Natural Product Synthesis

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Total Syntheses of (+)-Grandilodine C and (+)-Lapidilectine B and Determination of their Absolute Stereochemistry

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Abstract: *Enantioselective total syntheses of the Kopsia alkaloids (+)-grandilodine C and (+)-lapidilectine B were accomplished. A key intermediate, spirodiketone, was synthesized in 3 steps and converted into the chiral enone by enantioselective deprotonation followed by oxidation with up to 76% ee. Lactone formation was achieved through stereoselective vinylation followed by allylation and ozonolysis. The total synthesis of (+)-grandilodine C was achieved by palladium-catalyzed intramolecular allylic amination and ring-closing metathesis to give 8- and 5-membered heterocycles, respectively. Selective reduction of a lactam carbonyl gave (+)-lapidilectine B. The absolute stereochemistry of both natural products was thereby confirmed. These syntheses enable the scalable preparation of the above alkaloids for biological studies.*

The genus *Kopsia* is widely distributed in Southeast Asia. Numerous alkaloids from these plants have been considered attractive targets for synthetic studies owing to their unusual carbon skeletons and structural diversity.[1] Grandilodines[2a] (**1a–c**) and lapidiceltines[2b,c] (**2a–d**), which both have unique structures that includes three quaternary carbon centers on an indoline core and a polycyclic ring system, have been isolated from *Kopsia grandifolia* and *lapidilecta*, respectively (Figure 1). However, their limited availability from natural sources has been a major impediment to further biological studies.[2a] The scalable and efficient preparation of these alkaloids is an important goal because synthetic studies could lead to both potential methods for creating drug candidates and important tools for biological studies. However, only one example of the total synthesis of (±)-**2d** has been reported to date.[3]

Recently, we achieved a racemic and asymmetric total synthesis of lundurines, which are *Kopsia* alkaloids.[4] During our synthesis of **4a**[4a,b] and **4b**,[4c] we recognized that the synthetic intermediate **3** is a common basic structure of *Kopsia* alkaloids. This prompted us to propose a strategy using **3b** for the enantioselective total synthesis of (+)-grandilodine C (**1c**) and (+)-lapidilectine B (**2d**; Figure 2).

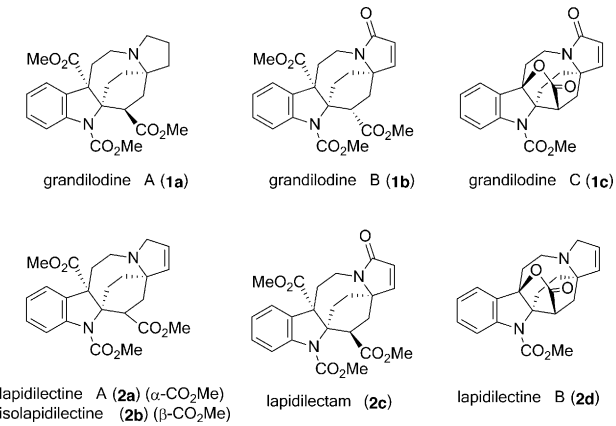

Figure 1. Selected *Kopsia* alkaloids.

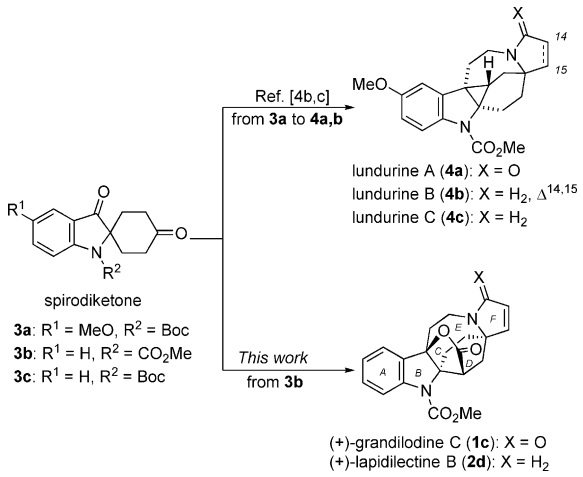

Figure 2. Synthetic targets and common intermediate **3**.

Since the spiroskeleton in **3** is considered to be a common structure among the related *Kopsia* alkaloids, we aimed for discriminative functionalization of two carbonyls in **8**, which is derived from **3b**, as shown in the retrosynthetic analysis (Scheme 1). Both the allylacetate and azide functionalities in **5** could be essential for construction of the E and F rings in **1c** and **2d**. The precursors of the lactone in **5** could be vinyl and hydroxy groups in **6**, which could be introduced by the addition of vinyl and allyl metal reagents to **8**. This sequential reaction is a key to controlling the stereogenic centers in **1c** and **2d**. The initial conjugated vinylation of **8** would proceed from the *Re* face (opposite the carbamate) to give **7**, and sequential allylation to the hindered benzylic carbonyl from the *Si* face would give the desired stereochemistry in **6**, as long

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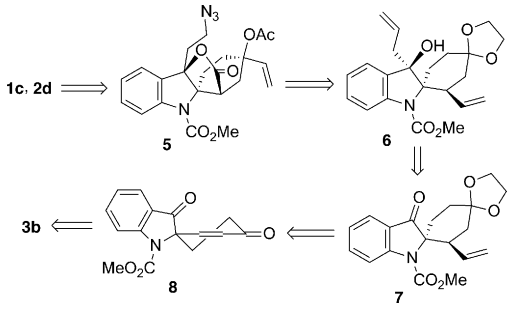
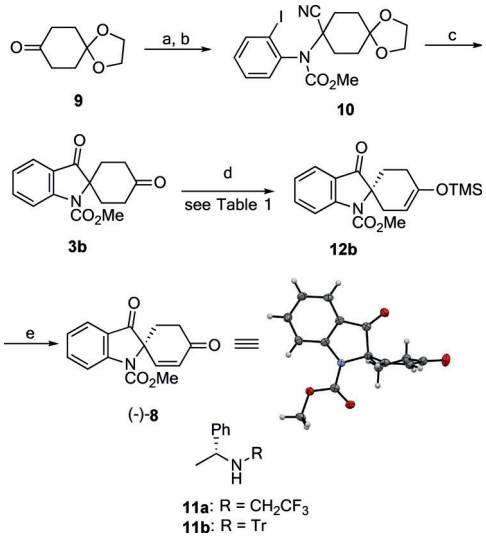


Scheme 1. Retrosynthetic analysis.

as the conformation of spirodiketone could be fixed as shown in **8**. The enone **8** could be obtained in an optically active form through enantioselective deprotonation followed by Saegusa–Ito oxidation of **3b**, as we previously reported with the related spirocyclohexanone.[4c]

To develop a more simple and efficient synthesis of **3b** compared to the previous 11-step synthesis,[4b] we chose the Strecker synthesis with the readily available cyclohexanone derivative **9** (Scheme 2). When **9** was reacted with TMSCN (1.2 equiv) and *o*-iodoaniline (1.0 equiv) in acetic acid, followed by N-acylation using $ClCO_2Me$ as a solvent in the presence of potassium carbonate (5.0 equiv) under reflux at 50 °C, **10** was obtained in 98 % yield. Attempted cyclization to **3b** under radical-,[5] Li-,[6] and Pd-mediated[7] conditions resulted in lower to moderate conversion, and we eventually concluded that a modified method with *i*PrMgCl (2.3 equiv) in THF at 0 °C[8] was the most effective for cyclization and this approach gave **3b** in 89 % yield of isolated product over 3 steps.



Scheme 2. Synthesis of (−)-**8**. Reagents and conditions: a) *o*-iodoaniline (1.0 equiv), TMSCN (1.2 equiv), AcOH, RT, overnight, 98 %, b) K_2CO_3 (5.0 equiv), $ClCO_2Me$, reflux, 72 h, 100 % (brsm, 33 % conversion), c) *i*PrMgCl (2.3 equiv), THF, 0 °C, 10 min then 1*N* HCl, 50 °C, overnight, 89 % (3 steps), d) chiral amine **11** (2.5 equiv), *n*BuLi (2.5 equiv), TMSCl (5.0 equiv), e) $Pd(OAc)_2$ (1.5 equiv), MeCN, RT, overnight. TMS = trimethylsilyl, brsm = based on recovered starting material, THF = tetrahydrofuran, Tr = trityl.

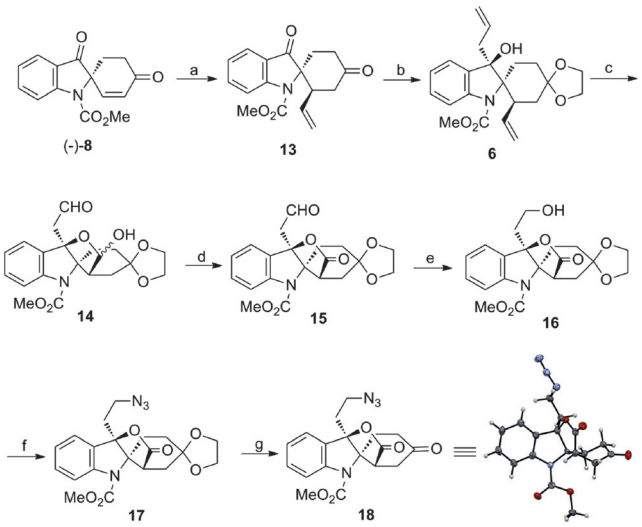
With spirodiketone **3b** in hand, we next focused on desymmetrization of **3b** to create a chiral quaternary carbon through enantioselective deprotonation[9–11] followed by Saegusa–Ito oxidation[12] to give **8** (Table 1). When **3b** was reacted with chiral lithium amides prepared from **11a**[9a,b] or **11b**[9c] with *n*BuLi, enantioselective deprotonation effectively proceeded to give **12b** by trapping with TMSCl. The *ee* values were evaluated after oxidation to the corresponding enone **8**. The *ee* values for **8** were influenced by the reaction temperature for both amines (**11a**,**b**), and up to 76 % *ee* was achieved at −100 °C (Table 1, entries 2 and 4). Chiral amines could be recovered in 80 % yield without any loss in optical purity; the enantiomeric excess of **8** was increased to 91 % by recrystallization, and its absolute configuration was confirmed to be *R* by X-ray crystallographic analysis, as shown in Scheme 2.[13] In the literature on the desymmetrization of 4-*tert*-butylcyclohexanone,[9a,b] chiral lithium amides from **11a**,**b** gave (*S*)-4-*tert*-butylcyclohexenone. In contrast to the results with a simple 4-monosubstituted cyclohexanone, it is difficult to predict the absolute stereochemistry in the asymmetric deprotonation of spirocyclic **3b** by chiral lithiumamides owing to the small energy difference between the two possible chair conformations of **3b**, as suggested by DFT calculations. When the methyl carbamate of **3b** was changed to a *tert*-butyloxycarbonyl (Boc) group, the enantioselectivity increased to 91 % *ee* under the same conditions as shown in Table 1, entry 2. These results might be explained by conformational fixation when using a more bulky carbamate.[14]

Table 1: Asymmetric deprotonation of **3b**.

Entry	Chiral amine	Conditions	(−)-**8**[a]
1	**11a**	−78 °C, 5 min	96 %, 56 % *ee*
2	**11a**	−100 °C, 5 min	96 %, 76 % *ee*
3	**11b**	−78 °C, 5 min	92 %, 65 % *ee*
4	**11b**	−100 °C, 5 min	85 %, 75 % *ee*

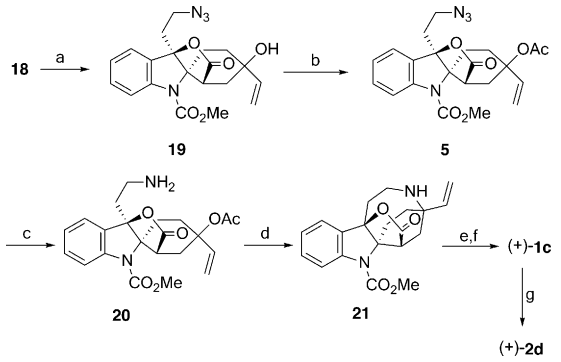
[a] $[\alpha]_D^{26}$ −245.8 ($CHCl_3$, *c*, 1.0, 76 % *ee*).

On the other hand, the carbamate group in enone **8** would be fixed to be in a pseudo-equatorial position, which would cause Cu-mediated conjugated vinylation from the *Re* face of the carbon–carbon double bond, exclusively. This vinyl group could also be important for controlling the stereoselectivity of the subsequent allylation from the *Si* face of the benzylic carbonyl plane in **13**. As expected, high diastereoselectivity was observed in the CuI-mediated vinylation of **8** to give **13** in 83 % yield together with a small amount of the 1,2-adduct. After acetalization of a carbonyl group, *Si*-face-selective allylation gave *tert*-alcohol **6** in 96 % yield as a single diastereomer. Subsequent ozonolysis of the two olefins gave an inseparable mixture of stereoisomeric hemiacetal **14**, which was oxidized to the corresponding lactone **15** by PDC. The instability of **15** led to hydride reduction without any purification, and the primary alcohol **16** was obtained in 33 % yield through a 3-step procedure. Mitsunobu azidation with DPPA[15] gave the corresponding azide **17** in 73 % yield and removal of ethyleneacetal gave **18**, the structure of which was confirmed by X-ray crystallographic analysis (Scheme 3).[13]



Scheme 3. Synthesis of **18**. Reagents and conditions: a) vinylMgBr (1.5 equiv), CuI (3.0 equiv), THF, −78 °C, 5 min, 83 %, b) $(TMSOCH_2)_2$ (1.5 equiv), TMSOTf (0.3 equiv), CH_2Cl_2, −78 °C, 3 h, then allylMgBr (2.0 equiv), −78 °C, 10 min, 96 %, c) O_3, CH_2Cl_2, −78 °C, 30 min, then Me_2S, RT, overnight, d) PDC (1.5 equiv), MS3 A, CH_2Cl_2, RT, 3 h, e) $NaBH_4$ (1.0 equiv), EtOH, −20 °C, 40 min, 33 % (3 steps), f) PPh_3 (1.5 equiv), DPPA (1.5 equiv), $(MeO(CH_2)_2O_2CN=)_2$ (1.5 equiv), THF, RT, overnight, 73 %, g) PTSA (1.0 equiv), acetone, 40 °C, overnight, quant. OTf = triflate, PDC = pyridinium dichromate, DPPA = diphenylphosphoryl azide, PTSA = toluene-*p*-sulfonic acid.

The final stage to complete the total synthesis of (+)-grandilodine C (**1c**) is the 6-step sequence outlined in Scheme 4. First, a mixture of stereoisomers of *tert*-allyl alcohol **19**, in a ratio of 6:1 as determined by ^{1}H NMR, was prepared by the stereo- and chemoselective addition of vinyl magnesium bromide to **18**. Although the stereochemistry of the tertiary hydroxy group in **19** has not yet been determined, the tertiary acetate **20** as a cyclization precursor was obtained



Scheme 4. Completion of total syntheses. Reagents and conditions: a) vinylMgBr (1.5 equiv), THF, −78 °C, 2 h, 86 %, d.r. = 6:1 (determined by ^{1}H NMR analysis), b) PTSA (0.5 equiv), Ac_2O, RT, 40 min, quant, c) PPh_3 (2.0 equiv), H_2O/THF, RT, overnight, quant, d) $Pd(PPh_3)_4$ (30 mol %), NEt_3, CH_3CN, 65 °C, 3 h, 70 %, e) CH_2=CHCOCl (10 equiv), *i*Pr_2NEt (20 equiv), CH_2Cl_2, 0 °C, overnight, f) Grubbs 2nd cat. (20 mol %), $(CH_2Cl)_2$, 50 °C, overnight, 92 % (2 steps), g) $Me_3O{\cdot}BF_4$, 2,6-di-*tert*-Bu Py, MS4 A, CH_2Cl_2, RT, 2 h, then $NaBH_4$, MeOH, 0 °C, 1 h.

by the acetylation[16] of **19** followed by a Staudinger reaction through **5** in quantitative yield. Eight-membered-ring formation was achieved by Pd-catalyzed intramolecular allylic amination to give **21** in 70 % yield. Sequential N-acylation followed by ring-closing metathesis (RCM) using Grubbs 2nd catalyst gave (+)-**1c** in 92 % yield (2 steps). Both the NMR spectra and the optical rotation value (+60.38, $CHCl_3$, *c* 0.08, 91 % *ee*, lit: +61, *c*, 0.55)[2a] of synthetic **1c** were in agreement with those of natural **1c**, and these results establish its structure along with the absolute stereochemistry of natural grandilodine C. Reductive removal of the lactam carbonyl in **1c** was accomplished through *O*-methylation and subsequent hydride reduction of the methyliminium ion (Me_3OBF_4 with 2,6-di-*tert*-Bu pyridine and then $NaBH_4$)[17] to give another natural product, (+)-lapidilectine B (**2d**), in 88 % yield, and its optical rotation was observed to be +35.6 (*c* 0.5, $CHCl_3$, lit: +7.6, *c*, 0.9).[2c]

In summary, we have accomplished the first total synthesis of (+)-grandilodine C (**1c**) in overall 8.4 % yield through 18 linear steps with determination of its absolute configuration. Furthermore, transformation of (+)-**1c** into (+)-lapidilectine B (**2d**) was achieved with determination of its absolute stereochemistry. The key points in this synthesis are 1) the facile preparation of spiroenone **8** from commercially available 1,4-cyclohexadione monoacetal by Strecker synthesis and enantioselective deprotonation, and 2) a stereoselective vinylation–allylation sequence to construct new stereocenters. This synthetic strategy demonstrates that the spirodiketone could be a versatile intermediate for the total synthesis of other related *Kopsia* alkaloids, and these syntheses are currently being explored in our laboratory.

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Keywords: alkaloids · fused-ring system · heterocycles · natural products · total synthesis

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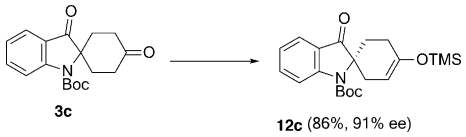
[13] The supplementary crystallographic data for this paper are available at CCDC 1409713 (**8**) and 1409714 (**18**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] Asymmetric deprotonation of **3c** with **11a** gave **12c** in 91 % *ee*.



3c **12c** (86%, 91% ee)

Reagents and conditions: **11a** (2.5 equiv), *n*BuLi (2.5 equiv) then TMSCl (5.0 equiv), −100 °C, 5 min.

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