

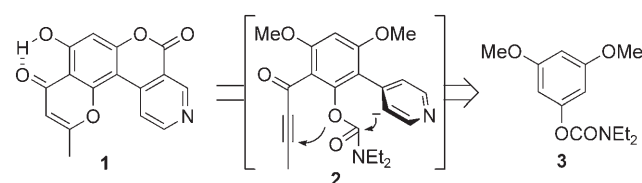
Synthetic Methods

Carbamoyl Translocations by an Anionic *ortho*-Fries and Cumulenolate α -Acylation Pathway: Regioselective Synthesis of Polysubstituted Chromone 3- and 8-Carboxamides**

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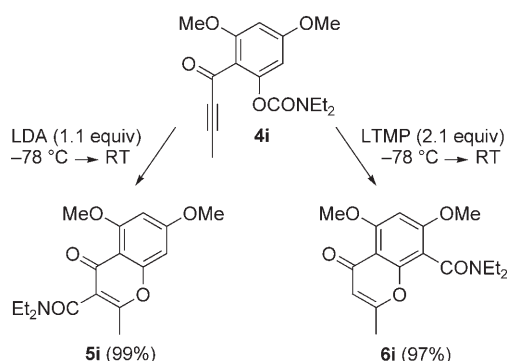
In memory of Albert I. Meyers

In an initial planned foray towards the total synthesis of schumanniphytine **1**,^[1] we envisaged (Scheme 1) a concise route incorporating a double intramolecular reaction



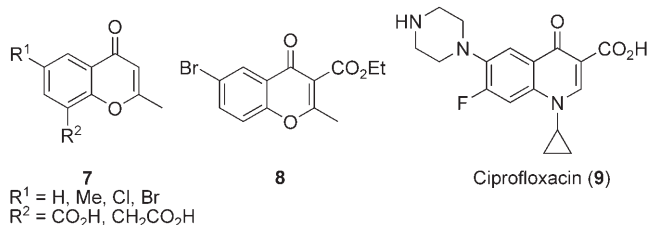
Scheme 1. Proposed retrosynthetic analysis of schumanniphytine (**1**).

sequence of a remote anionic-Fries rearrangement^[2] and a Michael addition (see intermediate **2**). While this concept was not placed to the test because of our failure to prepare the requisite precursor **2**,^[3] model studies on the conveniently synthesized 2-but-2-ynoyl aryl *O*-carbamate **4i** (Scheme 2) led to the discovery of two new anionic aryl *O*-carbamoyl rearrangements that give isomeric chromones **5i** and **6i** which proceed in essentially quantitative yield under standard conditions mediated by lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP), respectively. The original concept aside (Scheme 1), which represents a successful *ortho*-Fries/Michael addition reaction (**4i** $\rightarrow$ **6i**, Scheme 2), it was recognized that the chromone heterocycle represents major classes of natural products^[4] and is a key component for a plethora of bioactive molecules, commercial drugs, and agrochemicals.^[5] This realization



Scheme 2. Synthesis of chromone 3-carboxamide **5i** and 8-carboxamide **6i**.

gave us impetus to extend these initial studies.^[6] Herein we report the preliminary results of our synthetic and mechanistic findings which demonstrate: a) the preparation of 3- and 8-substituted chromones, systems represented by bioactive substances **7**^[7] and **8**^[8] which are difficult to access and are related to the important class of antibacterial 4-quinolone drugs ciprofloxacin (**9**),^[9] for which there is a



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[**] We acknowledge with gratitude the NSERC Canada for support through the Discovery Grant program. We warmly thank Merck Frosst Canada for unrestricted grant support. J.P. would like to thank the NSERC for an Undergraduate Student Research Award (USRA).

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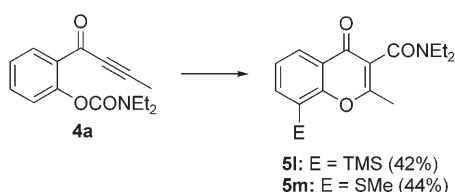
classical heterocyclic interconversion;^[10] b) repetitive metalation reactions which allow the construction of polysubstituted chromones (Table 1); and c) the intriguing and unprecedented involvement of a cumulenolate intermediate of **4i**^[11] in the anionic carbamoyl translocation reaction. Taken together, this work contributes to the increasing impact of carbanionic-mediated strategies in synthetic aromatic chemistry. By adaption of the approach used for the schumanniphytine alkaloid model compound study (**4i**, Scheme 2), a series of 2-but-2-ynoyl aryl *O*-carbamates **4a–k** were prepared^[12] and subjected to the strong base-mediated conditions. The results, which are summarized in Table 1, merit selected comment. Complications with the 1,2-addition of LDA to unhindered

Table 1: Synthesis of chromone 3-carboxamides **5a,c–k** and 8-carboxamides **6a,c–f,h–j**.

Entry	Substrate ^[a]	Base (equiv)	Product	Yield [%] ^[b]	Entry	Substrate ^[a]	Base (equiv)	Product	Yield [%] ^[b]
1		LTMP (1.5)		81	13		LTMP (1.5)		79 ^[f]
2		LTMP (1.2) sBuLi (2.3)		54 ^[c]	14		LTMP (1.5)		90
3		LTMP (1.1)		0	15		LTMP (5.0)		86
4		LTMP (2.1)		0	16		LDA (1.1)		99
5		LTMP (2.2)		93	17		LTMP (2.2)		97
6		LTMP (1.1) sBuLi (2.5)		44 ^[c]	18		LTMP (1.5)		90
7		LTMP (2.2)		85	19		LTMP (1.3) sBuLi (2.6)		36 ^[c]
8		LTMP (1.1) sBuLi (2.5)		46 ^[c]	20		LTMP (3.0)		65
9		LTMP (1.5)		92	21		LTMP (20)		0
10		LTMP (3.0)		84	[a] Prepared by DoM of the corresponding aryl O-carbamate. Conditions: sBuLi (1.2 equiv), –78 °C, 30 min; then MgBr₂·OEt₂ (2.5 equiv), –78 °C→0 °C; then <i>N</i>-methoxy-<i>N</i>-methylbut-2-ynamide (1.2 equiv), 0 °C→RT, 2 h; 61–77%. [b] Prepared by DoM of the corresponding aryl O-carbamate. Conditions: LTMP, –78 °C→RT, 2–12 h. [c] Conditions: LTMP, –78 °C, 10 min; then sBuLi, –78 °C→RT. [d] Conditions: sBuLi (1.2 equiv) –78 °C, 30 min; then CuCN·2LiCl (2 equiv), –78 °C, 30 min; then 2-butyne (2 equiv), –78 °C→RT, 1 h; 34–48%. [e] Prepared by metal-halogen exchange from the corresponding aryl bis-bromide. Conditions: tBuLi (2.1 equiv), –78 °C, 10 min; then MgBr₂·OEt₂ (2.5 equiv), –78 °C→0 °C; then <i>N</i>-methoxy-<i>N</i>-methylbut-2-ynamide (1.2 equiv), 0 °C→RT, 12 h. [f] LTMP, –78 °C→50 °C, 1 h. [g] Reaction performed at –100 °C.				
11		LTMP (1.1)		86					
12		LTMP (2.1)		93					

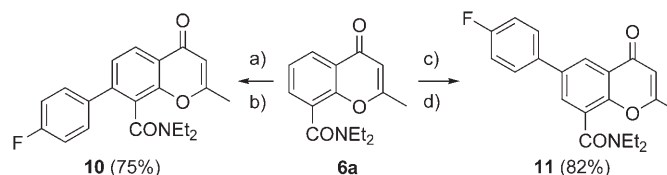
ynones led the use of LTMP, a more hindered base, for the remaining reactions of derivatives **4a–h**, **4j**, and **4k**. Conversions of unsubstituted and methyl-substituted *O*-carbamates **4a**, **4c**, and **4d** (entries 1, 5, and 7) as well as the methylenedioxy derivative **4j** (entry 18) proceed smoothly to give chromones **5a**, **5c**, **5d**, and **5j**, respectively, under LTMP conditions. However, their corresponding transformations into chromones **6a**, **6c**, **6d**, and **6j** (entries 2, 6, 8, and 19) require a sequential LTMP/*s*BuLi procedure: the second step with a stronger base was essential to achieve kinetic *ortho*-carbamoyl deprotonation to enable an *ortho*-Fries migration.^[13] The 3-fluoro compound **4b** (entries 3 and 4) failed to afford chromone **5b** or **6b**, presumably as a result of complications arising from benzyne formation.^[14] On the other hand, the lack of such presumed difficulties in the case of the bromosubstituted **4e** is noteworthy.^[15] not only is 3-carbamoylchromone **5e** (entry 9) obtained efficiently, but a known lateral metalation/carbamoyl migration^[16] gives the acetamide chromone **6e** (entry 10) in high yield. The chloro *O*-carbamates **4f** and **4g**, which were expected to cause less concern with respect to benzyne formation, smoothly underwent the isomeric carbamoyl transfer/Michael cyclization reactions to afford the expected products **5f**, **6f**, and **5g** (entries 11–13), respectively. Methoxy aryl *O*-carbamate **4h** (entry 15) required increased concentrations of LTMP (5 equiv) to favor formation of **6h**, presumably as a result of coordination and competitive directed *ortho*-metalation (DoM) arising from the presence of the OMe group.^[17] The original test substrate **4i** (entries 16 and 17) benefits from synergistic DoM^[18] to give **5i** and **6i** in the best overall yields for this general route. The biaryl *O*-carbamate **4k** (entry 20) furnishes the 8-aryl chromone **5k**, which is structurally related to several naturally occurring^[19] and synthetic^[20] antitumor agents. Structural differences notwithstanding, the unsuccessful conversion of **4k** (entry 21) into **6k** is indicative of the difficulties in proving that the (original untested concept) formation of **2** is a key step in the synthesis of schumannio-phytine (**1**).^[1]

The evidence that the formation of the C8 carbanion was possible under *s*BuLi conditions (entries 2, 6, 8, and 19) prompted us to investigate trapping experiments with other electrophiles at low temperatures. Thus, using sequential LTMP/*s*BuLi metalation of unsubstituted 2-but-2-ynyl phenyl *O*-carbamate (**4a**; Scheme 3) followed by TMSCl and MeSSMe treatment led to the formation of 8-silyl- and 8-thiomethylchromones **5l** and **5m**, respectively, in modest overall yields.



Scheme 3. One-pot DoM/chromone 3-carboxamide synthesis. Reagents and conditions: LTMP (1.3 equiv), THF, -78°C , 10 min; then *s*BuLi (2.5 equiv), -78°C , 30 min; then E = TMSCl or MeSSMe (2.5 equiv), $-78^{\circ}\text{C} \rightarrow \text{RT}$, 2 h. TMS = trimethylsilyl.

The availability of the new 8-carbamoylchromones **6** inspired us to perform additional DoM reactions. Thus, treatment of **6a** (Scheme 4) with LHMDs, to necessarily

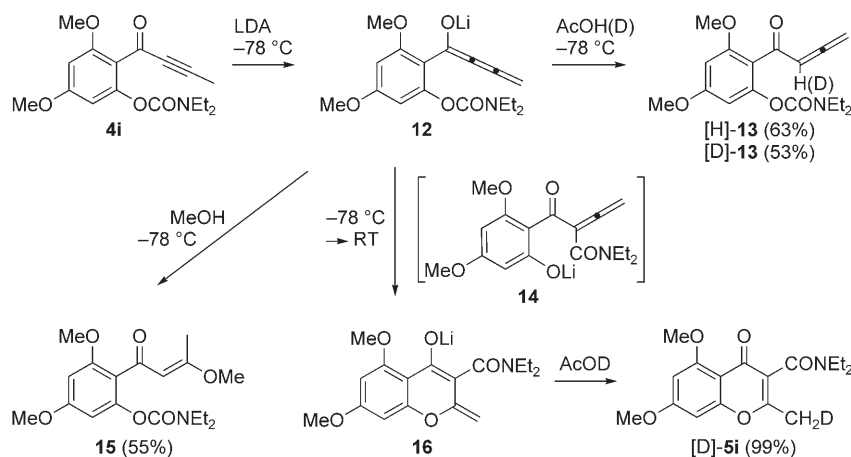


Scheme 4. Differential borylation and arylation of chromone **6a**.

Reagents and conditions: a) LHMDs (1.5 equiv), THF, -78°C , 10 min; then TMEDA (3 equiv), *s*BuLi (3 equiv), -78°C , 30 min; then B(OMe)₃ (4 equiv), -78°C , 1 h; b) [Pd₂(dba)₃] (0.01 equiv), S-Phos (0.02 equiv), 1-bromo-4-fluorobenzene (1.1 equiv), K₃PO₄ (2 equiv), PhMe, 100°C , 2 h; c) [Ir(OMe)(cod)]₂ (0.02 equiv), dtbpy (0.04 equiv), B₂pin₂ (0.6 equiv), hexanes, 80°C , 18 h; d) [Pd(PPh₃)₄] (0.02 equiv), 1-bromo-4-fluorobenzene (1.1 equiv), Na₂CO₃ (10 equiv), DME/H₂O (4:1), 80°C , 4 h. LHMDs = lithium hexamethyldisilazide, TME-DA = *N,N,N',N'*-tetramethylethylenediamine, dba = dibenzylideneacetone, S-Phos = dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl, cod = 1,5-cyclooctadiene, dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridyl, B₂pin₂ = bis(pinacolato)diboron, DME = 1,2-dimethoxyethane.

effect the formation of a protected dienolate,^[21] followed by DoM and treatment with B(OMe)₃ afforded the 7-borylated chromone, which was immediately subjected to modern Suzuki cross-coupling conditions^[22] to furnish the 7-(4-fluorophenyl)chromone **10** in reasonable yield. To provide regiochemical complementarity, advantage was taken of the substituent effects from the C–H activation/borylation route by using B₂pin₂ in the presence of an iridium catalyst.^[23] Thus, subjecting **6a** to one-pot borylation/Suzuki cross-coupling conditions^[24] afforded isomeric 6-(4-fluorophenyl)chromone **11** in very good yield.

A mechanistic study of the LDA-mediated reaction was undertaken on the high-yielding conversion of **4i** into [D]-**5i** (Scheme 5). First, treatment of **4i** with LDA (1.1 equiv) at -78°C for 1 hour and subsequent trapping with AcOH and AcOD at -78°C gave the 1,2-dienones (α -allenyl ketones) [H]-**13** and [D]-**13**, respectively in reasonable yields (21% monodeuterium incorporation was determined by ¹H NMR spectroscopy). This result confirms the generation of the kinetic cumulenolate intermediate **12** and its α -carbonyl protonation, in agreement with previous experimental and semiempirical calculations (MNDO).^[25] Treatment of **4i** with LDA (1.1 equiv, -78°C , 20 min) followed by quenching with MeOH at -78°C gave (2*E*)-aryl-3-methoxy-but-2-en-1-one **15** (confirmed by NOE experiments), which is the expected thermodynamically stable diastereomer resulting from α -carbonyl protonation and 1,4-addition of the generated methoxide.^[26,27] Allowing the cumulenolate **12** to warm to room temperature to promote carbamoyl transfer resulted in the appearance of a deep red solution indicative of the formation of the lithium dienolate **16**; this was confirmed by the rapid disappearance of color upon treatment with AcOD to give a clear solution and a high yield of [D]-**5i** (>95% deuterium incorporation was determined by ¹H NMR spec-



Scheme 5. Reactions of cumulenolate **12**.

troscopy). This result suggested a reaction pathway which proceeds via the buta-2,3-dienamide **14** followed by intramolecular Michael addition of the resulting phenolate and then protonation to give the chromone product **5i**.^[28] As suggested by the need for additional amounts of base for effective conversion of **4** into **6** (Table 1), this reaction may also involve the cumulenolate **12**, which undergoes anionic *ortho*-Fries rearrangement followed by protonation and Michael addition, although evidence for this suggestion is currently unavailable.

In conclusion, new general and regioselective syntheses of chromone derivatives **5** and **6** by anionic carbamoyl translocation reactions have been developed. The reactions, which involve sequential intramolecular anionic *ortho*-Fries rearrangement and Michael addition that proceed, as suggested by mechanistic studies (Scheme 5), via an intriguing cumulenolate **12**, provide routes to chromones which show uncommon and difficult to access C8 substitution^[7] as well as common and biologically significant^[8,9] 3-substitution patterns. The DoM reactions (Scheme 3) as well as the complementary *ortho*- and iridium catalyzed *meta*-borylation and Suzuki cross-coupling chemistry (Scheme 4) provide added conceptual and practical value for heterocyclic synthesis. As a proposed tenet, in juxtaposition with Brönsted or Lewis acid-mediated electrophilic substitution, this study and related aromatic carbanionic reactions^[18] offer advantages for allowing the introduction of varied substituents under mild conditions with regiochemical control. Potentially of more general significance, the observation of cumulenolate **12**, which represents a rarely studied species,^[25] provides impetus for increased attention in the synthesis of cumulenes and allenes,^[11] especially in view of recent developments in transition metal catalyzed reactions.^[11]

Received: September 21, 2007

Published online: February 11, 2008

Keywords: anionic reactions · heterocycles · metalation · organolithium reagents · synthetic methods

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- [13] The low yields of products **6c**, **6d**, and **6j** are undoubtedly due to competitive thermodynamically driven benzylic and methylenedioxy deprotonation which ultimately disfavors *ortho* to *O*-carbamate deprotonation and subsequent *ortho*-Fries rearrangement, even in the presence of excess LTMP (up to 8 equiv) and thus results, by default, in the formation of chromones **5**. In an attempt to trap a thermodynamically generated anion, treatment of **4j** under Martin conditions (**4j**/LTMP/TMSCl = 1:1.5:1.5–1:1.5:3, see T. D. Krizan, J. C. Martin, *J. Am. Chem. Soc.* **1983**, *105*, 6155–6157) led to several TMS products including those with benzylic and methylene bridge incorporation (^1H NMR spectroscopic evidence). For a viewpoint of the ability of the methylenedioxy group to prevent desired aromatic anionic chemistry under strong base conditions, see C. A. James, PhD thesis, University of Waterloo (Canada), **1998**.
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- [28] The observation that γ -proton abstraction and cumulenolate formation is obligatory in these reactions is further corroborated by the failure to obtain a chromone product upon treatment of 2-(3-phenylpropionyl)phenyl diethyl *O*-carbamate under LTMP reaction conditions.