

Combined Metalation–Cross Coupling Strategies: A Synthesis of Schumanniphytine by a Key Biaryl *O*-Carbamate Remote Anionic Fries Rearrangement

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Dedicated to the memory of Makoto Kumada^[‡]

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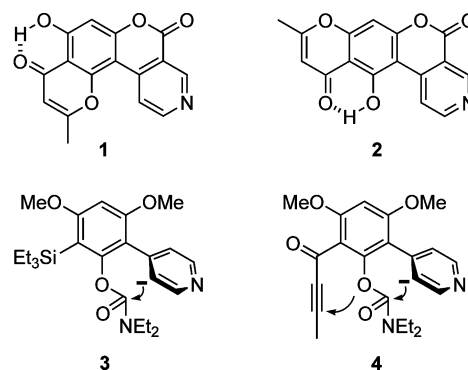
A short synthesis of the alkaloid schumanniphytine (**1**) starting from simple building blocks and involving directed *ortho* metalation (DoM), Suzuki–Miyaura cross coupling, and a key *ortho*-silicon-induced *O*-carbamate remote anionic Fries rearrangement (**3**) is described.

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Introduction

We disclose a synthesis of schumanniphytine (**1**), a representative of a minor class of alkaloids isolated^[1] from the root bark of *Schumanniphyton problematicum*, which shows central and autonomic system depressant properties and may have potential antiviral activity.^[2] Schumanniphytine co-occurs with isoschumanniphytine (**2**), into which it may be converted by base-catalyzed scission and reassembly of the pyrone ring.^[3] In spite of the rare tetracyclic pyranobenzopyranopyridine framework,^[4] schumanniphytine has elicited only a single total synthesis, reported by Kelly, which features a Stille cross-coupling reaction of a 4-stannylated nicotinate ester with an easily procurable 8-bromochromone.^[5]

Herein we describe a route that takes advantage of the directed *ortho* metalation (DoM)–Suzuki–Miyaura cross-coupling strategy^[6] and incorporates a key *ortho*-silicon-directed *O*-carbamate remote anionic Fries rearrangement (**3**) for construction of the lactone ring. Whereas a route towards schumanniphytine through an anionic remote Fries–Michael addition sequence (**4**) – a rational extension of concept **3**^[7] – proved unapproachable,^[8] initial model



studies^[9] confirmed correctness of concept and resulted in the development of new general and regioselective synthetic methodologies for 4*H*-1-benzopyran-4-ones (chromones), which is the subject of a separate communication.^[10]

Results and Discussion

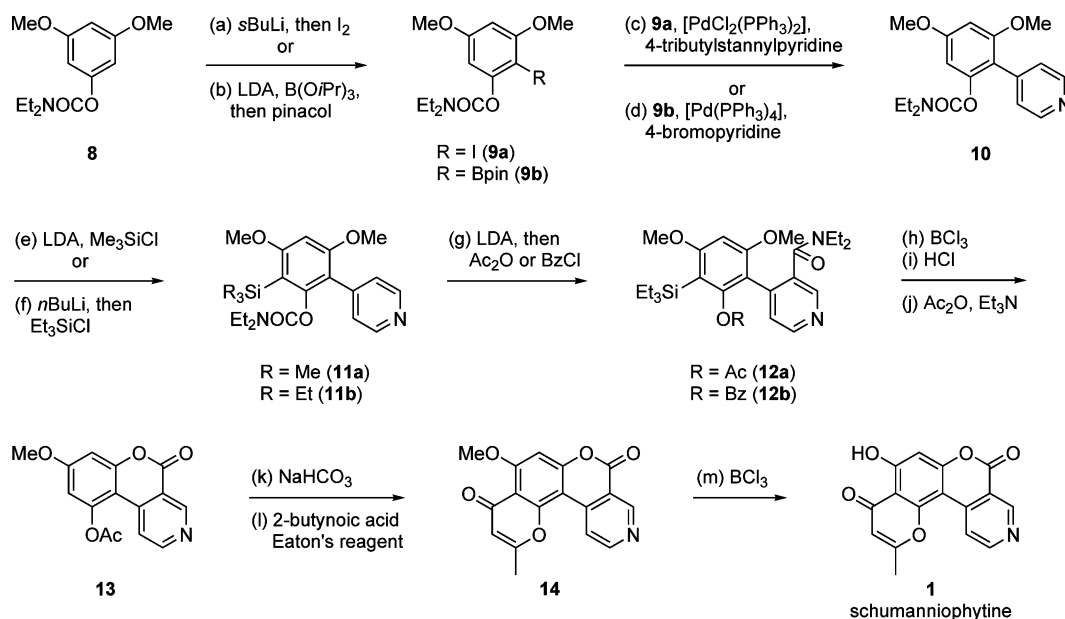
The synthesis of schumanniphytine was initiated (Scheme 1) by metalation of symmetrical *O*-carbamate **8**, whose regioselectivity takes advantage of the powerful carbamate-directed metalation group (DMG)^[11] to give, after iodination and boronation, intermediates **9a** and **9b**, respectively, in excellent yields. Stille cross coupling of **9a** with 4-tributylstannylpyridine^[12] or, more efficiently, Suzuki–Miyaura coupling of **9b** with commercial 4-bromopyridine hydrochloride led to azabiaryl **10**. The expected, regioselective second DoM reaction was followed by silylation with TMSCl and TESCl to afford highly hindered derivatives **11a** and **11b**, respectively.^[13] With silicon protection in

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[‡] Deceased: June 28, 2007. Like the sunrise, his work awakened the important theme of transition-metal-catalyzed cross coupling, which has momentarily enriched synthetic organic chemistry.

Supporting information for this article is available on the WWW under <http://www.eurjoc.org/> or from the author.



Scheme 1. Synthesis of schumanniphytine **1**. Reagents and conditions: (a) *s*BuLi (1.3 equiv.), TMEDA (1.3 equiv.), THF, -78°C , 10 min, then I_2 (1.5 equiv.), 86%; (b) LDA (1.2 equiv.), B(O*i*Pr)₃ (2.5 equiv.), THF, -78°C , 1 h, $\rightarrow 0^{\circ}\text{C}$, then 1 M HCl, pinacol (1.1 equiv.), 97%; (c) **9a**, [PdCl₂(PPh₃)₂] (0.1 equiv.), 4-tributylstannylpyridine (1.5 equiv.), DMF, 160°C , 1 h, 73%; (d) **9b**, [Pd(PPh₃)₄] (0.04 equiv.), 4-bromopyridine·HCl (1 equiv.), Na₂CO₃ (4 equiv.), DME/H₂O (2:1), 20 h, 99%; (e) LDA (3.5 equiv.), Me₃SiCl (4.5 equiv.), THF, $-78^{\circ}\text{C} \rightarrow \text{room temp.}$, 10 h, 94%; (f) *n*BuLi (1.2 equiv.), THF, -100°C , 5 min, then Et₃SiCl (2.5 equiv.), -100°C , 1.5 h, 91%; (g) LDA (4 equiv.), THF, $0^{\circ}\text{C} \rightarrow \text{room temp.}$, 1 h, then Ac₂O or BzCl (5 equiv.), $0^{\circ}\text{C} \rightarrow \text{room temp.}$, **12a** 75%, **12b** 65%; (h) BCl₃ (5 equiv.), CH₂Cl₂, 0°C , 30 min; (i) HCl (80 equiv.), EtOH/H₂O (1:1), 90°C , 12 h; (j) Ac₂O (5 equiv.), NEt₃ (5 equiv.), CH₂Cl₂, $0^{\circ}\text{C} \rightarrow \text{room temp.}$, 1 h, 84% for the three steps; (k) NaHCO₃ (10 equiv.), MeOH/H₂O (1:1), room temp., 4 h; (l) 2-butynoic acid (2 equiv.), P₂O₅/MsOH (1:10, 5 mL per mmol), 80°C , 12 h, 52% for the two steps; (m) BCl₃ (4 equiv.), CH₂Cl₂, 0°C , 30 min, 96%. Ac = acetyl, Bn = benzyl, DME = 1,2-dimethoxyethane, DMF = *N,N*-dimethylformamide, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

place, remote anionic Fries rearrangement of TES derivative **11b** resulted in smooth pyridine-ring carbamoyl translocation, to furnish, after direct acetylation and benzylation, aryl nicotinamides **12a** and **12b**, respectively.^[14] Although TMS derivative **11a** also underwent clean rearrangement to give the corresponding phenol in 80–90% yield, this product underwent rapid decomposition, which thus precluded its further synthetic use.^[15] In order to avoid alternative regiochemical lactonization of **12a** under acidic conditions,^[16] **12b** was subjected to treatment with BCl₃, which resulted in regioselective demethylation,^[17] to give, after acidic protodesilylation, debenzoylation, and reacylation (for convenient isolation), lactone **13** in high overall yield.

After numerous unsuccessful attempts to effect pyrone ring annulation,^[18] liberation of the free phenol from **13** by using sodium hydrogen carbonate followed by adaptation of the versatile Eaton's reagent (P₂O₅/MsOH, 1:10)^[19] gave the desired tetracycle **14**. To conclude, demethylation proceeded efficiently under BCl₃ conditions^[17] to furnish schumanniphytine (**1**), whose physical and spectroscopic properties were found to be in full accord with those of the natural product^[1,2a,3,5] (see Supporting Information).

Conclusions

A synthesis of schumanniphytine (**1**) involving a key *ortho*-silicon-induced remote anionic Fries rearrangement was

completed in 10 steps and 24% overall yield (optimum sequence, Scheme 1). The synthesis compares favorably with that described by Kelly^[5] (six steps and 5% overall yield). In view of the connections to DoM^[11] and cross-coupling strategies,^[6] the route provides opportunity for incorporation of functionality in the aromatic, pyridyl, and pyranil moieties for potential SAR profiling studies. This and related contributions from our^[20] and other laboratories^[21] further demonstrate the increasing value of carbanionic chemistry for the regioselective construction of aromatics and heteroaromatics.

Supporting Information (see footnote on the first page of this article): Full procedures and spectroscopic data for all compounds, React-IR diagram of DreM for **11b**.

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- [12] Handling and purification of this material proved difficult and was an unpleasant odiferous experience.
- [13] The hindrance is corroborated by the need to use –100 °C temperatures for the TESCl reaction owing to its slower reactivity over TMSCl, which thus allowed the faster (intramolecular) anionic *ortho*-Fries rearrangement to occur, see ref.^[8]
- [14] The migration was conveniently followed by React IR by observing the disappearance of the carbamoyl group ($\tilde{\nu}$ =1725 cm^{–1}) and the appearance of the amide carbonyl group stretching frequencies ($\tilde{\nu}$ =1635 cm^{–1}); the latter was only observed upon aqueous quench, which suggests the potential for trapping of the tetrahedral intermediate (see Supporting Information).
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