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Synthesis of the *Kopsia* alkaloids (±)-pauciflorine B, (±)-lahadinine B, (±)-kopsidasine, (±)-kopsidasine-*N*-oxide, (±)-kopsijasminilam and (±)-11-methoxykopsilongine

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Abstract—Pictet–Spengler condensation of **13** with tryptamine gave **14**, which was converted into **17**. Treatment of **17** with phenyl chloroformate resulted in **18**, which underwent transannular cyclization to give **19**. The more stable cyano-analog **22** was made by treating **18** with Tf_2O/DMAP to generate **18f**, and quenching the reaction with trimethylsilyl cyanide. Treatment of **22** with acryloyl chloride (excess) at 75°C gave **23**, which was directly treated with *N*-hydroxy-2-thiopyridone/Et_3N to give **24**. Irradiation of **24** in the presence of *t*-BuSH resulted in reductive decarboxylation to give **26** and a small amount of the 2-thiopyridyl ether **25**. Protection of the aniline nitrogen in **26** required the use of triphosgene/pyridine followed by methanol. The final step for the conversion of **27** into **28** required conjugate reduction of the α,β-unsaturated ester followed by α-hydroxylation and gave **28** (11,12-demethoxy lahadinine B). Exposure of **26** to $PhI(OAc)_2$/MeOH cleanly gave **26a**, which was directly reduced with Zn/AcOH to **29**. Conversion of **29** into **30** proceeded as before, and when **30** was treated with $AgBF_4$/THF followed by aqueous $NaHCO_3$ it was converted into (±)-kopsidasine **2**, completely characterized as its derived *N*-oxide **2a**. Treatment of **26** with $AgBF_4$/THF followed by aqueous $NaHCO_3$, gave **31**. Oxidation of **31** with *m*-chloroperoxybenzoic acid resulted in the *N*-oxide **32** which underwent fragmentation to give **33** when exposed to trifluoroacetic anhydride. When the diene **33** was treated with $Mn(dpm)_3$ (cat)/$PhSiH_3$/O_2 in isopropyl alcohol at 0°C, it was converted into kopsijasminilam **4**. Peracetic acid in EtOAc (10%) was used to quench the $AgBF_4$/THF conversion of **28** into **37**, and resulted in **42/42a** (4:1, 65%) along with small amounts of **38** and **41c**. Application of these procedures, with some modifications, to the 11,12-dimethoxy substituted systems gave (±)-lahadinine B **64**. Treatment of **64** with triethylsilane in the presence of trifluoroacetic acid cleanly converted it into 11-methoxykopsilongine **65** (93%). Treatment of (±)-lahadinine B **64** with $AgBF_4$/THF followed by work-up with EtOAc/$MeCO_3H$ (10%) gave (±)-pauciflorine **6** and the double bond isomer **6a**.

1. Introduction

The history of the kopsane alkaloids began with the isolation of kopsine **1** in 1890, Scheme 1.[1] Classical structural degradation studies of kopsine and structurally related alkaloids uncovered many remarkable chemical transformations,[2] but the structure of kopsine remained elusive until the advent of high-resolution mass spectrometry in the 1960s.[3] Confirmation of the correct structure for kopsine was obtained by X-ray crystallography.[4] During the last forty years or so there have been many reports of the isolation and structure determination of a large number of new *Kopsia* alkaloids with various degrees of oxidation.[5] The *Kopsia* alkaloids have attracted some attention as targets for total synthesis,[6] and our own efforts in this area in the 1980s was dominated by the use of indole-2,3-quinodimethanes as reactive intermediates for the synthesis of the more complicated kopsanes.[7]

In 1982 Hesse[8] reported the structure of kopsidasine **2** (and its derived *N*-oxide), which was the first example of a kopsane alkaloid where oxidation has taken place at C-21 resulting in the hemiaminal functionality. The structure of paucidactine A **3** further illustrates the varying and high degree of oxidation of the core kopsane skeleton that can take place.[9] The X-ray structure of the spirocyclic amide kopsijasminilam **4**, a possible 'Grob-type' fragmentation product of a hemiaminal has been described, thus placing the structural assignments on a firm basis.[10] In 1996 the structures of the *Kopsia* alkaloids pauciflorine A and B **5/6** were published,[11] and apart from their unusually strained structure, it was claimed that they selectively 'inhibited melanin synthesis of B16 melanoma cells at 13 μg mL^{-1} without any cytotoxicity towards the cultured cells'.

While the indole-2,3-quinodimethane strategy was applicable to the synthesis of kopsanes that lacked the hemiaminal

Keywords: *Kopsia* alkaloids; pauciflorine B; tryptamine.

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† Author for inquiries concerning the X-ray data. Complete crystallographic details for compounds **2a**, **6**, **18**, **19**, **19a**, **20**, **21**, **22b**, **28**, **35**, **36**, **39**, **40**, **42**, **42c** and **64** are deposited in the Cambridge data base.

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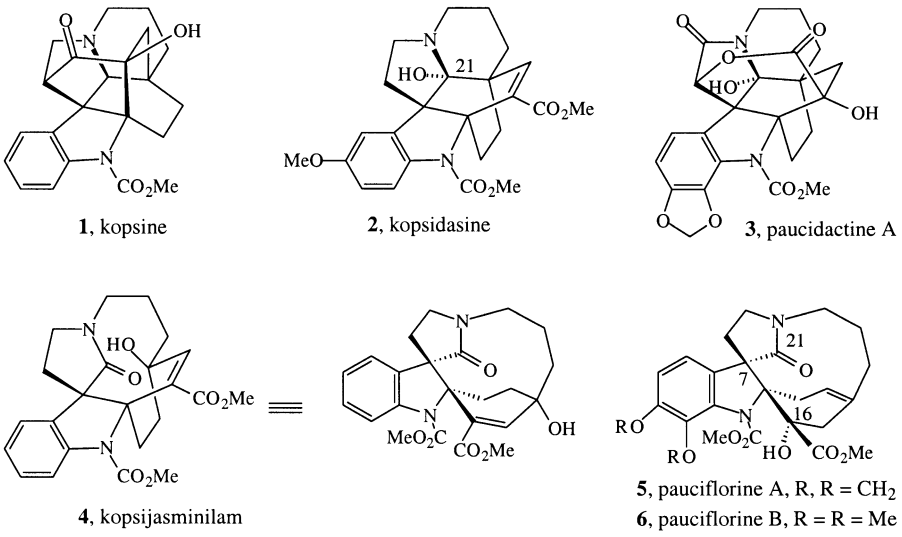
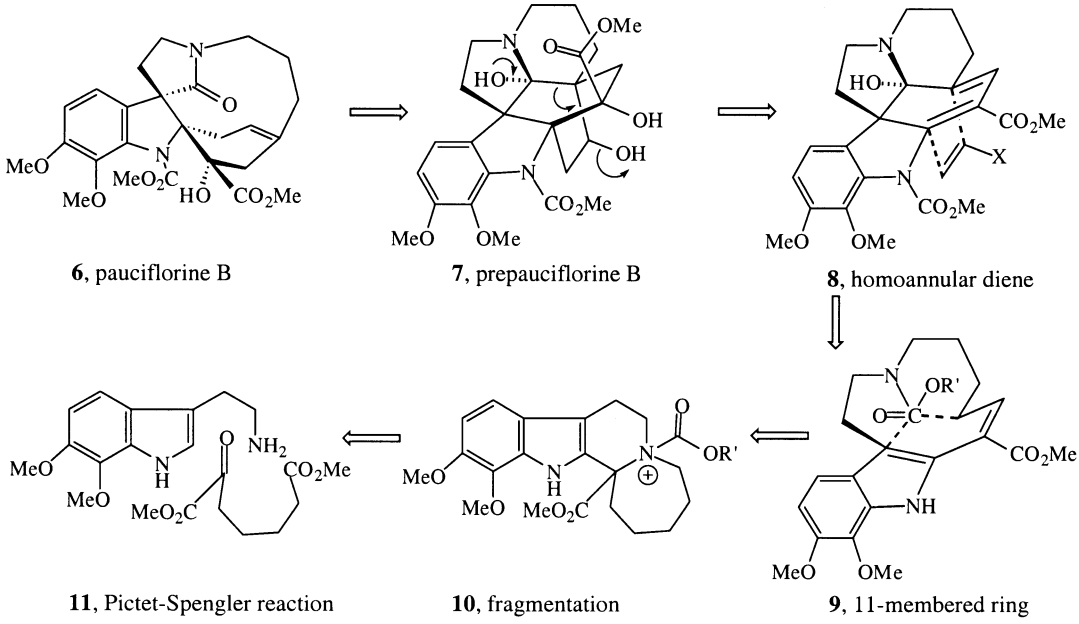


Scheme 1. Structures of some typical *Kopsia* alkaloids.

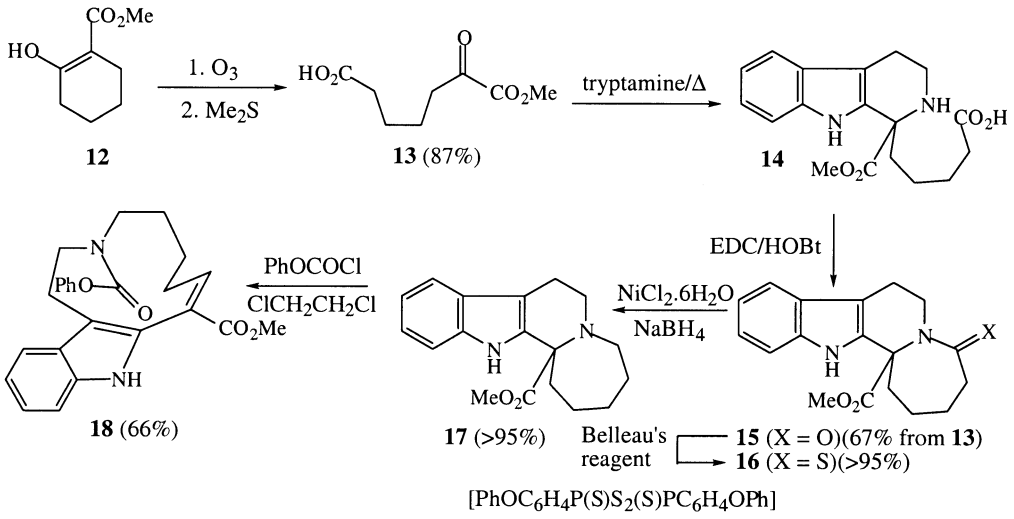
functionality,[7] this approach did not readily lend itself to these new structural types. Consequently, we adopted a completely different synthetic strategy that was based upon (at the time) a hypothetical biogenetic pathway.[12,13] Grob fragmentation of **7** leads to **6**. The structure of **7** is the classical *Kopsia* skeleton, which can be derived from **8**, Scheme 2. Two transannular cyclizations of **9** have the potential to provide a concise route to the homoannular diene **8**. Isogramine-type fragmentation of **10** should provide access to **9**,[14] and **10** is available from the classical Pictet–Spengler reaction of a tryptamine derivative and a pyruvate ester.[15]

2. Synthesis of the homoannular diene 19

All of our preliminary studies were conducted with tryptamine rather than the far less accessible 6,7-dioxygenated tryptamine derivatives. Ozonolysis of **12** followed by reductive work-up provided **13** (87%).[16] Pictet–Spengler condensation of **13** with tryptamine (containing 0.05 equiv. of tryptamine·HCl) gave **14**, which was treated, without purification, with 1-hydroxybenzotriazole/1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI)/Et_3N in dimethylformamide to give **15**. It should be noted that the use of the dimethyl ester derivative of **13** was unsuccessful because the methyl ester derivative of **14** could not be converted into **15**, and as a consequence the reactions in Scheme 3 are required. Belleau's reagent[17] converted **15** into **16**, and W-2 Raney Nickel or Ni_2B/H_2 desulfurization[18] gave **17**. Treatment of **17** with phenyl chloroformate/$ClCH_2CH_2Cl$ heated at reflux resulted in **18**, the structure of which was confirmed by X-ray crystallography. Several



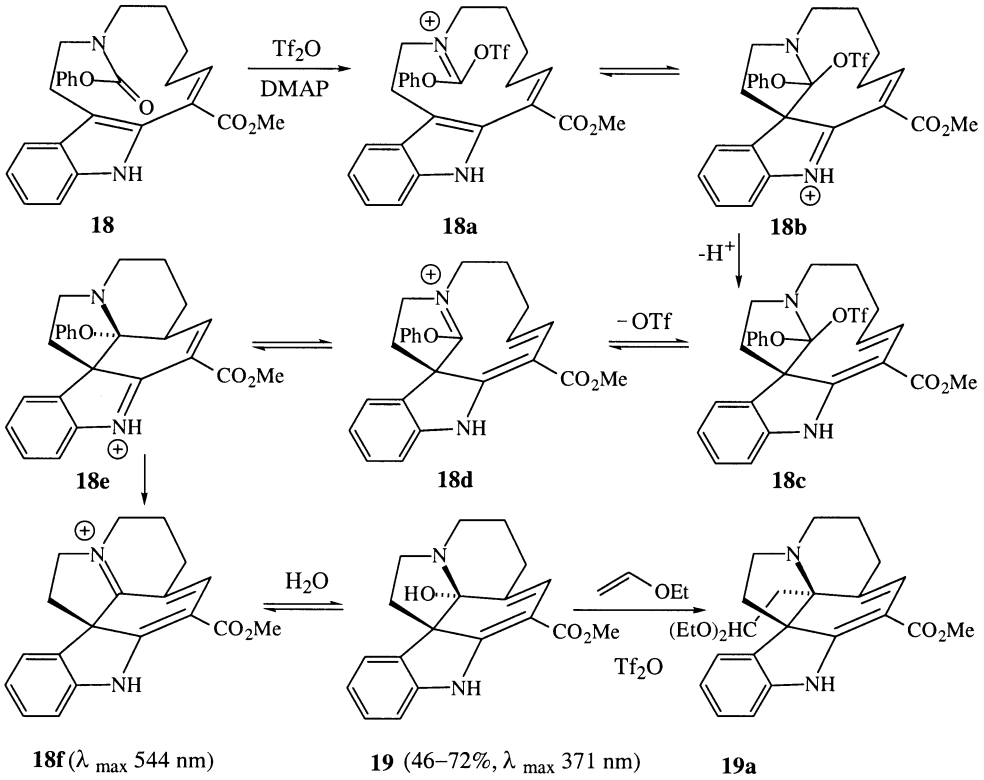
Scheme 2. Proposed biogenetic origin of pauciflorine and retrosynthetic analysis.



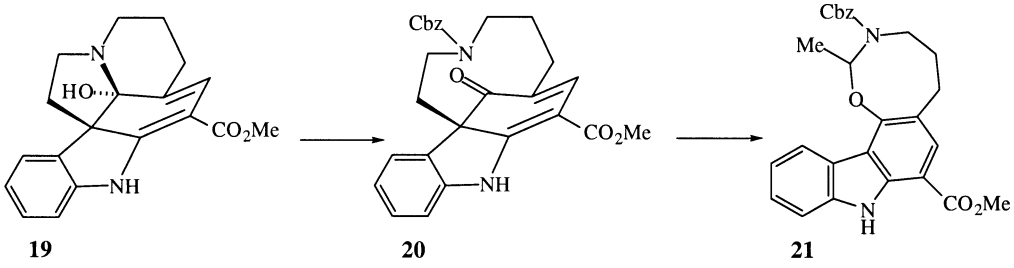
Scheme 3. Synthesis of tetracyclic amine **17** and fragmentation to give **18**.

other chloroformate induced fragmentations of **17** were tried, but phenyl chloroformate gave the best results.

It was anticipated that treatment of **18** with a powerful electrophile had the potential to cause both transannular reactions (**9** to give **8**, Scheme 2) to take place resulting in **19**, Scheme 4. Activation of **18** to give **18a** should result in **18b**, which on proton loss to **18c** and iminium ion formation generates **18d**, which can cyclize to give **18e**. The iminium ion **18e** can lose a proton and eliminate –OPh to give **18f**. In the event treatment of **18** with triflic anhydride in dichloromethane containing 4-dimethylaminopyridine heated at reflux[19] eventually gave a deep purple solution of the iminium ion **18f**. Quenching the purple solution with aqueous $NaHCO_3$ gave **19** as yellow crystals whose structure was confirmed by X-ray crystallography. Dissolving **19** in trifluoroacetic acid gave a purple solution (λ_{max} 544 nm). Treatment of **19** with trifluoromethanesulfonic anhydride in the presence of ethyl vinyl ether gave **19a** (X-ray). The yields of **19** were somewhat variable (46–72%), and the compound was not stable to chromatography other than neutral alumina.



Scheme 4. Formation of the homoannular diene **19**.



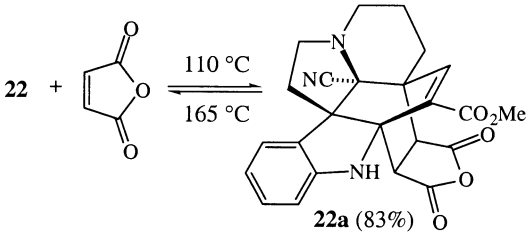
Scheme 5.

3. Reactions of the homoannular diene 19

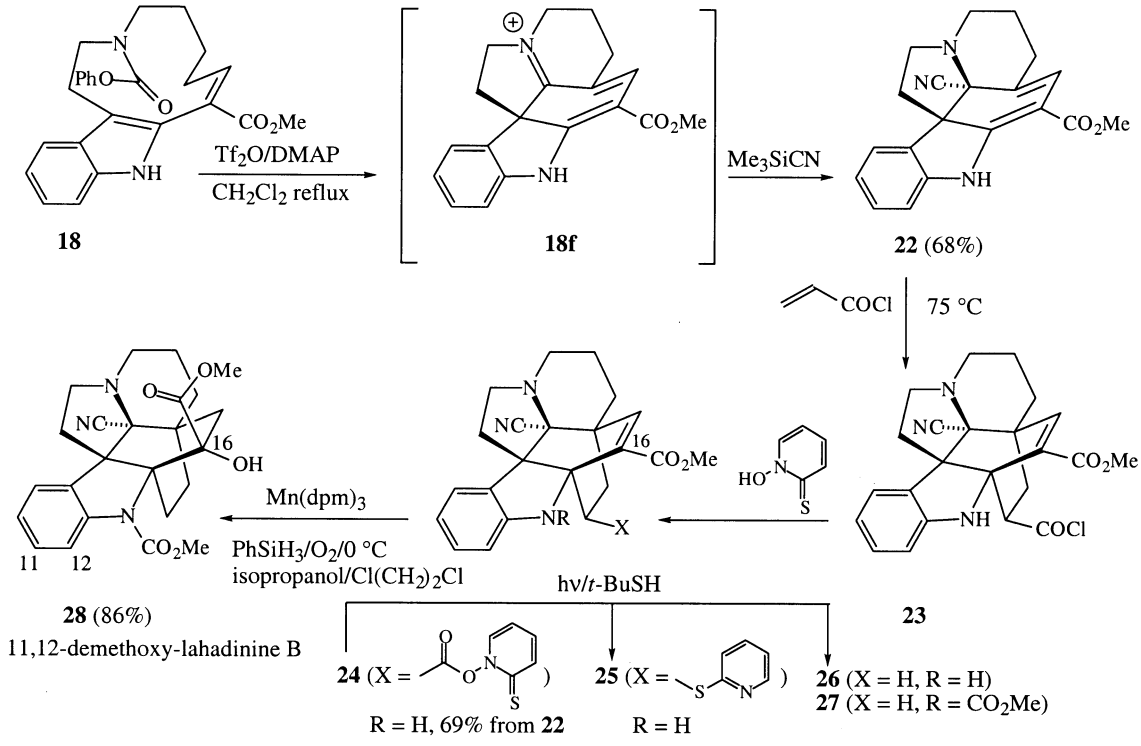
All attempted [2+4] cycloaddition reactions with the homoannular diene **19** were unsuccessful, and the only reaction pathway observed was the formation of carbazoles among otherwise complex mixtures. It was found that treatment of **19** with benzyl chloroformate in the presence of proton sponge resulted in formation of the *o*-cyclohexadienone **20** (95%), which also was resistant to [2+4] cycloaddition chemistry, Scheme 5. Heating **20**, for example, with maleic anhydride in toluene or xylene at reflux resulted in the formation of **21** (X-ray). It was evident that the hemiaminal hydroxyl group in **19** needed to be protected, or replaced with a more robust functional group.[20]

4. Synthesis of (±)-demethoxy-lahadinine B 28

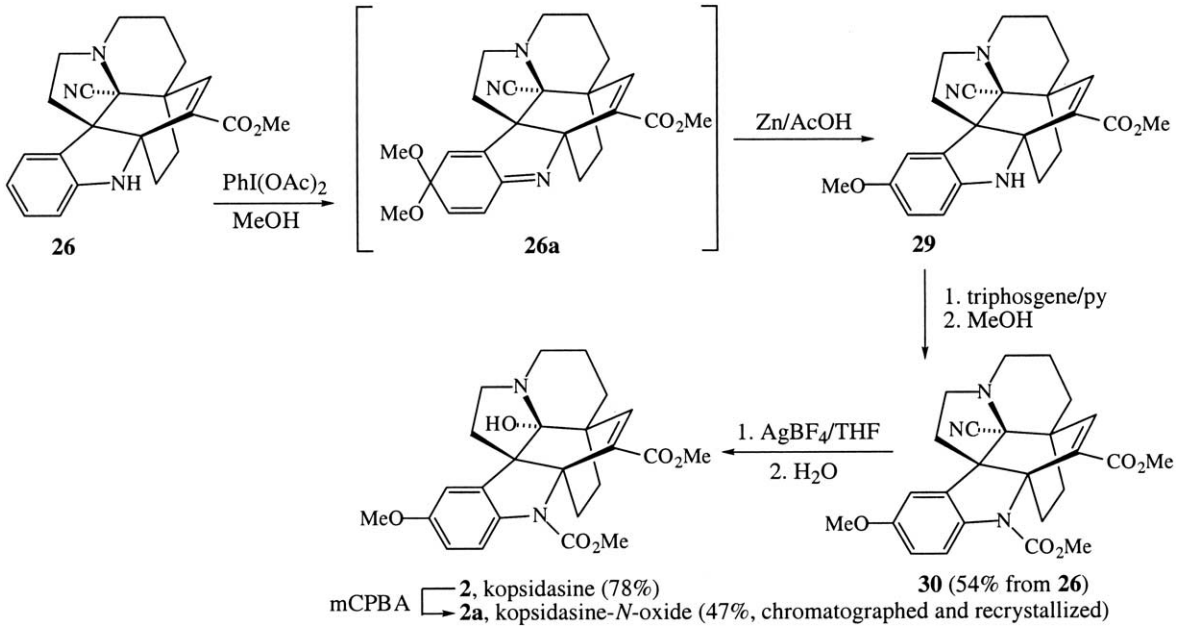
Initially, we found that replacing the hemiaminal hydroxyl group with an –OMe or –SPh (via acid catalyzed exchange) gave the required derivatives, but they were no better behaved in attempted [2+4] cycloaddition chemistry than **19**. Consequently, we made the more robust cyano-analog **22** by treating **18** with Tf_2O/DMAP to generate **18f**, and quenching the reaction with trimethylsilyl cyanide, Scheme 6. This procedure improved the yield of the homoannular diene derivative, and was more reproducible. In retrospect the choice of the cyano derivative **22** was somewhat fortuitous since we became aware that this functionality is present in the lahadinine *Kopsia* alkaloids. In 1997, Kam reported the isolation and structure determination of lahadinine B **64** from *Kopsia pauciflora*, Scheme 12.[21] Consequently, we could now consider the conversion of **22** into 11,12-demethoxylahadinine B **28**.



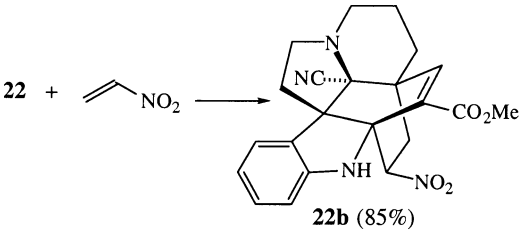
(1)



Scheme 6. Installation of 16α-hydroxyl group.



Scheme 7. Aniline α-methoxylation.



(2)

The improved stability of the homoannular diene **22** did indeed solve the above problems. For example, treatment of **22** with maleic anhydride in toluene at 100°C for 6 h gave the *endo*-adduct **22a** (83%), Eq. (1). Interestingly, heating **22a** at higher temperatures (165°C) resulted in the retro-Diels–Alder (or retro-Mannich) reaction to give back the starting materials. Also nitroethylene reacted with **22** at 75°C to give **22b** (85%) (X-ray), Eq. (2). Treatment of **22b** with *n*-Bu_3SnH/AIBN(cat)/PhH reflux gave a complex mixture that did not contain (by ^1H NMR) the expected adduct **26**. Consequently, we decided to use the very reactive acryloyl chloride as the dienophile.

Treatment of **22** with acryloyl chloride (excess) at 75°C gave **23**, which was directly treated with *N*-hydroxy-2-thiopyridone/Et_3N to give **24** (69% from **22**).[22] Irradiation of **24** in the presence of *t*-BuSH resulted in reductive decarboxylation to give **26** and a small amount of the 2-thiopyridyl ether **25**. Protection of the aniline nitrogen in **26** required the use of triphosgene/pyridine followed by methanol, as described by Danishefsky,[23] to give **27** (90%), and was used directly in the next step.

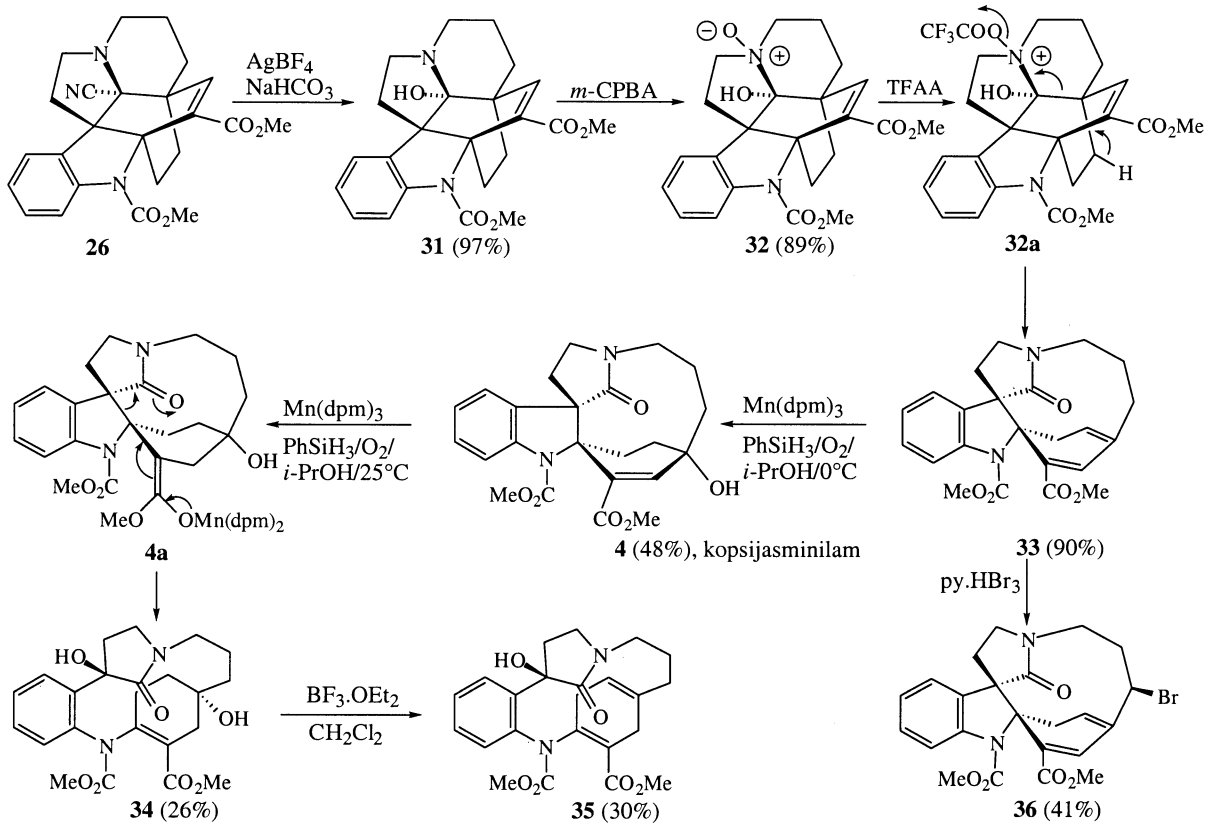
The final step for the conversion of **27** into **28** requires the conjugate reduction of the α,β-unsaturated ester followed by α-hydroxylation of the now saturated ester. In 1990, Isayama et al. reported a single step method for accomplishing the above.[24] Treatment of **27** with $PhSiH_3$(2.5 equiv.)/$Mn(dpm)_3$ (cat)/*i*-PrOH, $Cl(CH_2)_2Cl$ (2:1)/O_2 gave **28** (11,12-demethoxy lahadinine B) in 86% yield as a single stereoisomer whose structure and stereochemistry was confirmed by X-ray crystallography.[25]

5. Synthesis of (±)-kopsidasine 2 and (±)-kopsidasine-*N*-oxide 2a

It seemed reasonable to attempt to convert **26** into kopsidasine, and thus provide unequivocal evidence for its structure. Treatment of **26** with $Pb(OAc)_4$ or Frémys salt following literature protocols for the hydroxylation of tryptamines and tryptophans[26] did not proceed satisfactorily. Whereas, exposure of **26** to $PhI(OAc)_2$/MeOH cleanly gave **26a**, which was directly reduced with Zn/AcOH to **29**, Scheme 7.[27] Conversion of **29** into **30** proceeded as before, and when **30** was treated with $AgBF_4$/THF followed by aqueous $NaHCO_3$ it was converted into (±)-kopsidasine **2**. While the spectral data for **2** compared well with the literature,[3] an authentic sample of **2** was not available, whereas a sample of the derived *N*-oxide **2a** exists.[28] Consequently, **2** was converted into **2a** by treatment with *m*-chloroperoxybenzoic acid (mCPBA). Comparison of synthetic **2a** with natural **2a** by tlc (multiple elutions) and $^1H/^{13}C$ NMR confirmed their identity, and an X-ray crystal structure of **2a** unequivocally demonstrated the structure of **2a**.

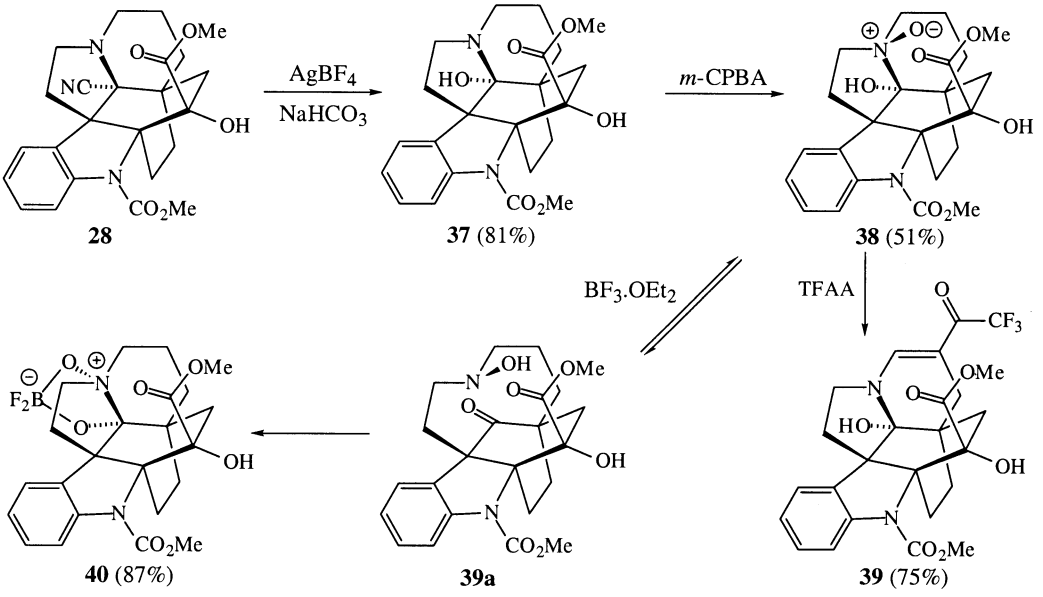
6. Synthesis of (±)-kopsijasminilam 4

Treatment of **26** with $AgBF_4$/THF followed by aqueous $NaHCO_3$[29] gave **31**, and now we were in a position to examine the Polonovski fragmentation, Scheme 8.[30] Oxidation of **31** with *m*-chloroperoxybenzoic acid (*m*-CPBA) resulted in the *N*-oxide **32** which underwent the required fragmentation to give **33** when exposed to trifluoroacetic

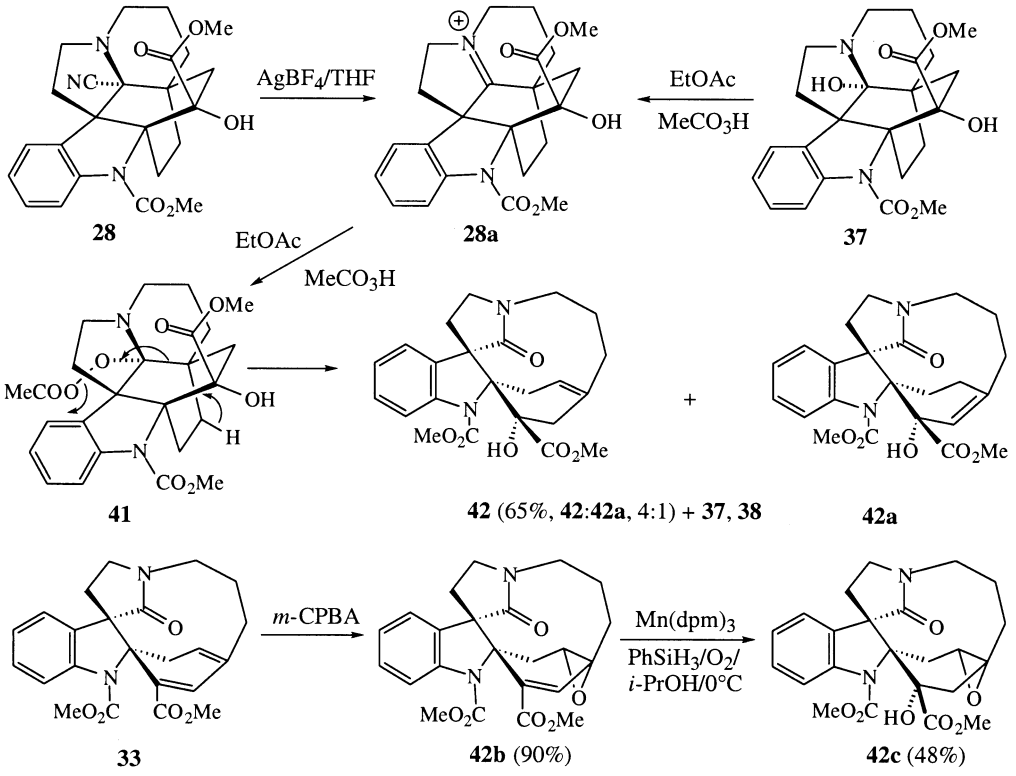


Scheme 8. Polonovski fragmentation.

anhydride (TFAA). When the diene **33** was treated with $Mn(dpm)_3$ (cat)/$PhSiH_3/O_2$ in isopropyl alcohol at 0°C, it was converted into kopsijasminilam **4** (after work-up with aqueous $Na_2S_2O_3$).[13] We had hoped that kopsijasminilam would react further with the above reduction–oxidation reagent to install the 16α-hydroxyl group. In the event, further exposure of **4** to $Mn(dpm)_3$ (cat)/$PhSiH_3/O_2$ 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 **4a** and oxidation α-to the amide resulted in **34**. Dehydration ($BF_3{\cdot}OEt_2$) of **34** gave **35** whose structure was confirmed by X-ray. Attempted protection of **33** through bromination of the diene with pyridinium tribromide gave **36** (X-ray).



Scheme 9.



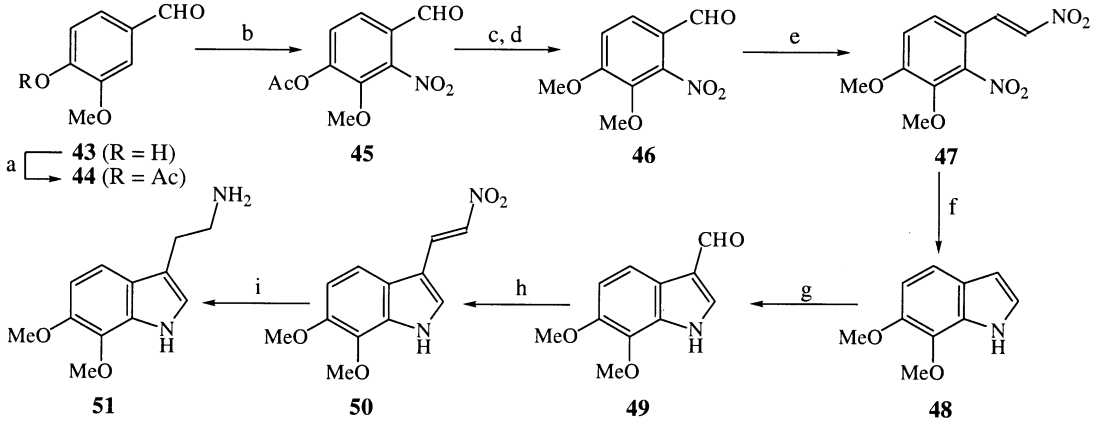
Scheme 10. Peroxyaminal fragmentation.

7. Attempted Polonovski fragmentations

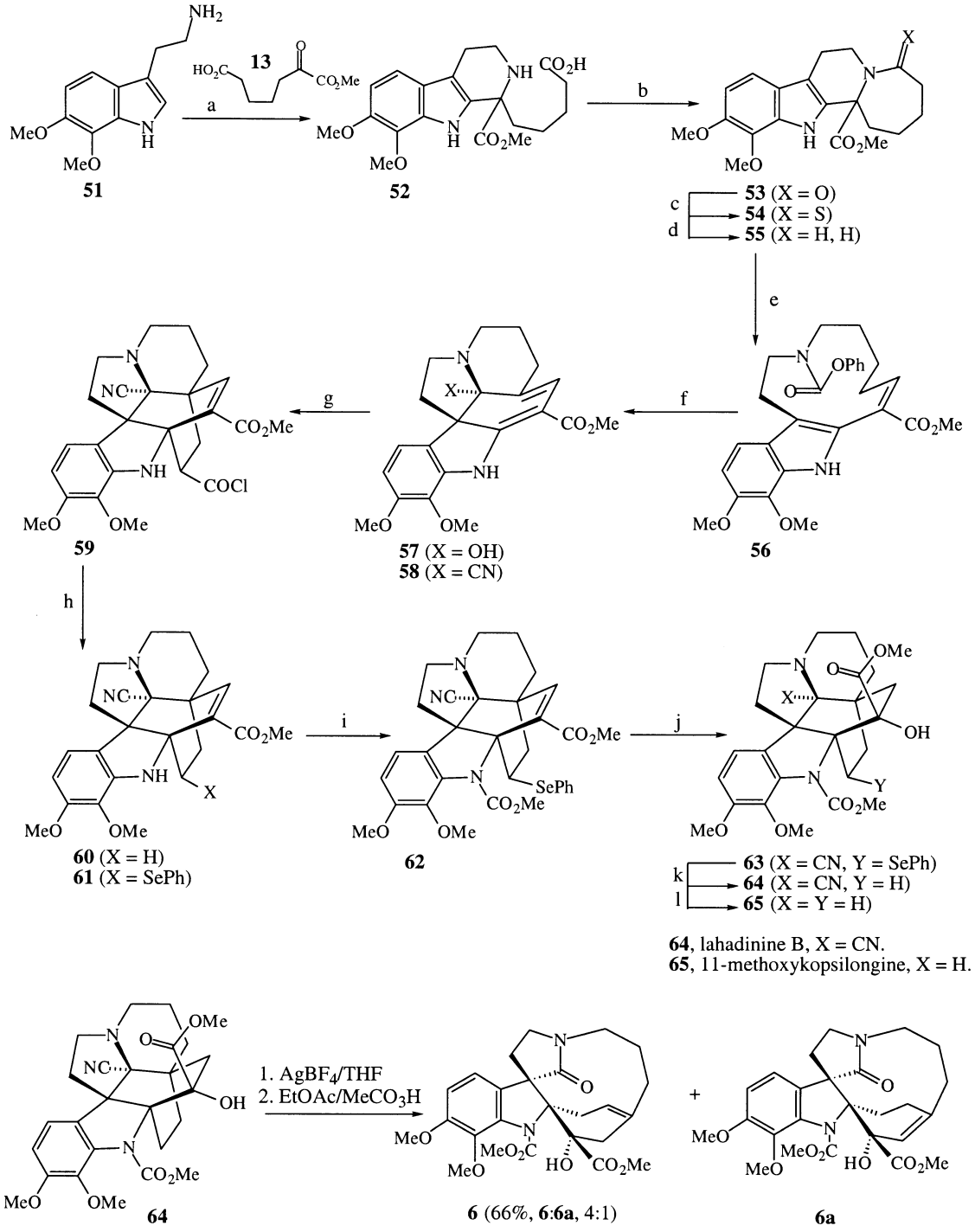
The above findings appeared to indicate that the 16α-hydroxy-ester functionality should be introduced before any attempted fragmentation process to the pauciflorine skeleton. Consequently, we first studied the Polonovski fragmentation of **38**, Scheme 9. Treatment of demethoxyl-ahadinine **28** with $AgBF_4$/THF followed by an aqueous $NaHCO_3$ work-up gave **37**, which was oxidized (*m*-CPBA) to a single *N*-oxide **38**. Exposure of **38** to TFAA/CH_2Cl_2 produced **39** (X-ray).[31] Attempted Polonovski rearrangement of **38** with $BF_3{\cdot}OEt_2$ gave a new *N*-oxide (presumably via **39a**) isolated as the BF_2-adduct **40** (X-ray). The adduct **40** on treatment with TFAA/CH_2Cl_2 gave an intractable mixture that did not contain any of **42** (as judged by the absence of the diagnostic signal for the alkene proton ^{1}H NMR δ 5.25, J=6.4 Hz).

8. Synthesis of (±)-11,12-Demethoxypauciflorine 42

On one occasion while converting **28** into **37**, the ^{1}H NMR spectrum of crude **37** was very clean, but after purifying **37** by chromatography over silica gel eluting with EtOAc/hexanes (1:2→1:1)/NEt_3 (1%), the eluents contained **37** and **38**, and very surprisingly, **42** and the derived epoxide **42c**! 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 **37**, **38**, **42** and



Scheme 11. 6,7-Dimethoxytryptamine **51**. (a) AcCl/py/100°C, **44** (96%). (b) Fuming HNO_3/<6°C, **45** (82%). (c) K_2CO_3/MeOH. (d) MeI/K_2CO_3/DMF/35°C, **46** (72% from **45**). (e) $MeNO_2$/KOH/DMF/EtOH/aqueous work-up HCl/0°C followed by Ac_2O/NaOAc/reflux, **47** (73%). (f) Fe/AcOH/EtOH/reflux, **48** (85%). (g) $POCl_3$/DMF/0–25°C, **49** (92%). (h) $MeNO_2$/NH_4OAc/reflux, **50** (100%). (i) $LiAlH_4$/THF/0°C to reflux, **51** (91%).



Scheme 12. (a) CF_3CO_2H(cat)/CH_2Cl_2/4 Å molecular sieves/0–23°C. (b) EDCI/HOBt/Et_3N/DMF/0–23°C, **53** (67%). (c) Belleau's reagent/THF/0–23°C, **54** (100%). (d) $NiCl_2{\cdot}6H_2O$/$NaBH_4$/THF/MeOH/0°C, **55** (77%). (e) PhOCOCl(15 equiv.)/$Cl(CH_2)_2Cl$/reflux/48 h, **56** (47%, 33% recovered **55**). (f) Tf_2O/DMAP/CH_2Cl_2/reflux, followed by aqueous $NaHCO_3$, **57** (18%), or work-up with TMSCN/DMAP/CH_2Cl_2, **58** (63%). (g) Acryloyl chloride/23°C/24 h. (h) 2-Thiopyridone-*N*-oxide(Na salt)/*t*-BuSH/CH_2Cl_2/*hv*, **60** (37%), or 2-thiopyridone-*N*-oxide(Na salt)/$(PhSe)_2$/CH_2Cl_2/*hv*, **61** (45%). (i) $KN(TMS)_2$/18-crown-6/THF/−78°C followed by CO_2 and Me_2SO_4, **62** (86%). (j) $Mn(dpm)_3$ (5 mol%)/$PhSiH_3$/O_2/*i*-PrOH/$Cl(CH_2)_2Cl$, **63** (83%). (k) Ph_3SnH/PhMe/reflux, **64** (94%). (l) CF_3CO_2H/Et_3SiH/CH_2Cl_2/23°C, **65** (93%).

small amounts of **42c**. On a fourth attempt only **37** 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 **28** into **37**, we obtained **42/42a** (4:1, 65%) along with small amounts of **38** and **42c**. The structures of **42** and **42c** were confirmed by X-ray crystallography. Epoxidation of **33** gave **42b**, which was treated with $Mn(dpm)_3$ (cat)/$PhSiH_3$/O_2 to give **42c**.

Since we know that neither *N*-oxide **38** nor **40** is the source of demethoxypauciflorine **42**, it is reasonable to suppose that the iminium ion intermediate **28a** in the conversion of **28** into **37** adds peracetic acid to generate **41** which fragments to give **42** and **42a** (Scheme 10).[32]

9. Synthesis of (±)-lahadinine B 64, (±)-11-methoxykopsilongine 65 and (±)-pauciflorine B 6

Acetylation of vanillin **43** gave **44**, which was nitrated following literature conditions to give **45** and a small amount of the 6-nitro-isomer (8:1 ratio of isomers).[33] Hydrolysis of **45** and *O*-methylation gave **46**,[34] which was exposed to the classical Henry reaction conditions to give **47**.[35] Reduction of **47** produced the indole **48**.[36] Vilsmeier formylation of **48** gave **49**, which was converted into **51** via **50** using conditions recently described by Corey[37] for the *N*-methyl derivative of **48**, Scheme 11.

Treatment of **51** with **13** under Pictet–Spengler reaction conditions that were satisfactory for tryptamine gave **52** (<10%) (Scheme 12). Whereas, exposure of a mixture of **51** and **13** to trifluoroacetic acid (cat) in dichloromethane in the presence of molecular sieves at 0–23°C gave **52**, which was directly (without purification) converted into **53** in 67% yield for the two steps. Belleau's reagent converted **53** into **54**, and Ni_2B/H_2 desulfurization gave **55**. The reaction of **55** with $PhOCOCl/ClCH_2CH_2Cl$ heated at reflux was very slow compared with the demethoxy series, but prolonged treatment (48 h) gave **56** (47%) and recovered **55** (33%). Attempts to drive the reaction to completion diminished the yield of **56**, and more reactive chloroformates such as 4-nitrophenyl chloroformate did not help.

Treatment of **56** with triflic anhydride in dichloromethane containing 4-dimethylaminopyridine heated at reflux, followed by quenching the purple solution with aqueous $NaHCO_3$ gave **57** (18%), whereas quenching the reaction with trimethylsilyl cyanide resulted in **58** (65%). Reaction of **58** with acryloyl chloride (excess) at 23°C gave **59**, which was directly treated with *N*-hydroxy-2-thiopyridone (Na salt), followed by irradiation in the presence of *t*-BuSH resulted in reductive decarboxylation to give **60** (37% from **58**). All attempts to convert **60** into 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 **59** into the phenylselenide derivative **61** (45% from **58**), we decided to examine its conversion into **62**. It was eventually found that $KN(SiMe_3)_2$/18-crown-6/CO_2/−78°C followed by dimethyl sulfate gave **62** (86%). This same procedure when applied to **60** 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 **62** into **63** was conducted with $Mn(dpm)_3$ (5 mol%)/$PhSiH_3$/O_2/*i*-PrOH/$Cl(CH_2)_2Cl$ and gave **63** in 83% yield. This reaction did not work at all on the unprotected adduct **61**. The final step involves reductive removal of the PhSe-substituent. This was achieved through treatment of **63** with triphenyltin hydride in toluene at reflux to give (±) lahadinine B **64** in 94% yield. Comparison of spectral data confirmed that the synthetic material was the same as the natural compound, apart from $[\alpha]_D$. The structure of **64** was confirmed by X-ray crystallography.[38]

Since we had established the structure of **64** to be correct, its conversion into **65** would provide unequivocal evidence for the correctness of the structure of **65**. Treatment of **64** with triethylsilane in the presence of trifluoroacetic acid cleanly converted it into 11-methoxykopsilongine **65** (93%).[39]

Treatment of (±)-lahadinine B **64** with $AgBF_4$/THF followed by work-up with EtOAc/$MeCO_3H$ (10%) gave (±)-pauciflorine **6** (66%) and the double bond isomer **6a** (21%). Crystallization of **6** from $MeOH/CH_2Cl_2$ gave crystals suitable for X-ray crystallography which confirmed the proposed structure.[40]

10. Experimental

10.1. Data for compounds

10.1.1. Methyl 2-oxo-6-carboxy-hexanoate 13. Ozone was bubbled through a solution of **12** (8.0 g, 51.2 mmol) in CH_2Cl_2 (340 mL) at −78°C for 3.5 h. Dimethyl sulfide (3.76 mL, 51.2 mmol) was added to the mixture, the solution warmed to room temperature, and stirred for 18 h. The solution was evaporated in vacuo to give a yellow liquid which was purified by chromatography over silica gel eluting with a gradient of EtOAc/hexanes containing 1% v/v acetic acid to give **13** as a white microcrystalline solid (8.4 g, 87%). IR (film) 3100, 2955, 1729, 1709 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 11.5–9.5 (1H, br s), 3.87 (3H, s), 2.88 (2H, br t, J=7.0 Hz), 2.40 (2H, br t, J=7.0 Hz), 1.74–1.64 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 179.0, 161.3, 52.9, 38.8, 33.5, 23.7, 22.2. HRMS calcd for $C_8H_{13}O_5$ (MH^+) 189.076. Found 189.076.

10.1.2. (±)-1-(4-Carboxy-butyl)-2,3,4,9-tetrahydro-1H-β-carboline-1-carboxylic acid methyl ester 14. A solution of **13** (1.65 g, 8.77 mmol) and tryptamine (1.41 g, 8.77 mmol) in 1,4-dioxane (22 mL) and benzene (22 mL) was heated at reflux for 24 h. Water was continuously removed by a Dean-Stark apparatus containing 4 Å molecular sieves. The cooled mixture was evaporated in vacuo to give **14** as a pale brown foam (3.0 g), which was subsequently used without purification. ^1H NMR indicated ca. 80–90% purity.

10.1.3. (±)-13b-Carbomethoxy-2,3,4,5,6,7,8,13,13b-octahydro-1H-azepino[1′,2′:1,2]pyrido[3,4-b]indol-5-one 15. A solution of crude **14** (2.89 g, <8.23 mmol) and 1-hydroxybenzotriazole monohydrate (1.39 g, 9.06 mmol) in DMF (100 mL) at 0°C was treated with a solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) (1.73 g, 9.05 mmol) and triethylamine (1.30 mL, 9.33 mmol) in DMF (100 mL). The resulting mixture was stirred at 0°C for 1 h, then at 23°C for 20 h, and treated with pH 7 buffer solution and water (total 1.2 L), and extracted

three times with EtOAc (600 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to yield an orange-brown solid (3.51 g). Flash chromatography over silica gel eluting with a gradient of EtOAc/hexanes gave **15** (1.73 g, 67% for two steps) as microscopic white cubes. Mp 209–209.5°C. IR (film) 3288, 2938, 1738, 1623 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.2 (1H, br s), 7.52 (1H, d, J=8 Hz), 7.34 (1H, d, J=8 Hz), 7.22 (1H, t, J=8 Hz), 7.13 (1H, t, J=8 Hz), 4.82 (1H, dt, J=12.8, 4.0 Hz), 3.81 (3H, s), 3.32 (1H, ddd, J=12.8, 8.8, 5.7 Hz), 2.90–2.75 (4H, m), 2.27 (1H, br t, J=12 Hz), 2.0–1.75 (4H, m), 1.70–1.55 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 172.2, 136.3, 131.8, 126.0, 122.8, 119.9, 118.7, 112.1, 111.1, 65.5, 53.3, 42.2, 40.9, 38.1, 25.6, 22.0, 20.6. HRMS calcd for $C_{18}H_{21}N_2O_3$ (MH^+) 313.155. Found 313.154.

10.1.4. (±)-13b-Carbomethoxy-2,3,4,5,6,7,8,13,13b-octahydro-1H-azepino[1′,2′:1,2]pyrido[3,4-*b*]indol-5-thione 16. To a solution of **15** (1.71 g, 5.49 mmol) in anhydrous THF (110 mL) at 0°C was added solid Belleau's reagent in one portion (1.89 g, 3.58 mmol). The resulting solution was stirred at 0°C for 10 min, allowed to warm to 23°C, and stirred for 6 h. Chromatographic grade silica (ca. 15 g) was added and the mixture evaporated in vacuo. Flash chromatography of the residue over silica gel eluting with a gradient of EtOAc/hexanes gave **16** as a pale lemon yellow microcrystalline solid (1.82 g, 100%). Recrystallization by diffusion of hexanes vapor into an Et_2O solution gave **16** as clear yellow prisms. Mp 160.5–161.5°C (dec). IR (film) 3396, 2948, 1732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.1 (1H, br s), 7.55 (1H, d, J=8 Hz), 7.35 (1H, d, J=8 Hz), 7.24 (1H, t, J=8 Hz), 7.16 (1H, t, J=8 Hz), 5.52 (1H, dt, J=13.3, 4.3 Hz), 4.07 (1H, ddd, J=13.3, 8.4, 5.1 Hz), 3.79 (3H, s), 3.63 (1H, ddd, J=14.6, 7.1, 2.3 Hz), 3.10–2.90 (2H, m), 2.79 (1H, ddd, J=14.6, 6.2, 3.0 Hz), 2.65 (1H, ddd, J=14.4, 11.8, 2.5 Hz), 2.06 (1H, ddd, J=14.4, 11.0, 3.4 Hz), 2.0–1.6 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 171.1, 136.3, 131.6, 125.7, 123.0, 120.1, 118.7, 111.9, 111.2, 69.6, 53.6, 51.9, 47.0, 38.9, 24.0, 23.7, 20.2. HRMS calcd for $C_{18}H_{21}N_2O_2S$ (MH^+) 329.132. Found 329.132.

10.1.5. (±)-13b-Carbomethoxy-2,3,4,5,6,7,8,13,13b-octahydro-1H-azepino[1′,2′:1,2]pyrido[3,4-*b*]indole 17. A freshly prepared aqueous suspension of W-2 Raney Nickel (19 g) was suspended five times in dry THF (25 mL), and the solvent decanted. To a vigorously stirred suspension of the washed metal in THF (30 mL) was added a pale yellow solution of **16** (1.82 g, 5.49 mmol) in THF (20 mL) dropwise at 23°C over 10 min; the color dissipated instantly. The mixture was filtered through a pad of Celite which was washed with EtOAc, and the filtrate evaporated in vacuo to give **17** (1.64 g, 100%) as white prisms. Mp 124–126°C. IR (neat) 3397, 2923, 2843, 1732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.1 (1H, br s), 7.50 (1H, dd, J=7.5, 1 Hz), 7.36 (1H, dd, J=7.5, 1 Hz), 7.18 (1H, dd, J=7.5, 1 Hz), 7.10 (1H, dd, J=7.5, 1 Hz), 3.74 (3H, s), 3.31 (1H, ddd, J=13.1, 11.0, 4.1 Hz), 3.20 (1H, ddd, J=13.1, 5.4, 1.8 Hz), 2.97–2.90 (2H, m), 2.87 (1H, ddd, J=15.4, 11.0, 5.4 Hz), 2.56 (1H, ddd, J=15.4, 4.1, 1.8 Hz), 2.49 (1H, ddd, J=15.0, 7.0, 3.0 Hz), 2.12 (1H, ddd, J=15.0, 9.0, 2.0 Hz), 1.75–1.55 (5H, m), 1.55–1.35 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 136.2, 133.5, 126.8, 121.9, 119.3, 118.4, 110.9, 66.6, 52.4, 50.5, 50.2, 39.4, 30.8, 29.2, 22.9, 19.8 (one signal not observed). HRMS calcd for $C_{18}H_{23}N_2O_2$ (MH^+) 299.176. Found 299.176.

Alternatively **16** can be desulfurized to give **17** using nickel boride. To a stirred solution of **16** (5.36 g, 16.34 mmol) and nickel(II) chloride hexahydrate (15.53 g, 65.36 mmol) in THF (100 mL) and MeOH (100 mL) at 0°C was added, portion wise, sodium borohydride (7.42 g, 196.09 mmol) over a period of 20 min. On addition the green solution immediately turned black. After complete addition of the sodium borohydride the mixture was stirred for a further 15 min before being filtered through a pad of Celite, washing with methanol (300 mL). The filtrate was concentrated in vacuo to ~50 mL of solvent, and partitioned between water (150 mL) and EtOAc (150 mL). The aqueous phase was extracted with EtOAc (3×150 mL) and the combined extracts washed with water (150 mL) and brine (150 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by chromatography over silica gel eluting with 25% EtOAc/hexanes containing 0.5% v/v triethylamine to give **17** (3.5 g, 79%, two steps).

10.1.6. (±)-5,8,9,10,11,14-Hexahydro-6H-7,14-diazacycloundeca[*a*]indene-7,13-dicarboxylic acid 13-methyl ester 7-phenyl ester 18. To a solution of **17** (233 mg, 780 μmol) in 1,2-dichloroethane (3.1 mL) was added phenyl chloroformate (979 μL, 7.80 mmol) and the mixture heated at reflux for 24 h. The solution became bright yellow within a few minutes and heavily clouded within 12 h. The mixture was cooled to 25°C, and excess saturated aqueous $NaHCO_3$ solution was added. The mixture was stirred vigorously for several hours and extracted three times with CH_2Cl_2. The combined extracts were washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo to yield an orange-brown oily solid. Flash chromatography over silica gel eluting with a gradient of EtOAc/hexanes gave **18** as a colorless, viscous oil which forms a white crystalline film in vacuo (216 mg, 66%). Crystals for X-ray analysis were grown by slow evaporation of a toluene solution to give **18** as clear, colorless cubes. Mp 170–171°C. IR (film) 3343, 2947, 1714 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 300 K) δ 8.10–8.01 (1H, br m), 7.65–7.58 (1H, br m), 7.38–6.97 (8H, br m), 6.30 (1H, d, J=7.8 Hz), 4.8–1.5 (12H, br m), 3.77–3.70 (3H, m). (500 MHz, d_8-toluene, 373 K) δ 7.46 (1H, dd, J=7.9, 0.9 Hz), 7.19 (0.8H, br s), 7.09 (1H, t, J=8.2 Hz), 7.11–6.94 (7H, obscured m), 6.81 (1H, t, J=7.4 Hz), 6.71 (1.2H, br s), 3.81 (2H, br t, J=5.7 Hz), 3.42 (3H, s), 3.12 (2H, br s), 2.92 (2H, t, J=5.7 Hz), 2.20–2.09 (4H, m), 1.65–1.49 (4H, m). ^{13}C NMR (75 MHz, d_8-toluene, 373 K) δ 166.9, 154.9, 152.8, 149.7, 137.4, 127.7, 124.7, 122.6, 121.9, 120.1, 111.3, 51.6, 50.5, 28.8, 27.2 (several signals not observed or obscured). HRMS calcd for $C_{25}H_{27}N_2O_4$ (MH^+) 419.197. Found 419.196.

10.1.7. (±)-12b-Hydroxy-2,3,6,11,12,12b-hexahydro-1H-6,12a-diazaindeno[7,1-*cd*]fluorene-5-carboxylic acid methyl ester 19. To a solution of **18** (143 mg, 341 μmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP) (125 mg, 1.03 mmol) in anhydrous CH_2Cl_2 (17 mL) at 0°C was added trifluoromethanesulfonic anhydride (287 μL, 1.71 mmol)

dropwise over 4 min. The mixture became bright yellow during the addition and a precipitate formed after ca. 1 equiv. had been added. After 10 min at 0°C the mixture was allowed to warm to 23°C for a further 10 min, and heated at reflux for 24 h (the mixture became olive-green, and after 10 min at reflux the solution became very deep purple in color). To the cooled mixture was added excess saturated aqueous $NaHCO_3$ solution, and the mixture stirred vigorously for ca. 30 min then extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to yield an orange-brown oil. Flash chromatography over neutral alumina eluting with a gradient of EtOAc/hexanes gave **19** (51 mg, 46%) as a yellow crystalline film. Recrystallization by diffusion of pentane vapor into an EtOAc solution gave **19** as yellow prisms suitable for X-ray analysis. Mp 184–185°C. UV ($CHCl_3$, 4.93×10^{-5} M) λ_{max} 371 (ϵ 11,300), 297 (ϵ 6900). (1%, v/v TFA in $CHCl_3$, 6.16×10^{-5} M) λ_{max} 544 (ϵ 1800), 370 (ϵ 11,500), 330 (ϵ 7900), 306 (ϵ 7300). IR (film) 3354, 2928, 2851, 1678, 1598 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.00 (1H, br s), 7.53 (1H, dd, J=7.5, 0.6 Hz), 7.21 (1H, td, J=7.5, 1 Hz), 6.97 (1H, td, J=7.5, 1 Hz), 6.88 (1H, d, J=7.5 Hz), 6.18 (1H, d, J=2.1 Hz), 3.78 (3H, s), 3.34 (1H, q, J=8.7 Hz), 3.28 (1H, td, J=13.6, 2.8 Hz), 3.03–2.86 (2H, m), 2.51 (1H, ddd, J=13.7, 4.7, 2.2 Hz), 2.5–2.3 (2H, m), 1.92–1.65 (3H, m), 1.53 (1H, ddd, J=13.1, 4.7, 2.3 Hz). (300 MHz, C_6D_6) δ 9.12 (1H, br s), 7.39 (1H, d, J=7.5 Hz), 6.92 (1H, t, J=7.5 Hz), 6.75 (1H, t, J=7.5 Hz), 6.43 (1H, d, J=2.1 Hz), 6.14 (1H, d, J=7.5 Hz), 3.53 (3H, s), 3.17 (1H, td, J=13.7, 2.7 Hz), 2.97 (1H, q, J=8.6 Hz), 2.64–2.48 (3H, m), 2.32–2.14 (2H, m), 1.70–1.50 (3H, m), 1.15 (1H, ddd, J=13.0, 5.0, 2.0 Hz). HRMS calcd for $C_{19}H_{20}N_2O_3$ (M^+) 324.147. Found 324.147. In some experiments the yield of **19** was as high as 72%, but this was not reproducible due to the instability of **19**. When the above reaction mixture was treated with trimethylsilyl cyanide to give **22**, the process becomes reproducible and improves the yield (see later).

10.1.8. Compound 20. To a solution of **19** (4.1 mg, 13 μmol) and proton sponge (8.2 mg, 38 μmol) in CH_2Cl_2 (2.0 mL) at 0°C was added dropwise benzyl chloroformate (4 μL, 28 μmol). The mixture was stirred at 0°C for 8 h, allowed to warm to 23°C for a further 18 h, and treated with excess saturated aqueous $NaHCO_3$ solution with vigorous stirring for a further 30 min. The mixture was extracted three times with CH_2Cl_2, the combined extracts washed with citric acid (0.5 M) and brine, dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography over silica gel eluting with 33% EtOAc/hexanes gave **20** (5.5 mg, 95%) as a deep orange oil. Crystals suitable for X-ray analysis were grown by slow evaporation of a toluene solution to give **20** as clear, orange hexagonal plates. Mp 185–188°C (dec, softens at 170°C). IR (film) 3313, 2923, 2853, 1652, 1612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (1H, br s), 7.92 (0.6H, d, J=7.5 Hz), 7.73 (0.4H, d, J=7.5 Hz), 7.45–7.3 (6H, m), 7.42 (0.6H, s), 7.40 (0.4H, s), 7.15–6.93 (2H, m), 5.25–4.95 (2H, m), 3.88 (3H, s), 3.82–3.65 (1H, m), 3.60 (0.6H, dd, J=14.8, 5.7 Hz), 3.50 (0.4H, dd, J=14.8, 5.7 Hz), 3.27 (0.4H, dd, J=14.8, 9.8 Hz), 3.17 (0.6H, dd, J=14.8, 9.8 Hz), 3.00–2.68 (2.6H, m), 2.50 (0.4H, dd, J=14.3, 10.0 Hz), 2.35–2.10 (1H, m), 2.1–1.6 (3H, m). Rotational doubling and broadening of some signals was observed. HRMS calcd for $C_{27}H_{27}N_2O_5$ (MH^+) 459.192. Found 459.191.

10.1.9. (±)-12b-(2,2-diethoxyethyl)-2,3,6,11,12,12b-hexahydro-1H-6,12a-diazaindeno[7,1-*cd*]fluorene-5-carboxylic acid methyl ester 19a. To a solution of the **19** (12.4 mg, 38.2 μmol) and DMAP (5.4 mg, 44 μmol) in anhydrous CH_2Cl_2 (3.8 mL) at 0°C was added a solution of trifluoromethanesulfonic anhydride in CH_2Cl_2 (221 μL, 42 μmol), causing the mixture to become deep orange. Ethyl vinyl ether (37 μL, 387 μmol) was added dropwise. The mixture was stirred at 0°C for 3 h and then allowed to warm to 23°C for a further 20 h. Excess pH 7 buffer solution was added and the mixture extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to yield a yellow oil. Flash chromatography over silica gel eluting with a gradient of EtOAc/hexanes gave **19a** (11.1 mg, 68%) as a yellow crystalline film. Crystals suitable for X-ray analysis were grown by slow diffusion of pentane vapor into an Et_2O solution gave **19a** as clear yellow plates. IR (film) 3387, 2928, 2866, 1674, 1633 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 9.37 (1H, br s), 7.45 (1H, d, J=7.2 Hz), 6.92 (1H, t, J=7.6 Hz), 6.79 (1H, t, J=7.4 Hz), 6.39 (1H, d, J=1.4 Hz), 6.24 (1H, d, J=7.7 Hz), 4.31 (1H, dd, J=6.5, 3.6 Hz), 3.60 (3H, s), 3.39–3.28 (1H, m), 3.22–3.12 (1H, m), 3.14–2.90 (4H, m), 2.75–2.61 (2H, m), 2.48 (1H, br q, J=9.0 Hz), 2.33 (1H, dd, J=14.3, 3.6 Hz), 2.3–2.1 (2H, m), 2.12 (1H, dd, J=14.3, 6.5 Hz), 1.70–1.53 (2H, m), 1.2–1.0 (1H, m), 1.02 (3H, t, J=7.0 Hz), 0.87 (3H, t, J=7.0 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 167.8, 166.2, 144.1, 134.8, 126.9, 124.5, 121.7, 117.2, 109.8, 100.8, 90.9, 66.5, 60.8, 60.1, 50.5, 47.7, 44.9, 40.4, 35.7, 30.2, 22.3, 15.4, 15.3 (two signals not observed or obscured). HRMS calcd for $C_{25}H_{32}N_2O_4$ (M^+) 424.236. Found 424.237.

10.1.10. Compound 21. A solution of the **20** (5.5 mg, 12 μmol) and phenyl vinyl sulfone (3.0 mg, 18 μmol) in anhydrous toluene (1.2 mL) was heated at 85–90°C for 12.5 h. No reaction had occurred as evidenced by TLC analysis, and the mixture was heated at reflux for a further 81 h. The mixture was evaporated in vacuo to yield a yellow oil. Flash chromatography over silica gel eluting with a gradient of EtOAc/hexanes gave **21** (3.1 mg, 56%) as a white crystalline film. Crystals suitable for X-ray analysis were grown in toluene by slow evaporation to give **21** as clear, colorless prisms. Mp 186–187°C. IR (film) 3366, 2919, 2851, 1703, 1699, 1608 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 300 K) δ 9.84 (0.6H, br s), 9.81 (0.4H, br s), 8.11 (0.4H, d, J=8.0 Hz), 8.08 (0.6H, d, J=8.0 Hz), 7.85 (0.6H, s), 7.82 (0.4H, s), 7.55–7.40 (2.4H, m), 7.32–7.23 (1.6H, m), 7.11–7.00 (1.6H, m), 6.88 (1.4H, t, J=7.6 Hz), 6.50–6.39 (1H, m), 6.29 (1H, d, J=7.4 Hz), 4.90 (0.4H, d, J=12.5 Hz), 4.82 (0.4H, d, J=12.5 Hz), 4.55 (0.6H, d, J=12.5 Hz), 4.46 (0.6H, d, J=12.5 Hz), 4.03 (1.2H, s), 4.01 (1.8H, s), 3.79 (1H, br t, J=14 Hz), 3.40 (1H, br t, J=12 Hz), 3.12–3.00 (1H, m), 2.78–2.66 (1H, m), 2.20–1.85 (2H, m), 1.81 (3H, d, J=6.0 Hz). Carbamate resonance causes doubling of signals. (500 MHz, d_8-toluene, 373 K) δ 9.61 (1H, br s), 8.17 (1H, br d, J=7.6 Hz), 7.80 (1H, s), 7.23 (1H, t, J=7.6 Hz), 7.15 (1H, t, J=7.5 Hz), 7.01 (1H, d, J=8 Hz), 6.95–6.75 (3H, br m), 6.7–6.35 (3H, br m),

4.65–4.35 (2H, br m), 3.78–3.63 (2H, br s), 3.66 (3H, s), 3.13 (1H, ddd, *J*=14.1, 12.0, 2.2 Hz), 2.94 (1H, td, *J*=13.3, 2.2 Hz), 2.50 (1H, br dd, *J*=13.3, 5.5 Hz), 1.67–1.60 (1H, m), 1.55 (3H, d, *J*=6.0 Hz). HRMS calcd for $C_{27}H_{26}N_2O_5$ (M^+) 458.184. Found 458.184.

10.1.11. (±)-12b-Cyano-2,3,6,11,12,12b-hexahydro-1H-6,12a-diazaindeno[7,1-*cd*]fluorene-5-carboxylic acid methyl ester 22. To a stirred solution of **18** (1.19 g, 2.84 mmol) and DMAP (1.04 g, 8.53 mmol) in anhydrous CH_2Cl_2 (110 mL) at 0°C under argon was added dropwise trifluoromethanesulfonic anhydride (2.35 mL, 14.2 mmol). When addition was complete the green solution was warmed to 23°C, and heated at reflux to give a deep purple solution. After 22 h at reflux the mixture was cooled to 23°C and trimethylsilyl cyanide (1.50 mL, 11.4 mmol) was added dropwise to the stirred solution. Solid DMAP (1.39 g, 11.4 mmol) was added portion wise to the solution resulting in the disappearance of the purple color and the formation of an orange/brown solution. Saturated aqueous $NaHCO_3$ (200 mL) solution was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (200 mL), and the combined extracts washed with water (200 mL) and brine (200 mL), dried ($MgSO_4$), and evaporated in vacuo. Purification by flash column chromatography over silica gel eluting with 25% EtOAc/hexanes gave **22** as a yellow solid (0.641 g, 68%). Mp 160°C (dec). IR (film) 3374, 2946, 2866, 2253, 1682, 1639 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.11 (1H, br s), 7.58 (1H, d, *J*=7.5 Hz), 7.23 (1H, td, *J*=7.5, 1.5 Hz), 7.00 (1H, td, *J*=7.5, 1.5 Hz), 6.90 (1H, d, *J*=7.5 Hz), 6.26 (1H, d, *J*=7.5 Hz), 3.79 (3H, s), 3.34 (1H, td, *J*=13.0, 2.5 Hz), 3.28 (1H, dd, *J*=17.0, 8.5 Hz), 3.14 (1H, m), 2.96 (1H, m), 2.52–2.35 (3H, m), 1.92–1.79 (2H, m), 1.60–1.53 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 161.7, 143.2, 132.3, 129.0, 124.0, 122.3, 119.8, 119.3, 117.3, 110.0, 91.2, 64.5, 59.0, 51.2, 46.7, 45.9, 39.6, 29.5, 20.4. HRMS calcd for $C_{20}H_{20}N_3O_2$ (MH^+) 334.156. Found 334.155.

10.1.12. Compound 22a. A mixture of **22** (93 mg, 0.279 mmol) and maleic anhydride (55 mg, 0.558 mmol) in degassed anhydrous toluene (2 mL) was heated in a sealed tube at 100°C for 6 h. The solvent was evaporated in vacuo, and the residue purified by flash column chromatography over silica gel eluting with 25% EtOAc/hexanes to give **22a** as a white solid (100 mg, 83%). Mp 180°C (dec). IR (film) 3382, 2951, 2864, 2256, 1855, 1779, 1719, 1609 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (1H, d, *J*=8.0 Hz), 7.19 (1H, td, *J*=8.0, 1.0 Hz), 6.95 (1H, s), 6.93 (1H, td, *J*=8.0, 1.0 Hz), 6.91 (1H, d, *J*=8.0 Hz), 5.51 (1H, br s), 3.82 (3H, s), 3.41 and 3.36 (2×1H, 2d, *J*=8.5 Hz), 3.33 (1H, m), 3.06 (1H, m), 2.87 (1H, m), 2.78 (1H, m), 2.73 (1H, m), 2.28 (1H, ddd, *J*=14.0, 7.0, 2.5 Hz), 2.10 (1H, td, *J*=14.0, 4.0 Hz), 1.90 (1H, m), 1.75 (1H, m), 1.64 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 168.8, 162.8, 147.4, 140.9, 134.8, 131.1, 129.1, 123.7, 121.5, 116.8, 112.1, 72.5, 68.8, 65.9, 52.7, 49.8, 48.4, 44.6, 43.8, 43.4, 36.9, 28.6, 16.7. HRMS calcd for $C_{24}H_{22}N_3O_5$ (MH^+) 432.156. Found 432.156.

10.1.13. Compound 22b. A mixture of the **22** (60 mg, 0.180 mmol) and nitroethylene (900 μL, 1 M soln in benzene, 0.900 mmol) was heated at 70°C in a sealed tube for 5 days. The solvent was removed by distillation under reduced pressure giving a beige solid. Purification by flash column chromatography over silica gel eluting with 25–35% EtOAc/hexanes gave **22b** as a pale yellow solid (62 mg, 85%) suitable for X-ray crystallography. Mp 180°C (dec). IR (film) 3393, 2947, 2861, 2253, 1716, 1611, 1550 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (1H, d, *J*=7.5 Hz), 7.17 (1H, td, *J*=7.5, 1.0 Hz), 7.16 (1H, s), 6.91 (1H, td, *J*=7.5, 1.0 Hz), 6.85 (1H, d, *J*=7.5 Hz), 5.19 (1H, br s), 4.95 (1H, dd, *J*=8.5, 6.0 Hz), 3.79 (3H, s), 3.31 (1H, m), 3.04 (1H, m), 2.84 (1H, td, *J*=7.5, 2.0 Hz), 2.72 (1H, m), 2.41 (1H, dd, *J*=14.0, 8.5 Hz), 2.36 (1H, m), 2.10 (1H, m), 2.02 (1H, m), 1.97–1.89 (2H, m), 1.77 (1H, m), 1.55 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 147.4, 144.1, 131.3, 131.1, 129.1, 123.4, 121.3, 117.4, 111.8, 82.9, 74.0, 68.3, 66.4, 52.3, 49.5, 44.5, 41.1, 37.5, 36.9, 30.6, 16.4. HRMS calcd for $C_{22}H_{23}N_4O_4$ (MH^+) 407.172. Found 407.172.

10.1.14. (±)-16-Anhydro-11,12-demethoxy-1-decarbomethoxylahadinine B 26. A mixture of **22** (0.273 g, 0.812 mmol) and acryloyl chloride (400 μL, 4.87 mmol) in degassed anhydrous toluene (3.3 mL) was heated in a sealed tube at 75°C for 5 days. The solvent was evaporated in vacuo to give a dark solid which was dried under high vacuum for 3 h. This residue was dissolved in anhydrous CH_2Cl_2 (2.5 mL), and a mixture of 2-mercaptopyridine-*N*-oxide (0.165 g, 1.30 mmol) and triethylamine (226 μL, 1.62 mmol) in anhydrous CH_2Cl_2 (1 mL) was added dropwise under argon with stirring in the absence of light for 2 h. The mixture was cooled to 0°C and *tert*-butyl thiol (700 μL) was added. The resultant mixture was irradiated with a tungsten lamp for 1.5 h, maintaining the temperature below 10°C with an ice/water bath. The solvents were evaporated in vacuo, and the residue partitioned between saturated aqueous $NaHCO_3$ (20 mL) and EtOAc (20 mL). The layers were separated and the aqueous extracted with EtOAc (20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL), and dried ($MgSO_4$). Purification by flash column chromatography over silica gel eluting with 20–50% EtOAc/hexanes gave **26** as a white solid (0.115 g, 39% over three steps). Mp 210–212°C. IR (film) 3365, 2944, 2859, 2251, 1713, 1609 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (1H, d, *J*=7.5 Hz), 7.08 (1H, td, *J*=7.5, 1.0 Hz), 6.95 (1H, s), 6.84 (1H, td, *J*=7.5, 1.0 Hz), 6.73 (1H, d, *J*=7.5 Hz), 4.34 (1H, br s), 3.80 (3H, s), 3.31 (1H, m), 3.02 (1H, m), 2.83 (1H, td, *J*=9.0, 1.5 Hz), 2.72 (1H, ddd, *J*=17.5, 9.0, 1.5 Hz), 2.28 (1H, ddd, *J*=13.5, 7.0, 1.5 Hz), 2.08 (1H, m), 1.98–1.80 (4H, m), 1.72 (1H, m), 1.46 (1H, m), 1.26 (1H, m), 1.13 (1H, ddd, *J*=13.0, 12.0, 6.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 149.3, 143.9, 135.3, 133.0, 128.0, 123.8, 120.3, 118.5, 110.9, 70.1, 68.7, 66.1, 52.1, 49.8, 44.8, 41.6, 37.4, 31.9, 31.4, 27.3, 16.5. HRMS calcd for $C_{22}H_{24}N_3O_2$ (MH^+) 362.187. Found 362.187.

10.1.15. (±)-16-Anhydro-11,12-demethoxylahadinine B 27. To a stirred solution of **26** (115 mg, 0.318 mmol) in a mixture of anhydrous CH_2Cl_2 (5.5 mL) and pyridine (1.2 mL) at 0°C under argon was added a solution of triphosgene (283 mg, 0.954 mmol) in anhydrous CH_2Cl_2 (2 mL) dropwise, resulting in a pink solution containing

some precipitate. After 10 min the mixture was allowed to warm to 23°C and stirred for 45 min resulting in complete dissolution of the precipitate. The mixture was recooled to 0°C, once again causing precipitation to occur, and anhydrous MeOH (2.5 mL) was added dropwise. The resultant clear solution was allowed to warm to 23°C. After a further 1 h, pH 7 phosphate buffer (50 mL) was added and the mixture extracted with EtOAc (2×50 mL). The combined extracts were washed with water (100 mL) and brine (100 mL) and dried ($MgSO_4$). Evaporation of the solvents in vacuo gave a yellow solid. Purification by flash column chromatography over silica gel eluting with 35–50% EtOAc/hexanes gave **27** as a white solid (120 mg, 90%). IR (film) 3350, 2953, 2858, 2254, 1714, 1690 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, 100°C) δ 7.75 (1H, d, J=7.5 Hz), 7.42 (1H, dd, J=7.5, 1.0 Hz), 7.28 (1H, td, J=7.5, 1.0 Hz), 7.12 (1H, td, J=7.5, 1.0 Hz), 6.84 (1H, s), 3.74 (3H, s), 3.72 (3H, s), 3.13 (1H, td, J=14.0, 3.0 Hz), 3.00 (1H, m), 2.76 (1H, td, J=9.0, 2.0 Hz), 2.64 (1H, m), 2.46 (1H, td, J=6.5, 2.0 Hz), 2.06 (1H, m), 1.95–1.81 (2H, m), 1.76–1.67 (2H, m), 1.61–1.50 (2H, m), 1.40 (1H, m), 1.29 (1H, td, J=12.5, 7.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6, 100°C) δ 164.2, 152.6, 141.0, 140.2, 134.3, 133.9, 127.6, 123.0, 122.7, 117.5, 114.2, 69.7, 67.4, 65.2, 51.7, 51.0, 48.9, 43.9, 40.1, 38.3, 30.3, 29.8, 23.4, 15.2. HRMS calcd for $C_{24}H_{26}N_3O_4$ (MH^+) 420.192. Found 420.192.

10.1.16. (±)-11,12-Demethoxylahadinine B 28. To a stirred solution of **27** (102 mg, 0.243 mmol) and $Mn(dpm)_3$ (4 mg, 0.010 mmol) in a mixture of isopropanol (2 mL) and 1,2-dichloroethane (1.5 mL) at 0°C was added dropwise phenylsilane (75 μL, 0.608 mmol). When addition was complete the green-brown solution was stirred under an oxygen balloon at 0°C for 10 min then at 23°C for 6 h. Saturated sodium thiosulfate solution was added slowly (20 mL), and after stirring for 5 min the mixture was extracted with EtOAc (2×20 mL), and the combined extracts washed with water (30 mL) and brine (30 mL). The solution was dried ($MgSO_4$), and evaporated in vacuo to give a beige solid. Purification by flash column chromatography over silica gel eluting with 25% EtOAc/hexanes gave **28** as a white crystalline solid (90 mg, 85%) suitable for X-ray crystallography. Mp 250–251°C. IR (film) 3284, 2948, 2253, 1736, 1682 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (1H, d, J=8.0 Hz), 7.51 (1H, td, J=8.0, 1.0 Hz), 7.31 (1H, s), 7.22 (1H, td, J=8.0, 1.0 Hz), 7.06 (1H, td, J=8.0, 1.0 Hz), 3.95 (3H, s), 3.72 (3H, s), 3.15–3.02 (4H, m), 2.96 (1H, m), 2.32 (1H, m), 1.97–1.87 (2H, m), 1.81–1.49 (6H, m), 1.45–1.37 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 156.5, 140.2, 135.1, 128.2, 123.8, 123.6, 118.3, 115.7, 76.1, 73.8, 68.2, 59.8, 53.6, 52.5, 49.1, 44.3, 39.3, 39.0, 36.5, 32.6, 28.6, 23.4, 19.8. HRMS calcd for $C_{24}H_{28}N_3O_5$ (MH^+) 438.203. Found 438.202.

10.1.17. (±)-16-Anhydro-11,12-demethoxy-13-methoxy-1-decarbomethoxylahadinine B 29. Iodobenzenediacetate (43 mg, 0.133 mmol) was added in one portion to a suspension of **26** (40 mg, 0.110 mmol) in MeOH (2 mL) at 0°C. After 45 min at 0°C the suspension became an orange solution. Zinc powder (36 mg, 0.554 mmol) was added and the orange solution became a yellow suspension. After stirring the mixture for 30 min at room temperature solid $NaHCO_3$ was added. The solvent was evaporated in vacuo and the resultant solid taken up in EtOAc and filtered. Evaporation of the solvent in vacuo gave the crude **29** (0.050 g) which was used immediately in the next step.

10.1.18. (±)-16-Anhydro-11,12-demethoxy-13-methoxylahadinine B 30. Triphosgene (98 mg, 0.332 mmol) in CH_2Cl_2 (1 mL) was added to a solution of **29** and pyridine (0.268 mL, 3.32 mmol) in CH_2Cl_2 (1 mL) at 0°C. The mixture was stirred at 0°C for a further 10 min, and warmed to room temperature and stirred for 45 min, resulting in complete dissolution of the precipitate. The mixture was cooled to 0°C and anhydrous MeOH (0.5 mL) was added dropwise. The resultant clear solution was allowed to warm to room temperature. After a further 2 h, pH 7 phosphate buffer (20 mL) was added, and the mixture extracted with EtOAc (3×20 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and evaporated in vacuo to give a brown solid. Purification by flash chromatography over silica gel, eluting with 50% EtOAc/hexanes gave **30** (27 mg, 54%). Mp 178–180°C. IR (film) 2949, 2250, 1715, 1686, 1610 cm^{-1}. ^1H NMR (500 MHz, DMSO-d^6, 373 K) δ 7.66 (1H, d, J=8.9 Hz), 6.98 (1H, d, J=2.7 Hz), 6.85 (1 H, dd, J=8.9, 2.7 Hz), 6.81 (1H, s), 3.76 (3H, s), 3.73 (3H, s), 3.69 (3H, s), 3.12 (1H, td, J=14.2, 3.1 Hz), 2.99 (1H, m), 2.76 (1H, td, J=8.7, 1.9 Hz), 2.64 (1H, m), 2.46 (1H, td, J=6.5, 1.9 Hz), 2.06 (1H, m), 1.96–1.85 (1H, m), 1.81 (1H, td, J=12.9, 2.5 Hz), 1.77–1.65 (2H, m), 1.61–1.54 (2H, m), 1.40 (1H, m), 1.29 (1H, td, J=12.3, 6.9 Hz). ^{13}C NMR (125 MHz, DMSO-d^6, 373 K) δ 164.2, 155.5, 152.6, 139.9, 135.0, 134.5, 134.4, 117.6, 114.9, 112.9, 109.1, 78.5, 69.7, 67.3, 65.1, 55.1, 51.5, 51.0, 48.8, 43.8, 38.0, 30.2, 29.7, 23.3, 15.2. HRMS calcd for $C_{25}H_{27}N_3O_5$ (MH^+) 449.195. Found 449.195.

10.1.19. (±)-Kopsidasine 2. Silver tetrafluoroborate (67 mg, 0.338 mmol) in anhydrous THF (1 mL) was added to a solution of **30** (38 mg, 0.0846 mmol) in anhydrous THF (1 mL) at room temperature. Over a period of 1 h the yellow solution became orange and a yellow suspension formed. Saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture stirred for 10 min. The mixture was extracted with EtOAc (3×20 mL), and the combined extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated in vacuo. Flash chromatography over silica gel, eluting with 50–75% EtOAc/hexanes and 1% v/v triethylamine gave **2** as a colorless glass, (29 mg, 78%). IR (film) 3417, 2950, br 1713, 1686, 1613 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (1H, br d, J=7.6 Hz), 6.84–6.70 (3H, m), 3.77 (3H, s), 3.75 (3H, s), 3.68 (3H, s), 3.25–3.15 (1H, m), 2.79 (1H, m), 2.70 (1H, t, J=9.0 Hz), 2.59 (1H, m), 2.38–2.27 (1H, m), 1.93–1.57 (8H, m), 1.38–0.98 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 156.4, 153.7, 143.4, 136.6, 136.3, 135.3, 116.1, 115.6, 112.2, 109.5, 91.37, 71.3, 62.4, 55.6, 51.8, 47.2, 43.4, 42.2, 30.1, 29.6, 29.4, 23.6, 16.3. HRMS calcd for $C_{24}H_{29}N_2O_6$ (MH^+) 441.203. Found 441.202. The spectral data are in good agreement with the literature values.

10.1.20. (±)-Kopsidasine-*N*-oxide 2a. To a solution of kopsidasine **2** (29 mg, 0.0659 mmol) in CH_2Cl_2 (2 mL) was added *m*-chloroperoxybenzoic acid (24 mg, 0.0988 mmol) in CH_2Cl_2 (2 mL). The resultant yellow solution was stirred at room temperature for 4 h. Water (5 mL) was

added and the mixture extracted with CH_2Cl_2 (2×5 mL). The combined extracts were washed with 1% NaOH (10 mL), dried (Na_2SO_4), and evaporated in vacuo to give a yellow glass which was purified by flash chromatography over silica gel eluting with 3% MeOH/$CHCl_3$ and 1% v/v triethylamine. Recrystallization of the product from Et_2O/MeOH gave colorless crystals of **2a** (14 mg, 46%) suitable for X-ray crystallography. Mp 168–170°C. IR (film) 3374, 2953, br 1715, 1612 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 313 K) δ 7.82 (1H, br m), 7.43 (1H, d, J=2.5 Hz), 6.75 (1H, br d, J=7.5 Hz), 6.67 (1H, br s), 3.78, 3.77 (9H, 2 s), 3.48 (1H, br d, J=13.0 Hz), 3.35–3.17 (2H, m), 3.14 (1H, br t, J=8.7 Hz), 2.40 (1H, m), 2.17–1.71 (8H, m), 1.31–1.25 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$, 313 K) δ 165.6, 156.7, 137.7, 115.6, 114.2, 111.2, 102.6, 71.4, 61.2, 59.1, 55.6, 52.1, 45.9, 43.6, 35.6, 30.2, 29.6, 27.4, 20.1 (several signals obscured or not observed). HRMS calcd for $C_{24}H_{29}N_2O_7$ (MH^+) 457.197. Found 457.198.

10.1.21. (±)-16-Anhydro-11,12-demethylenedioxypaucifinine 31. Silver tetrafluoroborate (341 mg, 1.75 mmol) in anhydrous THF (4 mL) was added to a solution of **26** (147 mg, 0.351 mmol) in anhydrous THF (4 mL) at room temperature. Over a period of 1 h the yellow solution became orange and a yellow suspension formed. Saturated aqueous $NaHCO_3$ (15 mL) was added and the mixture stirred for 10 min. The mixture was extracted with EtOAc (3×30 mL), and the combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography over silica gel eluting with 50–75% EtOAc/hexanes and 1% v/v triethylamine gave **31** as a white foam (139 mg, 97%). IR (film) 3492, 2936, br 1714, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (1H, br m), 7.23 (2H, br m), 7.03 (1H, t, J=7.2 Hz), 6.87 (1H, br m), 3.95–3.65 (6H, br m), 3.27–3.17 (1H, m), 2.80 (1H, m), 2.72 (1H, t, J=8.7 Hz), 2.61 (1H, m), 2.38–2.31 (1H, m), 1.96–1.50 (8H, m), 1.34–1.00 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 153.7, 143.8, 142.7, 135.5, 135.0, 127.5, 123.5, 122.9, 115.4, 91.1, 77.2, 71.2, 62.3, 60.3, 51.8, 47.2, 43.4, 42.2, 36.8, 29.7, 29.4, 16.2. HRMS calcd for $C_{23}H_{27}N_2O_5$ 411.192. Found 411.192.

10.1.22. (±)-16-Anhydro-11,12-demethylenedioxypaucifinine-*N*-oxide 32. To a solution of **31** (139 mg, 0.339 mmol) in CH_2Cl_2 (4 mL) was added a solution of *m*-chloroperoxybenzoic acid (108 mg, 0.441 mmol) in CH_2Cl_2 (4 mL). The resultant yellow solution was stirred at room temperature for 1.5 h. Water (10 mL) was added and the mixture extracted with CH_2Cl_2 (2×20 mL). The combined extracts was washed with 1% NaOH solution (15 mL), dried (Na_2SO_4), and evaporated in vacuo to give a yellow glass. Flash chromatography over silica gel eluting with 5% MeOH/$CHCl_3$ containing 1% v/v triethylamine gave **32** as a white foam (128 mg, 89%). IR (film) 2952, 1718, 1601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (1H, br m), 7.80 (1H, d, J=7.5 Hz), 7.21 (1H, br t, J=7.5 Hz), 7.06 (1H, t, J=7.5 Hz), 6.72 (1H, br m), 3.90–3.68 (6H, m), 3.49 (1H, m), 3.40–3.00 (3H, m), 2.40 (1H, m), 2.16–1.66 (8H, m), 1.36–1.29 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 136.8, 128.0, 126.0, 124.0, 114.7, 102.4, 77.2, 71.1, 61.2, 59.0, 52.1, 45.8, 43.5, 35.7, 30.0, 27.3, 20.0 (several signals not observed or obscured). HRMS calcd for $C_{23}H_{27}N_2O_6$ (MH^+) 427.187. Found 427.187.

10.1.23. (±)-16,17-Anhydro-11,12-demethoxypauciflorine B 33. Trifluoroacetic anhydride (0.169 mL, 1.19 mmol) was added to a solution of **32** (102 mg, 0.239 mmol) in CH_2Cl_2 (3 mL) at −30°C. The solution was allowed to warm to 0°C over 30 min and stirred for a further 1 h at room temperature. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated in vacuo to give **33** as a yellow foam, which was used directly in the next reaction. (The ^1H NMR of the crude product showed the diene **33** to be present in >90%). IR (film) 2949, br 1711, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.92, 7.49 (1H, br d, J=8.1 Hz), 7.30–6.97 (4H, m), 5.80 (1H, br s), 4.04 (1H, t, J=13.2 Hz), 3.95–3.65 (7H, m), 3.57 (1H, m), 3.15–2.87 (3H, m), 2.76–2.59 (1H, m), 2.47 (1H, m), 2.20 (1H, br t, J=12.9 Hz), 2.00–1.65 (3H, m). HRMS calcd for $C_{23}H_{25}N_2O_5$ (MH^+) 409.176. Found 409.176.

10.1.24. (±)-16,17-Anhydro-11,12-demethoxy-15-bromopauciflorine B 36. To a solution of **33** (33 mg, 0.0808 mmol) in $CHCl_3$ (1 mL) at −60°C was added pyridinium hydrogen bromide perbromide (25 mg, 0.0808 mmol). After 1 h the solution was warmed to room temperature, and after a further 3 h the mixture was quenched with saturated aqueous sodium bisulphite (5 mL). The aqueous phase was extracted with $CHCl_3$ (3×10 mL), and the combined extracts were washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4) and the solvents evaporated in vacuo to give an orange film. Purification by flash chromatography over silica gel eluting with 50% EtOAc/hexanes gave **36** a white glass (25 mg, 63%). Recrystallization from ether/MeOH gave colorless crystals suitable for X-ray crystallography (16 mg, 41%). Mp 160–162°C. IR (film) 2942, 1712, 1685, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

10.1.25. (±)-Kopsijasminilam 4. Phenylsilane (15 μL, 0.122 mmol) was added to a solution of **33** (20 mg, 0.049 mmol) and $Mn(dpm)_3$ (1 mg, 0.002 mmol) in isopropanol (0.75 mL) and 1,2-dichloroethane (0.5 mL) at −30°C. The brown solution was placed under an oxygen atmosphere and stirred for a further 1 h at −30°C then at 0°C for 1 h. At this point more phenylsilane (15 μL, 0.122 mmol) and $Mn(dpm)_3$ (1 mg, 0.002 mmol) were added, and the mixture warmed to room temperature for 1 h. Triethylphosphite (9.2 μL, 0.053 mmol) was added and the mixture stirred for 45 min open to the atmosphere. Evaporation of the solvents in vacuo gave a brown oil which was purified by flash chromatography over silica gel eluting with 50% EtOAc/hexanes, increasing to 100% EtOAc to give **4** as a colorless glass, (10 mg, 48%). IR (film) 3418, 1712, 1697, 1600 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 and 7.48 (1H, br d, J=8.3 Hz), 7.21 (1H, m), 7.10 (1H, br m), 7.04 (1H, t, J=7.3 Hz), 7.01 (1H, s), 4.08 (1H, br t, J=13.4 Hz), 3.82–3.71 (6H, m), 3.64 (1H, br s), 3.48 (1H,

m), 2.98 (1H, dd, *J*=14.1, 3.7 Hz), 2.86 (1H, t, *J*=9.5 Hz), 2.44 (1H, m), 2.36–1.60 (8H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 166.5, 153.5, 145.6, 140.7, 130.7, 129.9, 128.7, 124.9, 123.6, 115.4, 69.6, 69.3, 60.3, 52.7, 52.3, 43.9, 42.3, 41.3, 32.9, 31.2, 26.2, 22.5. HRMS calcd for $C_{23}H_{27}N_2O_6$ (MH^+) 427.187. Found 427.186.

10.1.26. Compounds 34 and 35. Phenylsilane (114 μL, 0.931 mmol) was added to a solution of **33** (76 mg, 0.186 mmol) and $Mn(dpm)_3$ (5 mg, 0.002 mmol) in isopropanol (0.75 mL) and 1,2-dichloroethane (0.5 mL) at 0°C. The brown solution was placed under an oxygen atmosphere and allowed to warm to room temperature and stirred for a further 18 h. Triethyl phosphite (79 μL, 0.465 mmol) was added, and the mixture was stirred for 45 min open to the atmosphere. Evaporation of the solvents in vacuo gave a brown oil which was purified by flash chromatography over silica gel eluting with 0–50% MeOH/$CHCl_3$ to give **34** as a colorless glass (22 mg, 26%). IR (film) 3418, 1712, 1680, 1637, 1600 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, d, *J*=8.1 Hz), 7.45 (1H, t, *J*=8.1 Hz), 7.31 (1H, t, *J*=7.8 Hz), 6.96 (1H, d, *J*=7.5 Hz), 4.00 (1H, m), 4.00–3.65 (2H, m), 3.76 (3H, s), 3.64 (3H, s), 3.46 (2H, m), 3.07 (1H, m), 2.79 (1H, d, *J*=13.5 Hz), 2.60–2.00 (4H, m), 1.99–1.25 (5H, m). A solution of the diol **34** (21 mg, 0.047 mmol) in CH_2Cl_2 (0.5 mL) at room temperature was treated with $BF_3{\cdot}Et_2O$ (6.5 μL, 0.052 mmol). A precipitate immediately formed which redissolved after 10 min. After 1 h at room temperature the mixture was quenched with water (3 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and the solvents evaporated in vacuo to give a yellow oil. Purification by flash chromatography over silica gel eluting with 5% MeOH/$CHCl_3$ gave the product **35** as a colorless solid (6 mg, 30%). Recrystallization from ether/MeOH gave colorless crystals suitable for X-ray analysis. Mp 159–161°C. IR (film) 3389, 1715, 1694, 1681 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (1H, dd, *J*=8.0, 1.5 Hz), 7.40 (1H, td, *J*=8.5, 1.5 Hz), 7.31 (1H, td, *J*=7.5, 1.5 Hz), 7.05 (1H, dd, *J*=7.5, 1.5 Hz), 5.48 (1H, d, *J*=6.5 Hz), 3.78 (3H, s), 3.86–3.50 (2H, m), 3.70 (3H, s), 3.20–3.10 (2H, m), 3.06–2.82 (3H, m), 2.77 (1H, dd, *J*=14.0, 5.0 Hz), 2.58 (1H, m), 2.47–2.39 (1H, m), 2.24 (1H, m), 2.12 (1H, dt, *J*=13.0, 3.5 Hz), 1.94 (1H, dd, *J*=15.0, 9.0 Hz), 1.83 (1H, dd, *J*=15.0, 7.0 Hz), 1.72 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 134.9, 133.8, 131.1, 130.5, 129.9, 128.8, 127.9, 127.1, 125.2, 119.9, 78.7, 53.5, 52.4, 44.7, 44.2, 35.7, 30.4, 29.7, 28.1, 22.7 (two signals not observed). HRMS calcd for $C_{23}H_{27}N_2O_6$ (MH^+) 427.187. Found 427.185.

10.1.27. (±)-11,12-Demethylenedioxypaucifinine 37. Silver tetrafluoroborate (338 mg, 1.74 mmol) in anhydrous THF (5 mL) was added to a solution of **28** (152 mg, 0.347 mmol) in anhydrous THF (5 mL) at room temperature. Over a period of 1 h the yellow solution became orange/brown and a suspension formed. Saturated aqueous $NaHCO_3$ (15 mL) was added and the mixture was stirred for 10 min. The mixture was extracted with EtOAc (3×30 mL), and the combined extracts were washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated in vacuo to give a yellow oil. Flash chromatography over silica gel eluting with 35–50% EtOAc/hexanes and 1% v/v triethylamine gave **37** as a white solid (120 mg, 81%). Mp 182–182°C. IR (film) 3499, 3288, 1732, 1681, 1599 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, d, *J*=8.1 Hz), 7.34 (1H, s), 7.26 (1H, d, *J*=7.2 Hz), 7.16 (1H, t, *J*=7.5 Hz), 7.02 (1H, t, *J*=7.5 Hz), 3.95 (3H, s), 3.72 (3H, s), 3.25–3.10 (2H, m), 3.07–2.97 (1H, m), 2.95–2.77 (2H, m), 2.32–2.18 (1H, m), 2.07–1.98 (1H, m), 1.93–1.40 (9H, m), 1.33–1.22 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 156.5, 140.7, 136.1, 127.2, 123.7, 123.5, 115.8, 90.6, 74.8, 74.3, 59.5, 53.3, 52.3, 47.7, 43.0, 41.5, 36.3, 36.2, 31.6, 28.8, 23.2, 17.1. HRMS calcd for $C_{23}H_{28}N_2O_6$ (M^+) 428.195. Found 428.193.

10.1.28. (±)-11,12-Demethylenedioxypaucifinine-*N*-oxide 38. To a solution of **37** (120 mg, 0.280 mmol) in CH_2Cl_2 (4 mL) was added a solution of *m*-chloroperoxybenzoic acid (83 mg, 0.336 mmol) in CH_2Cl_2 (4 mL) at 0°C. The resultant yellow solution was stirred at 0°C for 20 min. Water (10 mL) was added and the mixture extracted with CH_2Cl_2 (2×20 mL). The combined extracts were washed with 1% NaOH solution (15 mL), dried (Na_2SO_4), and the solvents were evaporated in vacuo to give a yellow glass. Flash chromatography over silica gel eluting with 5% MeOH/$CHCl_3$ containing 1% v/v triethylamine gave **38** as a yellow oil (63 mg, 51%). IR (film) 3278, 1731, 1679 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, d, *J*=7.5 Hz), 7.72 (1H, br s), 7.52 (1H, d, *J*=8.1 Hz), 7.18 (1H, t, *J*=8.1 Hz), 7.07 (1H, t, *J*=7.2 Hz), 3.97 (3H, s), 3.83 (1H, m), 3.76 (3H, s), 3.59 (1H, br d, *J*=13.5 Hz), 3.45–3.24 (3H, m), 3.06 (1 H, br d, *J*=15.9 Hz), 2.95–2.80 (1H, m), 2.34–2.24 (1H, m), 2.15–2.09 (1H, m), 1.95–1.20 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 156.8, 140.5, 134.3, 127.8, 127.2, 124.3, 114.8, 103.4, 74.7, 73.7, 62.5, 60.5, 53.5, 52.8, 45.7, 43.1, 36.9, 33.6, 29.8, 29.0, 22.2, 18.8. HRMS calcd for $C_{23}H_{29}N_2O_7$ (MH^+) 445.197. Found 445.197.

10.1.29. Compound 39. Trifluoroacetic anhydride (0.242 mL, 1.70 mmol) was added to a solution of **38** (63 mg, 0.141 mmol) and pyridine (114 μL, 1.41 mmol) in CH_2Cl_2 (2.5 mL) at −10°C. After stirring at −10°C for 1 h saturated aqueous $NaHCO_3$ (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), and the combined extracts were washed with 1% NaOH (15 mL), brine (15 mL), dried (Na_2SO_4), and evaporated in vacuo to give a yellow oil. Chromatography over silica gel eluting with 35% EtOAc/hexanes gave **39** product as a colorless glass (47 mg, 75%). Recrystallization from ether/MeOH gave colorless crystals suitable for X-ray analysis. Mp 205–207°C. IR (film) 3310, 1737, 1681 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

10.1.30. Compound 40. To a solution of **38** (62 mg, 0.139 mmol) in CH_2Cl_2 (1 mL) at 0°C was added $BF_3{\cdot}Et_2O$

(27 μL, 0.209 mmol). After 45 min at 0°C saturated aqueous $NaHCO_3$ (3 mL) was added and the resultant mixture extracted with CH_2Cl_2 (3×10 mL). The combined extracts were washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4), and evaporated in vacuo. Purification by flash chromatography over silica eluting with 5% MeOH/$CHCl_3$ gave **40** as a colorless glass (60 mg, 87%). Recrystallization from ether/MeOH gave colorless crystals suitable for X-ray analysis. Mp 158–160°C. IR (film) 3277, 1736, 1681, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (1H, d, J=7.5 Hz), 7.60 (1H, d, J=8.1 Hz), 7.45 (1H, br s), 7.27 (1H, t, J=8.1 Hz), 7.13 (1H, t, J=7.5 Hz), 4.06–4.00 (2H, m), 3.96 (3H, s), 3.86–3.55 (5H, m), 3.75 (3H, s), 2.83 (1H, br d, J=16.2 Hz), 2.60–1.40 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 156.3, 140.2, 130.6, 128.7, 126.1, 123.8, 115.8, 112.9, 74.9, 73.5, 65.6, 59.8, 58.9, 53.7, 52.8, 44.5, 37.9, 34.5, 29.8, 22.4, 21.9, 13.8. HRMS calcd for $C_{23}H_{28}{}^{11}BN_2O_7F_2$ (MH^+) 493.196. Found 493.195.

10.1.31. (±)-11,12-Demethoxypauciflorine B 42 and (±)-11,12-demethoxy-17,20-isopauciflorine B 42a. Silver tetrafluoroborate (0.135 g, 0.697 mmol) in anhydrous THF (1.5 mL) was added to a solution of **28** (61 mg, 0.139 mmol) in anhydrous THF (1.5 mL) at room temperature. After 15 min a solution of peracetic acid (0.146 mL, 0.697 mmol, 32% in acetic acid) in EtOAc (15 mL) was added. The brown suspension turned yellow and after 30 min saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was extracted with EtOAc (3×20 mL), and the combined extracts were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), and evaporated in vacuo to give a yellow glass. Purification by flash chromatography over silica gel eluting with 35–50% EtOAc/hexanes gave a white solid (39 mg, 65%) as a mixture of double bond isomers. A portion of the mixture was separated by preparative chromatography using multiple elutions with 35% EtOAc/hexanes to give **42** as a white solid (8 mg) which was recrystallized from ether/MeOH to give colorless crystals suitable for X-ray analysis. Further purification gave **42a** as a white solid (3 mg).

42: Mp dec >180°C, melts 247–249°C. IR (film) 3195, 1732, 1681, 1603 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

42a: Mp 182–184°C. IR (film) 3205, 1732, 1681, 1603 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

10.1.32. Epoxide 42b. *m*-Chloroperoxybenzoic acid (74 mg, 0.301 mmol) was added to a solution of the diene **33** (82 mg, 0.200 mmol) in CH_2Cl_2 (2 mL) at 0°C. The solution was stirred for 1 h at 0°C and quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined extracts were washed with 0.5% NaOH solution (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated in vacuo to give a yellow foam **42b** (78 mg, crude 92%). (NMR shows >90% epoxide). IR (film) 2931, 1716, 1693, 1601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.92, 7.50 (1H, br d, J=8.1 Hz), 7.40–6.95 (4H, m), 4.21 (1H, t, J=13.8 Hz), 4.00–3.60 (6H, m), 3.52–3.40 (2H, m), 3.30–2.95 (2H, m), 2.71–2.55 (1H, m), 2.50–2.40 (1H, m), 2.35–2.15 (1H, m), 2.00–1.50 (4H, m), 1.43–1.30 (1H, m). HRMS calcd for $C_{23}H_{25}N_2O_6$ (MH^+) 425.171. Found 425.170.

10.1.33. (±)-11,12-Demethoxy-19,20-oxapauciflorine B 42c. Phenylsilane (9 μL, 0.0766 mmol) was added to a solution of the epoxide **42b** (13 mg, 0.0306 mmol) and $Mn(dpm)_3$ (1 mg, 0.001 mmol) in isopropanol (0.75 mL) and 1,2-dichloroethane (0.25 mL) at 0°C. The brown solution was placed under an oxygen atmosphere and stirred for a further 10 min at 0°C then at room temperature for 18 h. Triethylphosphite (6 μL, 0.0337 mmol) was added and the mixture was stirred for 45 min open to the atmosphere. Evaporation of the solvents in vacuo gave a brown oil which was purified by flash chromatography over silica gel eluting with 75% EtOAc/hexanes to give **42c** as a white solid, (6 mg, 48%). Mp 225–227°C. IR (film) 3206, 2926, 1731, 1681, 1603 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.69 (1H, br s), 7.45 (1H, d, J=8.1 Hz), 7.20 (1H, t, J=7.5 Hz), 7.07 (1H, t, J=7.5 Hz), 6.98 (1H, d, J=7.2 Hz), 4.24 (1H, br t, J=13.2 Hz), 3.95 (3H, s), 3.85–3.77 (1H, m), 3.75 (3H, s), 3.37 (1H, t, J=10.2 Hz), 3.13 (1H, d, J=6.3 Hz), 3.06–2.97 (1H, m), 2.82 (1H, d, J=14.7 Hz), 2.68 (1H, dd, J=14.4, 6.0 Hz), 2.55–2.35 (2H, m), 2.28–1.97 (1H, m), 2.05–1.85 (1H, m), 1.75–1.55 (2H, m), 1.37–1.20 (2H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) $^{\delta}$ 174.1, 172.9, 157.4, 140.3, 134.2, 128.3, 124.4, 124.2, 116.2, 82.3, 75.6, 63.2, 59.3, 57.3, 53.7, 52.7, 44.7, 43.0, 35.5, 33.4, 30.4, 29.5, 21.6. HRMS calcd for $C_{23}H_{27}N_2O_5$ (MH^+) 443.183. Found 443.182.

10.1.34. 6,7-Dimethoxyindole 48. A 500 mL three-necked round bottom flask fitted with a condenser, a mechanical stirrer and a rubber septum was charged with iron powder (37.6 g), acetic acid (57 mL), EtOH (73 mL) and heated to 95°C with vigorous stirring. A suspension of **47** (4.00 g, 15.7 mmol) in acetic acid (84 mL) was added to the refluxing mixture over a period of 25 min, and stirring was continued for 2.5 h. The mixture was allowed to cool, and filtered through Celite into an aqueous solution of sodium metabisulfite (30.1 g in 280 mL of water). The solid residues were washed with EtOH (50 mL), and CH_2Cl_2 (250 mL). The aqueous and organic layers were

separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined extracts were washed successively with saturated aqueous $NaHCO_3$ (5×150 mL), water (2×150 mL), and dried ($MgSO_4$), filtered and evaporated in vacuo to give a pale yellow solid. Purification by flash column chromatography over silica gel eluting with CH_2Cl_2 gave **48** as pale pink blades (2.349 g, 85%). Mp 99–101°C (lit.[36] 102–103°C). IR (film) 3414, 3103, 2993, 2967, 2933, 2836, 1632 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, br s), 7.28 (1H, d, J=8.5 Hz), 7.11 (1H, dd, J=3.1, 2.6 Hz), 6.85 (1H, d, J=8.6 Hz), 6.47 (1H, dd, J=3.2, 2.2 Hz), 4.00 (3H, s), 3.92 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 134.4, 130.4, 124.4, 123.8, 115.4, 108.6, 102.6, 60.8, 57.4. HRMS calcd for $C_{10}H_{12}NO_2$ (MH^+) 178.087. Found 178.086.

10.1.35. 6,7-Dimethoxyindole-3-carboxaldehyde 49. To DMF (11 mL) at 0°C was added phosphorus oxychloride (8.1 mL, 87.3 mmol) dropwise over 13 min. The solution was stirred for a further 75 min, and treated with a solution of 6,7-dimethoxyindole **48** (5.151 g, 29.1 mmol) in DMF (11 mL) dropwise to give a yellow solution. The mixture was warmed to ambient temperature and stirred for a further 80 min, a further portion of DMF (25 mL) was added, and the yellow suspension was poured into ice-water (500 mL) and stirred overnight. The aqueous solution was neutralized with saturated aqueous $NaHCO_3$, and extracted with EtOAc (4×150 mL). The combined extracts were washed with water (5×50 mL), dried ($MgSO_4$), filtered and evaporated in vacuo to give a pale brown crystalline solid. Purification by flash column chromatography over silica gel eluting with 25% EtOAc (3:1) gave **49** as pale pink cubes (5.463 g, 92%). Mp 132–135°C. IR (film) 3108, 2945, 2838, 1625 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 10.01 (1H, s), 9.06 (1H, br s), 7.95 (1H, d, J=8.7 Hz), 7.78 (1H, d, J=3.0 Hz), 7.02 (1H, d, J=8.7 Hz), 4.02 (3H, s), 3.95 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 148.4, 135.3, 134.1, 131.3, 120.0, 116.8, 110.8, 61.1, 57.0. HRMS calcd for $C_{11}H_{12}NO_3$ (MH^+) 206.082. Found 206.083.

10.1.36. 6,7-Dimethoxy-3-(2-nitroethenyl)indole 50. A solution of **49** (1.011 g, 4.93 mmol) and NH_4OAc (1.140 g, 14.80 mmol) in nitromethane (20.0 mL) was heated at reflux for 40 min to give a red solution. The cooled mixture was diluted with water (30 mL), and extracted with CH_2Cl_2 (5×50 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo to give **50** as a red oil (1.22 g, 100%) that solidified on standing. No further purification was required. IR (film) 3311, 2936, 1611, 1516 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.82 (1H, br s), 7.74 (1H, d, J=13.5 Hz), 8.24 (1H, d, J=13.5 Hz), 7.60 (1H, d, J=2.3 Hz), 7.41 (1H, d, J=8.6 Hz), 7.02 (1H, d, J=8.7 Hz), 4.04 (3H, s), 3.96 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 134.6, 134.1, 133.6, 132.1, 132.0, 120.4, 115.4, 110.2, 109.9, 61.1, 57.0. HRMS calcd for $C_{12}H_{13}N_2O_4$ (MH^+) 249.088. Found 249.088.

10.1.37. 6,7-Dimethoxytryptamine 51. To a stirred suspension of $LiAlH_4$ (97 mg, 2.556 mmol) in THF (5 mL) at 0°C was added a solution of **50** (127 mg, 0.512 mmol) in THF (5 mL) dropwise over a period of 30 min, and the mixture was heated at reflux for 1 h. The mixture was allowed to cool to room temperature and quenched by dropwise addition of water. The mixture was poured into saturated aqueous Rochelle's Salt (20 mL) and stirred overnight. The solution was extracted with EtOAc (5×20 mL), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo to give a brown oil. Purification by flash column chromatography over silica gel eluting with CH_2Cl_2/MeOH (10:1+1% triethylamine) gave **51** as a pale brown oil (103 mg, 91%) that solidified on standing. IR (film) 3355, 2933, 2835, 1629 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (1H, br s), 7.20 (1H, d, J=9 Hz), 6.92 (1H, s), 6.81 (1H, d, J=9 Hz), 3.96 (3H, s), 3.89 (3H, s), 2.99 (2H, br t, J=6 Hz), 2.85 (2H, br t, J=6 Hz), 2.80 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 134.4, 130.9, 124.2, 121.9, 113.6, 133.3, 107.9, 60.7, 57.4, 41.8, 28.7. HRMS calcd for $C_{12}H_{16}N_2O_2$ (M^+) 220.121. Found 220.122.

10.1.38. (±)-1-(4-Carboxy-butyl)-7,8-dimethoxy-2,3,4,9-tetrahydro-1H-β-carboline-1-carboxylic acid methyl ester 52. A mixture of **51** (1.131 g, 5.141 mmol), **13** (0.966 g, 5.141 mmol) and 4 Å molecular sieves (ca. 5 g) in CH_2Cl_2 (28 mL) at 0°C was treated with trifluoroacetic acid (0.080 mL, 1.042 mmol) dropwise then allowed to warm to room temperature and stirred for 24 h. The mixture was filtered through Celite and washed with MeOH (200 mL). The filtrate was evaporated in vacuo to afford **52** a brown oil (2.0 g) used subsequently without further purification.

10.1.39. (±)-13b-Carbomethoxy-16,17-dimethoxy-2,3,4,5,6,7,8,13,13b-octahydro-1H-azepino[1′,2′:1,2]pyrido-[3,4-*b*]indol-5-one 53. To a solution of crude **52** (2.0 g) and 1-hydroxybenzotriazole monohydrate (1.389 g, 10.282 mmol) in DMF (104 mL) at 0°C was added a solution of EDCI (1.971 g, 10.282 mmol) and Et_3N (1.43 mL, 10.282 mmol) in DMF (67 mL). The resulting mixture was stirred at 0°C for 1 h, and at room temperature for 24 h, treated with pH 7 buffer solution and water (400 mL), and extracted with EtOAc (5×150 mL). The combined extracts were successively washed with water (3×200 mL), dried (Na_2SO_4), filtered and evaporated in vacuo to give a brown oil. Purification by flash chromatography over silica gel eluting with 25% EtOAc/hexanes (1:1) gave (1.234 g, 67%). Crystallization by slow evaporation of hexane/EtOAc gave **53** as colorless cubes. Mp 192–193°C. IR (film) 3284, 2935, 1735, 1628 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, br s), 7.15 (1H, d, J=8.6 Hz), 6.85 (1H, d, J=8.7 Hz), 4.77 (1H, dt, J=13.0, 4.0 Hz), 4.00 (3H, s), 3.91 (3H, s), 3.79 (3H, s), 3.32 (1H, dt, J=13.1, 7.2 Hz), 2.8 (4H, m), 2.3 (1H, m), 1.97 (1H, m), 1.85 (1H, m), 1.62 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 171.9, 147.6, 134.4, 131.3, 130.7, 122.6, 133.5, 112.4, 108.4, 65.5, 60.8, 57.3, 53.2, 42.1, 40.5, 37.9, 25.4, 22.0, 20.6. HRMS calcd for $C_{20}H_{25}N_2O_5$ (MH^+) 373.176. Found 373.176.

10.1.40. (±)-13b-Carbomethoxy-16,17-dimethoxy-2,3,4,5,6,7,8,13,13b-octahydro-1H-azepino[1′,2′:1,2]pyrido-[3,4-*b*]indol-5-thione 54. To a solution of **53** (1.808 g, 5.079 mmol) in dry THF (110 mL) at 0°C was added solid Belleau's reagent (1.75 g, 4.70 mmol) in one portion. The resulting solution was stirred at 0°C for 10 min, and allowed to warm to room temperature and stirred for 15 h.

Chromatographic grade silica gel (ca. 15 g) was added, and the mixture evaporated in vacuo. Purification by flash chromatography over silica gel eluting with 25% EtOAc/hexanes gave **54** as a pale yellow solid (1.970 g, 100%). Crystallization by slow evaporation of EtOAc gave **54** as clear, pale yellow prisms. Mp 209–210°C. IR (film) 3317, 2937, 2836, 1735, 1632 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, br s), 7.18 (1H, d, J=8.5 Hz), 6.87 (1H, d, J=8.7 Hz), 5.45 (1H, dt, J=13.3, 4.3 Hz), 4.10 (1H, m), 4.00 (3H, s), 3.92 (3H, s), 3.79 (3H, s), 3.61 (1H, dd, J=14.5, 4.4 Hz), 3.00–2.75 (3H, m), 2.66 (1H, m), 2.07 (1H, m), 2.00–1.60 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 170.9, 147.8, 134.4, 131.0, 130.9, 122.2, 133.5, 112.3, 108.7, 69.6, 60.8, 57.3, 53.6, 51.8, 47.0, 38.7, 24.0, 23.7, 20.3. HRMS calcd for $C_{20}H_{25}N_2O_4S$ (MH^+) 389.154. Found 389.153.

10.1.41. (±)-13b-Carbomethoxy-16,17-dimethoxy-2,3,4,5,6,7,8,13,13b-octahydro-1H-azepino[1′,2′:1,2]pyrido-[3,4-*b*]indole 55. A solution of thiolactam **54** (1.970 g, 5.077 mmol) and $NiCl_2{\cdot}6H_2O$ (4.827 g, 20.308 mmol) in THF (50 mL) and MeOH (50 mL) at 0°C was treated with $NaBH_4$ (2.881 g, 76.155 mmol) portion wise, an immediate color change from green to black was observed. Stirring was continued for 5 min until the effervescence had subsided. The mixture was filtered through celite, and washed through with MeOH (250 mL). The solvent was evaporated in vacuo to give a blue-gray solid which was partitioned between EtOAc (150 mL) and water (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×100 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo to give a yellow oil. Purification by flash chromatography over silica gel eluting with 33% EtOAc/hexanes (2:1) gave **55** as a white solid (1.400 g, 77%). Crystallization by slow evaporation from EtOAc gave **55** as clear, colorless cubes. Mp 126–127°C. IR (film) 3337, 2929, 2837, 1735, 1718, 1628 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (1H, br s), 7.14 (1H, d, J=8.5 Hz), 6.82 (1H, d, J=8.7 Hz), 4.01 (3H, s), 3.92 (3H, s), 3.72 (3H, s), 3.29 (1H, dt, J=11.1, 4.2 Hz), 3.17 (1H, dd, J=13.2, 5.1 Hz), 2.91 (2H, m), 2.85 (1H, m), 2.50 (2H, m), 2.10 (1H, m), 1.68 (5H, m), 1.43 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 147.2, 134.4, 133.1, 130.5, 123.5, 113.2, 111.0, 107.9, 66.6, 60.8, 57.5, 52.3, 50.3, 50.2, 39.2, 30.8, 29.1, 22.8, 19.7. HRMS calcd for $C_{20}H_{27}N_2O_4$ (MH^+) 359.197. Found 359.197.

10.1.42. (±)-5,8,9,10,11,14-Hexahydro-6H-15,16-dimethoxy-7,14-diazacycloundeca[*a*]indene-7,13-dicarboxylic acid 13-methyl ester 7-phenyl ester 56. A solution of **55** (87 mg, 0.243 mmol) in 1,2-dichloromethane (2.0 mL) at room temperature was treated with phenyl chloroformate (0.239 mL, 1.905 mmol) and the mixture heated at reflux for 48 h. The mixture was cooled to room temperature, excess saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture stirred vigorously for several hours then extracted with CH_2Cl_2 (5×20 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo to give a dark brown oil. Purification by flash chromatography over silica gel eluting with 25% EtOAc/hexanes gave **56** (55 mg, 47%) as a yellow oil that solidified on standing. The amine **55** was also recovered (29 mg, 33%). IR (film) 3348, 2934, 2836, 1715, 1631, 1593 cm^{-1}. ^1H NMR (500 MHz, d_8-toluene, 100°C) δ 7.64 (1H, s), 7.10 (1H, t, J=8.1 Hz), 7.2 (2H, dd, J=8.5, 0.6 Hz), 6.95 (3H, br m), 6.81 (1H, t, J=6.8 Hz), 6.64 (1H, d, J=8.3 Hz), 3.84 (3H, s), 3.80 (2H, br m), 3.58 (3H, s), 3.39 (3H, s), 3.14 (2H, br m), 2.89 (2H, br m), 2.10 (2H, br m), 1.53 (4H, br m). ^{13}C NMR (125 MHz, d_8-toluene, 100°C) δ 166.7, 154.5, 152.6, 148.0, 136.1, 131.7, 125.9, 124.6, 121.9, 114.7, 110.5, 60.4, 58.0, 51.5, 50.4, 27.2, some signals obscured. HRMS calcd for $C_{20}H_{31}N_2O_6$ (MH^+) 479.218. Found 479.218.

10.1.43. (±)-12b-Cyano-7,8-dimethoxy-2,3,6,11,12,12b-hexahydro-1H-6,12a-diazaindeno[7,1-*cd*]fluorene-5-carboxylic acid methyl ester 58. A solution of **56** (192 mg, 0.402 mmol), and DMAP (147 mg, 1.203 mmol) in CH_2Cl_2 (9.3 mL) at 0°C was treated with trifluoromethanesulfonic anhydride (0.337 mL, 2.003 mmol) dropwise to give an olive green solution. The mixture was stirred for a further 20 min at 0°C, warmed to room temperature, and stirred for a further 30 min. The mixture was heated at reflux for a further 22 h to give a dark purple solution. The solution was cooled to ambient temperature, stirred for 1.5 h and treated with a solution of trimethylsilyl cyanide (0.214 mL, 1.608 mmol) and DMAP (147 mg, 1.203 mmol) in CH_2Cl_2 (2.0 mL) dropwise to give an orange-brown solution. After stirring for a further 45 min, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture stirred for a further 1 h. The mixture was extracted with CH_2Cl_2 (4×50 mL), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo to give an orange-brown solid. Purification by flash chromatography over silica gel eluting with 35% EtOAc/hexanes gave **58** as a yellow solid (99 mg, 63%). Mp 207–209°C. IR (film) 3397, 2945, 2867, 2838, 2253, 1682, 1634, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.10 (1H, br s), 7.24 (1H, d, J=8.2 Hz), 6.53 (1H, d, J=8.2 Hz), 3.91 (3H, s), 3.86 (3H, s), 3.81 (3H, s), 3.30 (2H, m), 3.17 (1H, d, J=13.8 Hz), 2.95 (1H, dt, J=11.1, 2.52 Hz), 2.45 (3H, m), 1.90 (2H, m), 1.57 (1H, br d, J=13.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 161.7, 153.3, 136.7, 133.5, 125.8, 120.2, 119.1, 118.8, 117.5, 105.8, 91.6, 64.7, 60.9, 59.2, 56.1, 51.2, 46.6, 45.9, 39.7, 29.5, 20.5. HRMS calcd for $C_{22}H_{24}N_3O_4$ (MH^+) 394.177. Found 394.176.

10.1.44. (±)-16-Anhydro-1-decarbomethoxylahadinine B 60. A solution of **58** (41 mg, 0.104 mmol) in freshly distilled acryloyl chloride (1.0 mL) was stirred in a sealed tube at ambient temperature in the dark for 24 h then concentrated under reduced pressure to yield a pale brown solid. The crude solid was dissolved in dichloromethane (1.0 mL, with 1.0 mL wash over) and added to a suspension of pre-dried 2-mercaptopyridine *N*-oxide, sodium salt (23 mg, 0.156 mmol; tech., 90%) in dichloromethane (1.0 mL) at 0°C in the dark. The mixture was stirred for 5 min, warmed to room temperature, stirred for a further 2 h, cooled to 0°C, and treated with *tert*-butyl thiol (0.7 mL, excess). The mixture was irradiated with a tungsten lamp for 1.75 h (the reaction temperature was kept between 0 and 20°C). After irradiation the mixture was concentrated under reduced pressure to give a yellow solid. Purification by flash column chromatography on silica gel eluting with hexane–EtOAc 2:1 gave **60** as a colorless oil (16 mg, 37%). IR (film) 3354, 2942, 2858, 2251, 1714, 1623 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37 (s, 1H),

7.23 (d, J=8.2 Hz, 1H), 6.51 (d, J=8.3 Hz, 1H), 4.61 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 3.42 (t, J=12 Hz, 1H), 3.14 (d, J=12 Hz, 1H), 2.95 (t, J=9 Hz, 1H), 2.84 (q, J=9 Hz, 1H), 2.43 (dd, J=15, 6 Hz, 1H), 2.05 (m, 4H), 1.71 (bm, 1H), 1.57 (bm, 1H), 1.35 (m, 2H), 1.00 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4, 152.5, 143.7, 143.0, 135.3, 134.4, 127.1, 118.5, 103.5, 77.1, 70.8, 68.8, 65.8, 60.3, 55.8, 51.8, 49.8, 44.8, 41.5, 37.6, 31.8, 31.3, 27.4, 16.5. HRCIMS calcd for $C_{24}H_{28}N_2O_4$, (MH^+) 422.208. Found 422.208.

10.1.45. (±)-16-Anhydro-1-decarbomethoxy-18-selenophenyllahadinine B 61. A solution of **58** (81 mg, 0.2061 mmol) in freshly distilled acryloyl chloride (2.0 mL) was stirred in a sealed tube at ambient temperature in the dark for 24 h, and concentrated under reduced pressure to yield a pale brown solid **59**. The crude solid was dissolved in CH_2Cl_2 (2.0 mL, with 2.0 mL wash over) and added to a suspension of pre-dried 2-mercaptopyridine *N*-oxide sodium salt (50 mg, 0.3017 mmol, tech., 90%) in CH_2Cl_2 (3.5 mL) at 0°C in the dark. The mixture was stirred for 5 min, warmed to room temperature, stirred for a further 1.75 h, cooled to 0°C and treated with a solution of diphenyl diselenide (371 mg, 1.19 mmol) in CH_2Cl_2 (3.0 mL). The yellow solution was irradiated with a tungsten lamp for 30 min (the reaction temperature was kept between 0 and 20°C). After irradiation the mixture was evaporated in vacuo to give a yellow solid. Purification by flash column chromatography over silica gel eluting with 50% EtOAc/hexanes gave **61** as a colorless oil (49 mg, 41%). IR (film) 3380, 2943, 2859, 2839, 2251, 1718, 1622, 1578 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (2H, d, J=7.6 Hz), 7.20 (3H, m), 7.08 (1H, d, J=8.2 Hz), 7.05 (1H, s), 6.40 (1H, d, J=8.2 Hz), 3.88 (3H, s), 3.82 (3H, s), 3.75 (3H, s), 3.29 (1H, br t, J=12.2 Hz), 3.02 (1H, br d, J=13.7 Hz), 2.83 (1H, t, J=7.6 Hz), 2.71 (1H, q, J=8.3 Hz), 2.52 (1H, dd, J=14.0, 8.6 Hz), 2.36 (1H, dd, J=14.2, 7.2 Hz), 1.95 (2H, m), 1.85 (2H, m), 1.50 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 152.7, 144.0, 142.2, 134.7, 134.1, 133.8, 129.1, 128.3, 127.7, 126.4, 118.3, 118.1, 104.1, 73.9, 68.5, 67.0, 60.3, 55.9, 52.0, 49.6, 44.6, 43.3, 41.9, 41.5, 38.1, 30.8, 16.1. HRMS calcd for $C_{30}H_{32}N_3O_4Se^{80}$ (MH^+) 578.156. Found 578.152.

10.1.46. (±)-16-Anhydro-18-selenophenyllahadinine B 62. A solution of **61** (17 mg, 0.0295 mmol) and 18-crown-6 (12 mg, 0.0454 mmol) in THF (1.0 mL) at −78°C, under argon, was treated with a solution of $KN(SiMe_3)_2$ (0.088 mL, 0.0442 mmol, 1.0 M solution in toluene) to give an orange-brown solution. The solution was stirred for a further 10 min, and CO_2 gas was passed over the mixture for 10 min to give a pale yellow solution. The CO_2 inlet was removed, dimethyl sulfate (0.012 mL, 0.127 mmol) was added, and stirring continued for 15 min at −78°C. The mixture was allowed to warm to room temperature, stirred for a further 30 min and treated with pH 7 phosphate buffer solution (5 mL). The mixture was extracted with CH_2Cl_2 (5×15 mL), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo to give a pale brown oil. Purification by flash column chromatography over silica gel eluting with 50% EtOAc/hexanes gave **62** (16 mg, 86%). IR (film) 2948, 2858, 2251, 1802, 1718, 1610 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (2H, d, J=6.5 Hz), 7.20 (4H, m), 6.74 (1H, d, J=8.3 Hz), 6.60 (1H, s), 4.00 (1H, t, J=7.9 Hz), 3.90 (3H, s), 3.85 (6H, br s), 3.83 (3H, s), 3.23 (1H, br t, J=12.4 Hz), 2.98 (2H, dd, J=14.1, 6.5 Hz), 2.81 (1H, t, J=8.4 Hz), 2.68 (1H, q, J=8.3 Hz), 1.95 (2H, m), 1.73 (3H, m), 1.41 (1H, br d, J=11.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 153.9, 153.7, 138.6, 138.3, 134.4, 133.8, 133.7, 129.4, 128.9, 128.5, 127.3, 118.1, 108.2, 75.4, 68.9, 67.4, 60.8, 56.1, 53.0, 52.4, 50.1, 44.5, 40.8, 40.6, 39.9, 38.6, 30.7, 15.6, 14.1. HRMS calcd for $C_{32}H_{34}N_3O_6Se^{80}$ (MH^+) 636.161. Found 636.161.

10.1.47. (±)-18-Selenophenyllahadinine B 63. A dark brown solution of **62** (7 mg, 0.0110 mmol) and tris(dipivaloylmethanato)manganese(III) (3 mg, 0.0071 mmol) in isopropanol (0.2 mL) and 1,2-dichloroethane (0.5 mL) at 0°C was treated with phenylsilane (50 μL, 0.402 mmol) causing the mixture to turn pale brown. The solution was placed under an atmosphere of oxygen and stirred for a further 10 min at 0°C. The mixture was warmed to room temperature and stirred for 7 days. The solution was treated with aqueous 1 M $Na_2S_2O_3$ (3 mL) and extracted with CH_2Cl_2 (5×10 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated in vacuo to give a pale brown oil. Purification by flash column chromatography over silica gel eluting with 50% EtOAc/hexanes gave **63** (6 mg, 83%). Mp 249°C (dec). IR (film) 3351, 2948, 2362, 1740, 1680 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 153.7, 138.8, 133.0, 132.8, 130.8, 130.7, 128.8, 126.1, 117.9, 117.4, 107.8, 79.3, 74.1, 67.9, 62.5, 60.0, 56.2, 53.5, 52.3, 49.1, 44.3, 43.4, 41.3, 40.2, 38.9, 37.6, 32.2, 29.6, 20.7. HRMS calcd for $C_{32}H_{36}N_3O_7Se^{80}$ (MH^+) 654.172. Found 654.172. Used directly in the next stage.

10.1.48. (±)-Lahadinine B 64. A solution of **63** (7 mg, 0.011 mmol) in toluene (0.75 mL) heated at reflux was treated with a solution of triphenyltin hydride (18 mg, 0.051 mmol) in toluene (0.75 mL), and stirred for a period of 24 h in the dark. The cooled mixture was evaporated in vacuo, and purified by flash column chromatography over silica gel eluting with 50% EtOAc/hexanes to give **64** (6 mg, 83%) as a white solid. Crystallization by slow evaporation from a solution in CH_2Cl_2/MeOH (2:1, v/v) gave **64** as colorless needles suitable for X-ray crystallography. IR (film) 2917, 2848, 2352, 1738, 1732, 1714, 1694, 1682, 1651 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (1H, d, J=8.2 Hz), 6.61 (1H, d, J=8.4 Hz), 6.60 (1H, d, J=0.6 Hz), 3.87 (3H, s), 3.84 (3H, s), 3.73 (3H, s), 3.72 (3H, s), 3.04 (4H, m), 2.92 (1H, ddd, J=9.0, 6.6, 1.8 Hz), 2.39 (1H, ddd, J=13.4, 10.8, 1.6 Hz), 1.98 (1H, ddd, J=12.2, 9.2, 6.8 Hz), 1.87 (1H, ddd, J=12.8, 10.2, 9.0 Hz), 1.73 (1H, ddd, J=13.4, 10.5, 8.3 Hz), 1.70 (1H, m), 1.56 (5H, m), 1.43 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 157.0, 153.6, 137.9, 133.7, 130.2, 118.5, 117.9, 106.9, 75.3, 73.7, 68.4, 60.1, 59.6, 56.0, 53.5, 52.4, 49.1, 44.3, 39.5, 39.2, 36.7, 32.5, 28.3, 24.9, 20.3. HRMS calcd for $C_{26}H_{32}N_3O_7$ (MH^+) 498.224. Found 498.225 (Fig. 1).

10.1.49. (±)-11-Methoxykopsilongine 65. A solution of lahadinine B **64** (3.5 mg) in dichloromethane (1.3 mL) at 0°C under an atmosphere of argon was treated with trifluoroacetic acid (450 μL) to give a very pale green/brown solution. After stirring for a further 5 min the mixture

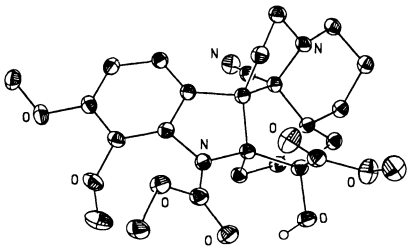


Figure 1. ORTEP of lahadinine B, **64**.

was treated with triethylsilane (450 μL), stirred for a further 15 min, and warmed to ambient temperature and stirred for a further 4 days. The mixture was treated with saturated aqueous sodium hydrogen carbonate (4 mL) and extracted with dichloromethane (4×15 mL). Purification by flash column chromatography over silica gel (hexane/EtOAc 1:1 then neat EtOAc) gave **65** (3.5 mg, 93%) as a pale brown oil. IR (film) 3322, 2929, 2855, 1732, 1682, 1613 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.92 (1H, br m), 6.64 (1H, s), 6.54 (1H, d, J=8.2 Hz), 3.89 (3H, s), 3.82 (3H, s), 3.74 (3H, s), 3.73 (3H, s), 3.06 (2H, m), 2.95 (1H, br m), 2.89 (1H, dd, J=14.9, 2.0 Hz), 2.79 (1H, br m), 2.36 (2H, m), 2.17 (1H, br m), 1.78 (2H, m), 1.63 (2H, m), 1.47 (1H, ddd, J=7.8, 11.1, 13.3 Hz), 1.28 (2H, m), 1.05 (1H, br t, J=11.1 Hz), 1.40 (1H, d, J=14.5 Hz). HRCMS calcd for $C_{25}H_{32}N_2O_7$ (MH^+) 473.229. Found 473.229.

10.1.50. (±)-Pauciflorine B 6 and (±)-17,20-isopauciflorine B 6a. A solution of lahadinine B **64** (5 mg, 0.010 mmol) in THF (0.4 mL), at ambient temperature under an atmosphere of argon, was treated with a solution of silver tetrafluoroborate (26 mg, 0.134 mmol) in THF (0.1 mL) to give an orange/brown solution. After stirring the mixture for a further 20 min, a solution of peracetic acid (10 mL, 32% wt in acetic acid, 0.048 mmol) in EtOAc (0.8 mL) was added to the mixture to give a pale yellow solution. After stirring for a further 1 h the mixture was treated with saturated aqueous sodium hydrogen carbonate (2 mL), and extracted with CH_2Cl_2 (4×10 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give a pale brown oil. Purification by flash column chromatography over silica gel (CH_2Cl_2/MeOH 60:1) gave pauciflorine B **6** (3.2 mg, 66%) as a colorless oil, and **6a** (1.0 mg, 21%). Slow evaporation of a CH_2Cl_2/MeOH solution of pauciflorine B provided crystals suitable for X-ray crystallography. IR (film) 3240, 2923, 2850, 1732, 1688, 1679, 1601 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 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, 6.7 Hz), 2.48 (1H, d, J=19.4 Hz), 2.24 (2H, m), 2.05 (3H, m), 1.50 (1H, m). HRCMS calcd for $C_{25}H_{31}N_2O_8$ (MH^+) 487.208. Found 487.208 (Fig. 2).

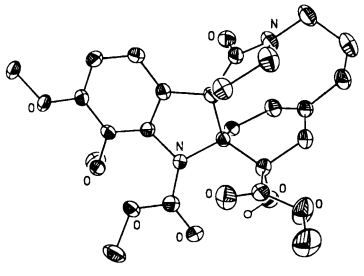


Figure 2. ORTEP of pauciflorine B, **6**.

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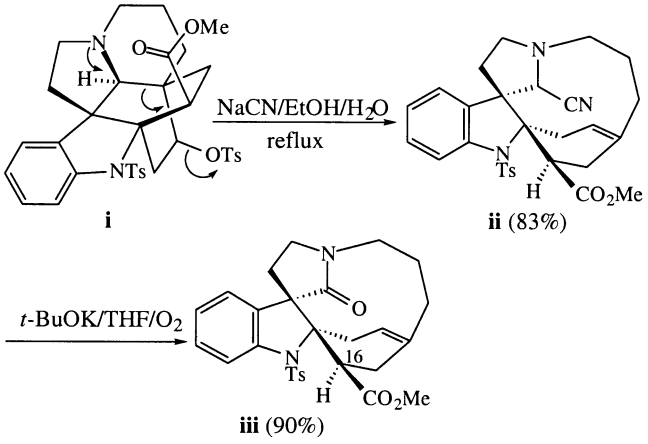

i **ii** (83%) **iii** (90%)

Compound **iii** was converted into **33** and hence into kopsijasminilam **4** using the $Mn(dpm)_3/PhSiH_3/O_2$ reaction.
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