** is used in the cycloaddition, unreacted (*S*)-**3b** was recovered in 96% isolated yield (Scheme 3).

Installation of the α,β-unsaturated methyl ester was accomplished in a stepwise fashion. Cycloadduct **4** was converted to the cyanohydrin, which upon elimination furnished the α,β-unsaturated nitrile **5** in 60% isolated yield over two steps. Chemoselective reduction of the α,β-

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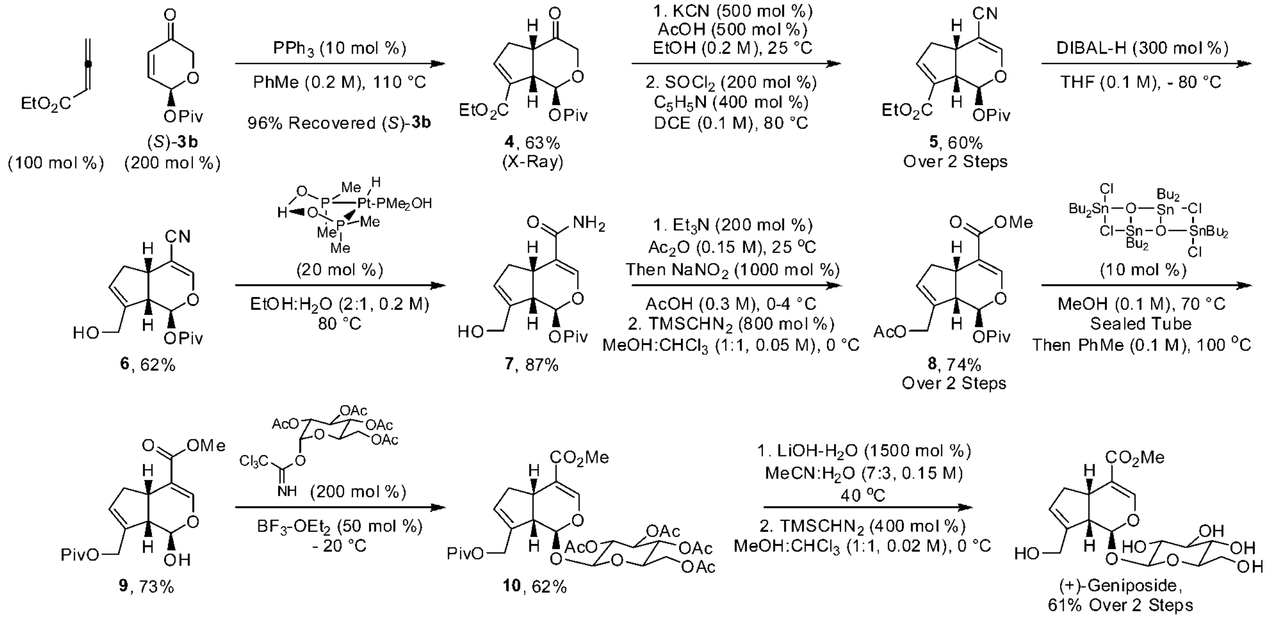
Scheme 3. Conversion of (*S*)-**3b** to (+)-Geniposide **1** via Phosphine-Catalyzed [3 + 2] Cycloaddition



[a] See Supporting Information for detailed experimental procedures.

unsaturated ethyl ester of compound **5** using DIBAL-H delivered the allylic alcohol **6** in 62% yield. Further conversion of nitrile **6** to the methyl ester was difficult due to the sensitivity of the enol moiety to acid, as well as the base sensitivity of the pivalate. Using the Ghaffer−Parkins catalyst,[22] hydration of nitrile **6** to the primary amide **7** was accomplished in 87% isolated yield. Nitrosation of amide **7** resulted in hydrolysis to furnish the carboxylic acid.[23] During the course of this reaction, the primary alcohol was converted to the acetate. Exposure of the carboxylic acid to TMS−diazomethane delivered the methyl ester **8** in 74% yield over two steps (Scheme 3).

To complete the synthesis of (+)-geniposide **1**, installation of the *β*-glucoside was required. Quite serendipitously, it was found that upon exposure of methanolic solutions of compound **8** to Otera's catalyst[24] acetate removal was accompanied by transfer of the pivaloyl moiety to provide lactol **9** in 73% yield as a 5:1 mixture of epimers at the lactol carbon. Compound **9** was independently prepared from commercially available (+)-genipin **2**, thus corroborating its structural assignment and providing a convenient source of forefront material. Glycosidation of lactol **9** employing the trichloroacetimidate as the glycosyl donor delivered the *β*-glucoside **10** in 62% yield as a single diastereomer. Global deprotection of **10** using aqueous lithium hydroxide in acetonitrile[25] provided (+)-geniposide **1** in 61% isolated yield, the spectral data of which corresponded to that of previously reported material (Scheme 3).[26]

In summary, we report an asymmetric synthesis of the iridoid glucoside (+)-geniposide **1** in 14 steps. A key feature of our synthetic strategy involves rapid construction of the *cis*-fused cyclopenta[c]pyran iridoid ring system employing a phosphine-catalyzed intermolecular [3 + 2] cycloaddition. Unlike typical intermolecular cycloadditions employing acrylates, fumarates, and maleates, which provide adducts as mixtures of regio- and diastereoisomers, the unique structural features of γ-heteroatom-substituted enones **3** combine high levels of reactivity with excellent regio- and stereocontrol.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). Single-crystal X-ray diffraction data for the 4,5-dichlorophthalimide adduct of (*S*)-**3a** and the cycloadduct **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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