ORGANIC LETTERS

2011
Vol. 13, No. 14
3710–3713

# An Efficient Synthesis of the Protected Carbohydrate Moiety of Brasilicardin A

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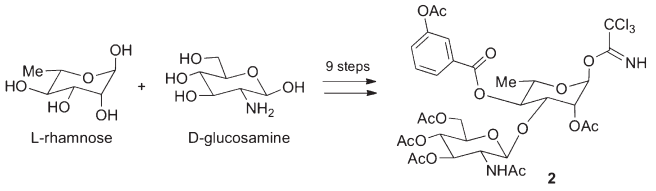
**Received May 20, 2011**

## ABSTRACT




**A synthesis of the protected carbohydrate moiety 2 of Brasilicardin A starting from L-rhamnose and D-glucosamine is described. The disaccharide was synthesized using a TMSOTf-mediated glycosylation of the 2-phthalimido-2-deoxyglucose donor 5 and the 3-hydroxyl group of the protected L-rhamnose derivative 4, which already bears the 3-hydroxybenzoate unit. The imidate 2 was coupled via TMSOTf-mediated glycosidation with cholesterol as a model aglycone followed by the selective cleavage of all the acetate groups to give the Brasilicardin A analogue 16.**

Brasilicardin A (**1**, Figure 1), isolated from the cultured broth of the actinomycete *Norcardia brasiliensis* IFM0406, is a tricyclic terpenoid consisting of an anti/syn/anti perhydrophenanthrene skeleton with a sugar moiety and an amino acid side chain attached.[1] The carbohydrate moiety is a dissacharide consisting of an L-rhamnose with a $\beta$-*N*-acetylglucosamine unit attached to the 3-hydroxyl and a 3-hydroxybenzoate unit attached to the 4-hydroxyl. This unusual carbohydrate is also a key structural feature of the related natural product Brasilicardin B.[2] Based on both $^{1}H-^{13}C$ and $^{1}H-^{1}H$ coupling constants, the stereochemistry at each anomeric position of the sugar moieties was assigned: $\alpha$ at the anomeric position of rhamnose and $\beta$ on the *N*-acetylglucosamine.[1] Brasilicardin A was found to exhibit immunosuppressive as well as cytotoxic activity against several different cell lines.[1−3] Structure−activity relationship (SAR) studies on analogues of **1** revealed the importance of the glucosamine and 3-hydroxybenzoate substituents at the 3- and 4-positions of the rhamnose for immunosuppressive activity.[3]

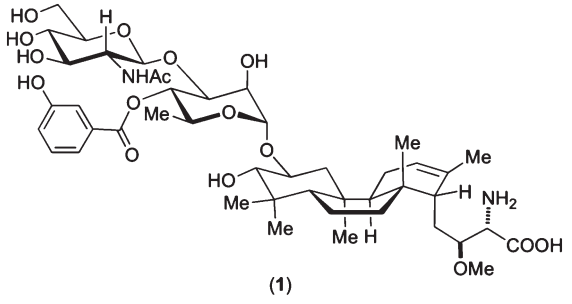



**Figure 1.** Structure of Brasilicardin A (**1**).

Our synthetic strategy toward Brasilicardin A (**1**) is illustrated in Scheme 1. We planned to introduce the sugar moiety in one of the last steps of the synthesis of **1** via the TMSOTf-promoted glycosylation of the glycosyl donor **2** and the protected terpenoid aglycone **3** via the method of Schmidt.[4] In order to minimize the length of the synthesis, we opted to use acetates as the

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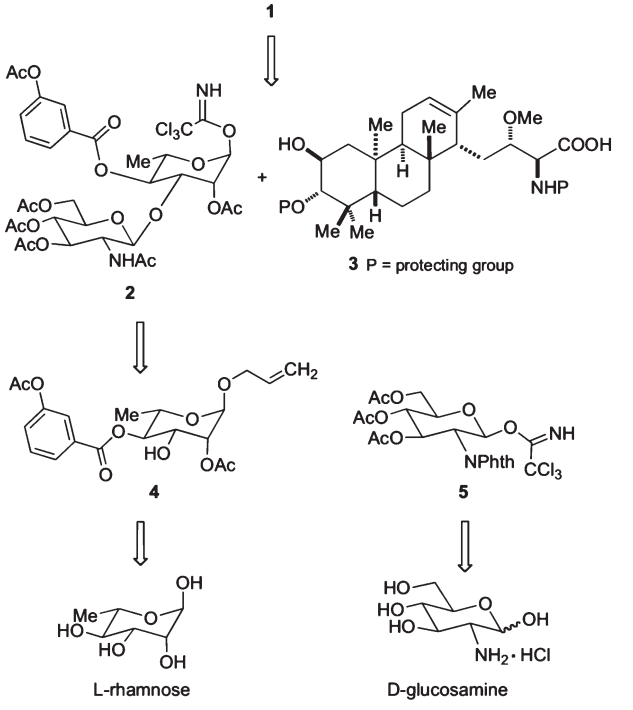
(4) (a) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed.* **1980**, *19*, 731–732. (b) Zhu, X; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934.

10.1021/ol2013704 
**Published on Web 06/16/2011**

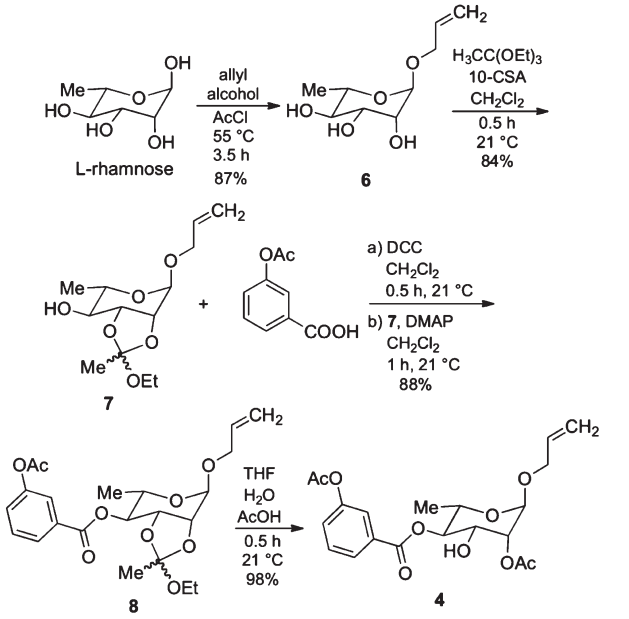
protecting group for the five hydroxyl functions even though there was a possible problem in retaining the integral benzoate moiety of the final product while cleaving the acetates. However, we reasoned that the benzoate group, being situated between two equatorial groups, would be quite hindered toward nucleophilic attack and thus likely to survive acetate removal, which would significantly shorten the synthesis. The donor **2** would arise from TMSOTf-mediated coupling of the known 2-phthalimido-2-deoxyglucose donor **5**[5] and the protected L-rhamnose derivative **4**. As the protecting group for the 2-amine of glucosamine, we chose the phthaloyl group since it is known to selectively afford $\beta$-glycosides in couplings with alcohols in the presence of a Lewis acid.[6,7] Compound **4** could be synthesized in four steps from the commercially available L-rhamnose monohydrate.

**Scheme 1.** Synthetic Strategy for the Preparation of **1**




In the first step in the synthesis of the L-rhamnose acceptor **4** (Scheme 2), the anomeric position of the L-rhamnose was protected with an allyl group to give **6** in 87% yield. The allyl α-L-rhamnopyranoside (**6**) was transformed into the 2,3-ortho ester **7** by reaction with triethyl orthoacetate in the presence of a catalytic amount of 10-camphorsulfonic acid in 84% yield. Compound **7** was a mixture of two diastereomers, which were not separated but used as a mixture. Acylation with 3-acetyloxybenzoic acid, which was prepared according to Zhang et al.,[8] using DCC/DMAP coupling conditions furnished the ester **8** in 88% yield. Treatment of **8** with a 1:1:3 mixture of THF/water/acetic acid at 21 °C resulted in the regioselective ring opening of the acid labile ortho ester to afford the desired 2-acetyloxy 3-hydroxy derivative **4** in 98% yield.[9] This acetyloxy group is required to ensure neighboring group participation in the later glycosylation, which favors the formation of the desired 1,2-trans linked product.[7] The $^1$H NMR of **4** clearly indicated a downfield shift of the H-2 signal from 3.95 ppm in the $^1$H NMR spectrum of compound **6** to 5.11 ppm caused by the acetyloxy substituent at this position.

**Scheme 2.** Synthesis of the Glycosyl Acceptor **4**




Scheme 3 shows the synthesis of the 2-phthalimido-2-deoxyglucose donor **5**. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-$\beta$-D-glucopyranose (**9**) was synthesized from commercially available D-glucosamine HCl in two steps and 61% yield via the method of Minuth et al.[10] Selective anomeric deacetylation of **9** was achieved in 69% yield using ethylene diamine and acetic acid, following the protocol of Zhang and Kovac.[11] The hemiacetal **10** was activated by treatment with trichloroacetonitrile and DBU to give the trichloroacetimidate **5** in 81% yield.

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(7) Paulsen, H. *Angew. Chem., Int. Ed.* **1982**, *21*, 155–173.

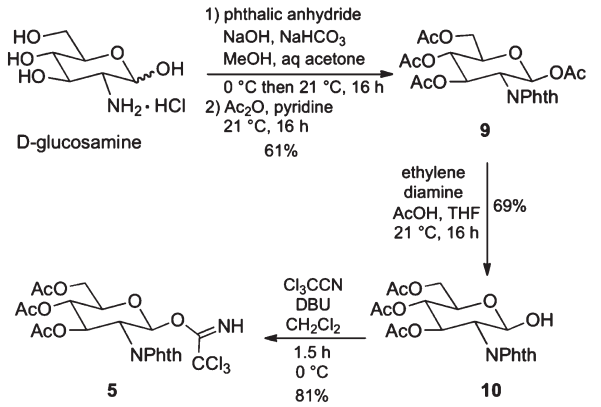
(8) Zhang, B.-S.; Wang, W.; Shao, D.-D.; Hao, X.-Q.; Gong, J.-F.; Song, M.-P. *Organometallics* **2010**, *29*, 2579–2587.

(9) (a) Paulsen, H.; Lorentzen, J. P. *Liebigs Ann. Chem.* **1986**, 1586–1599. *Carbohydr. Res.* **1987**, *165*, 207–337. (b) King, J. F.; Allbutt, A. D. *Tetrahedron Lett.* **1967**, *8*, 49–54. *Can. J. Chem.* **1970**, *48*, 1754–1769.

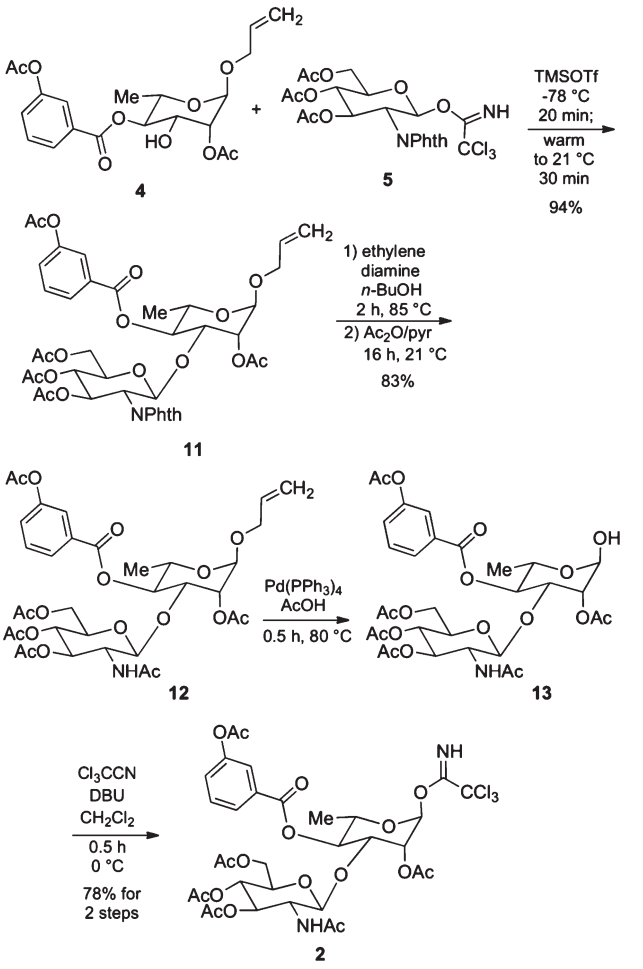
(10) Minuth, T.; Irmak, M; Groschner, A; Lehnert, T; Boysen, M. M. K. *Eur. J. Org. Chem.* **2009**, 997–1008.

(11) Zhang, J.; Kovac, P. *J. Carbohydr. Chem.* **1999**, *18*, 461–469.

**Scheme 3.** Synthesis of the Glycosyl Donor **5**




**Scheme 4.** Synthesis of the Trichloroacetimidate **2**




The synthesis of the desired protected carbohydrate moiety **2** of Brasilicardin A (Scheme 4) involved the coupling of the 2-phthalimido glucosamine donor **5** and the glycosyl acceptor **4** in dichloromethane at −78 °C, mediated by a catalytic amount of TMSOTf, to afford the disaccharide **11** in 94% yield. Under these conditions, only the formation of the desired $\beta$-anomer was observed (the NMR spectra showed $^3J_{1,2} = 8.4$ Hz, indicating that H-1 is in the α-orientation). The phthaloyl group was removed from **11** by treatment with ethylene diamine in *n*-butanol at 85 °C followed by acetylation with acetic anhydride in pyridine to furnish compound **12** in 83% yield for the two steps. The ester bond of the benzoate group was stable under these hydrolysis conditions. To our surprise, the signal of the methyl group of the acetamido moiety showed a dramatic upfield shift in the proton NMR ($\delta = 1.14$ ppm). Removal of the allyl protecting group on the anomeric oxygen was achieved in good yield by heating the allyl ether **12** with 0.5 equiv of $Pd(PPh_3)_4$ in acetic acid at 80 °C. Finally, the hemiacetal **13** was converted to the desired trichloroacetimidate **2** using trichloroacetonitrile and DBU. The structure of compound **2** was proven by X-ray crystallographic analysis[12] (Figure 2). The X-ray structure clearly confirms the stereochemistry at both anomeric positions, namely α for the rhamnose and $\beta$ for the glucosamine unit. Moreover, the X-ray data offer a good explanation for the upfield shift of the methyl group of the NHAc moiety, namely that it lies below the phenyl ring of the 3-acetyloxybenzoate moiety and is thus deshielded. This orientation is supported by an intramolecular hydrogen bond between the N−H group of the amide and the C=O group of the acetyl protecting group of the 3-hydroxybenzoate moiety. The length of the hydrogen bond interaction is 2.13 Å.

For the synthesis of Brasilicardin A (**1**), we would need to couple this disaccharide unit and then deprotect the acetate protecting groups without any unforeseen problems arising, especially deprotection of the benzoate group. Therefore we decided to test the coupling of the imidate **2** on a model aglycone using a TMSOTf-mediated

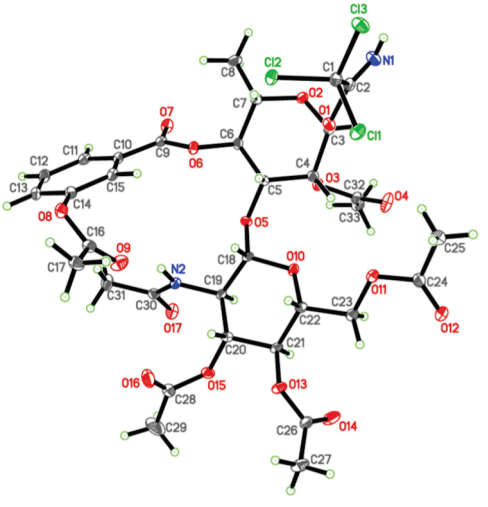
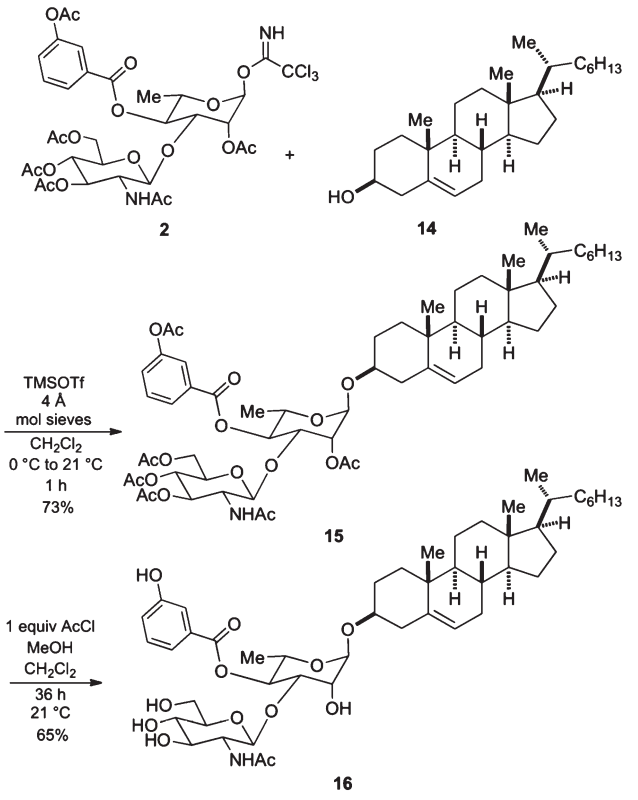


**Figure 2.** Ortep plot of imidate **2**.

(12) We thank Dr. Saeed Khan (UCLA) for the X-ray structural analysis.

**Scheme 5.** Coupling of **2** with Cholesterol (**14**) and Deprotection




glycosylation. As the model aglycone, we chose the common steroid cholesterol (**14**) since it has a secondary equatorial hydroxyl group like the Brasilicardin A aglycone, e.g., **3**. The addition of TMSOTf was carried out at 0 °C, and the reaction was stirred for 1 h at 21 °C to furnish a mixture of the desired α-anomer **15** and its β-anomer in a ratio of 9:1 (Scheme 5). Both anomers could be separated via flash chromatography on silica gel, and the desired α-anomer **15** was thus obtained in 73% yield. The α-stereochemistry at the anomeric center was determined by the direct $^{1}H-^{13}C$ coupling constant of C-1 of the rhamnose unit ($^{1}J_{CH}$ = 170.5 Hz).[13] Finally, under mild conditions, i.e., addition of 1 equiv of acetyl chloride to a solution of compound **15** in 1:1 MeOH/dichloromethane (to generate an equiv of HCl), selective cleavage of all of the acetate groups in the presence of the benzoate was achieved.[14] In this manner, we were able to isolate the desired Brasilicardin A analogue **16** in 65% yield as a pure compound.

In summary, we have described the synthesis of the carbohydrate moiety of Brasilicardin A in a protected form, compound **2**, in nine steps and in an overall yield of 38% from commercial L-rhamnose. Coupling of this imidate **2** to a model aglycone was achieved in good yield with the desired α-anomer as the major product. Investigation of the biological activity of **16** and the synthesis of both Brasilicardin A and its simpler analogues are currently in progress.

**Acknowledgment.** P.K. gratefully acknowledges support by the Deutsche Forschungsgemeinschaft (KO 4111/1-1). We also thank CNSI-Abraxis (UCLA) for financial support of this research. The authors thank Dr. Saeed Khan for obtaining and analyzing the X-ray crystallographic data and Dr. John Greaves, Director, Mass Spectrometry Facility, University of California, Irvine, for the HRMS data.

**Supporting Information Available.** Experimental procedures and proton and carbon NMR for all new compounds and X-ray crystallographic data (cif file) for compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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