Total Synthesis of the *Kopsia lapidilecta* Alkaloid (±)-Lapidilectine B

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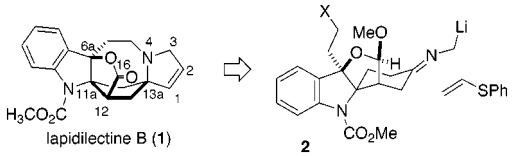
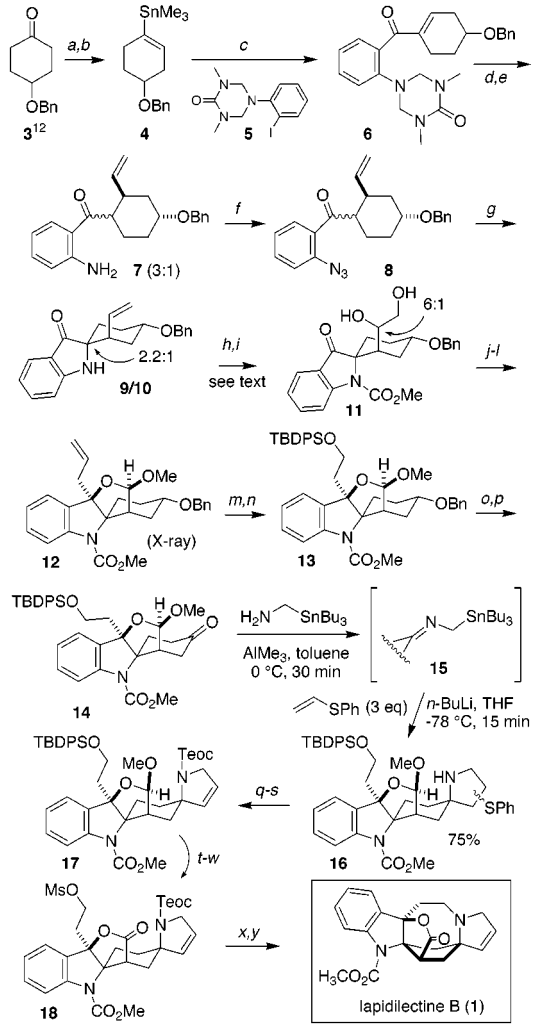
The genus *Kopsia* (*Apocynaceae*, subfamily *Plumerioideae*) is comprised of about 30 species that grow in South and Southeast Asia.[1,2] Lapidilectine B (**1**) is one of several 5,6,12,13-tetrahydro-11a,13a-ethano-3*H*-pyrrolo[1′,2′:1,8]azocino[5,4-*b*]indoles that have been isolated from this genus of plants.[3−5] It was isolated by Awang, et al. from the leaves of the tree *Kopsia lapidilecta* in 1992, and its structure was elucidated by two-dimensional NMR experiments.[3,4,6] The absolute configuration of lapidilectine B is proposed to be as shown based on biogenesis and a positive Cotton effect.[3] Although there are no reports on the pharmacological effects of *Kopsia lapidilecta* alkaloids, various medicinal uses of other *Kopsia* alkaloids have been reported, including the treatment of rheumatoid arthritis, dropsy, tonsillitis, and hypertension.[2,5,7] No synthetic studies on *Kopsia lapidilecta* alkaloids have been reported.[8] We report herein the first total synthesis of a *Kopsia lapidilecta* alkaloid, namely (±)-lapidilectine B (**1**). Notable elements of the synthesis are the assembly of the pyrroline ring by the cycloaddition of a 2-azaallyllithium (**2**) with the acetylene equivalent phenyl vinyl sulfide[9] (Scheme 1) and the assembly of a key 1,2-dihydro-3*H*-indol-3-one (an "indoxyl") via a Smalley cyclization[10,11] of an azido enolate. Further, an intramolecular *N*-alkylation is used to generate the perhydroazocine ring.



A mixture of *cis*- and *trans*-cyclohexane-1,4-diol was monobenzylated and oxidized to give the known[12] ketone **3** (Scheme 1). Formation of the enol triflate of **3**[13] followed by stannylation according to Wulff and co-workers[14] gave **4**. Stille carbonylative coupling[15,16] of **4** with the known iodoaniline derivative **5**[15] gave the enone **6**. Conjugate addition of a vinyl group, which would eventually supply the carbonyl group at C-16 of lapidilectine B, was accomplished using vinylmagnesium bromide under Lipshutz's conditions,[17,18] producing a 3:1 mixture of diastereomeric ketones **7** after hydrolysis of the perhydro-1,3-dimethyl-1,3,5-triazin-2-one protecting group. Both stereoisomers of **7** bore a *trans* relationship between the vinyl and benzyloxy groups, as

Scheme 1[a]



[a] LDA, THF, −78 °C; $PhNTf_2$, 0 °C, 2 h (82%). [b] $(Me_3Sn)_2$, LiCl, cat. $Pd(PPh_3)_4$, THF, reflux, 5 h (91%). [c] CO (80 psi), cat. $Pd_2(dba)_3$, Ph_3As, LiCl, 4 Å molecular sieves, NMP, 70 °C, 12 h (98%). [d] 3 equiv (2-thienyl)Cu(CN)Li, 3 equiv $CH_2{=}CH_2MgBr$, $BF_3{\cdot}OEt_2$, THF, −78 °C, 10 h (84%). [e] 10 equiv concd HCl, MeOH, rt, 30 min (68%). [f] 3 equiv concd HCl, 2 equiv $NaNO_2$, EtOH, 0 °C, 30 min; 4 equiv NaN_3 in H_2O. [g] 5 equiv KOH ^{i}PrOH, 15 °C, 1 h (68%, two steps). [h] *t*-BuLi, THF, −78 to −50 °C, 1 h; 2 equiv MeOCOCl, 0 °C, 1 h (89%). [i] OsO_4, *N*-methylmorpholine *N*-oxide, acetone, rt, 8 h (87%). [j] 3.1 equiv allylmagnesium bromide, THF, −40 °C to rt, 3 h. [k] $NaIO_4$, aq THF, pH 7, rt, 3 h (75%, two steps). [l] 5 equiv camphorsulfonic acid, MeOH, rt, 2 h (82%). [m] O_3, pyridine, CH_2Cl_2, MeOH, −78 °C, 5 min; $NaBH_4$ (80−87%). [n] TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 3 h (88%). [o] $Pd(OH)_2$, cyclohexene, EtOH, reflux, 4 h (82−92%). [p] tetra-*n*-propylammonium perruthenate, *N*-methylmorpholine-*N*-oxide, 4 Å molecular sieves, CH_2Cl_2, rt, 1 h (95%). [q] TeocCl, $^i Pr_2NEt$, CH_2Cl_2, rt, 1 h (91%). [r] *m*-CPBA (1 equiv), $NaHCO_3$, CH_2Cl_2, −30 °C to rt, 2 h (88%). [s] pyridine, $Cl_2C{=}CCl_2$, 140 °C, 4 h (85%). [t] BCl_3, CH_2Cl_2, −10 °C, 1 h. [u] PCC, Celite, CH_2Cl_2, rt, 2 h (45%, two steps). [v] HF·pyridine, THF, rt, 2 h (88%). [w] MsCl, $^i Pr_2NEt$, CH_2Cl_2, −10 °C to rt, 30 min (92%). [x] TFA, CH_2Cl_2, rt, 1 h. [y] $^i Pr_2NEt$, MeCN, 60 °C, 10 h; 3 equiv DBU (45%, two steps).

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(6) The CAS name of lapidilectine B is [6a*R*-(6aα,11a*β*,12α,13a*β*)]-5,6,-12,13-tetrahydro-16-oxo-11*H*-6a,12-(epoxymethano)-11a,13a-ethano-3*H*-pyrrolo[1′,2′:1,8]azocino[5,4-*b*]indole-11-carboxylic acid methyl ester. The researchers who isolated this alkaloid (Awang, et al., refs 3, 4) use a different numbering system, shown in parentheses after the corresponding CAS numbers: 1(15), 2(14), 3(3), 4(4), 6a(7), 11a(2), 13a(20).
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verified by the relative configuration of a later compound in the synthesis (i.e., **12**, vide infra). Diazotization of the aniline **7** followed by displacement with sodium azide gave the *o*-azido ketone **8**.[19,20] Treatment of **8** with KOH according to Smalley and co-workers[10,11] caused cyclization to the diastereomeric 1,2-dihydro-3*H*-indol-3-ones **9** (shown) and **10** (not shown) in good overall yield from the aniline **7**. The major diastereomer **9** was subjected to *N*-acylation and dihydroxylation to give the diol **11** as a 6:1 mixture of diastereomers. Allylation of the ketone, oxidative cleavage of the diol, and methyl acetal formation produced a single diastereomer of **12**, whose structure was verified by X-ray crystallography. The minor amino ketone **10** from the Smalley cyclization could also be transformed into **12**, except that the benzyloxy-bearing stereocenter had the opposite configuration.[21] Ozonolysis of **12**, reduction, and silylation gave **13**, which was debenzylated and oxidized[22] to afford the pivotal ketone **14**. Condensation of a solution of **14** in toluene with (aminomethyl)tributylstannane[23] in the presence of trimethylaluminum[9b] generated a solution of the (2-azaallyl)stannane **15**, which was diluted with THF and treated sequentially with phenyl vinyl sulfide and *n*-BuLi at −78 °C. The spirocyclic pyrrolidine **16** was isolated as a mixture of regio- and stereoisomers (or amide rotamers)[24] in 75% yield based on the ketone **14**. Protection of **16** as its Teoc derivative followed by oxidation of the sulfide to the sulfoxide and elimination gave the 3-pyrroline **17** in good overall yield.[24] Hydrolysis of the methyl acetal with aqueous acid was problematic, but demethylation with boron trichloride provided the lactol, which was oxidized to a lactone with PCC. Deprotection of the alcohol and mesylation afforded **18**. Finally, Teoc removal with CF_3CO_2H followed by heating the trifluoroacetate salt with Hünig's base gave (±)-lapidilectine B (**1**), which exhibited physical data identical to those of the natural alkaloid, spectra of which were kindly provided by Dr. Khalijah Awang of the University of Malaya.[25]

In summary, the first total synthesis of (±)-lapidilectine B has been accomplished, which also represents the first synthesis of a member of the 5,6,12,13-tetrahydro-11a,13a-ethano-3*H*-pyrrolo-[1′,2′:1,8]azocino[5,4-*b*]indole class of alkaloids. The pivotal 2-azaallyl anion cycloaddition proceeded in good yield and facial selectivity to produce the spirocyclic pyrrolidine substructure. Other key steps include the first implementation of Smalley's method for 1,2-dihydro-3*H*-indol-3-one (indoxyl) synthesis in a natural product setting, and a successful intramolecular *N*-alkylation to generate the perhydroazocine nucleus of this alkaloid. Further studies on the use of these methods for the synthesis of related *Kopsia* alkaloids are underway.

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Supporting Information Available: Experimental procedures and characterization data for **1**, **6**, **9**, **10**, and **16**; photocopies of spectra of synthetic and natural lapidilectine B; variable temperature ^{1}H NMR spectra of lapidilectine B (PDF). Crystallographic data for **12** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Methyl carbamate formation, osmylation, bis(trimethylsilyl) ether formation, allylmagnesium bromide addition, desilylation, and periodate cleavage gave an aldehyde that spontaneously epimerized and formed a cyclic hemiacetal, which was converted to the methyl acetal **12** (but epimeric at the benzyloxy group). See: Mi, Y. Ph.D. Thesis, University of Michigan, 1999.

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(24) The mixture **16**, which showed nine acetal methine protons in its ^{1}H NMR spectrum, could be separated by chromatography on silica gel into two fractions. The first fraction, which contained one-third of the product, was found to be the 4-(phenylthio)pyrrolidine as either a mixture of two diastereomers or two amide rotamers. The second fraction, accounting for two-thirds of the material, was found to be the 3-(phenylthio)pyrrolidine, again as either two diastereomers or two amide rotamers. This fraction also contained less than 10% of other isomers. It was not necessary to separate the isomers of **16** to proceed further. Examination of the alkenes **17** and **18** showed that they were 4:1 and 7:1 mixtures of diastereomers at the spiro carbon C(13a), respectively, providing evidence that the diastereofacial selectivity in the 2-azaallyl anion cycloaddition (producing **16**) was reasonable.

(25) In the original work on the isolation of lapidilectine B, several impurities in the ^{1}H NMR spectrum were noted. We also observed these peaks but were able to show that they were due to carbamate rotamers by variable temperature ^{1}H NMR spectroscopy. See the Supporting Information.