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# **Total Synthesis of Millingtonine**

Patrick D. Brown, and Andrew L. Lawrence\*

**Abstract:** Millingtonine is a glycosidic alkaloid that exists as a pair of pseudo-enantiomeric diastereomers. Consideration of the likely biosynthetic origins of this unusual natural product has resulted in the development of a seven-step total synthesis. Results from this synthetic work provide evidence in support of a proposed network of biosynthetic pathways that can account for the formation of several phenylethanoid natural products.

In 1996 Yamasaki and co-workers isolated the alkaloid millingtonine (1) from Millingtonia hortensis, an ornamental Bignonia plant more commonly known as the Indian Cork Tree.<sup>[1]</sup> Millingtonine (1) was isolated as a mixture of two diastereomeric alkaloids, which contain a molecular framework not previously known to exist in the natural world. Conceptually, but not biosynthetically (vide infra), millingtonine (1) can be considered to consist of a racemic aglycone core that is 'resolved' into two pseudo-enantiomeric diastereomers by the attachment of a pair of  $\beta$ -D-glucopyranosyl units. Biosynthetically, millingtonine (1) is likely constructed from two shikimate-derived C<sub>6</sub>C<sub>2</sub> units, linked together by an ornithine-derived C<sub>4</sub>N unit (Scheme 1). No biosynthetic pathway towards millingtonine (1) has been proposed and, as commented upon by the isolation team, "the mechanism of insertion of this (C<sub>4</sub>N) unit between the two  $C_6C_2$ units is unknown".<sup>[1]</sup>

There has been one previous total synthesis of millingtonine (1), reported in 2012 by the research groups of Ley, Kirschning and Baxendale.<sup>[2]</sup> The execution of a total synthesis of this alkaloid is an impressive achievement, with the intermediate structures en-route to millingtonine (1) reported to be *"exceedingly prone"* to rearrangement reactions. In total, the Ley-Kirschning-Baxendale synthesis required twelve linear steps from commercially available materials (sixteen steps in total) and produced milligram quantities of material. We were hopeful that if we could gain new insight into how nature synthesizes millingtonine (1) we might be able to develop a new, more step-economical, synthetic strategy.

Our previous biomimetic studies on other phenylethanoid natural products provided some important clues as to the potential origins of millingtonine (1).<sup>[3]</sup> We considered that a phenylethanoid glycoside **2**, which contains an ornithine-derived *N*-linked putrescine unit, might represent a reasonable biosynthetic precursor. Our biosynthetic proposal, which is shown in Scheme 2, involves a network of pathways that can

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account for the formation of several structurally distinct natural products isolated from Bignoniaceae plants: cornoside (3),<sup>[4]</sup> rengyolone (4),<sup>[5]</sup> incarviditone (5),<sup>[6]</sup> incarvilleatone (6),<sup>[7]</sup> incargranine B (7),<sup>[8]</sup> and millingtonine (1).<sup>[1]</sup>



**Scheme 1.** Structure and retro-biosynthetic analysis of millingtonine (1). Glc = D-glucopyranosyl.

In our proposal, diamine 2 can undergo an oxidative dearomatization to form imine 8 (Scheme 2; Pathway 1), which following hydrolysis would give the known para-quinol natural product cornoside (3). It has been shown that cleavage of the glycosidic bond in cornoside (3) results in concomitant oxa-Michael cyclisation to give the racemic natural product rengyolone (4).<sup>[9]</sup> We previously investigated a biomimetic domino-Michael dimerization of rengyolone (4) to access incarviditone (5),[3a] a racemic homochiral dimer. From our synthetic studies we were able to reassign the relative stereochemistry of incarviditone (5) and isolate an unexpected racemic heterochiral dimer, which was subsequently reported as a natural product named incarvilleatone (6).<sup>[7]</sup> An alternative biosynthetic pathway from diamine 2 (Scheme 2; Pathway 2) involves oxidative deamination to give amino-aldehyde 9, which would be expected to undergo intramolecular condensation to give enamine 10. We predicted enamine 10 would then undergo rapid dimerization with its corresponding iminium ion 11, which formed the basis of our previous structural reassignment and biomimetic synthesis of incargarnine B (7).[3b]



Scheme 2. Proposed network of biosynthetic pathways towards a family of plant-derived phenylethanoid natural products, including millingtonine (1). Glc = D-glucopyranosyl.

With these two divergent biosynthetic pathways in mind we recognized the possibility that the two pathways could reconverge to give millingtonine (1) (Scheme 2; Pathway 3). Thus, a Michael reaction between enamine 10 and cornoside (3) would give an intermediate iminium ion 12, which would rapidly ringclose through an *oxa*-Mannich reaction to give millingtonine (1). Therefore, in our proposed biogenesis, the two diastereomers of millingtonine (1) are the result of a lack of stereochemical influence exerted by the sugars of enamine 10 and cornoside (3) in a crossed-dimerization, rather than a late-stage glucosidation of a racemic aglycone.

In our previous work (Scheme 3),[3b] the incargranine B framework (13) was accessed through a biomimetic domino Mannich/SEAr (electrophilic aromatic substitution) reaction sequence, initiated by acidic-deprotection of acetal-protected amino-aldehyde 14.<sup>[10]</sup> It was envisaged that having para-quinol 15<sup>[11]</sup> present under these acidic deprotection conditions would allow for a biomimetic crossed-dimerization to occur to give the millingtonine framework. However, after extensive experimentation, screening various acidic reaction conditions, no crossed-dimerizations could be achieved. Only formation of the incargranine B and dia-incargranine B aglycone structures (13 & 16) was observed. It was concluded that the domino Mannich/SEAr reaction sequences, en-route to the incargranine B frameworks, are too fast for crossed-dimerization to compete. We considered, however, that a window of opportunity for crossed-dimerization might exist if an N-aryl enamine (akin to **17**) could be accessed whilst avoiding formation of the highly electrophilic *N*-aryl iminium species (akin to **18**).



**Scheme 3.** Previously reported biomimetic synthesis of the incargranine B aglycone **13**.<sup>(3b)</sup> TBS = *tert*-butyldimethylsilyl.



Scheme 4. Biomimetic total synthesis of millingtonine (1). Boc = *tert*-butyloxycarbonyl, TMSOTf = trimethylsilyl trifluoromethanesulfonate, Glc = D-glucopyranosyl, Piv = pivaloyl, TFA = trifluoroacetic acid.

Many strategies were investigated before we settled upon an alkene isomerization approach, using transition-metal hydride catalysis.<sup>[12]</sup> Thus, commercially available 4-aminophenethyl alcohol 19 was protected as an acid-labile tert-butoxycarbamate before a B-selective glucosidation was achieved, using the pivalovI-protected trichloroacetimidate 20 (Scheme 4).<sup>[13]</sup> Under the acidic glucosidation reaction conditions deprotection of aniline 21 occurred in situ to give the pivaloyl-protected glucoside 22 in 53-55% yield over the two steps. Condensation of aniline 22 with (Z)-1,4-dichlorobut-2-ene then gave N-aryl-2,5dihydropyrrole 23 in 50-52% yield.<sup>[14]</sup> It was found that the commercially available RhHCO(PPh<sub>3</sub>)<sub>4</sub> was a competent catalyst for the isomerization of skipped enamine 23 into the conjugated enamine 24.<sup>[15]</sup> All efforts to purify and isolate enamine 24, however, were met with failure. Therefore, the search for suitable reaction conditions for cross-dimerization of enamine 24 with para-quinol 25, which was prepared in 4 steps from tyrosol,[16] were pursued using freshly prepared solutions of enamine 24. Pyrrolidine was investigated, in the hope of establishing an iminium-organocatalytic cycle,<sup>[17]</sup> and gratifyingly led to crossed-dimerization for the first time, albeit in very low yield. Control experiments, however, revealed that the beneficial effect of adding pyrrolidine was down to the unexpected formation of an aminal intermediate 26.[15] Furthermore, inclusion of pyrrolidine at the beginning of the rhodium-hydride-catalyzed isomerization reaction was found to result in quantitative

conversion of alkene 23 to aminal 26.[18] Pivaloyl-protected cornoside 25 was then added to this freshly prepared solution resulting in the formation of a 1:1 diastereomeric mixture of crossed-dimers 27 in 50% isolated vield. Formation of the cis.svn.cis-isomers 27 was an unexpected and presumably kinetically controlled outcome, as we anticipated the desired cis,anti,cis ring system would be thermodynamically more favorable. Our kinetic versus thermodynamic reasoning was shown to be sound, as exposure of the cis.svn.cis-isomers 27 to acidic conditions resulted in isomerization to the desired cis,anti,cis-isomers 28 in 56-73% yield (Scheme 4). Presumably this isomerization occurs via an acid-catalyzed retro-oxa-Mannich/iminium-epimerization/oxa-Mannich reaction sequence. Finally, removal of the pivaloyl groups under basic conditions gave over 50 mg of millingtonine (1) in 67% yield. Thus we had successfully synthesized millingtonine (1) in a longest linear sequence of seven steps from commercially available materials (ten steps in total), which compares favorably to the previous state-of-the-art.[2]



Scheme 5. a, Mechanistic speculation for our successful crossed-dimerization. b, Plausible biosynthetic pathway towards dia-millingtonine (33) involving vitamin B6 (*i.e.*, pyridoxal phosphate) as a co-enzyme. Glc = D-glucopyranosyl.

The successful crossed-dimerization of aminal 26 with paraquinol 25 (Scheme 4) stands in stark contrast to the exclusive homo-dimerization observed when using acetal 14 (Scheme 3). Our failure to cross-dimerize acetal 14 was attributed to the formation of a highly reactive N-aryl iminium species 18, which leads to very fast and essentially irreversible domino Mannich/S<sub>E</sub>Ar reaction sequences (Scheme 3). In our successful crossed-dimerization, however, we still isolate an 14% yield of homo-dimers (29 and 30) (Scheme 4), indicating that an N-aryl iminium ion must still be formed under these reaction conditions. How then can crossed-dimerization compete? One possible explanation is that it is more favourable for the endocyclic C-N bond of aminal 26 to cleave, in preference to the exocyclic C-N bond, to give the acyclic iminium ion 31 (Scheme 5a). Therefore, the problematic N-aryl iminium species is present at lower concentration and can also be rapidly trapped by the pyrrolidine. Thus enamine 32, which would also be expected to be more nucleophilic than the N-aryl enamine 24, has a sufficient window of opportunity to react with para-quinol 25 (Scheme 5a). It is interesting to consider whether this might, therefore, be indicative of a similar mechanism operating within the plant. Might pyrrolidine be mimicking the coenzyme-role of vitamin B6 (i.e., pyridoxal phosphate) in an interrupted oxidativedeamination reaction of diamine 2 (Scheme 5b)?[19]

In summary, through synthesis alone we have been able to probe the feasibility of our proposed biogenesis of millingtonine (1). We have been able to obtain evidence in support of a unified

network of biosynthetic pathways that can account for the formation of a family of phenylethanoid natural products. Crucially, these new biosynthetic insights have enabled the development of a highly step-economical total synthesis of millingtonine (1). Central to the development of this successful synthesis was the use of transition-metal hydride catalysis to access an otherwise unstable biomimetic intermediate, an approach we envisage will prove applicable to other biomimetic studies. The future isolation of the *cis*,*syn*,*cis*-isomer of millingtonine, namely dia-millingtonine (33), from the natural environment would represent a new case of 'natural product anticipation' – an essentially unique benefit of following biomimetic strategies in synthesis.<sup>[20]</sup>

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