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A Combined Tamaru Allylation/Olefin Cross-Metathesis Approach for the Total Syntheses of (±)-Paniculidine B, (±)-Paniculidine C, and 2-Methylcarbazole

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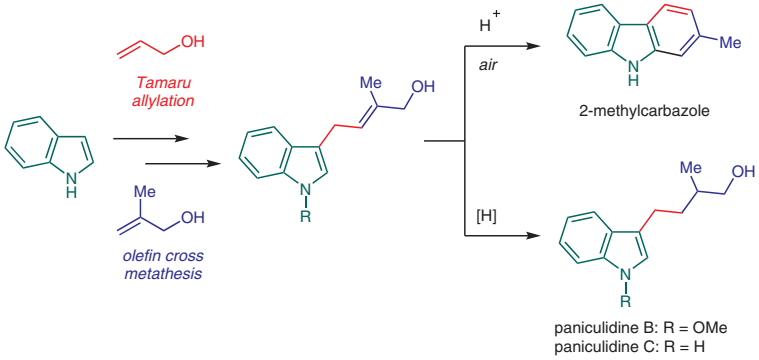

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Abstract A concise approach to the total syntheses of racemic paniculidines B and C is described. The route features a combined Tamaru allylation/olefin cross-metathesis sequence for the regiocontrolled synthesis of prenylindole intermediates. In addition, we report a transformation of the prenylated indole into 2-methylcarbazole catalyzed by sulfonic acid-functionalized silica gel.

Key words prenylindoles, Tamaru allylation, cross-metathesis, carbazoles, total synthesis, alkaloids

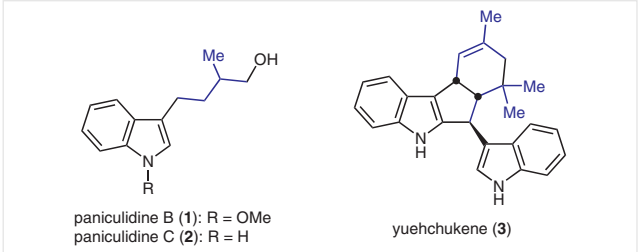

Figure 1 Prenylindole-type alkaloids from *Murraya paniculata*

Murraya paniculata (Linn.) Jack, commonly known as orange jessamine, is an evergreen shrub found widely throughout tropical and subtropical Asia. Folk-medicine practitioners have long exploited various parts of this plant as therapeutic agents. The reported pharmacological effects, such as antidiarrheal, antinociceptive, and antiinflammatory activities imply considerable biomedical potential for chemical constituents of *M. paniculata*.[1] The search for bioactive substances in this plant has led to the identification of some alkaloids featuring a biogenetically uncommon 3-prenylindole motif. These alkaloids, among many others, include paniculidine B (**1**),[2] paniculidine C (**2**),[3] and yuehchukene (**3**)[4] (Figure 1). From a chemotaxonomic standpoint, Kinoshita and co-workers have suggested that **1** and **2** are biosynthetically related to the apparent dimeric alkaloid **3**.[5] Intriguingly, Chakraborty suggested that 3-prenylated indoles might be biosynthetic precursors for naturally occurring 2-methylcarbazole derivatives.[6]

The unique structural features and possible roles in the biosynthesis of carbazole alkaloids have stimulated several laboratories to conceive synthetic strategies for the synthesis of prenylindoles. In 1985, Somei and Ohnishi achieved the first total synthesis of racemic paniculidine B (**1**) in seven steps; the route involves the use of a modified Heck reaction[7] for the introduction of an oxoalkyl side chain onto the *N*-methoxyindole framework.[8] On the other hand, the Kinoshita group described the first total synthesis of paniculidine C (**2**) via a Japp–Klingemann reaction, followed by a Fisher indolization.[9] Selvakumar and Rajulu disclosed an eight-step synthesis of racemic **1** employing a novel conversion of an *ortho*-substituted nitroarene into a highly functionalized *N*-methoxyindole; they also completed the synthesis of paniculidine C (**2**) through a facile hydrogenolysis of the N–OMe bond of **1**.[10] Significantly, Moissenkov and co-workers accomplished the first asymmetric synthesis of paniculidine C (**2**) based on a chiron approach.[11] Nevertheless, new routes featuring the employment of catalytic, operationally simple transformations are still highly desirable.

Nature conducts selective normal or reverse prenylation of indoles with an array of prenyltransferases under remarkably mild conditions.[12] From a synthetic perspective, the selective incorporation of a prenyl or *tert*-prenyl group into one position of indole raises issues of chemoselectivity and regioselectivity.[13] Despite these challenges, a few efficacious reaction systems for the C3-prenylation of indoles

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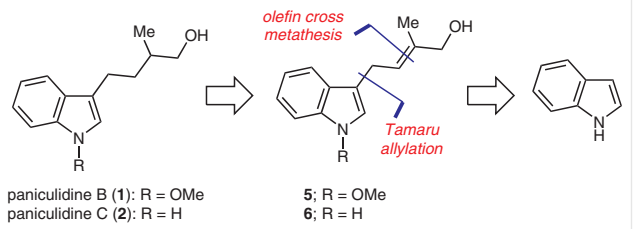
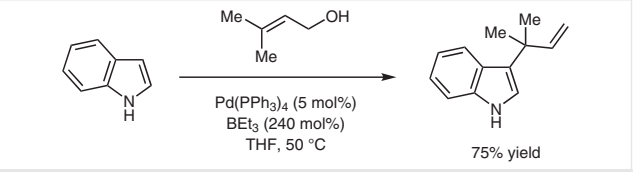
have been disclosed.[14] In our quest for syntheses of prenylated alkaloids, we sought to develop a formal C3-prenylation of indole involving sequential catalytic Tamaru allylation and olefin cross-metathesis (Scheme 1).[15] Here, we report a concise total syntheses of (±)-paniculidines B (**1**) and C (**2**), and we present an unexpected synthesis of 2-methylcarbazole (**4**) from the common 3-prenylindole intermediate **6**.



Scheme 1 Retrosynthetic analysis of **1** and **2**

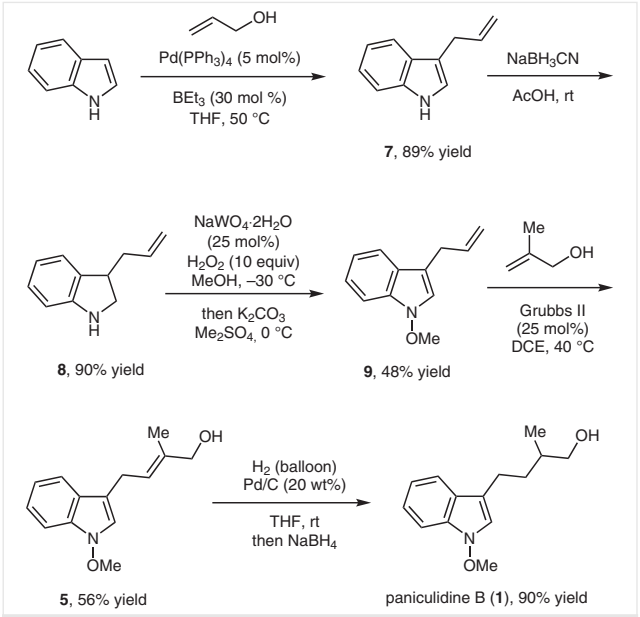
Our synthesis commenced with a palladium-catalyzed Tamaru allylation[16] to give the known 3-allylindole (**7**) in 89% yield (Scheme 2). Reduction of **7** with sodium cyanoborohydride in acetic acid furnished the corresponding indoline **8**. By applying a modified Somei oxidation,[17] we were able to convert compound **8** into 3-allyl-1-methoxyindole (**9**) in moderate yield without affecting the alkene moiety. To our delight, the terminal alkene groups of **9** and 2-methylprop-2-en-1-ol underwent a cross-metathesis reaction in the presence of the Grubbs second-generation catalyst (Grubbs II)[18] to give enol **5** containing a hydroxyprenyl fragment. In this case, the use of the Grubbs first-generation catalyst under various conditions delivered the desired product **5** in low yields (<10%).



Equation 1 C3-tert-prenylation of indole

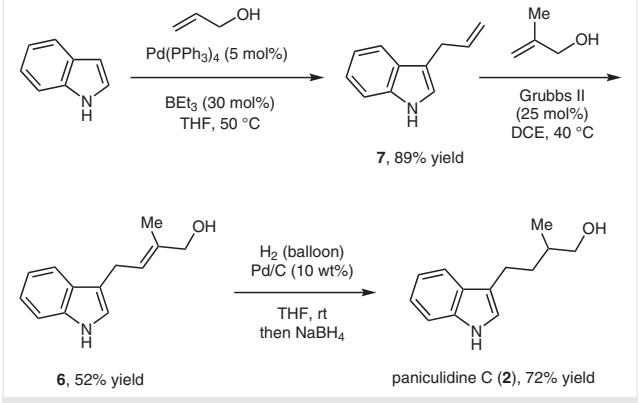
Note that Tamaru and co-workers have shown that the reaction of indole with 3-methylbut-2-en-1-ol (prenyl alcohol) resulted in the exclusive generation of C3-*tert*-prenylated indole in good yield (Equation 1).[16] Therefore, our designed normal-prenylation sequence, which conveniently facilitates completely regioselective installation of a prenyl group at the C3 position of indoles, is complementary to Tamaru's method.

Our initial attempts to execute selective hydrogenation of the trisubstituted alkene **5** encountered difficulties due to the labile nature of the N–OMe bond under reductive conditions. After much experimentation, we found that a judicious selection of solvent was critical in realizing the desired reduction in a chemoselective manner. By treating compound **5** in THF[19] with Pd/C under a hydrogen atmosphere (balloon) and then with sodium borohydride, paniculidine B (**1**) was successfully obtained in 90% yield.[20] The spectral data (IR, ^{1}H and ^{13}C NMR, and mass spectra) of the synthetic compound **1** were in good agreement with those of the natural product, as reported in the literature.[2]



Scheme 2 Total synthesis of (±)-paniculidine B (**1**)

Borrowing from our experiences in the synthesis of **1**, we also completed a short synthesis of paniculidine C (**2**) in racemic form by taking advantage of the two-step formal prenylation sequence (Scheme 3). Our synthetic material **2** proved identical to the naturally occurring compound, based on spectral comparisons (IR, ^{1}H NMR, and mass spectra).[3]



Scheme 3 Total synthesis of (±)-paniculidine C (**3**)

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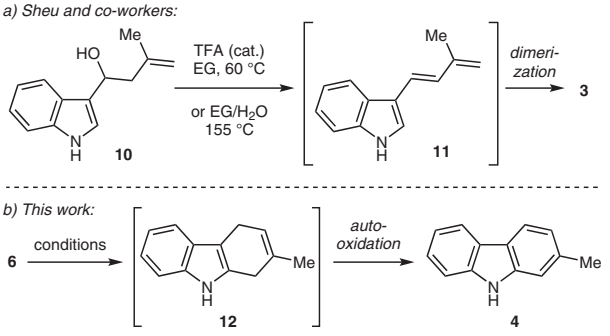
Several research groups have reported racemic syntheses of yuehchukene (**3**) through the biomimetic dimerization of 3-isoprenylindole (**11**) or its synthetic equivalents (e.g., **10**) under acidic or neutral conditions.[21] Inspired by Sheu's studies ,[22] we surmised that allylic alcohol **6** might be first converted into diene **11** through an E1-type elimination and this would then undergo dimerization to give **3**. In the event, the trifluoroacetic acid-catalyzed reaction of **6** did not proceed to any noticeable extent (Table 1, entry 1).[23] The conversion of **6** in ethylene glycol (EG)–water failed to give **3**, but instead furnished 2-methylcarbazole (**4**)[24] as the sole identifiable product in 7% yield (entry 2).[25] The unexpected formation of the carbazole nucleus illustrates the distinctive reactivity of the allyl alcohol **6** compared with the analogous homoallyl alcohol **10** under thermal conditions. This intriguing finding prompted us to examine a few more variations in the reaction parameters. The use of triflic acid in acetonitrile resulted in the formation of a complex mixture (entry 3).[26] With the application of sulfonic acid functionalized silica gel (HO-SAS) as a heterogeneous Brønsted acid catalyst,[27] compound **4** was also generated (entry 4), and we observed that the reaction conducted in polar protic solvent at an elevated temperature was relatively more efficient (entries 4–6).[28] A plausible mechanism that might account for the formation of **4** entails an initial Friedel–Crafts-type spirocyclization and a subsequent 1,2-alkyl migration, followed by an autooxidative aromatization.[29] From a biosynthetic perspective, our preliminary results provide an intriguing piece of experimental evidence supporting the view that 2-methylcarbazole-based alkaloids might be formed from 3-prenylated indoles.[30]

In summary, we accomplished concise total syntheses of (±)-paniculidines B (**1**) and C (**2**) from indole in 19.4% and 33.3% overall yield, respectively. Although the individual catalytic protocols are well established, our indirect C3-prenylation sequence of indole is the first to showcase the use of a combined Tamaru allylation/olefin cross-metathesis process. Whereas the attempts to convert **6** into yuehchukene (**3**) were unfruitful, we discovered an unprecedented route to 2-methylcarbazole (**4**), albeit with modest efficiency. This experiment suggests a possible biosynthetic link between 3-prenylated indoles and 2-methylcarbazole alkaloids.

Table 1 Sheu's Synthesis of Yuehchukene (**3**) by a Dehydrative Dimerization of **10**, and the Conversion of **6** into 2-Methylcarbazole (**4**)



Entry	Conditions	Yield[a] (%) of **4**
1	TFA (20 mol%), EG, 60 °C, 72 h (N_2)	NR[b]
2	EG/H_2O (v/v = 20/1), 155 °C, 72 h (air)	7[c]
3	triflic acid (10 mol%), MeCN, 0 °C, 0.5 h (air)	–[d]
4	HO-SAS (10 mol%), EG, 155 °C, 3 h (air)	13[c]
5	HO-SAS (10 mol%), *p*-xylene, 145 °C, 10 h (air)	4[c]
6	HO-SAS (10 mol%), DMF, 155 °C, 72 h (air)	4[e]

[a] Isolated yield.
[b] No reaction (^{1}H NMR analysis).
[c] Compound **6** was fully consumed; the remaining mass balance consisted of intractable material.
[d] Complex mixture.
[e] Compound **6** was partially consumed.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591739.

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(20) **Paniculidine B (1)**
A mixture of compound **5** (46 mg, 0.2 mmol) and 20 mass% Pd/C (9 mg) was stirred in THF (4 mL) under H_2 (balloon) at r.t. for 6 h. The mixture was filtered through a short pad of Celite, which was washed with THF (2 × 5 mL). To the stirred filtrate was added $NaBH_4$ (8 mg, 0.2 mmol) at r.t. After 3 h, the reaction was quenched with sat. aq NH_4Cl (10 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography [silica gel, MeOH–CH_2Cl_2 (1:80)] to give a colorless oil; yield: 42 mg (90%). Note: $NaBH_4$ was added in this step to reduce a minor amount of aldehyde in the crude mixture, presumably generated via alkene isomerization of **5** under the hydrogenation conditions.
IR ($CHCl_3$): 3688, 1603, 1460 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (ddd, *J* = 7.9, 1.0, 1.0 Hz, 1 H), 7.41 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 1 H), 7.24 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1 H), 7.11 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1 H), 7.06 (d, *J* = 1.0 Hz, 1 H), 4.05 (s, 3 H), 3.57 (dd, *J* = 10.4, 5.8 Hz, 1 H), 3.50 (dd, *J* = 10.0, 6.3 Hz, 1 H), 2.82 (dddd, *J* = 14.7, 10.0, 5.6, 1.0 Hz, 1 H), 2.72 (dddd, *J* = 14.7, 9.8, 6.3, 0.9 Hz, 1 H), 1.91–1.83 (m, 1 H), 1.79–1.70 (m, 1 H), 1.53 (dddd, *J* = 13.4, 9.8, 8.0, 5.6 Hz, 1 H), 1.40 (br s, 1 H), 1.03 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.79, 123.96, 122.31, 120.43, 119.37, 119.13, 112.96, 108.32, 68.21, 65.44, 35.50, 33.41, 22.43, 16.53. HRMS (EI): *m/z* [M^+] calcd for $C_{14}H_{19}NO_2$: 233.1416; found: 233.1410.
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