

Synthetic Studies toward
Lapidilectine-Type *Kopsia* Alkaloids

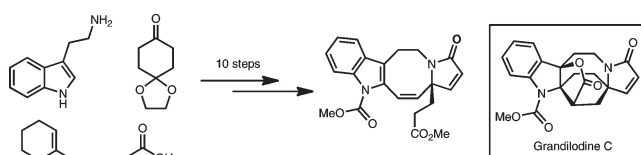
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ABSTRACT

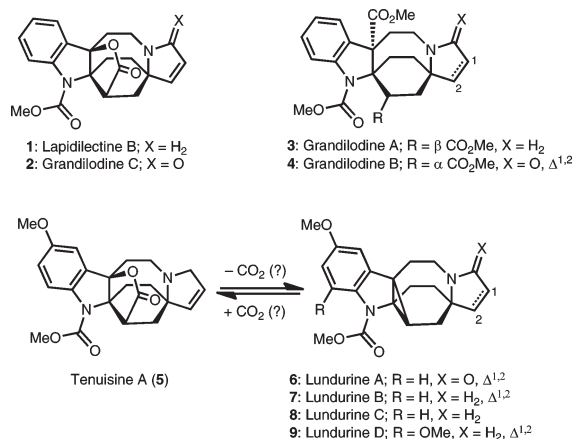


A rapid synthesis of the tetracyclic core of *Kopsia* indole alkaloids related to lapidilectine B, grandilodine C, and tenuisine A is reported. Key to the success of this route was an efficient and scalable Ugi four-component coupling to install all the necessary carbons found in the natural products.

Alkaloids isolated from the *Kopsia* genus of flowering plant, representative examples of which are shown in Figure 1, demonstrate a wide range of structural diversity as well as pharmacological activities.¹ Extracts from *Kopsia* have been used in traditional treatments for various ailments including rheumatoid arthritis, edema, tonsillitis, and hypertension. Lapidilectine B (**1**), grandilodine C (**2**),² and lundurine B (**7**) show multidrug resistance (MDR) reversing effects in vincristine-resistant KB cancer cells,³ whereas lundurines A (**6**) and C (**8**) show selective cytotoxicity toward B16 melanoma cells.

A majority of the synthetic efforts aimed at these compounds have been focused on the lundurine class of molecules.⁴ The most advanced approach, which arrives at the tetracyclic core of lundurine using creative ring closing metathesis reactions, was recently reported by Martin and co-workers.⁵

In addition, an elegant total synthesis of lapidilectine B (**1**) was achieved by Pearson and co-workers in 2001 and

Figure 1. Selected *Kopsia* alkaloids.

featured an inventive use of a 2-azaallyllithium ion in a [3 + 2] cycloaddition.⁶ To date, no synthetic efforts have been reported toward the tenuisines⁷ or grandilodines.

We were drawn to these compounds as synthetic targets because of their unique structures, which offered opportunities

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(2) For the isolation of the grandilodines, see: Yap, W.-S.; Gan C.-Y.; Low, Y.-Y.; Choo, Y.-M.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2011**, *74*, 1309–1312.

(3) Kam, T.-S.; Lim, K. H.; Yoganathan, K. *Tetrahedron* **2004**, *60*, 10739–10745.

(4) (a) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358–1373. (b) Donets, P. A.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Org. Lett.* **2009**, *11*, 3618–3621. (c) Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 9015–9020.

(5) Orr, S. T.; Tian, J.; Niggemann, M.; Martin, S. F. *Org. Lett.* **2010**, *13*, 5104–5107.

(6) (a) Pearson, W. H.; Mi, Y.; Lee, I. Y.; Stoy, P. *J. Am. Chem. Soc.* **2001**, *123*, 6724–6725. (b) Pearson, W. H.; Lee, I. Y.; Mi, Y.; Stoy, P. *J. Org. Chem.* **2004**, *69*, 9109–9122.

(7) For the isolation of the tenuisines and an account of their structural revision, see ref 3.

for new synthetic tactics, as well as their potential as starting points for new pharmaceuticals. Furthermore, our analysis of the subset of *Kopsia* alkaloids illustrated in Figure 1 indicated a close structural relationship, which could inform a unified strategy for their syntheses.

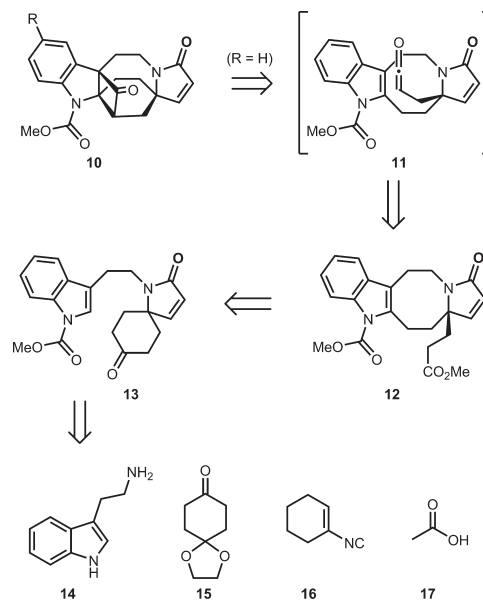
In our analysis of the subset of *Kopsia* alkaloids depicted in Figure 1, it seemed plausible that the fused cyclopropane in the lundurines (see **6–9**) could arise, synthetically (or even biosynthetically), from a decarboxylation of a related tenuisine type precursor (e.g., **5**).⁸ Alternatively, the microscopic reverse, i.e., carboxylation of the cyclopropane moiety of a lundurine precursor (e.g., **7**), could provide an entry to tenuisines such as **5**. A similar relationship can be envisioned between fused γ -lactone compounds **1** or **2** and their respective cyclopropane-containing congeners, which are yet to be isolated. Furthermore, a selective carbanion opening of the γ -lactone moiety in **1** or **2** could lead to **3** and **4**, respectively.

In order to test aspects of this unified synthetic plan, we sought a versatile synthetic precursor that could give access to either the fused γ -lactone or cyclopropane framework. Fused cyclobutanone **10** (Scheme 1) engendered exciting possibilities for its conversion to a γ -lactone (as in **1** or **2** with R = H; or **5** with R = OMe) using a Baeyer–Villiger type oxidation⁹ or to a fused cyclopropane (as in **6–9**; R = OMe) using a C–C bond activation/decarbonylation sequence.¹⁰ As such, **10** was selected as the penultimate target.

We envisioned cyclobutanone **10** arising from ester **12** (if R = H) via ketene intermediate **11** by a [2 + 2] cycloaddition.¹¹ Tetracycle **12** could in turn arise from spiro-fused α,β -unsaturated lactam derivative **13** by cleavage of the cyclohexanone ring and functionalization of the indole C-2 position. The cleavage step could, in principle, be rendered enantioselective by a desymmetrization of ketone **13**. Tryptamine-derived lactam **13** could in turn arise from a four-component Ugi coupling¹² of **14**, **15**, **16**, and **17**.

Our synthetic studies commenced with the Ugi four-component coupling (Scheme 2), which led to adduct **18** in 95% yield. The virtues of this coupling reaction are many fold. First, in this single step, we install all the carbons of the lapidilectine-type *Kopsia* alkaloid framework. Second, the product precipitates out of the reaction mixture and only requires filtration to be obtained free of impurities. Third, the reaction can be conducted on a large scale (> 200 g) without compromising yield.¹³ The Armstrong isocyanide (**16**)¹⁴ was selected for the Ugi coupling on the

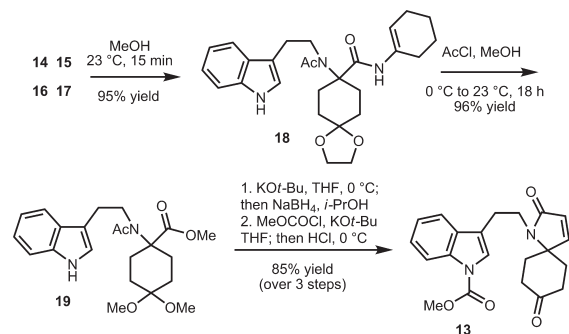
Scheme 1. Retrosynthetic Analysis of Cyclobutanone Precursor



basis of the elegant synthetic studies of Sorensen and Seike on FR901483, which showed (as we found) that the Ugi product (**18**) could easily be converted to the corresponding methyl ester (see **19**).¹⁵ Thus, treatment of **18** with methanolic HCl provided methyl ester **19**, whereby the esterification was attended by a transketalization to the dimethylketal.

Following the Sorensen protocol, subjection of acetamide ester **19** to KO t -Bu in THF effected a Dieckmann condensation. Selective reduction of the ketone group (NaBH₄) and elimination of the resulting hydroxy group (activated as the carbonate) provided spiro-fused lactam **13** in excellent yield over three steps (Scheme 2). The accompanying protection of the indole nitrogen made the handling of this compound straightforward. Of note, the conversion of **19** to **13** can be consistently performed on a > 5 g scale without appreciable depression in yield.

Scheme 2. Synthesis of Spiro-lactam **13**



(8) Kam and co-workers (see ref 3) isolated the lundurine and tenuisine compounds from the same plant source, lending credence to a biogenetic connection between these natural products.

(9) Krow, G. R. *Org. React.* **1993**, *43*, 251–798.

(10) For a review on this type of C–C bond activation: Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740–7752.

(11) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793–811.

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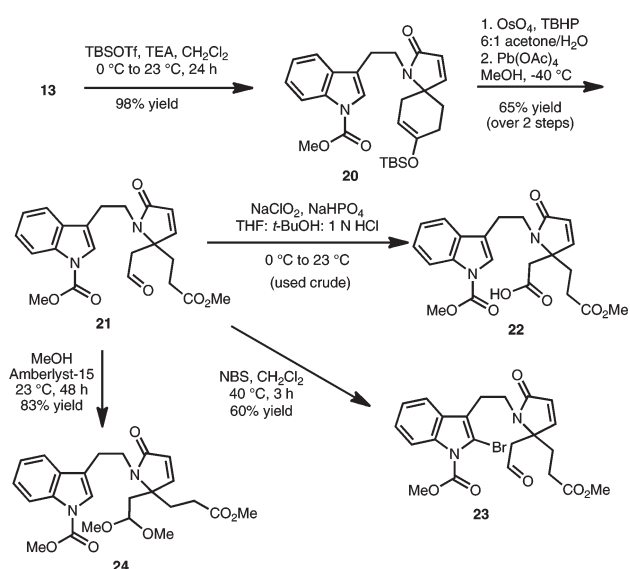
(13) Performed by B.G.P. in the Process Group at Eli Lilly, Indianapolis.

(14) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574–2583.

(15) Seike, H.; Sorensen, E. J. *Synlett* **2008**, 695–701.

With efficient access to **13**, we have investigated several strategies for the synthesis of the tetracyclic core of the lapidilectines and structurally related alkaloids (i.e., **12**, Scheme 1). These studies began with the conversion of **13** to **20** by TBS silyl enol ether formation (Scheme 3), which proceeded in excellent yield. Oxidative opening of the six-membered ring was effected using the two-stage protocol of dihydroxylation (OsO_4 , TBHP) followed by $\text{Pb}(\text{OAc})_4$ -mediated cleavage in the presence of methanol, which afforded aldehyde ester **21**. In preparation for cyclization studies en route to the tetracyclic core structure (eqs 1–3), **21** was converted to acid **22** employing a Pinnick

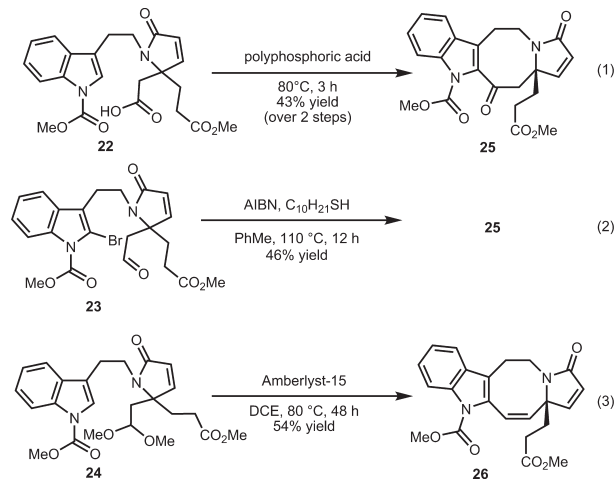
Scheme 3. Oxidative Opening of Spirocycle **20**



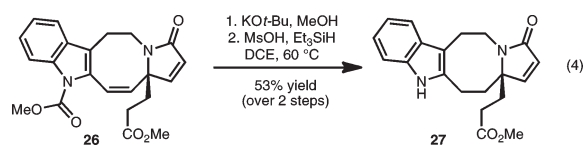
oxidation;¹⁶ to C-2 bromo-indole **23** using NBS; and to dimethylacetal **24** under standard acetalization conditions.

As shown in eqs 1–3, the lapidilectine-type tetracyclic core, varying only in the oxidation level about the eight-membered ring, can be successfully realized from each of these precursors (i.e., **22**, **23**, and **24**). Tetracycle **25** was directly accessible from crude acid **22** in 43% yield using a polyphosphoric acid mediated Friedel–Crafts acylation (eq 1).¹⁷ Despite the modest yield of this transformation, the usual ‘two-step’ Friedel–Crafts protocol, involving treatment of the corresponding acid chloride with a Lewis acid (e.g., AlCl_3), was less efficient and resulted in significant polymerization. Alternatively, aldehyde **23** was successfully

converted to keto-tetracycle **25** (eq 2) in 46% yield upon treatment with AIBN and dodecyl thiol ($\text{C}_{10}\text{H}_{21}\text{SH}$), presumably via an acyl radical intermediate.¹⁸ We have found this particular protocol for the formation of **25** to be effective (as compared to starting from acid **22**) because it generally leads to less byproduct formation. A Friedel–Crafts type transformation could also be initiated from dimethyl acetal **24** using Amberlyst-15 as the source of acid (eq 3) to afford **26** in 54% yield.¹⁹ The mass balance of the material was accounted for by aldehyde **21**, which likely arises from a competing hydrolysis of the acetal group. Attempts to effect the conversion of **24**→**26** using Lewis acids or other protic acids resulted only in the hydrolysis of the acetal, which reverts back to aldehyde **21**.



In preparation for the exploration of endgame scenarios, tetracycle **26** was converted to **27** (eq 4) by cleavage of the carbamate group and selective removal of the alkene group by ionic reduction using methanesulfonic acid and triethylsilane.²⁰ Our current efforts are focused on the selective conversion of the methyl ester group of **27** to an ‘activated ester’ to study our proposed ketene generation/cycloaddition (see **12**→**10**, Scheme 1).



We have also briefly explored opportunities to render our strategy enantioselective. In this regard, our initial efforts have focused on the desymmetrization of spiroketones related to **13** (see **28**, Table 1). The control of the single tertiary amine spiro stereocenter would guide the installation of the three additional stereocenters in the target natural products, which would substantially simplify the diastereoselectivity challenge. As a proof of concept for stereoselective desymmetrization, the enantioselective

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(17) (a) Owton, W. M.; Brunavs, M. *Synth. Commun.* **1991**, *21*, 981–987. (b) Wood, J. L.; Pujanauskis, B. G.; Sarpong, R. *Org. Lett.* **2009**, *11*, 3128–3131.

(18) (a) Yoshikai, K.; Hayama, T.; Nishimura, K.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2005**, *70*, 681–683. (b) For a recent application in a complex molecule synthesis, see: Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (c) Tetracycle **25** was obtained in approximately 85% purity.

(19) Ballini, R.; Gabrielli, S.; Palmieri, A.; Petrini, M. *Adv. Synth. Catal.* **2010**, *352*, 2459–2462.

(20) Larson, G. L.; Fry, J. L. *Org. React.* **2008**, *1*–737.

(21) O’Brien, P. J. *Chem. Soc., Perkins Trans. 1* **1998**, 1439–1457.

(22) (a) Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* **1995**, *36*, 5465–5468. (b) Of note, diminished enantioselectivity is generally observed in the absence of the LiCl additive (compare, for example, entries 5 and 6).

Table 1. Enantioselective Desymmetrization of **28**

entry	amine	additive (1 equiv)	% ee
1	A	LiCl	31
2	A	LiCl, HMPA	24
3	B	LiCl	6
4	C	LiCl	24
5	D	LiCl	39
6	D	—	18
7	E	LiCl (2 equiv)	12

deprotonation of ketone **28** was investigated with a range of chiral, nonracemic kinetic amine bases (see Table 1).²¹ Our brief survey has revealed that the amide base generated from amine **D**, in the presence of LiCl (1 equiv),²² yields enol carbonate **29** in 39% ee and 60% yield (entry 5). This preliminary result, albeit in modest ee, could provide the basis for the development of an enantioselective synthesis of lapidilectine and related *Kopsia* alkaloids.

In conclusion, we have developed an effective and scalable synthetic sequence to the tetracyclic core of *Kopsia* alkaloids related to lapidilectine. The synthetic sequence features a highly enabling Ugi four-component coupling to install all the carbons found in these natural products. The reported strategy holds high potential for providing a unified approach to the subset of *Kopsia* alkaloids depicted in Figure 1. In addition, preliminary results on enantioselective deprotonation of a spirocyclic ketone provides a proof of concept for the possible enantioselective syntheses of these natural products.

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Supporting Information Available. Experimental details and characterization for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.