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# Synthesis of (±)-demethoxypauciflorine B and (±)-pauciflorine B from (±)-11,12-demethoxylahadinine B and (±)-lahadinine B, respectively via a peroxycarbanolamine fragmentation reaction

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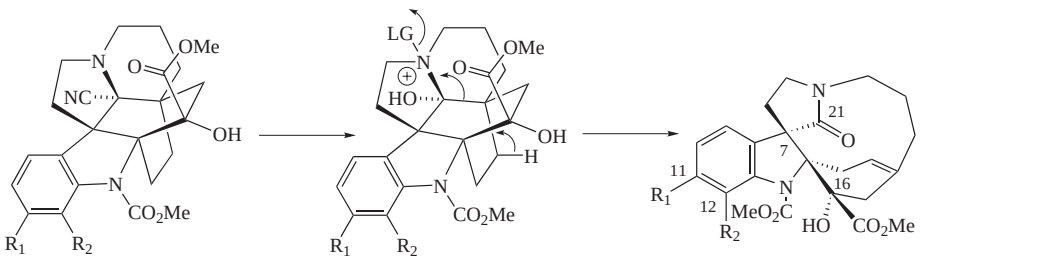
**Abstract**—Conversion of 11,12-demethoxylahadinine B **3** and lahadinine B **2** into 11,12-demethoxypauciflorine B **6** and pauciflorine B **5**, respectively, was achieved by treatment with $AgBF_4$/THF followed by EtOAc/$MeCO_3H$. 

In 1997 Kam reported the isolation and structure determination of two cyano-substituted indole alkaloids from *Kopsia pauciflora* which were named lahadinine A **1** and lahadinine B **2**, respectively (Scheme 1).[1] We have reported the synthesis of the 11,12-demethoxy analog **3**,[2] and more recently completed the synthesis of **2**.[3] In 1996 the structures of the *Kopsia* alkaloids pauciflorine A and B **4/5** were published,[4] and we have embarked upon a strategy for their synthesis, which was in part, based on a biogenetic speculation.[2,5]

It appears plausible that the pauciflorines are derived from the lahadinines by fragmentation of the carbon–carbon bond adjacent to the *tert*-amine as indicated in **1a**. The leaving group (LG) indicated on the *tert*-amine **1a** is most conveniently an activated *N*-oxide. With this in mind we began by converting **7**[2] into **8** by treatment with $AgBF_4$/THF followed by aqueous $NaHCO_3$,[6] and examining the Polonovski fragmentation (Scheme 2).[7] Oxidation of **8** with *m*-chloroperoxybenzoic acid (*m*-CPBA) resulted in the *N*-oxide **9** which underwent the required fragmentation to give **10** when exposed to trifluoroacetic anhydride (TFAA).

When the diene **10** was treated with a catalytic amount of tris(dipivaloylmethanato)manganese(III) [abbreviated to $Mn(dpm)_3$]/$PhSiH_3$/$O_2$ in isopropyl alcohol at 0°C, with the expectation that **6** would be formed, it was converted into kopsijasminilam **11** (after work-up




**1**, lahadinine A, $R_1$, $R_2$ = -$OCH_2O$-
**2**, lahadinine B, $R_1$ = $R_2$ = OMe
**3**, 11,12-demethoxylahadinine, $R_1$ = $R_2$ = H

**1a**

**4**, pauciflorine A, $R_1$, $R_2$ = -$OCH_2O$-
**5**, pauciflorine B, $R_1$ = $R_2$ = OMe
**6**, 11,12-demethoxypauciflorine, $R_1$ = $R_2$ = H

**Scheme 1.**

*Keywords*: lahadinine; pauciflorine; peracetic acid; Polonovski fragmentation; peroxycarbanolamine fragmentation.

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† Author for inquiries concerning the X-ray data for compounds **5**, **6**, **14**, **15**, **17**, **21** and **22**

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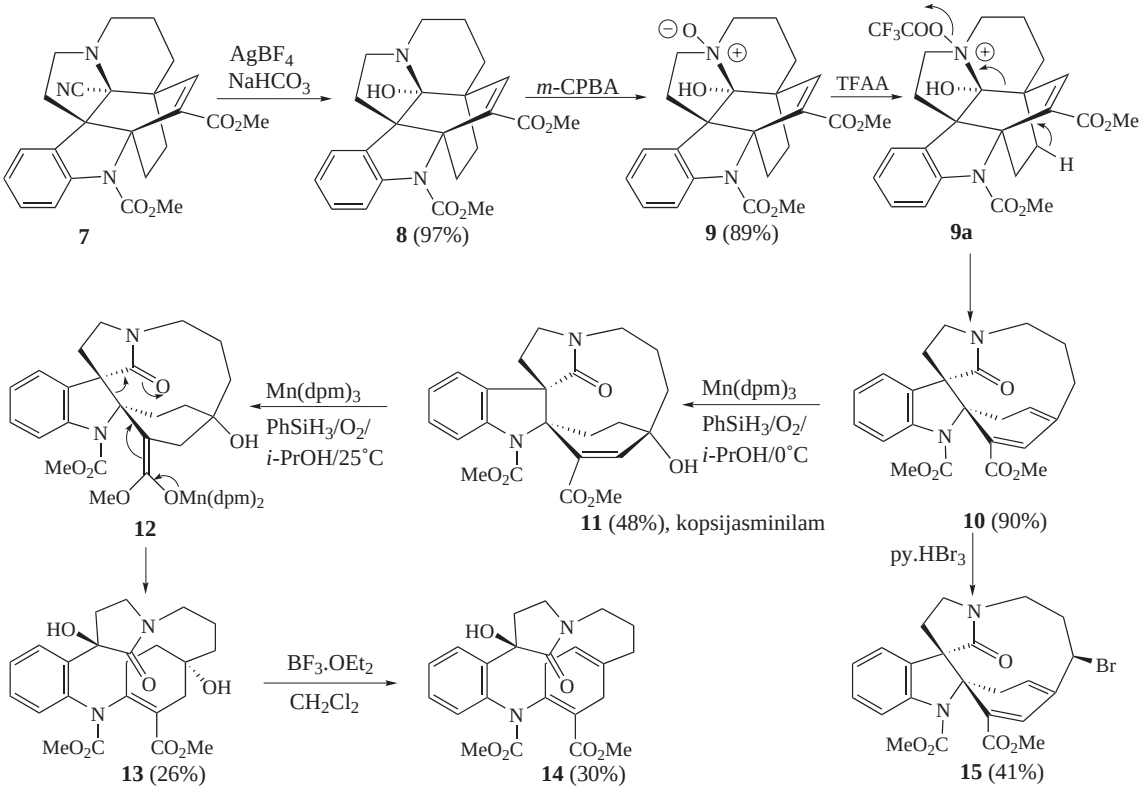
with aqueous $Na_2S_2O_3$) (Scheme 2).[8,9] Further exposure of **11** to $Mn(dpm)_3]/PhSiH_3/O_2$ in isopropyl alcohol at 25°C did not result in the expected α-hydroxy ester, but rather fragmentation of the putative $Mn(dpm)_2$-enolate **12** and oxidation α- to the amide resulted in **13**. Dehydration ($BF_3{\cdot}OEt_2$) of **13** gave **14** whose structure was confirmed by X-ray. Attempted protection of **10** through bromination of the diene with pyridinium tribromide gave **15** (X-ray).

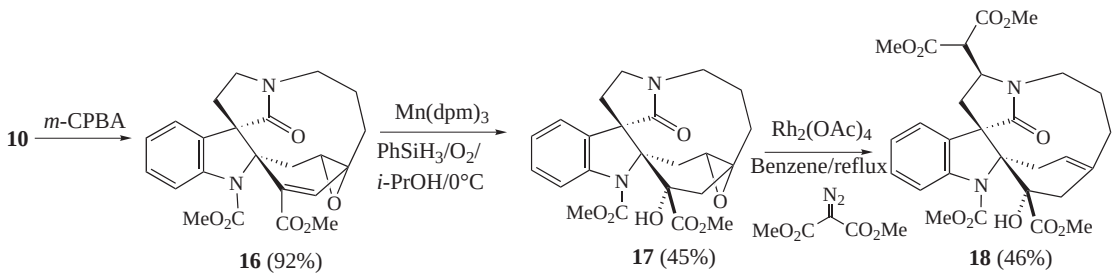
In a further effort to make use of the diene **10** it was treated with *m*-CPBA to give **16** (Scheme 3). Conjugate reduction of **16** and α-hydroxylation gave **17**, without the fragmentation alluded to above. Exposure of **17** to the Ganem epoxide deoxygenation procedure[10] resulted in deoxygenation of the epoxide, but unfortunately the dimethylmalonyl carbenoid had also inserted adjacent to the nitrogen atom of the pyrrolidine amide resulting in **18**. Consequently, we abandoned efforts to convert **10** into **6**.

The above findings appeared to indicate that the α-hydroxyester functionality should be introduced before any attempted fragmentation process to the pauciflorine skeleton. Consequently, we first studied the Polonovski fragmentation of **20** (Scheme 4). Treatment of demethoxylahadinine **3** with $AgBF_4$/THF followed by aqueous $NaHCO_3$ work-up and extraction with EtOAc gave **19**, which was oxidized (*m*-CPBA) to a single *N*-oxide **20**. Exposure of **20** to $TFAA/CH_2Cl_2$ produced **22** (structure by X-ray). Attempted Polonovski rearrangement of **20** with $BF_3{\cdot}OEt_2$ gave a new *N*-oxide (presumably via **20a**) isolated as the $BF_2$-adduct **21** (structure by X-ray). The adduct **21** on treatment with $TFAA/CH_2Cl_2$ gave an intractable mixture that did not contain any of **6** (as judged by the absence of the diagnostic signal for the alkene proton $^1H$ NMR: $\delta$ 5.25, $J = 6.4$ Hz).

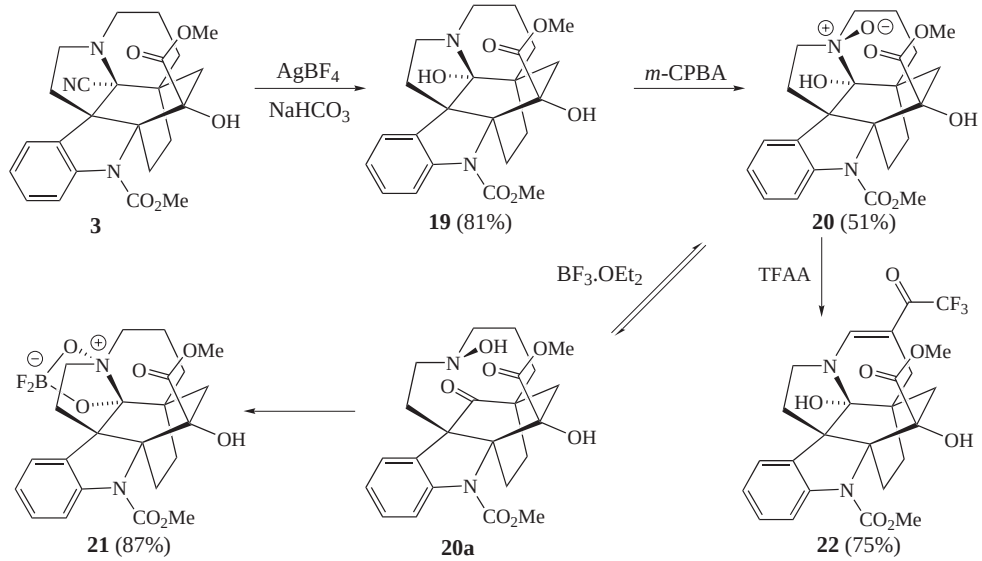
At this stage a curious and eventually explainable transformation took place (Scheme 5). On one occasion



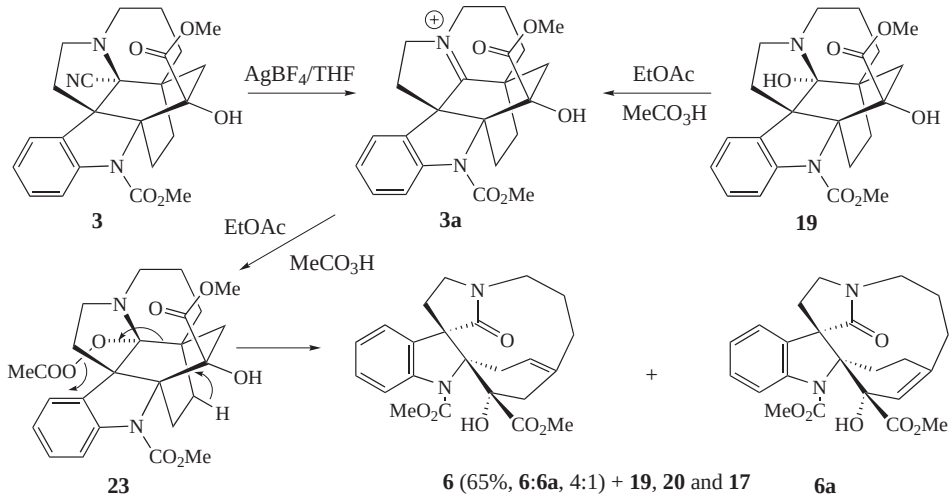

**Scheme 2.**




**Scheme 3.**




**Scheme 4.**



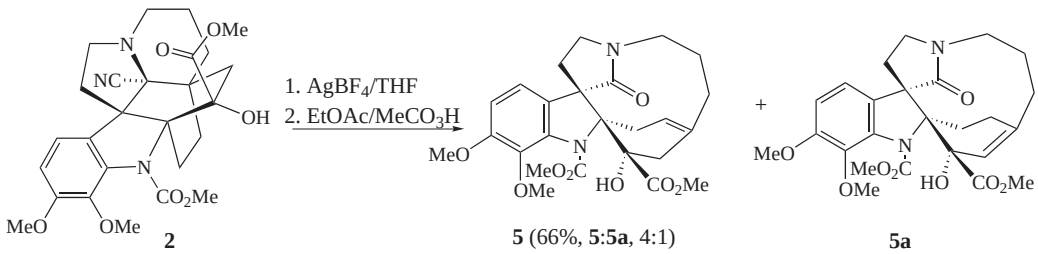

**Scheme 5.**

while converting **3** into **19**, the $^1$H NMR spectrum of crude **19** was very clean, but after purifying **19** by chromatography over silica gel eluting with EtOAc/hexanes (1:2→1:1)/$NEt_3$ (1%), the eluents contained **19** and **20**, and very surprisingly, **6** and the derived epoxide **17**! Furthermore, we also observed that all of the triethylamine used in the chromatography had been oxidized to triethylamine *N*-oxide. This experiment was reproduced three times, and each time we isolated **19**, **20**, **6** and small amounts of **17**. On a fourth attempt only **19** was formed. It would appear that the simplest explanation consistent with these observations is that the EtOAc used during chromatography contained a finite amount of a peracid (most likely peracetic acid). Indeed, when we deliberately added peracetic acid to EtOAc (10%) and used it to quench the $AgBF_4$/THF conversion of **3** into **19**, we obtained **6**/**6a** (4:1, 65%) along with **20** and **17**. The structures of **6** and **17** were confirmed by X-ray. We have subsequently detected peracid impurities in EtOAc using standard peroxide testing protocols at the level of approximately 0.5 mg/L.

Since we know that neither *N*-oxide **20** nor **21** is the source of demethoxypauciflorine **6**, it is reasonable to suppose that the iminium ion intermediate **3a** in the conversion of **3** into **19** adds peracetic acid to generate **23** which fragments to give **6** and **6a**.[11]

Treatment of (±)-lahadinine B **2** with $AgBF_4$/THF followed by work-up with EtOAc/$MeCO_3H$ (10%) gave (±)-pauciflorine **5** and the double-bond isomer **5a** (4:1) in 66% yield (Scheme 6). Crystallization of **5** from $MeOH/CH_2Cl_2$ gave crystals suitable for X-ray crystallography which confirmed the proposed structure.[12,13]

The peroxycarbanolamine fragmentation process takes place under exceptionally mild conditions since the central σ-bond that is broken is aligned *trans*-coplanar to the indicated hydrogen atom and to the O–O bond.




**Scheme 6.**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12. Dr. Kam is thanked for $^1H$ and $^{13}C$ NMR spectra of **5**.
13. Data for **15**: Mp 160–162°C. IR (film) 2942, 1712, 1685, 1600 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.93, 7.50 (1H, d, $J=7.8$ Hz), 7.40–6.90 (4H, m), 6.04 (1H, br d, $J=3.6$ Hz), 4.59 (1H, br d, $J=11.1$ Hz), 4.06 (1H, t, $J=13.5$ Hz), 3.95–3.60 (6H, m), 3.50 (1H, m), 3.30–1.50 (8H, m). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 175.6, 166.3, 152.6, 140.5, 134.5, 133.1, 132.2, 128.8, 124.7, 124.2, 123.9, 123.8, 115.1, 73.2, 60.4, 58.8, 52.2, 52.0, 44.5, 42.0, 35.5, 31.0, 29.3. HRMS calcd for $C_{23}H_{24}N_2O_5Br$ ($MH^+$) 487.087. Found 487.085. Data for **22**: Mp 205–207°C. IR (film) 3310, 1737, 1681 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.62 (1H, d, $J=8.4$ Hz), 7.58 (1H, s), 7.53 (1H, d, $J=9.0$ Hz), 7.27 (1H, t, $J=8.4$ Hz), 7.07 (1H, t, $J=7.5$ Hz), 4.04 (1H, m), 3.97 (3H, s), 3.72 (3H, s), 3.39 (1H, dd, $J=11.1$, 6.9 Hz), 2.85 (1H, br s), 2.52 (1H, d, $J=17.4$ Hz), 2.34 (1H, t, $J=10.5$ Hz), 2.22 (1H, d, $J=17.1$ Hz), 2.12 (1H, m), 2.08 (1H, s), 1.95 (1H, m), 1.75–1.50 (5H, m). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 172.1, 156.4, 146.1, 140.7, 132.2, 128.5, 124.2, 123.4, 116.2, 89.4, 77.2, 74.6, 73.7, 60.1, 53.7, 52.6, 49.6, 41.1, 40.2, 34.0, 26.8, 26.4, 23.1 (two signals not observed). HRMS calcd for $C_{25}H_{26}N_2O_7F_3$ ($MH^+$) 523.169. Found 523.167 Data for **6**: Mp softens >180°C, melts 247–249°C. IR (film) 3195, 1732, 1681, 1603 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.90 (1H, d, $J=1.5$ Hz), 7.51 (1H, d, $J=8.0$ Hz), 7.18 (1H, td, $J=7.5$, 1.5 Hz), 7.04 (1H, td, $J=7.5$, 1.0 Hz), 6.94 (1H, d, $J=8.0$ Hz), 5.27 (1H, d, $J=6.0$ Hz), 4.05 (1H, br t, $J=13.5$ Hz), 3.96 (3H, s), 3.80 (3H, s), 3.70 (1H, m), 3.31 (1H, td, $J=10.5$, 2.0 Hz), 3.12 (1H, br d, $J=17.0$ Hz), 2.95 (1H, dt, $J=14.0$, 2.5 Hz), 2.88 (1H, br d, $J=19.0$ Hz), 2.71 (1H, dd, $J=16.5$, 6.5 Hz), 2.53 (1H, ddd, $J=16.0$, 9.0, 2.5 Hz), 2.45 (1H, br d, $J=18.5$ Hz), 2.26 (2H, m), 2.11 (1H, m), 1.89 (1H, m), 1.52 (1H, m). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 175.3, 173.3, 157.5, 140.5, 134.7, 130.5, 128.2, 124.5, 124.3, 122.2, 116.2, 81.9, 75.6, 59.9, 53.6, 52.6, 44.3, 42.8, 37.0, 36.0, 30.4, 29.8, 21.6. HRMS calcd for $C_{23}H_{27}N_2O_6$ ($MH^+$) 427.187. Found 427.187.16. Data for **6a**: Mp 182–184°C. IR (film) 3205, 1732, 1681, 1603 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.71 (1H, s), 7.49 (1H, d, $J=7.5$ Hz), 7.17 (1H, td, $J=7.5$, 1.5 Hz), 7.03 (1H, td, $J=7.5$, 1.0 Hz), 6.96 (1H, d, $J=7.5$ Hz), 6.60 (1H, br s), 4.03 (1H, m), 3.97 (3H, s), 3.80 (3H, s), 3.39 (1H, m), 3.17 (1H, t, $J=9.5$ Hz), 2.85 (1H, m), 2.51 (3H, m), 2.39 (1H, m), 2.20 (2H, m), 2.09 (2H, m), 1.75 (2H, m). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 174.9, 172.8, 157.1, 143.1, 140.9, 134.4, 128.1, 124.6, 124.3, 119.6, 115.8, 82.7, 74.1, 59.7, 53.5, 52.7, 44.8, 34.3, 32.1, 29.7, 28.2, 22.1, 21.1. HRMS calcd for $C_{23}H_{27}N_2O_6$ ($MH^+$) 427.187. Found 427.186. Data for **5:** IR (film) 3240, 2923, 2850, 1732, 1688, 1679, 1601 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 8.05 (1H, d,

$J=1.9$ Hz), 6.67 (1H, d, $J=8.4$ Hz), 6.64 (1H, d, $J=8.4$ Hz), 5.23 (1H, d, $J=6.4$ Hz), 4.03 (1H, t, $J=12.8$ Hz), 3.86 (3H, s), 3.86 (3H, s), 3.80 (3H, s), 3.72 (3H, s), 3.64 (1H, q, $J=9.9$ Hz), 3.25 (1H, t, $J=10.2$ Hz), 3.06 (1H, d, $J=17.5$ Hz), 2.87 (3H, m), 2.68 (1H, dd, $J=16.4$ and 6.7 Hz), 2.48 (1H, d, $J=19.4$ Hz), 2.24 (2H, m), 2.05 (3H, m), 1.50 (1H, m). HRMS calcd for $C_{25}H_{31}N_2O_8$ ($MH^+$) 487.208. Found 487.208.