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# A Total Synthesis of Millingtonine A

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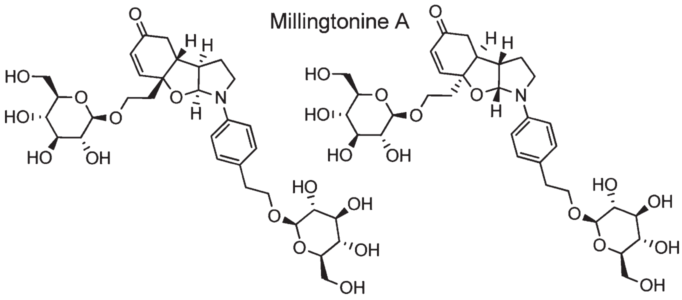
## ABSTRACT



**A total synthesis of millingtonine A, a diglycosylated alkaloid, has been accomplished. Millingtonine A possesses a unique racemic tricyclic core structure not known from any other natural or synthetic source until now. The synthesis features a key bond-forming radical Ueno–Stork cyclization to form the heterocyclic core.**

Millingtonine A (**1**), a glycosidal alkaloid, was first isolated in Thailand from the methanolic extract of the flower buds of *Millingtonia hortensis*.[1] The structural elucidation was subsequently achieved through a combination of chemical and spectroscopic methods. Millingtonine A is uniquely a racemic tricyclic aglycon that has a trans configuration of the two outermost rings to the central hydrofuran core. The two pendant hydroxyethane groups are both glycosylated with D-glucose in its $\beta$-anomer form. To date, little is known about the biological profile of millingtonine A (**1**); however, *Millingtonia hortensis* is an important source of herbal medicine in Southeast Asia as the plant is cultivated throughout the area and used for the treatment of tuberculosis or sinusitis and as an antiasthmatic agent.[2] The aqueous methanolic leaf extracts of *Millingtonia hortensis* have also been screened against a series of bacterial strains and yeast cultures demonstrating comparable antimicrobial activity to gentamycin and nystatin.[3] In addition, numerous other pharmacologically active substances have been isolated from different parts of the plant, such as scutellarein and hispidulin from the petals of the plant, acetyl oleanolic acid from the fruits, and $\beta$-sitosterol from the heartwood and bark. Isolated extracts containing novel molecular architectures are of general interest as potential leads for new pharmaceuticals. Consequently, millingtonine's promising but yet undefined biological activity together with the unique core structure and the fact that no previous syntheses have been reported makes it an attractive target for total synthesis.

Retrosynthetically, we devised a convergent strategy allowing the rapid and parallel synthesis of the different building blocks as outlined below (Scheme 1).

Accordingly, we anticipated that millingtonine A (**1**) could be derived from diol **2** via a late-stage glycosidation employing trichloroacetimidate **3** followed by a final global deprotection. The corresponding glycosyl donor **3** could in turn be accessed in two steps from commercially available D-glucose pentaacetate **9**. The main heterocyclic core **2** would be obtained from racemic amine **4** and bromide **5** via a Hartwig–Buchwald coupling reaction. Finally, the main fragment **4** would be prepared from the tertiary alcohol **8** and enamine **7** through a Ueno–Stork cyclization.[4]

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(1) Hase, T.; Ohtani, K.; Kasai, R.; Yamasaki, K.; Picheansoonthon, C. *Phytochemistry* **1996**, *41*, 317–321.

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(3) Jetty, A.; Iyengar, D. S. *Pharmaceut. Biol.* **2000**, *38*, 157–160.

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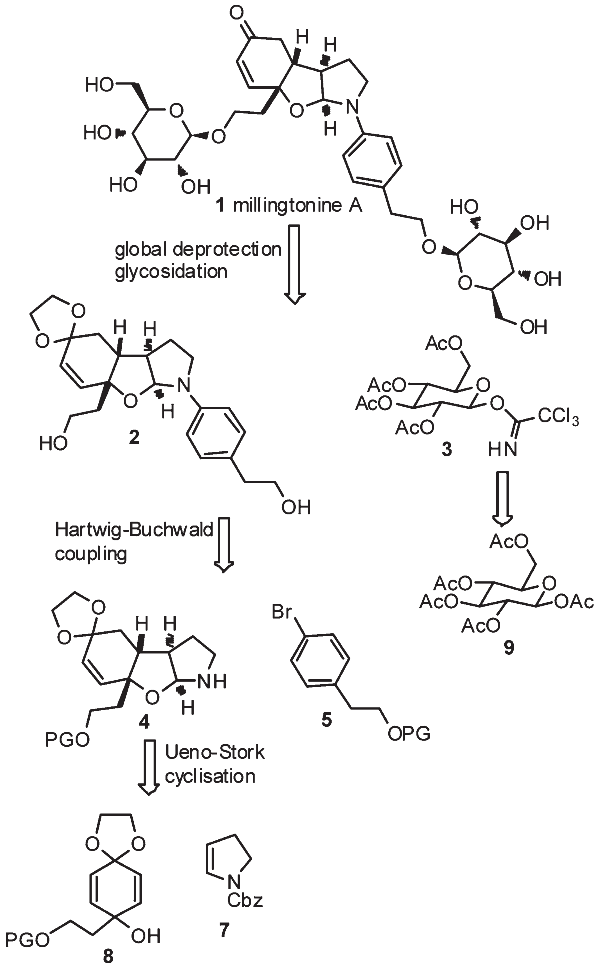
**Scheme 1.** Retrosynthetic Analysis

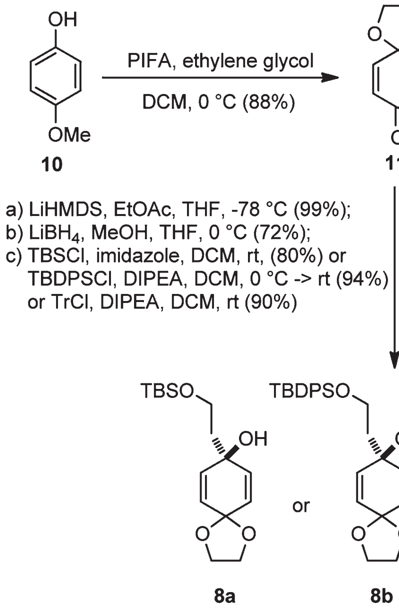


The preparation of protected diol **8** began from *p*-hydroxyanisol (**10**) employing a one-pot oxidation/protection protocol as described by Wong and co-workers[5] to afford ketoketal **11**. In a subsequent sequence, the freshly prepared ketone **11** was reacted with a preformed solution of ethyl acetate lithium enolate to form a $\beta$-hydroxy ester followed by lithium borohydride reduction and selective protection of the resulting primary alcohol. Three different protecting groups were selected to assess their influence on the stereochemical outcome of the Ueno–Stork cyclization, namely, the TBS ether **8a**, the TBDPS ether **8b**, and the trityl ether **8c** (Scheme 2).

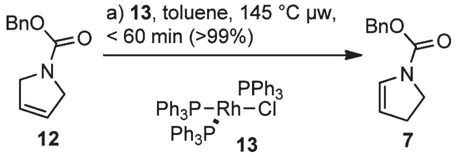
The second partner needed for the Ueno–Stork cyclization is enamine **7**, which can be readily obtained from commercial 1-Cbz-2,5-dihydro-1*H*-pyrrole (**12**) by isomerization (Scheme 3).

We found that the pyrrole **12** on treatment with Wilkinson's catalyst[6] (**13**) under microwave irradiation was easily isomerized to the conjugated molecule **7**. Interestingly, the use of microwave heating was found particularly beneficial in forming enamine **7** (60 min, 1.25 mol % catalyst). The corresponding classical reflux conditions using an oil bath gave only incomplete conversion even when much higher loadings of catalyst were used.

**Scheme 2.** Synthesis of Fragment **8**



**Scheme 3.** Synthesis of Pyrrole **7**



In the next stage of the synthesis, the fragments **8a**–**c** and **7** were coupled in a two-step procedure (Scheme 4). First, the enamine derivative **7** was brominated yielding a transient bromonium/iminium ion which was trapped in situ by the corresponding tertiary alcohol **8a**–**c**. Then the resultant intermediate bromide **14a**–**c** was further reacted without isolation via a tin hydride mediated radical cyclization to form an easily separable mixture of amines **15a**–**c** (mixture of *cis*/*trans* relative ring junctures). After intensive optimization studies, a yield of 86% over the two consecutive steps was achieved with a *cis*/*trans* ring ratio of 1:2.7. The structure elucidation of the two configurational isomers of **15** (*cis* and *trans*) was deteremined on the basis of detailed $^1$H NMR anaylsis and NOE experiments of the tricycle **15c**. In compound **15c**, multiple conclusive NOE couplings between H1′–H2′–H7–H2 in the *cis* product were observed, whereas only NOE contacts between

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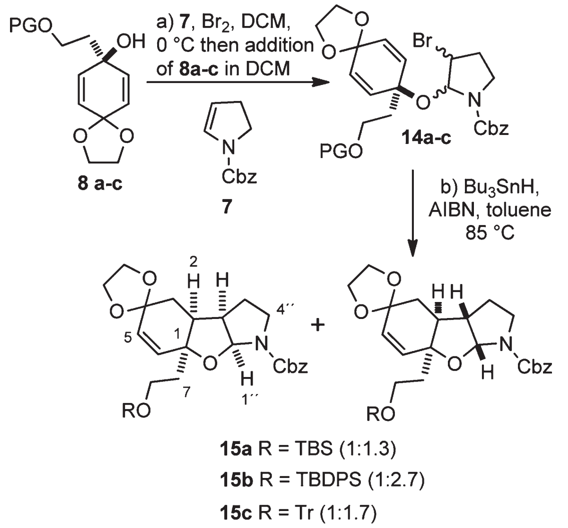
(4) (a) Ueno, Y.; Chino, K.; Wantanabe, M.; Moyira, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564–5566. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741–3742.

(5) Tran-Huu-Dau, M.-E.; Wartchow, R.; Winterfeldt, E.; Wong, Y.-S. *Chem.—Eur. J.* **2001**, *7*, 2349–2369.

(6) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711–1732.

H1′−H2′ and H2−H7 for the corresponding *trans* product were recorded.[7]

**Scheme 4.** Ueno−Stork Cyclization toward Amines **15a−c**



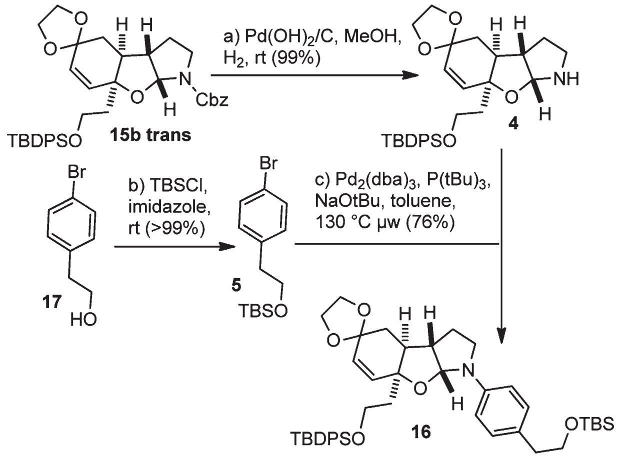
By inspection of the data (Scheme 4), a general stereochemical trend for the cyclization reaction can be identified, namely, that the larger the protecting group the higher the selectivity. Although due to cost they were not evaluated here potentially larger protecting groups such as −Si(TMS)$_3$ or −Si(TES)$_3$ could be investigated.

Following construction of the tricyclic ring system the Cbz-group was removed to obtain amine **4** which was then subjected to a Hartwig-Buchwald coupling reaction to form the silyl protected diol **16** (Scheme 5). For this process only the *trans* isomer **15b** was used consistent with the stereochemistry of the final natural product.

When palladium on charcoal was used as the reduction catalyst, this resulted in only loss of the dioxolane ring, while the Cbz-group remained intact. At elevated temperatures double bond reduction was also apparent. Consequently, we investigated the use of Pearlman's catalyst[8] (Pd(OH)$_2$/C), which gave the desired amine **4** in essentially quantitative yield at ambient temperature in only 60 min using a hydrogen pressure of less than 1 bar.

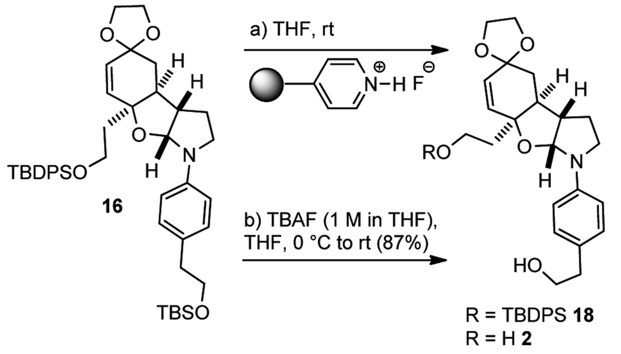
Although palladium-catalyzed allylation of amines is well-known, arylation of aminals has not been reported. Nevertheless, we found that aryl bromides with Pd$_2$(dba)$_3$, (*o*-biphenyl)P($t$-Bu)$_2$, and NaO-*t*-Bu[9] or other ligands such as P($t$-Bu)$_3$, (*rac*)-BINAP, P(otolyl)$_3$, and (*o*-biphenyl)-Pcy$_2$[10] proved effective for this transformation. However, the catalytic system which gave the best result was Pd$_2$-(dba)$_3$, P($t$Bu)$_3$ and NaO-*t*-Bu in toluene under microwave heating, which afforded a 76% yield of the protected diol **16**.

**Scheme 5.** Synthesis of Protected Aglycon **16**



In order to obtain the racemic aglycon **2**, both silyl protecting groups had to be removed. Initially a polymer supported HF.pyridine complex[11] was selected since HF·pyridine is known[12] to deprotect TBDPS-silyl ethers. However, in our case, only deprotection of the TBS-silyl ether occurred to yield **18** (Scheme 6). Thus, we resorted to the use of TBAF in THF to afford the bis-diol **2** ready for glycosidation.

**Scheme 6.** Silyl Deprotection toward Diol **2**



Glycosidation of diol **2** was first investigated with trichloracetimidate **3**, which in turn was obtained via a known literature procedure in two steps from pentaacetate **9**.[13]

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(7) See the Supporting Information for more details.

(8) (a) Carpes, M. J. S.; Cesar, P.; Miranda, M. L.; Correia, C. R. D. *Tetrahedron Lett.* **1997**, *38*, 1869–1872. (b) Takahata, H.; Kubota, M.; Ihara, K.; Okamoto, N.; Momose, T.; Azer, N.; Eldefrawi, A. T.; Eldefrawi, M. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3289–3301.

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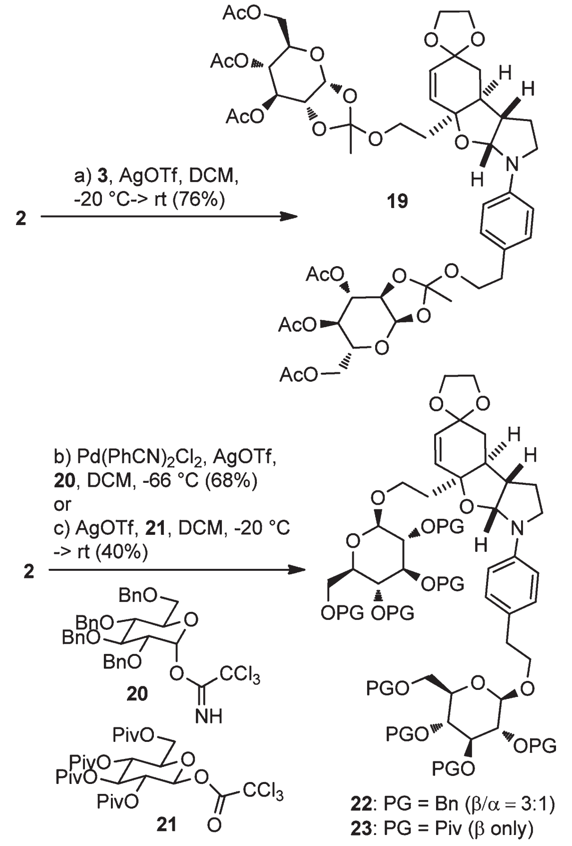
(10) (a) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451–8458. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416.

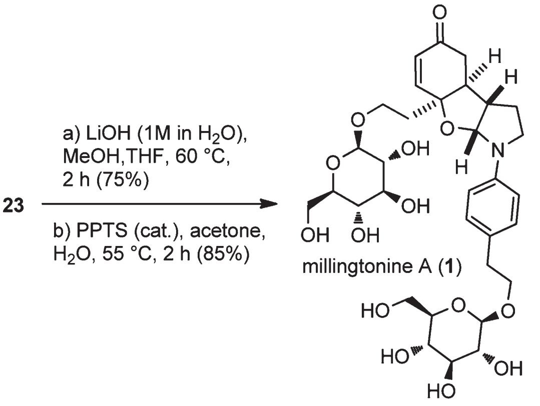
(11) (a) Gregorcic, A.; Zupan, M. *J. Fluorine Chem.* **1984**, *24*, 291–302. (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195.

(12) Takahashi, D.; Hirono, S.; Hayashi, C.; Igarashi, M.; Nishimura, Y.; Toshima, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 10096–10100.

**Scheme 7.** Glycosidation of Diol **2**



**Scheme 8.** Final Deprotection Steps toward Millingtonine A (**1**)



Unfortunately, attempted glycosidation using AgOTf as the activator[14] at −20 °C furnished only the bis-*ortho* ester **19** (Scheme 7). All successive attempts to rearrange this *ortho*-ester to the alternative di-$\beta$-glycoside were unsucessful. Many alternative methods for the glycosylation of diol **2** via the use of glycosyl sulfides, glycosyl sulfoxides, glycosyl bromides, and glycosyl trichloroacetimidates in each case with the pivaloyl, benzoate, or acetate protecting groups and various activators led to low yields and/or poor selectivity.

Finally, diglycosidation was achieved to give the benzyl- or pivaloyl-protected structure in reasonable yields and high $\beta/\alpha$ ratio (Scheme 7). Indeed, in the case of the pivaloyl-protected system the $\beta$-anomer was formed exclusively. Therefore, considering the high anomeric ratio and since we anticipated selective deprotection of the benzyl groups of compounds **22** could be problematic (due to the presence of the internal double bond), it was decided to attempt the synthesis with compound **23** (Scheme 8). First, the pivaloyl groups were removed by treatment with aqueous LiOH in THF/MeOH at 60 °C, and then cleavage of the dioxolane was conducted with PPTS in a mixture of acetone and water to finally afford millingtonine A (**1**). The spectral analysis of this material matched that of the previously isolated natural product.[7]

In conclusion, the route described constituted a longest linear synthesis of 12 steps giving millingtonine A (**1**) in 6.2% overall yield. Of particular note, although not discussed in this paper, was the considerable lability of the intermediate structures which were exceedingly prone to rearrangement at each stage of the synthetic scheme. Consequently realization of this total synthesis is a considerable synthetic achievement. The analysis of the accompanying rearrangements and the elucidation of the resulting chemical architectures will be discussed in detail at a later date.

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**Supporting Information Available.** Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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