Glycocinnasperimicin D Synthetic Studies: Synthesis of Cinnamoyl Glycosides via Iodination-Heck Reaction Sequence Starting from Phenyl Glycosides

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Abstract: A new approach for the synthesis of cinnamoyl glycoside has been developed via iodination-Heck reaction sequence starting from phenyl glycoside. Successful application of this procedure accomplished the construction of the right core structure of aminosugar antibiotic, glycocinnasperimicin D.

Key words: antibiotics, cinnamoyl glycoside, glycosylation, Heck reaction, palladium

In 1985, Umezawa et al. reported the isolation of a novel antibiotic, glycocinnasperimicin D, from the fermentation broth of *Nocardia* strain.[1] Its structure was elucidated by spectroscopic studies as represented in Figure 1, which clarified that this aminosugar antibiotic belongs to a member of glycocinnamoylspermidine. The more complex relative with an additional 2,4-diaminopentose is LL-BM123β [cinodine β, (**2**)], which was isolated and identified at Lederle Laboratories.[2] Glycocinnasperimicin D (**1**) has demonstrated broad antibacterial spectrum and several unique structural features; the left portion is 2-ureidopentose and the right part is 2,4-diamino-2,4,6-trideoxy-α-D-glucopyranose with *p*-cinnamoyl spermidine aglyson. These two amino sugars are joined with urea glycosyl linkage. The interesting structure and small availability of **1** from natural sources promoted us to pursue the synthetic work of **1**.[3] In this manuscript, we describe a new approach to cinnamoyl glycosides and its application for the synthesis of right segment of **1**.

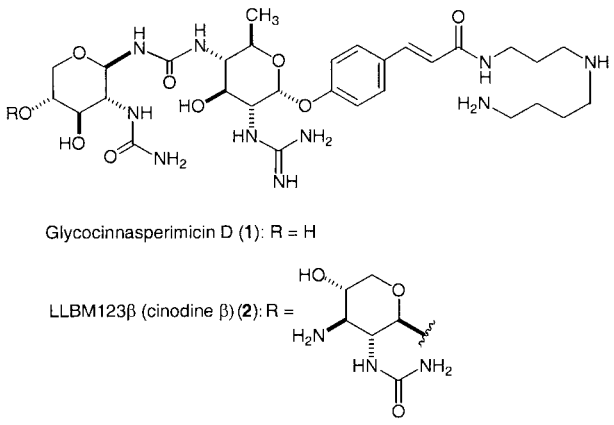

Figure 1

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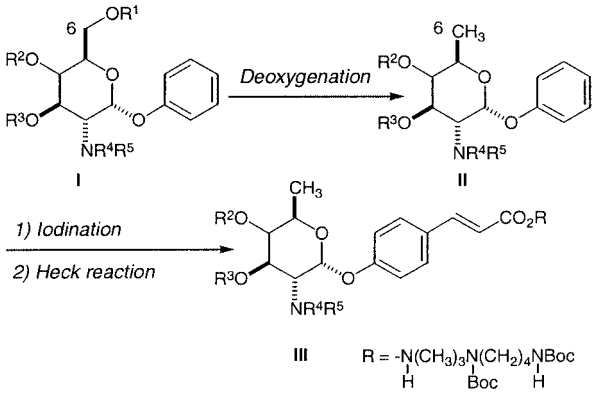
During our synthetic endeavor, we soon recognized that glycosylation of a highly functionalized pyranose, such as 2,4-diamino-2,4,6-trideoxy-D-glucopyranose or its equivalents, with *p*-hydroxycinnamic acid derivatives is quite problematic due to a poor nucleophilic nature of the phenol bearing an electron-withdrawing group.[4] To circumvent this problem, we developed a synthetic plan which involves a new approach for the synthesis of cinnamoyl glycosides (Scheme 1).

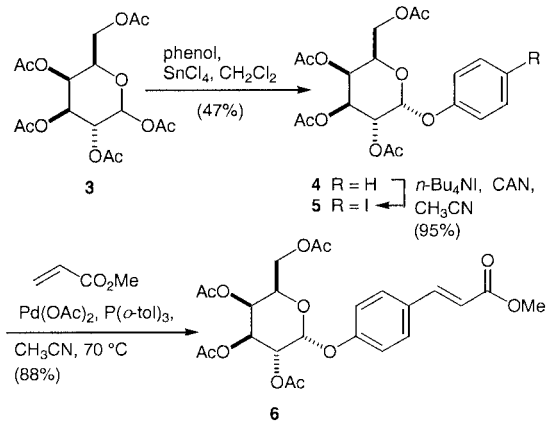


Scheme 1

Starting from α-phenyl glycoside I, initial efforts focused on the deoxygenation of C-6 hydroxy group.[5] Iodination of the resulting phenyl 6-deoxy-glycoside II followed by the Heck reaction with acrylamide containing spermidine moiety would offer a highly convergent tactic to the right subunit of **1**. In our initial attempts to explore this strategy, we focused on the synthesis of cinnamoyl α-D-galactopyranoside (Scheme 2).

Phenyl α-D-galactopyranoside **4** was readily prepared by Lewis acid catalyzed glycosylation of pentaacetate **3** with phenol in 47% yield after recrystallization.[6] A screen of several iodination agents revealed that cerium (IV)-promoted iodination is an optimal solution.[7] In practice, treatment of **4** with ceric ammonium nitrate (CAN) and iodine salt (n-Bu_4NI) in MeCN at 70 °C for 24 h furnished iodophenyl galactoside **5** in 95% yield. The Heck reaction of **5** with methyl acrylate [$Pd(OAc)_2$, P(o-tol)$_3$, CH_3CN, 70 °C] proceeded smoothly to furnish α-cinnamoyl galactoside **6** in 88% yield.[8]

We examined the generality of this cinnamoyl glycoside synthesis using a variety of phenyl glycosides (Table 1).

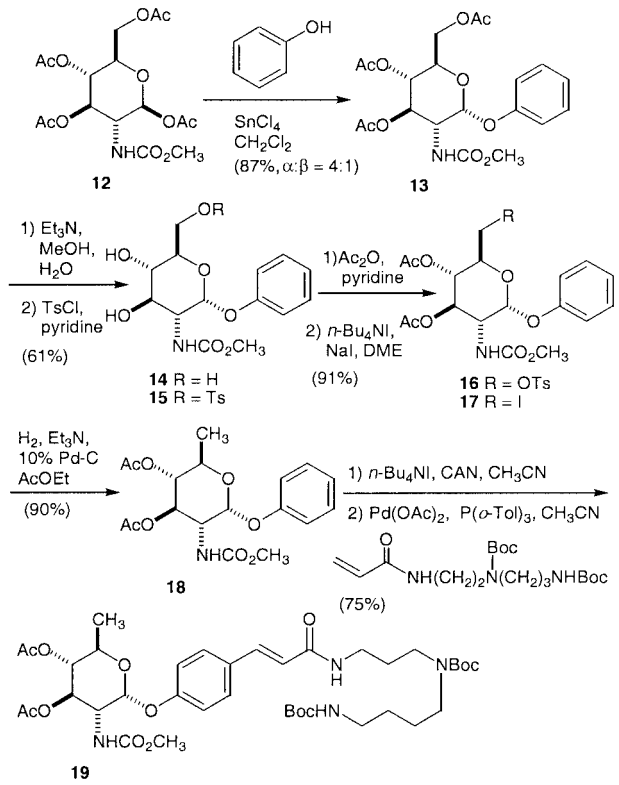


Scheme 2

Ready availability of each phenyl glycoside and good overall yield over two steps make this approach highly acceptable.[9]

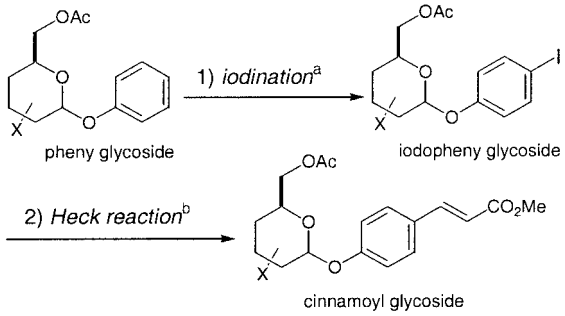
With an efficient route to cinnamoyl glycoside established, we turned our attention to the right core synthesis of glycocinnasperimicin D (Scheme 3).

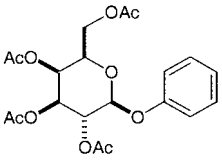
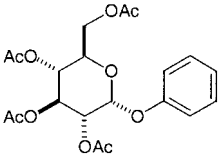
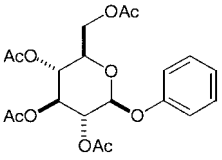
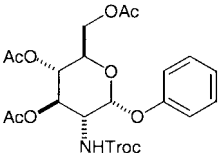
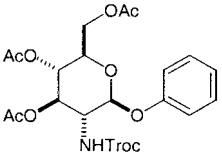
Glycosylation of glucosamine derivative **12** with phenol catalyzed with tin (IV) chloride in CH_2Cl_2 proceeded smoothly to afford a 4:1 anomeric mixture of phenyl glycosides (87%).[10] Following purification of α-anomer **13** by chromatography, hydrolysis of acetyl groups in **13** (Et_3N, MeOH, H_2O) and selective tosylation (TsCl, pyridine) of the triol **14** furnished tosylate **15** (61% in two



Scheme 3

Table 1 Cinnamoyl Glycoside Synthesis Using a Variety of Phenyl Glycosides

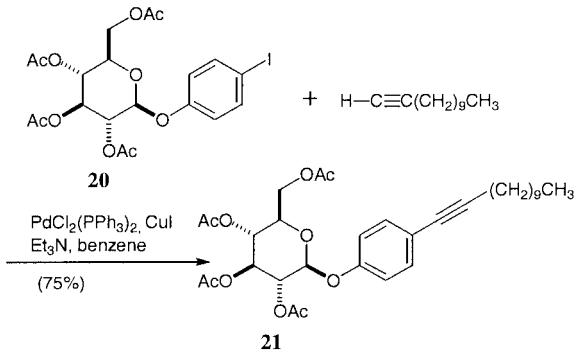


Entry	Phenyl glycoside	Iodination yield (%)	Heck reaction (%)
A		92	92
B		96	87
C		94	89
D		96	84
E		93	87

[a] CAN (3.0 equiv), *n*-Bu_4NI (1.5 equiv), CH_3CN, 70 °C, 24 h.
[b] Methyl acrylate (3.0 equiv), 30 mol% $Pd(OAc)_2$, 50 mol% P(*o*-tol)$_3$, Et_3N (5.0 equiv), CH_3CN, 70 °C, overnight.

steps). Acetylation of two hydroxy groups in **15** (Ac_2O, pyridine) followed by the S_N2 displacement (*n*-Bu_4NI, NaI, DME) produced iodide **17** (91% yield over two steps). Reductive hydrogenolysis of **17** (H_2, 10% Pd-C, Et_3N, EtOAc) then furnished 6-deoxy pyranose **18** in good yield (90%). Finally, iodination of phenyl glycoside **18** followed by the Heck reaction with acrylylspermidine successfully constructed the right core structure of glycocinnasperimicin D, and the product, 2-amino-6-deoxy-α-D-glucocinnamoyl spermidine **19**, was isolated in 75% yield.[11]

During these synthetic works, we recognized that iodophenyl glycosides, prepared from readily available phenyl glycosides by high-yielding iodination process, are particularly attractive synthons for the synthesis of substituted phenyl glycosides (Scheme 4). In fact, introduction of 1-dodecyne onto the phenyl ring in **20** was achieved efficiently by the Sonogashira cross-coupling reaction [1-dodecyne, $PdCl_2(PPh_3)_2$, CuI, Et_3N, benzene] to provide a useful amphilic carbohydrate derivative **21** for the nonionic detergents in 75% yield.[12] This example demonstrates synthetic potential of iodophenyl glycosides.[13]



Scheme 4

In conclusion, a new approach for the synthesis of cinnamoyl glycoside was established, and successful application of this method accomplished the construction of the right core structure found in glycocinnasperimicin D. Furthermore, palladium-catalyzed reaction successfully demonstrated synthetic potential of iodophenyl glycosides.

General Procedure for the Synthesis of Cinnamoyl Glycosides via Iodination-Heck Reaction Sequence

A solution of phenyl galactoside **4** (500 mg, 1.18 mmol), tetra-*n*-butylammonium iodide (654 mg, 1.77 mmol) and CAN (1.94 g, 3.54 mmol) in MeCN (20 mL) was heated at 70 °C for 24 h. The resulting yellow solution was poured into sat. aq $NaHCO_3$, and the aq layer was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over anhyd Na_2SO_4, and then concentrated. The resulting residue was purified by silica gel chromatography (stepwise gradient of 25% to 30% EtOAc–hexane) to afford the iodophenyl galactoside **5** (613 mg, 1.11 mmol, 95%) as a white solid.

A dry Schlenk flask was charged with **5** (80 mg, 0.15 mmol), methyl acrylate (40 μL, 0.44 mmol), tri-*o*-tolylphosphine (18 mg, 0.073 mmol), Et_3N (0.10 mL, 0.73 mmol), and MeCN (2.0 mL). The solution was degassed by two freeze-thaw cycles. After cooling the Schlenk flask at –78 °C, palladium(II) acetate (9.0 mg, 0.040 mmol) was placed on the resulting solidified reaction mixture. The Schlenk flask was evacuated and then heated at 70 °C overnight. After cooling to r.t., the reaction mixture was poured into sat. aq NH_4Cl, and the aq layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated, and purified by silica gel chromatography (stepwise gradient of 25% to 30% EtOAc–hexane) to furnish α-cinnamoyl galactoside **6** (65 mg, 88%) as a white crystalline mass.

Acknowledgment

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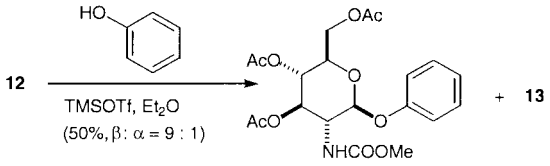
(3) For the synthetic studies of LL-BM123β, see the references: (a) Araki, K.; Miyazawa, K.; Hashimoto, H.; Yoshimura, J. *Tetrahedron Lett.* **1982**, *23*, 1705. (b) Araki, K.; Kawa, M.; Saito, Y.; Hashimoto, H.; Yoshimura, J. *Bull. Chem. Soc, Jpn.* **1986**, *59*, 3137. (c) Araki, K.; Hashimoto, H.; Yoshimura, J. *Carbohydr. Res.* **1982**, *109*, 143.
(4) (a) Oyama, K.; Kondo, T. *Synlett* **1999**, 1627; and references therein. (b) See also ref.[3c]
(5) We avoid glycosylation with iodophenol, because our preliminary experiments showed that catalytic hydrogenolysis of 6-iodo-glycopyranose is the most simple and high-yielding method for multigram synthesis of 6-deoxy glycopyranose. For recent examples of C6-deoxygenation: Medgyes, A.; Farkas, E.; Liptak, A.; Pozsgay, V. *Tetrahedron* **1997**, *53*, 4159.
(6) This acid-catalyzed glycosylation initially led to the formation of an anomeric mixture of phenyl galactosides. Prolonged reaction time (4 d) resulted in a gradual decrease of the β-isomer proportion and concomitant increase in the formation of α-anomer.
(7) Sugiyama, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2847.
(8) (a) Bromination of β-phenyl glucoside **9** (Br_2, CH_2Cl_2, –5 °C) and the Heck reaction of the resultant brominated glycosylated aromatic with alkenes has been reported by Lepoittevin et al.: Mabic, S.; Lepoittevin, J.-P. *Tetrahedron Lett.* **1995**, *36*, 1705. (b) In our case, bromophenyl glycosides, prepared (NBS, DMF, r.t.) in good yields, were found to be poor substrates for the Heck reaction.
(9) Although cinnamoyl glycosides are known as important natural products, their synthesis suffer from the low nucleophilicity of *p*-hydroxycinnamic acid derivatives. For example: Takada, N.; Kato, E.; Ueda, K.; Yamamura, S.; Ueda, M. *Tetrahedron Lett.* **2002**, *43*, 7655.
(10) We have found the reversal of selectivity in this glycosylation using TMSOTf and Et_2O (Scheme 5).



Scheme 5

(11) Spectroscopic data of **19**; $[\alpha]_D^{26}$ = +98.9 (*c* 1.09, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.17 (d, *J* = 6.5 Hz, 3 H), 1.40–1.90 (m, 6 H), 1.44 (s, 9 H), 1.48 (s, 9 H), 2.05 (s, 3 H), 2.07 (s, 3 H), 3.08–3.25 (br s, 4 H), 3.25–3.40 (br s, 4 H), 3.64 (s, 3 H), 3.93 (dq, *J* = 10.5, 6.5 Hz, 1 H), 4.18 (td, *J* = 10.5, 3.5 Hz), 4.50–4.70 (br s, 1 H), 4.94 (dd, *J* = 10.5, 9.5 Hz, 1 H), 5.11 (d, *J* = 10.0 Hz, 1 H), 5.37 (dd, *J* = 10.5, 9.5 Hz, 1 H),

5.54 (d, *J* = 3.5 Hz, 1 H), 6.37 (d, *J* = 15.5 Hz, 1 H), 7.04–7.10 (3 H), 7.44–7.52 (2 H), 7.57 (d, *J* = 15.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.1, 20.47, 20.53, 25.5, 27.2, 27.5, 28.19, 28.23, 35.6, 39.9, 43.2, 46.5, 52.3, 53.9, 66.3, 70.7, 73.1, 79.0, 79.7, 95.6, 116.4, 120.2, 129.2, 129.8, 139.4, 156.0, 156.5, 157.0, 166.1, 169.7, 171.2.

(12) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *23*, 4467. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Tohda, Y.; Hagihara, N. *Synthesis* **1980**, 627.

(13) For recent examples of the Sonogashira reacton using iodophenyl α-D-mannopyranoside for the efficient synthesis of sugar-rods and cyclodextrin-based cluster mannosides, see: (a) Roy, R.; Das, S. K.; Santoyo-Gonzalez, F.; Hernandez-Mateo, F.; Dam, T. K.; Brewer, C. F. *Chem.–Eur. J.* **2000**, *6*, 1757. (b) Ortega-Caballero, F.; Gimenez-Martinez, J. J.; Vargas-Berenguel, A. *Org. Lett.* **2003**, *14*, 2389.