DOI: 10.1002/ejoc.200701116

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

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Dedicated to the memory of Makoto Kumada[‡]

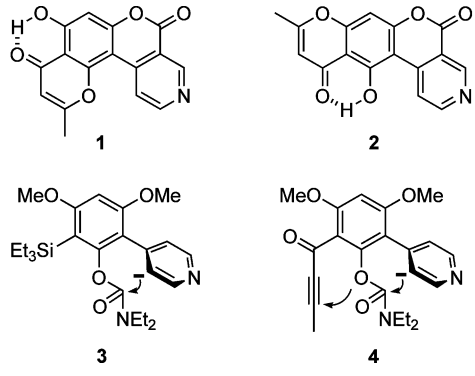
Keywords: Total synthesis / Metalation / Directed remote metalation / C–C coupling

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

Introduction

We disclose a synthesis of schumanniophytine (**1**), a representative of a minor class of alkaloids isolated[1] from the root bark of *Schumanniophyton problematicum*, which shows central and autonomic system depressant properties and may have potential antiviral activity.[2] Schumanniophytine co-occurs with isoschumanniophytine (**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] schumanniophytine 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 (D*o*M)–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 schumanniophytine 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 schumanniophytine 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 D*o*M 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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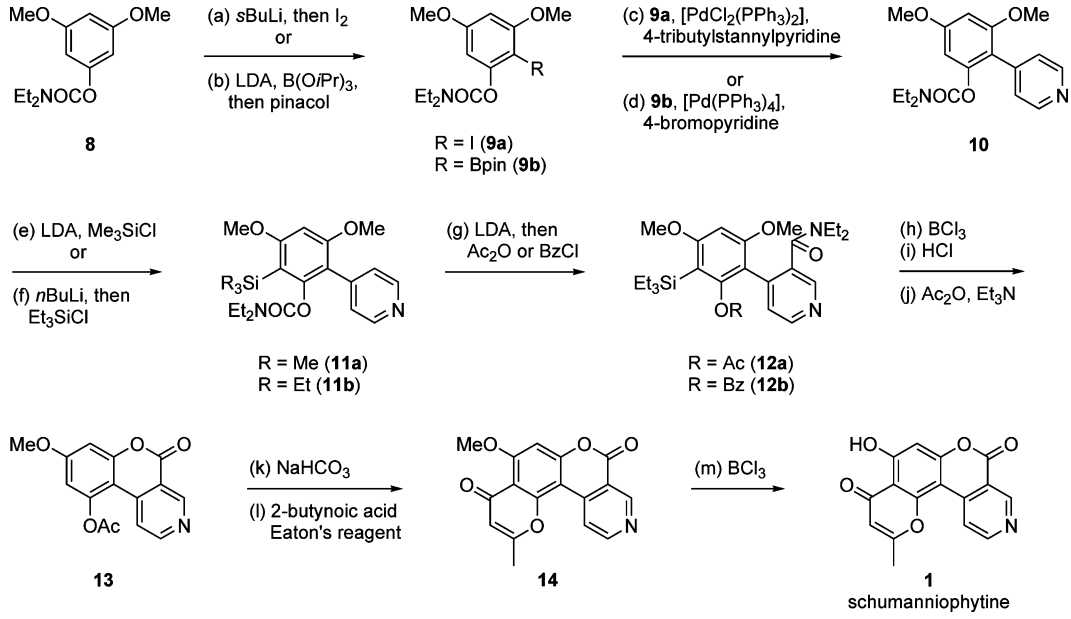
[‡] Deceased: June 28, 2007. Like the sunrise, his work awakened the important theme of transition-metal-catalyzed cross coupling, which has momentously enriched synthetic organic chemistry.
Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.



Scheme 1. Synthesis of schumanniophytine **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.), $B(OiPr)_3$ (2.5 equiv.), THF, –78 °C, 1 h, → 0 °C, then 1 M HCl, pinacol (1.1 equiv.), 97%; (c) **9a**, $[PdCl_2(PPh_3)_2]$ (0.1 equiv.), 4-tributylstannylpyridine (1.5 equiv.), DMF, 160 °C, 1 h, 73%; (d) **9b**, $[Pd(PPh_3)_4]$ (0.04 equiv.), 4-bromopyridine·HCl (1 equiv.), Na_2CO_3 (4 equiv.), DME/H_2O (2:1), 20 h, 99%; (e) LDA (3.5 equiv.), Me_3SiCl (4.5 equiv.), THF, –78 °C → room temp., 10 h, 94%; (f) *n*BuLi (1.2 equiv.), THF, –100 °C, 5 min, then Et_3SiCl (2.5 equiv.), –100 °C, 1.5 h, 91%; (g) LDA (4 equiv.), THF, 0 °C → room temp., 1 h, then Ac_2O or BzCl (5 equiv.), 0 °C → room temp., **12a** 75%, **12b** 65%; (h) BCl_3 (5 equiv.), CH_2Cl_2, 0 °C, 30 min; (i) HCl (80 equiv.), EtOH/H_2O (1:1), 90 °C, 12 h; (j) Ac_2O (5 equiv.), NEt_3 (5 equiv.), CH_2Cl_2, 0 °C → room temp., 1 h, 84% for the three steps; (k) $NaHCO_3$ (10 equiv.), MeOH/H_2O (1:1), room temp., 4 h; (l) 2-butynoic acid (2 equiv.), P_2O_5/MsOH (1:10, 5 mL per mmol), 80 °C, 12 h, 52% for the two steps; (m) BCl_3 (4 equiv.), CH_2Cl_2, 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 benzoylation, 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 BCl_3, which resulted in regioselective demethylation,[17] to give, after acidic protodesilylation, debenzylation, 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 (P_2O_5/MsOH, 1:10)[19] gave the desired tetracycle **14**. To conclude, demethylation proceeded efficiently under BCl_3 conditions[17] to furnish schumanniophytine (**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 schumanniophytine (**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 D*o*M[11] and cross-coupling strategies,[6] the route provides opportunity for incorporation of functionality in the aromatic, pyridyl, and pyranyl 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**.

Acknowledgments

We thank NSERC Canada for support through the Discovery Grants program and Merck Frosst Canada for unrestricted grant support. We are grateful to the Canadian Foundation for Innovation (CFI) for infrastructure support to establish our high-field NMR and HRMS facilities.

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[11] For recent reviews on the D*o*M reaction and its connection to cross-coupling chemistry, see: a) T. Macklin, V. Snieckus in *Handbook of C–H Transformations* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**, vol. 1, pp. 106–118; b) C. G. Hartung, V. Snieckus in *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, pp. 330–367.

[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).

[15] M. A. Reed, V. Snieckus, unpublished results.

[16] Although compound **12a**, upon treatment with ICl, gave the corresponding *ipso*-Friedel–Crafts product in 89% yield (Z. Zhao, V. Snieckus, *Org. Lett.* **2005**, *7*, 2523–2526), attempts to effect *ipso-ortho*-Fries and *ipso*-Friedel–Crafts acylation on both **12a** and **12b**, respectively, as a prelude for chromone ring annulation, resulted only in desilylation and other undesired products, see ref.[8]

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[18] Subjection of compound **13** to classical Lewis acid Fries rearrangement [H. Heaney, *Comprehensive Organic Synthesis* (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, vol. 2, pp. 733–752] followed by reacylation afforded a 1:1 mixture of the corresponding 9- and 7-acetyl derivatives. Attempts to effect a Baker–Venkataraman chromone ring syntheses (I. Hirao, M. Yamaguchi, M. Hamada, *Synthesis* **1984**, 1076–1078. For use in natural product synthesis, see S. Gattinoni, L. Merlini, S. Dallavalle, *Tetrahedron Lett.* **2007**, *48*, 1049–1051) on the 9-acetyl derivative as well as on the corresponding C-10 phenol afforded **14** albeit in low and poorly reproducible yields, see ref.[8] Attempts to adapt recent electrophilic Meldrum's acid chemistry were also unsuccessful, see: E. Fillion, A. M. Dumas, B. A. Kuropatwa, N. R. Malhotra, T. C. Sitler, *J. Org. Chem.* **2006**, *71*, 409–412.

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Received: November 27, 2007
Published Online: February 11, 2008

