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# Synthesis of (±)-lahadinine B and (±)-11-methoxykopsilongine†

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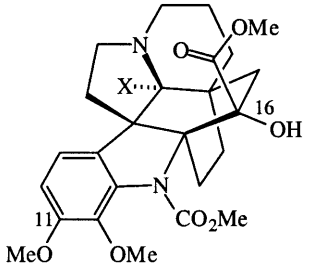
**Abstract**

6,7-Dimethoxytryptamine **11** was converted into the homoannular diene **19** which underwent a Diels–Alder reaction with acryloyl chloride to give **20**. Subsequent radical decarboxylation in the presence of $(PhSe)_2$ provided **22**, which was converted into (±)-lahadinine B **1** and (±)-11-methoxykopsilongine **2**, thus confirming their structures. 

*Keywords:* Kopsia alkaloids; 6,7-dimethoxytryptamine; lahadinine B; 11-methoxykopsilongine.

In 1997 Kam reported the isolation and structure determination of the cyano-substituted indole alkaloid lahadinine B **1** from *Kopsia pauciflora* (Eq (1)).[1] During the course of our recent studies on the synthesis of 11,12-demethoxylahadinine B and related Kopsia alkaloids[2,3] we established a strategy that should, in principle, be applicable to the synthesis of **1** and the related alkaloid 11-methoxykopsilongine **2**.[4]




(1)

**1**, Lahadinine B, X = CN.
**2**, 11-Methoxykopsilongine, X = H.

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† Dedicated to Harry H. Wasserman on the occasion of his 80th birthday.

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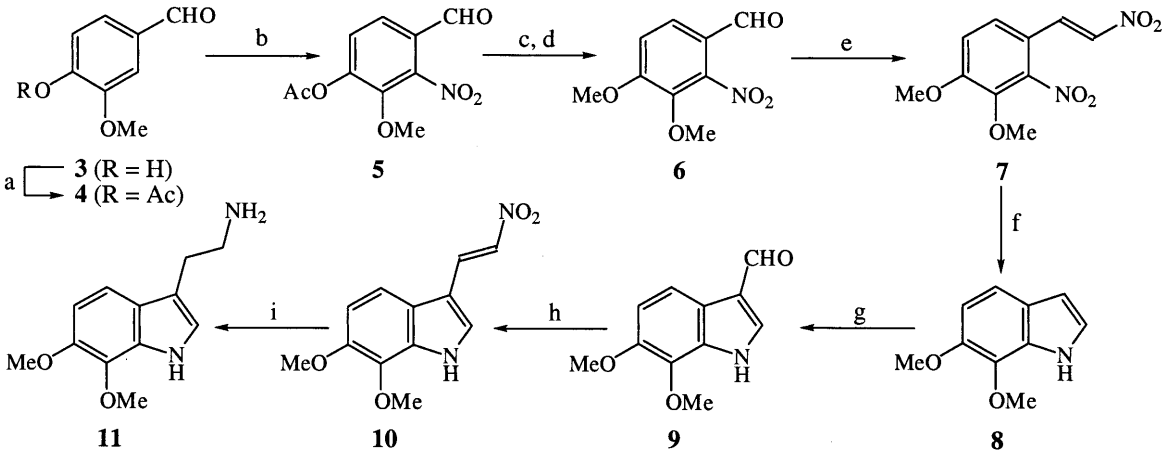
While our previous research started with tryptamine, we now required a convenient synthesis of 6,7-dimethoxytryptamine **11** (Scheme 1). While the sequence of reactions from tryptamine to 11,12-demethoxylahadinine B, eventually, after some optimization, worked reasonably well, it was not a foregone conclusion that the dimethoxy analog would be so cooperative. Indeed, the ability of electron-rich indole derivatives to undergo facile C3 protonation and subsequent dimerization forewarned us that the reactions conditions, and possible whole strategy might require radical modifications to be successful.

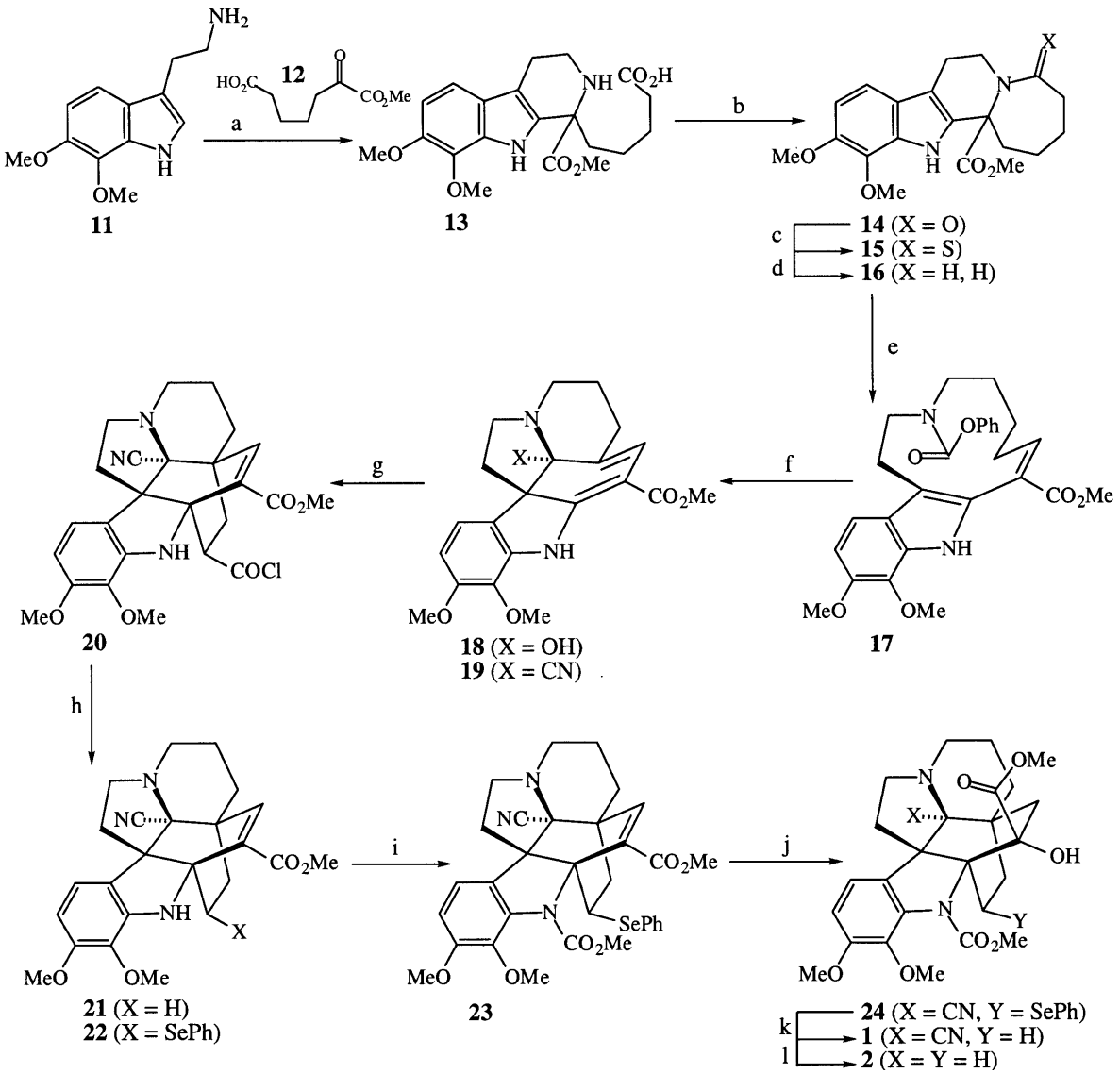



Scheme 1. (a) AcCl/py/100°C, **4** (96%). (b) Fuming $HNO_3$/<6°C, **5** (82%). (c) $K_2CO_3$/MeOH. (d) MeI/$K_2CO_3$/DMF/35°C, **6** (72% from **5**). (e) $MeNO_2$/KOH/DMF/EtOH/aq. work-up HCl/0°C followed by $Ac_2O$/NaOAc/reflux, **7** (73%). (f) Fe/AcOH/EtOH/reflux, **8** (85%). (g) $POCl_3$/DMF/0–25°C, **9** (92%). (h) $MeNO_2$/$NH_4OAc$/reflux, **10** (100%). (i) $LiAlH_4$/THF/0°C to reflux, **11** (91%)

Acetylation of vanillin **3** gave **4**, which was nitrated following literature conditions to give **5** and a small amount of the 6-nitro-isomer (8:1 ratio of isomers).[5] Hydrolysis of **5** and *O*-methylation gave **6**,[6] which was exposed to the classical Henry reaction conditions to give **7**.[7] Reduction of **7** produced the indole **8**.[8] Vilsmeier formylation of **8** gave **9**, which was converted into **11** via **10** using conditions recently described by Corey[9] for the *N*-methyl derivative of **8** (Scheme 1).

Treatment of **11** with **12** under Pictet–Spengler reaction conditions that were satisfactory for tryptamine, gave **13** (<10%) (Scheme 2), whereas exposure of a mixture of **11** and **12** to trifluoroacetic acid (cat.) in dichloromethane in the presence of molecular sieves at 0–23°C gave **13**, which was directly (without purification) converted into **14** in 67% yield for the two steps. Belleau's reagent[10] converted **14** into **15**, and $Ni_2B/H_2$ desulfurization[11] gave **16**. The reaction of **16** with PhOCOCl/$ClCH_2CH_2Cl$ heated at reflux was very slow compared with the demethoxy series,[3] but prolonged treatment (48 h) gave **17** (47%) and recovered **16** (33%). Attempts to drive the reaction to completion diminished the yield of **17**, and more reactive chloroformates such as 4-nitrophenyl chloroformate did not help.

Treatment of **17** with triflic anhydride in dichloromethane containing 4-dimethylaminopyridine heated at reflux, followed by quenching the purple solution with aqueous $NaHCO_3$ gave **18** (18%), whereas quenching the reaction with trimethylsilyl cyanide resulted in **19** (65%). Reaction of **19** with acryloyl chloride (excess) at 23°C gave **20**, which was directly treated with *N*-hydroxy-2-thiopyridone (Na salt),[12] followed by irradiation in the presence of *t*-BuSH resulted in reductive decarboxylation to give **21** (37% from **19**). All attempts to convert **21** into




Scheme 2. (a) $CF_3CO_2H$(cat.)/$CH_2Cl_2$/4 Å molecular sieves/0–23°C. (b) EDCI/HOBt/$Et_3N$/DMF/0–23°C, **14** (67%). (c) Belleau's reagent/THF/0–23°C, **15** (100%). (d) $NiCl_2{\cdot}6H_2O$/$NaBH_4$/THF/MeOH/0°C, **16** (77%). (e) PhOCOCl (15 equiv.)/$Cl(CH_2)_2Cl$/reflux/48 h, **17** (47%, 33% recovered **16**). (f) $Tf_2O$/DMAP/$CH_2Cl_2$/reflux, followed by aqueous $NaHCO_3$, **18** (18%), or work-up with TMSCN/DMAP/$CH_2Cl_2$, **19** (63%). (g) Acryloyl chloride/23°C/24 h. (h) 2-Thiopyridone-*N*-oxide (Na salt)/*t*-BuSH/$CH_2Cl_2$/hv, **21** (37%), or 2-thiopyridone-*N*-oxide (Na salt)/$(PhSe)_2$/$CH_2Cl_2$/hv, **22** (45%). (i) $KN(TMS)_2$/18-crown-6/THF/−78°C followed by $CO_2$ and $Me_2SO_4$, **23** (86%). (j) $Mn(dpm)_3$ (5 mol%)/$PhSiH_3$/$O_2$/*i*-PrOH/$Cl(CH_2)_2Cl$, **24** (83%). (k) $Ph_3SnH$/PhMe/reflux, **1** (94%). (l) $CF_3CO_2H$/$Et_3SiH$/$CH_2Cl_2$/23°C, **2** (93%)

its derived N–$CO_2Me$ adduct using a variety of conditions such as pyridine/triphosgene/MeOH, pyridine/$COCl_2$/MeOH, NaH/$COCl_2$/MeOH, KH/18-crown-6/$COCl_2$/MeOH, DMAP/$ClCO_2Me$ and KH/18-crown-6/$ClCO_2Me$ all failed, presumably because of steric hindrance. Since we had also converted **20** into the phenylselenide derivative **22** (45% from **19**), we decided to examine its conversion into **23**. It was eventually found that $KN(SiMe_3)_2$/18-crown-6/$CO_2$/−78°C, followed

by dimethyl sulfate gave **23** (86%). This same procedure when applied to **21** was unsuccessful! It can be speculated that the PhSe– substituent coordinates the $-NCO_2K$ intermediate sufficiently to allow *O*-methylation before decarboxylation.

The conjugate reduction–oxidation reaction to convert **23** into **24** was conducted with tris-(dipivaloylmethanato)manganese(III) (5 mol%)/$PhSiH_3$/$O_2$/*i*-PrOH/$Cl(CH_2)_2Cl$ and gave **24** in 83% yield.[13] This reaction did not work at all on the unprotected adduct **22**. The final step involves reductive removal of the PhSe– substituent. This was achieved through treatment of **24** with triphenyltin hydride in toluene at reflux to give (±)-lahadinine B in 94% yield. Comparison of spectral data confirmed that the synthetic material was the same as the natural compound,[14] apart from $[\alpha]_D$. The structure of **1** was confirmed by X-ray crystallography.

Since we had established the structure of **1** to be correct, its conversion into **2** would provide unequivocal evidence for the correctness of the structure of **2**. Treatment of **1** with triethylsilane in the presence of trifluoroacetic acid cleanly converted it into **2** (93%).

## Acknowledgements

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14. Professor Kam is thanked for copies of spectra of **1**.