Tetrahedron 65 (2009) 6730–6738

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Application of an amidyl radical cascade to the total synthesis of (±)-fortucine leading to the structural revision of kirkine

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ARTICLE INFO

Article history:
Received 12 January 2009
Received in revised form 7 April 2009
Accepted 7 April 2009
Available online 16 April 2009

Dedicated with admiration to Professor Larry E. Overman

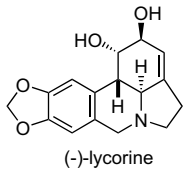
ABSTRACT

A radical cascade initiated by a nitrogen-centred (amidyl) radical was developed, allowing the rapid construction of galanthan frameworks. It was applied to a concise, stereo/regio-selective and tin-free total synthesis of the natural product (±)-fortucine. This in turn resulted in the correction of the structure of kirkine.

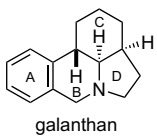
1. Introduction

Over the past decade, drug discovery from medicinal plants has played a large role in furnishing new drugs and drug leads against various diseases. There are numerous pharmacologically active compounds that belong to the Amaryllidaceae family, which includes nearly 500 structurally diverse alkaloids showing significant biological activity.[1]

Lycorine alkaloids[2] were isolated from the Amaryllidaceae family. These alkaloids have long been known for their medicinal virtues[3] and show antineoplastic, antimitotic, insect antifeedant, and antiviral activities. They also inhibit growth and cell division in higher plants, protein and DNA synthesis in murine cells and in vivo growth of a murine transplantable ascite tumour. Tests for antifungal and antimicrobial activities demonstrated that bacteria are resistant to lycorine whereas yeasts are sensitive to it.[4]



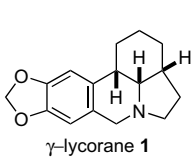
(-)-lycorine



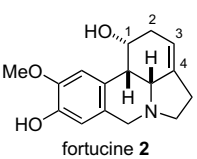
galanthan

Ever since the structure of lycorine was first described in 1955,[5] the tetracyclic galanthan framework common to lycorine alkaloids has been the subject of intense research.[1] Most lycorine alkaloids have a trans-B,C-ring junction; however, some compounds have a cis-B,C-ring junction, notably γ-lycorane **1**, fortucine (kirkine, **2**) and siculinine **3** (Fig. 1).[4c,1]

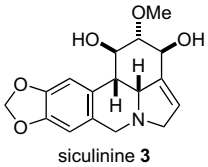
Fortucine **2** was isolated from the *Fortune* variety of narcissus by a Russian group in 1988.[6a] Bastida et al. subsequently isolated kirkine from *Crinum kirkii*, a common grassland plant from East Africa used as a purgative, rat poison and for the treatment of sores.[7] They assigned to kirkine the same structure as fortucine **2**.[6b] Notwithstanding that the Spanish study is more recent, it was apparently conducted without knowledge of the work by the Russian group. Furthermore, the respective NMR spectra show discrepancies between the two compounds, which cannot be readily explained, even when taking into consideration the fact that the NMR spectra were recorded under different conditions. We decided to undertake the total synthesis of structure **2** to clarify this anomaly and to provide sufficient quantities of **2** to explore its biological activity. We also sought to establish a general strategy to access galanthan



γ–lycorane **1**



fortucine **2**



siculinine **3**

Figure 1. Lycorine type alkaloids.

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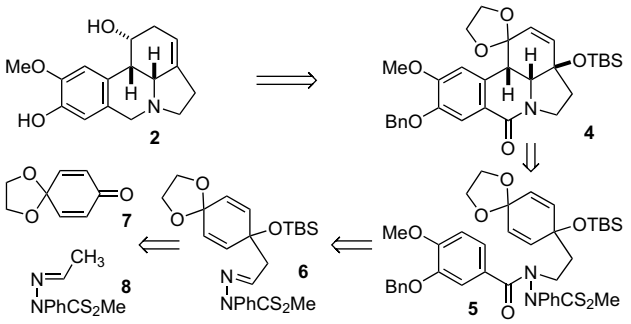
doi:10.1016/j.tet.2009.04.027



Scheme 1. Retrosynthetic analysis of fortucine **2**.

frameworks with a cis-B,C-ring junction. In the present article we give a full account of our work.[8]

Our synthetic approach to structure **2** (henceforth fortucine) is based on a radical cascade that is initiated by the generation of an amidyl radical that undergoes cyclisation on to the neighbouring alkene followed by an oxidative cyclisation on to the aromatic ring (Scheme 1). This cascade is designed to form rings B and D in one step. Moreover, we expected the cyclisations to be stereoselective leading to the requisite cis-B,C-ring junction, as well as regioselective to give *para* (as opposed to *ortho*) cyclisation with respect to the benzyloxy group. Precursor **6** is constructed by the union of *p*-benzoquinone ethylene-monoketal **7**[9] with the azaenolate of hydrazone **8**.[10] Hydrazone **6** can be a useful building block for the formation of lycorine type alkaloids, through reduction and benzoylation of the ensuing hydrazide to give key intermediates such as **5**.

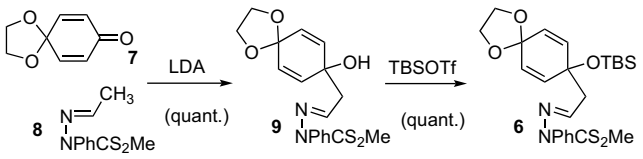
2. Results and discussion

We began the synthesis by trapping the azaenolate derived from hydrazone **8** with *p*-monoketal **7** to provide alcohol **9** in a quantitative yield. Such a satisfying result was not expected, since neither 1,4-addition onto the enone nor intramolecular cyclisation of the azaenolate onto the thiocarbonyl group were observed. The azaenolate of **8** was stable at −78 °C, and it was indeed possible to trap it with a variety of α,β-unsaturated ketones. These coupled products can in principle be used to construct dihydropyrroles via iminyl radicals,[11] and galanthan frameworks via amidyl radicals[12] through cyclisations onto the neighbouring alkenes (Scheme 2).

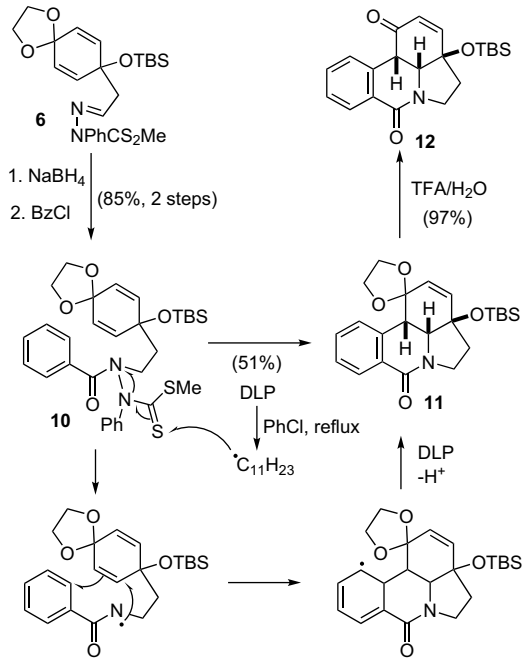
At this point we attempted the direct transformation of alcohol **9** into the radical precursor **5** via reduction and reaction with an appropriate aroyl chloride, but the free di-allylic tertiary alcohol was too unstable to undergo the benzoylation reaction. We therefore decided to protect it as a silyl ether, and attempted to prepare silyl ether **6** in the same pot by quenching the coupling reaction of hydrazone **8** with monoketal **7** with TBSOTf as opposed to the addition of aqueous NH_4Cl. In the event, it proved necessary to isolate and purify alcohol **9** and to react it with TBSOTf in a separate step to afford silyl ether **6** in an acceptable yield.

2.1. Model study

A model study was first carried out in which ring A was replaced by a phenyl ring. Hydrazone **6** was reduced with $NaBH_4$ and then



Scheme 2. Synthesis of silyl ether **6**.



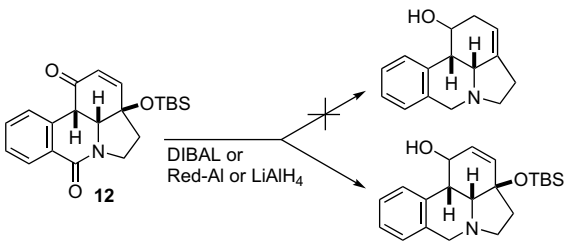
Scheme 3. Synthesis of pentacycle **12**.

treated with benzoyl chloride to yield radical precursor **10**. Pleasingly, treatment of radical precursor **10** in refluxing chlorobenzene with lauroyl peroxide (DLP, 2.0 equiv) effected the desired radical cascade to give pentacycle **11** in 51% yield. Even though we have studied this type of cyclisation before,[12] we were delighted (but not surprised) to see that the cascade process had occurred stereoselectively to give the all-cis cyclised product. The protected-ketone was then unmasked by treatment with TFA in water to give enone **12** in 97% yield (Scheme 3).

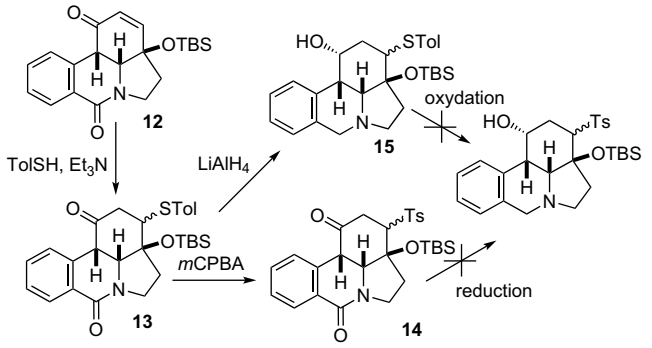
At this point, we examined the reductive elimination of the allylic silyl ether and the concomitant migration of the double bond. Unfortunately, treatment of **12** with DIBAL, Red-Al, or $LiAlH_4$ only gave an amino alcohol (Scheme 4).

We then attempted treating **12** with zinc in AcOH, $NiCl_2/NaBH_4$, SmI_2 and Ca/NH_3, but these reactions led to the decomposition of **12** or reduction of the enone double bond without the elimination of the silyl ether, which would have led to the installation of the double bond in the desired $\Delta_{3,4}$ location.

Notwithstanding the failure to induce reductive elimination of the silyl ether, we decided to explore Wittig, Peterson and Julia chemistry to install the requisite $\Delta_{3,4}$ double bond. To this end, we attempted the 1,4-addition of triphenylphosphine and triorganosilyl cuprates, but without success. By contrast, the addition of *p*-methylthiophenol onto **12** gave thioether **13** in a good yield. Oxidation of sulfide **13** to the sulfone **14** by *m*-CPBA was possible, but the reaction was not very clean. Moreover, subsequent reduction with $LiAlH_4$, DIBAL or $BH_3\cdot THF$ was not successful and we



Scheme 4. Reduction with aluminium based reagents.



Scheme 5. Routes to model sulfone.

observed the β-elimination of the sulfone moiety. We also tried to reduce both amide and ketone prior to the oxidation of sulphide **15**, but neither *m*-CPBA in the presence of TFA nor treatment with $AcOH/AcO_2H$ gave the desired product (Scheme 5).

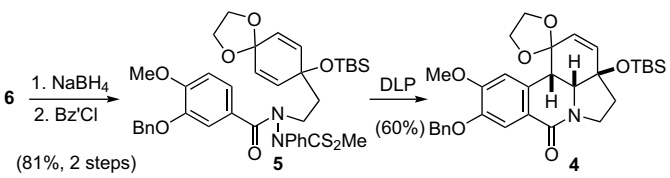
2.2. Total synthesis of (±)-fortucine

Despite these setbacks in the model studies, we decided to concentrate our efforts on the real system by introducing the appropriate ring A of fortucine **2** via the acylation of the intermediate hydrazide with 3-benzyloxy-4-methoxybenzoyl chloride (Bz′Cl, Scheme 6) to give amidyl radical precursor **5** in 81% from hydrazone **6**. Treatment of this substance in refluxing 1,2-dichloroethane with lauroyl peroxide (DLP, 1.4 equiv) effected the radical cascade to give pentacycle **4** in 60% yield. We were pleased to note that the yield of this reaction increased with scale (optimal at 1–2 mmol).[10] Gratifyingly, pentacycle **4** was obtained with complete stereoselectivity to afford the cis ring junction. Oxidative cyclisation on to the aromatic ring occurred regioselectively in a 14:1 ratio (*para*/*ortho* with respect to the benzyloxy group), the steric clash between the ethylene ketal and benzyloxy functionality being sufficient in disfavouring the undesired *ortho* cyclisation.

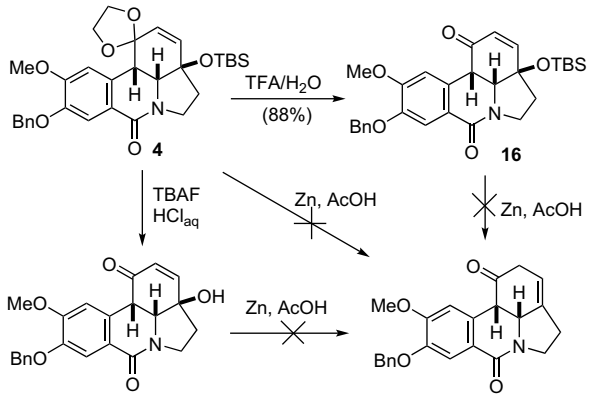
The formation of densely functionalized pentacycle **4** in five steps is remarkably efficient. The structural diversity of lycorine type alkaloids generally originates from functional groups on rings A and C. The strategic positioning of the alkene and the protected-ketone in **7** as well as the choice of the aryl chloride in the formation of **5** can potentially be used to target other complex members of the lycorine alkaloids (see Section 2.4).

The remaining task was to carry out a reductive cleavage of the allylic silyl ether with the migration of the double bond ($\Delta_{2,3} \rightarrow \Delta_{3,4}$), and the installation of an axial alcohol at C-1. Treatment of pentacycle **4** with TFA/H_2O gave enone **16** in 88% yield. As anticipated from the model study, all our efforts to induce direct reductive elimination of the TBSO-group failed (Scheme 7).

First, the silyl ether in pentacycle **4** was deprotected with TBAF to give tertiary alcohol **17**, which was then converted into a mesylate group and the ketone unmasked with TFA. Compound **18** thus obtained was subjected to zinc in acetic acid but this furnished the undesired conjugated ketone **18a**. In another approach, the tertiary



Scheme 6. Synthesis of pentacycle **4**.

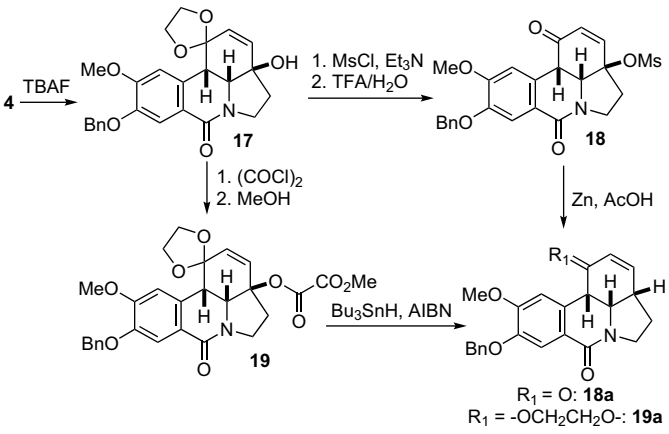


Scheme 7. Attempts at direct reductive elimination.

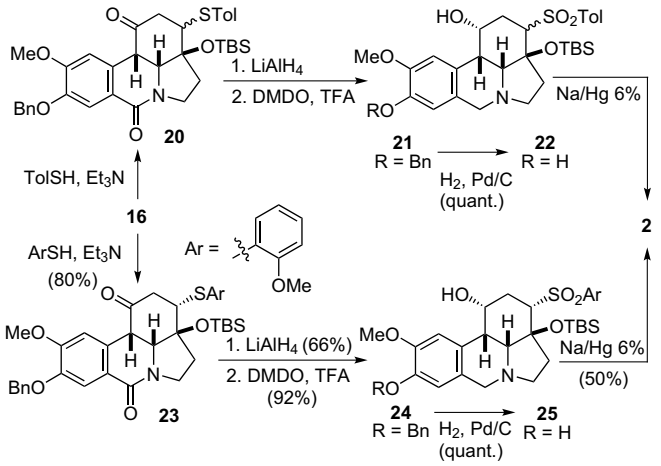
alcohol was converted into oxalate **19** and treated with tributyltin hydride and a small amount of AIBN. We hoped that the intermediate tertiary allylic radical in this variation of the Barton-McCombie deoxygenation[13] would react on C-4, which appeared to be the less hindered position. Unfortunately, only the unwanted deoxygenated isomer **19a** was observed (Scheme 8).

At this point, we decided to pursue more persistently the addition of thiols, which was explored in the model study. Addition of *p*-methylthiophenol to **16** gave thioether **20** as a mixture of diastereoisomers. It was now necessary to oxidise the sulphide and reduce both amide and ketone. The previous results from the model study led us to believe that the reduction should be carried out prior to the oxidation. Thioether **20** was treated with $LiAlH_4$ to reduce both the amide and the ketone to the tertiary amine and alcohol, respectively. After many attempts to oxidise the sulphide group, we found that dimethyldioxirane in the presence of TFA to protect the tertiary amine was the most satisfactory. Having in hand sulfone **21**, we tried to provoke direct elimination of TBSO– and sulfone groups, but the phenol had to be unmasked by hydrogenolysis over Pd/C (**22**) before processing to the Julia-type olefination using 6% Na/Hg amalgam to finally give fortucine (**2**). However, the fact that addition of *p*-methylthiophenol to enone **16** was not diastereoselective complicated considerably the interpretation for the NMR spectra. The NMR spectra of our first batch of compound **2**, recorded with a very small amount of product, did not match with those described in Bastida's paper[6b] but matched the Russian spectral data (Scheme 9).[6a]

In order to better clarify the NMR of our intermediates, we decided to replace *p*-methylthiophenol by the more bulky 2-methoxythiophenol and obtained thioether **23** from enone **16** in



Scheme 8. Replacement of TBSO– with leaving groups.



Scheme 9. Synthesis of fortucine **2**.

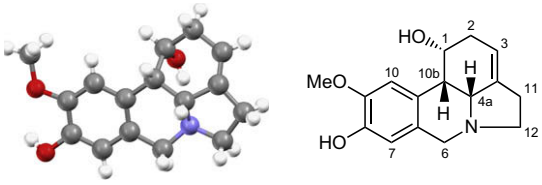


Figure 2. X-ray crystallographic structure of fortucine **2**.

80% yield as one diastereoisomer. As expected, the reduction of ketone with $LiAlH_4$ occurred stereoselectively from the convex face to deliver exclusively the axial alcohol in 66% yield. Mechanical loss in the isolation of the polar amino alcohol is presumably the cause for the relatively modest yield. Oxidation of the sulfide group with DMDO/TFA furnished sulfone **24** in 92% yield. Hydrogenolysis over Pd/C unmasked quantitatively phenol **25**, which was subjected to Julia-type olefination using 6% Na/Hg amalgam to give finally the target molecule fortucine **2** in 50% yield. Product stemming from desulfonylation without elimination of the TBSO– group was also observed in the crude mixture, explaining in part the moderate yield in the last step.

2.3. Revision of the structure of kirkine

The structure of our synthetic (±)-fortucine was unambiguously confirmed by X-ray crystallography (Fig. 2).

Table 1
Differences between ^{1}H NMR spectra of fortucine/kirkine

Authentic fortucine[a,6a]	Fortucine **2**[b]	Protons	Fortucine **2**[c]	Authentic kirkine[d,6b]
4.25	4.30	1	4.27	4.37
2.30–2.60	2.40–2.50	2	2.31	2.34–2.46
5.52	5.55	3	5.47	5.87
2.68	2.71	4a	3.24	4.24
3.27–3.87	3.30–3.90	6	3.45–3.66	4.40–4.61
6.53	6.57	7	6.53	6.60
6.79	6.80	10	7.18	7.08
2.95	3.00	10b	3.19	3.52
2.30–2.60	2.30–2.50	11	2.40–2.67	2.81–2.87
2.30–2.60	2.30–3.30	12	2.40–3.00	3.71–3.83
3.83	3.85	OMe	3.81	3.87

[a] Recorded on 360 MHz in $CDCl_3$.
[b] Recorded on 400 MHz in $CDCl_3$ at −27 °C.
[c] Recorded on 400 MHz in CD_3OD at −20 °C.
[d] Recorded on 500 MHz in CD_3OD.

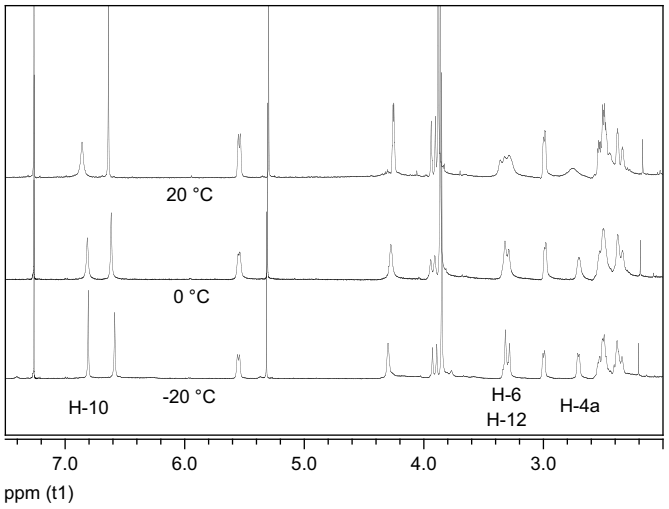


Figure 3. ^{1}H NMR spectra of **2** at low temperatures.

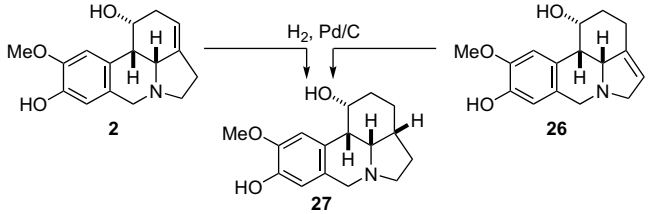
The NMR spectrum of our product was consistent with the data of the Russian group[6a] but not with those of Bastida et al.[6b] (Table 1). An authentic sample of kirkine, kindly supplied by Prof. Bastida, proved different from our synthetic material (by TLC and NMR). Prominent differences observed involved protons in the cis-junction (4a and 10b), those next to the nitrogen (6 and 12) and in the vicinity of the double bond (3 and 11).

Interestingly, protons 10 (in the vicinity of the alcohol), 4a, 6 and 12 (adjacent to the nitrogen) of the ^{1}H NMR spectrum in our study were ill resolved, apparently due to slow conformational changes in ring C as indicated by molecular modelling. A better resolution was obtained by recording the spectra at −27 °C, at which point the compound was essentially frozen in its most stable conformation (Fig. 3).

It appeared that kirkine and fortucine were either diastereoisomers or positional isomers of the double bond. In order to distinguish between these two possibilities, we subjected our synthetic material and authentic kirkine to catalytic hydrogenation and obtained the same compound **27** by NMR, TLC and HRMS (the only difference being that the synthetic sample is racemic). We therefore concluded that kirkine must have structure **26**, which contains a double bond in the same location as siculinine **3**.[6c] Structure **26** is the only isomer compatible with the NMR spectra and which would lead to **27** upon catalytic hydrogenation (Scheme 10).

2.4. Hydrazone 6 as a building block for the synthesis of pyrrolophenanthridine alkaloids

The pyrrolo[3,2,1-*de*]phenanthridine ring system **28** constitutes the core structural framework of the pyrrolophenanthridine alkaloids.[14] Oxoassoanine **29**, assoanine **30**, hippadine **31** and pratosine **32** are members of the pyrrolophenanthridine class of compounds



Scheme 10. Hydrogenation of synthetic fortucine **2** and authentic kirkine.

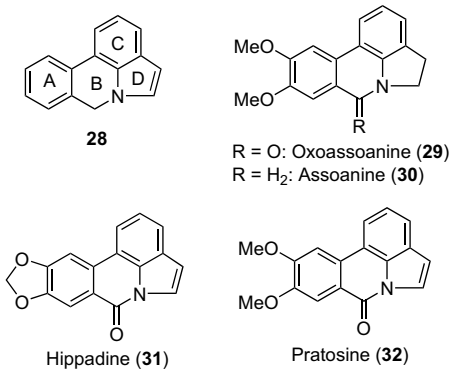
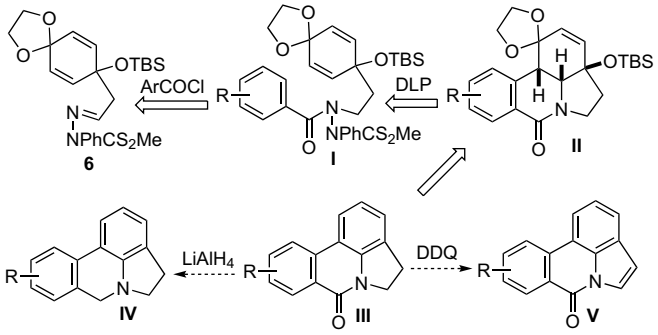


Figure 4. Pyrrolophenanthridine alkaloids.

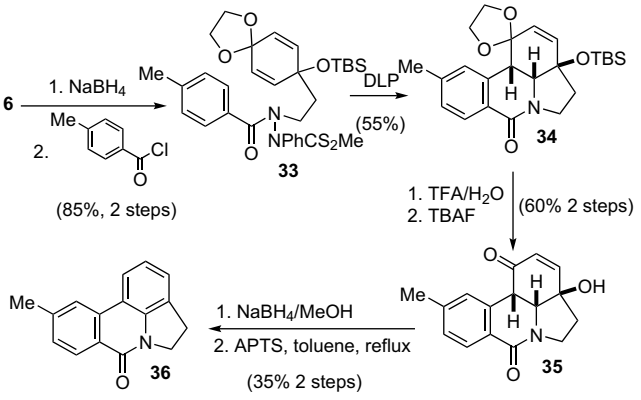


Scheme 11. Strategic approach to Pyrrolophenanthridine alkaloids.

(Fig. 4). They are isolated from various species of Amaryllidaceae[15] and present potentially useful pharmacological activities.[16]

Hydrazone **6** could in principle be utilised as a synthetic building block to access this class of compounds. Aromatic ring A can be introduced via acylation of the hydrazide with an appropriate aryl chloride to get radical precursor **I**. The radical cascade should provide tetracyclic structure **II** as previously demonstrated and pyrrolophenanthridine alkaloids **III** can then be obtained by aromatisation of ring C. Related compounds could also be obtained by further reduction (**IV**) or oxidation (**V**) (Scheme 11).

In a preliminary study, and in order to define the conditions for the aromatisation of ring C, we decided to use *p*-tolyl chloride for the formation of amidyl radical precursor **33**. The ketone and tertiary alcohol in **34** were unmasked to give **35**. Reduction with $NaBH_4$ and subsequent treatment with APTS in refluxing toluene yielded **36** with the desired pyrrolophenanthridine structure (Scheme 12).



Scheme 12. Model study towards pyrrolophenanthridine.

3. Conclusion

In summary, we have implemented a short first total synthesis of (±)-fortucine **2** (12 steps, 9% overall yield) and corrected the structure of kirkine, which should now be revised to **26**. The strategy is noteworthy for its stereo/regio-selective radical cascade and the multifaceted use of hydrazone **8**. We also have explored briefly the possibility of reaching pyrrolophenanthridine alkaloids by a radical cascade.

4. Experimental

4.1. General

All reactions requiring anhydrous conditions were conducted under an inert atmosphere. Glassware, syringes and needles were dried at 120 °C and allowed to either cool in a desiccator over $CaCl_2$, or under a positive pressure of Ar before use. THF was distilled from benzophenone ketyl; CH_2Cl_2, MeOH, and NEt_3 from CaH_2. Reactions were monitored by TLC, using plates pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator. Visualisation of reaction components was achieved with 254 nm light, and with anisaldehyde, vanillin or Dragendorff reagent. Organic layers were dried using $MgSO_4$. Column chromatography was carried out on Kieselgel 60 (40–63 μm). Petroleum ether refers to the fraction of petroleum boiling between 30 °C and 40 °C. IR spectra were recorded as thin films. Melting points were recorded on a Kofler hot block, and are uncorrected. ^1H and ^{13}C NMR spectra of compounds were recorded in $CDCl_3$ at 25 °C. Chemical shifts are reported relative to $CDCl_3$ (δ_H 7.26, δ_C (central line of *t*) 77.23). Coupling constants (*J*) are given in hertz, multiplicities are given as multiplet (m), singlet (s), doublet (d), triplet (t), quartet (q), or broad (br). COSY, HSQC, NOESY and DEPT were use to aid spectral assignments.

4.2. Hydrazone (8)

Acetaldehyde (3.80 mL, 68.0 mmol) was added to a solution of 1-(methylthio)thiocarbonyl-1-phenyl-hydrazine[17] (795 mg, 4.01 mmol) in EtOH (15 mL). After 2 h 30 min, the mixture was concentrated in vacuo, and purified by flash column chromatography (gradient elution: 0–20% Et_2O/petroleum ether) to give hydrazone **8** (881 mg, 98%) as a brown crystalline solid. R_f=0.3 (Et_2O/petroleum ether; 10%); mp 37–40 °C; ν_{max}/cm^{-1} 2913, 2359, 1631, 1594, 1486, 1399, 1359, 1320, 1219, 1167, 1134, 1069, 1036, 959, 929; ^1H NMR (400 MHz, $CDCl_3$) 7.57–7.52 (2H, m, 2*CH*Ar), 7.50–7.45 (1H, m, C*H*Ar), 7.18–7.15 (2H, m, 2C*H*Ar), 6.79 (1H, q, *J*=5.4 Hz, NC*H*), 2.62 (3H, s, S*CH*$_3$), 2.01 (3H, d, *J*=5.4 Hz, NCH*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 202.0 (*C*S_2), 145.8 (NCH), 139.6 (*Cq*), 130.5 (2CHAr), 129.6 (*C*HAr), 129.2 (2*C*HAr), 19.1 (CS_2CH_3), 18.8 (NCHCH_3); *m*/*z* (CI) 225 ($M+H^+$, 100%) Found: M, 224.0445. $C_{10}H_{12}N_2S_2$ requires M, 224.0442.

4.3. Alcohol (9)

n-BuLi (3.54 mL, 1.6 M in THF, 5.67 mmol) was added dropwise to a stirred solution of diisopropylamine (0.88 mL, 6.24 mmol) in THF (8 mL) at −78 °C. After 15 min, a solution of hydrazone **8** (1.27 g, 5.67 mmol) in THF (15 mL) was added dropwise to the reaction mixture and stirred for 1 h. After that time, a solution of *p*-benzoquinone ethylene-monoketal (**7**)[9] (288 mg, 1.89 mmol) in THF (6 mL) was added dropwise. After 15 min, saturated aqueous solution of NH_4Cl (30 mL) was added to the reaction mixture and allowed to warm to 20 °C. The aqueous layer was extracted with Et_2O (3×50 mL), and the combined organic extracts were washed with brine (150 mL). The organic layer was dried, concentrated in vacuo, and purified by flash column chromatography (gradient

elution: 0–100% Et_2O/petroleum ether) to give recovered excess hydrazone **8** (807 mg, 95%) and alcohol **9** (708 mg, 99%) as a white crystalline solid. R_f=0.6 (Et_2O); mp 134–136 °C; ν_{max}/cm^{-1} 3398, 2885, 2361, 1488, 1390, 1324, 1218, 1116, 1069, 1013, 965; ^1H NMR (400 MHz, $CDCl_3$) 7.53–7.49 (2H, m, 2C*H*Ar), 7.46–7.42 (1H, m, C*H*Ar), 7.16–7.13 (2H, m, 2C*H*Ar), 6.60 (1H, t, *J*=5.7 Hz, NC*H*), 5.95 (2H, d, *J*=10.5 Hz, 2CH=C*H*), 5.73 (2H, d, *J*=10.5 Hz, 2CH=C*H*), 3.99 (4H, s, 2OCH_2), 3.10 (1H, s, O*H*), 2.59 (2H, d, *J*=5.7 Hz, NCHCH_2), 2.59 (3H, s, SCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 202.3 (*C*S_2), 144.5 (NCH), 139.0 (*Cq*), 135.4 (2*C*H=CH), 130.3 (2*C*HAr), 129.5 (*C*HAr), 129.1 (2*C*HAr), 127.8 (2*C*H=CH), 98.7 (OCO), 67.1 (*C*OH), 65.3 (OCH_2), 65.1 (OCH_2), 42.9 (NCHCH_3), 19.1 (SCH_3); *m*/*z* (CI) 377 (M+H^+, 20%), 225 (100%) Found: M, 376.0918. $C_{18}H_{20}O_3N_2S_2$ requires M, 376.0916.

4.4. Silyl ether (6)

2,6-Lutidine (6.36 mL, 54.6 mmol) and TBSOTf (6.02 mL, 26.2 mmol) were added to a stirred solution of alcohol **9** (4.11 g, 10.9 mmol) in CH_2Cl_2 (70 mL). After 1 h 15 min, H_2O (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (3 ×200 mL). The combined organic extracts were sequentially washed with 0.1 M aqueous HCl (3×400 mL), saturated aqueous solution of $NaHCO_3$ (2×400 mL) and brine (400 mL). The organic layer was dried, concentrated in vacuo and purified by flash column chromatography (20% Et_2O/petroleum ether) to give silyl ether **6** (5.36 g, 100%) as a white crystalline solid. R_f=0.2 (Et_2O/petroleum ether; 20%); mp 84–86 °C; ν_{max}/cm^{-1} 3036, 2954, 2927, 2883, 2855, 2360, 1593, 1488, 1471, 1408, 1388, 1325, 1253, 1220, 1116, 1070, 1014, 969, 946; ^1H NMR (400 MHz, $CDCl_3$) 7.54–7.50 (2H, m, 2C*H*Ar), 7.46–7.42 (1H, m, C*H*Ar), 7.17–7.15 (2H, m, 2C*H*Ar), 6.78 (1H, t, *J*=5.9 Hz, NC*H*), 5.88 (2H, d, *J*=10.2 Hz, 2C*H*=CH), 5.75 (2H, d, *J*=10.2 Hz, 2C*H*=CH), 4.03 (2H, d, *J*=3.2 Hz, OCH_2), 4.02 (2H, d, *J*=3.2 Hz, OCH_2), 2.60 (3H, s, SCH_3), 2.55 (2H, d, *J*=5.9 Hz, NCHCH_2), 0.70 (9H, s, SiC(CH_3)$_3$), −0.04 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 202.4 (*C*S_2), 145.9 (NCH), 139.4 (*Cq*), 136.1 (2CH=CH), 130.4 (2*C*HAr), 129.5 (*C*HAr), 129.1 (2*C*HAr), 127.1 (2*C*H=CH), 98.9 (OCO), 69.2 (*Cq*), 65.5 (OCH_2), 65.0 (OCH_2), 45.8 (NCHCH_2), 25.7 (3SiCCH_3), 19.1 (SCH_3), 18.0 (SiC(CH_3)$_3$), −2.8 (2SiCH_3); *m*/*z* (CI) 491 (M+H^+, 100%), 355 (20%), 238 (10%) Found: M, 490.1769. $C_{24}H_{34}O_3N_2S_2Si$ requires M, 490.1780.

4.5. Pentacycle (4)

$NaBH_4$ (2.31 g, 61.13 mmol) was added portion wise over 1 h to a stirred solution of silyl ether **6** (1.00 g, 2.04 mmol) in MeOH (20 mL) and THF (20 mL) at 0 °C. The reaction mixture was heated to reflux for 30 min. After cooling, H_2O (30 mL) was added and the mixture was concentrated in vacuo to remove MeOH. The aqueous layer was then extracted with Et_2O (2×50 mL) and the combined organic extracts were washed with brine (100 mL), dried and concentrated in vacuo to give the hydrazide as yellow oil.

Oxalyl chloride (2.85 mL, 32.61 mmol) was added to a stirred mixture of 3-benzyloxy-4-methoxybenzoic acid (2.14 g, 8.15 mmol) and DMF (three drops) in CH_2Cl_2 (25 mL). After 1 h 30 min, the reaction mixture was concentrated in vacuo to give 3-benzyloxy-4-methoxybenzoyl chloride as a yellow crystalline solid, which was used in the next step without further purification.

The above 3-benzyloxy-4-methoxybenzoyl chloride was added portion wise to a stirred mixture of the above hydrazide, DMAP (50 mg, 0.41 mmol) and Et_3N (3.39 mL, 24.46 mmol) in CH_2Cl_2 (20 mL). After 24 h, H_2O (50 mL) and saturated aqueous solution of $NaHCO_3$ (50 mL) were added to the reaction mixture, and the aqueous layer was extracted with in CH_2Cl_2 (2×50 mL). The organic layer was dried, concentrated in vacuo and the crude material was triturated with ether. The mixture was filtered to remove acid anhydride, the filtrate was then concentrated in vacuo and purified by flash column chromatography (gradient elution: 0–5% EtOAc/toluene) to give radical precursor **5** (1.21 g, 81% over two steps) as a yellow foam; R_f=0.4 (EtOAc/toluene; 8%).

Radical precursor **5** (951 mg, 1.30 mmol) was dissolved in 1,2-dichloroethane (10.3 mL) and lauroyl peroxide (DLP, 100 mg portions, 700 mg, 140%) was added into the reaction mixture at 1 h intervals for 7 h. Immediately after the first addition of DLP, the reaction mixture was heated to reflux for 7 h. After cooling, the resulting solution was concentrated in vacuo and directly purified by column chromatography (gradient elution: 0–100% EtOAc/petroleum ether) to give pentacycle **4** (427 mg, 60%) as a colourless foam. R_f=0.4 (EtOAc); ν_{max}/cm^{-1} 2928, 2856, 2360, 1654, 1602, 1508, 1450, 1388, 1350, 1293, 1261, 1218, 1129, 1051, 1009, 950; ^1H NMR (400 MHz, $CDCl_3$) 7.67 (1H, s, *H*-7), 7.48–7.46 (2H, m, 2C*H*Ar), 7.38–7.34 (2H, m, 2C*H*Ar), 7.31–7.27 (1H, m, C*H*Ar), 6.89 (1H, s, *H*-10), 5.82 (1H, dd, *J*=10.2, 1.7 Hz, *H*-3), 5.74 (1H, d, *J*=10.2 Hz, *H*-2), 5.24 (1H, d, *J*=11.9 Hz, OCH_2Ph), 5.17 (1H, d, *J*=11.9 Hz, OCH_2Ph), 4.00 (1H, dd, *J*=3.9, 1.5 Hz, *H*-4a), 3.92 (3H, s, OCH_3), 3.91–3.88 (1H, m, *H*-12), 3.75–3.62 (3H, s, OCH_2CH_2O), 3.31 (1H, d, *J*=3.9 Hz, *H*-10b), 3.25 (1H, dt, *J*=11.8, 7.1 Hz, *H*-12), 2.44–2.39 (1H, m, OCH_2-CH_2O), 2.33–2.15 (1H, m, *H*-11), 2.15–2.08 (1H, m, *H*-11), 0.86 (9H, s, 3SiCCH_3), 0.15 (3H, s, SiCH_3), 0.15 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 163.6 (*C*-6), 151.5 (*Cq*), 147.8 (*Cq*), 136.8 (*Cq*), 131.5 (*C*-3), 130.6 (*C*-2), 130.0 (*Cq*), 128.7 (2*C*HAr), 128.1 (*C*HAr), 127.8 (2*C*HAr), 125.5 (*Cq*), 112.1 (*C*-7), 112.1 (*C*-10), 103.6 (OCO), 76.4 (*Cq*), 71.0 (OCH_2Ph), 66.3 (OCH_2CH_2O), 64.6 (OCH_2CH_2O), 63.7 (*C*-4a), 56.4 (OCH_3), 42.2 (*C*-12), 41.8 (*C*-10b), 38.4 (*C*-11), 25.8 (3SiCCH_3), 18.1 (SiC(CH_3)$_3$), 2.1 (SiCH_3), 2.1 (SiCH_3); *m*/*z* (CI) 550 (M+H^+, 100%), 285 (15%) Found: M, 549.2536. $C_{31}H_{39}O_6NSi$ requires M, 549.2547.

4.6. Ketone (16)

A mixture of H_2O (15 mL) and TFA (15 mL) was added to a stirred solution of pentacycle **4** (427 mg, 0.78 mmol) in THF (3.5 mL). After 1 h, the reaction mixture was diluted with EtOAc (100 mL), the organic layer was washed with H_2O (50 mL), cautiously basified by washing with saturated aqueous solution of Na_2CO_3 (3×100 mL), washed with brine (200 mL), dried, concentrated in vacuo and purified by flash column chromatography (gradient elution: 0–50% EtOAc/petroleum ether) to give ketone **16** (346 mg, 88%) as a colourless foam. R_f=0.5 (EtOAc/petroleum ether; 50%); ν_{max}/cm^{-1} 2928, 1684, 1651, 1601, 1511, 1149, 1385, 1352, 1293, 1255, 1221, 1136; ^1H NMR (400 MHz, $CDCl_3$) 7.61 (1H, s, *H*-7), 7.48–7.45 (2H, m, 2C*H*Ar), 7.38–7.34 (2H, m, 2C*H*Ar), 7.31–7.27 (1H, m, C*H*Ar), 6.88 (1H, s, *H*-10), 6.72 (1H, dd, *J*=10.2, 2.2 Hz, *H*-3), 6.15 (1H, d, *J*=10.2 Hz, *H*-2), 5.21 (1H, d, *J*=12.1 Hz, OCH_2Ph), 5.17 (1H, d, *J*=12.1 Hz, OCH_2Ph), 4.27 (1H, dd, *J*=4.3, 2.1 Hz, *H*-4a), 3.97 (3H, s, OCH_3), 3.96–3.90 (1H, m, *H*-12), 3.70 (1H, d, *J*=4.3 Hz, *H*-10b), 3.29–3.21 (1H, m, *H*-12), 2.27–2.22 (2H, m, *H*-11), 0.90 (9H, s, 3SiCCH_3), 0.20 (3H, s, SiCH_3), 0.18 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 194.7 (*C*-1), 163.0 (*C*-6), 152.3 (*Cq*), 148.0 (*Cq*), 146.8 (*C*-3), 136.7 (*Cq*), 130.1 (*C*-2), 129.0 (*Cq*), 128.6 (2*C*HAr), 128.0 (*C*HAr), 127.6 (2*C*HAr), 121.8 (*Cq*), 113.0 (*C*-10), 112.0 (*C*-7), 75.6 (*Cq*), 70.9 (OCH_2Ph), 63.9 (*C*-4a), 56.2 (OCH_3), 45.2 (*C*-10b), 42.1 (*C*-12), 37.5 (*C*-11), 25.6 (3SiCCH_3), 18.0 (SiC(CH_3)$_3$), −2.1 (SiCH_3), −2.2 (SiCH_3); *m*/*z* (CI) 506 (M+H^+, 100%) Found: M, 505.2282. $C_{29}H_{35}O_5NSi$ requires M, 505.2285.

4.7. Thioether (23)

Ketone **16** (150 mg, 0.30 mmol) and *o*-methoxythiophenol (0.90 mL, 7.41 mmol) were dissolved in THF (5.9 mL) and Et_3N (1.05 mL, 7.41 mmol) was added. After 1 h 15 min, the mixture was concentrated in vacuo, and purified by flash column chromatography (gradient elution: 0–40% EtOAc/petroleum ether) to give thioether **23** (153 mg, 80%) as a colourless foam. R_f=0.5 (EtOAc/petroleum ether; 40%); ν_{max}/cm^{-1} 2952, 2932, 2858, 2360, 2336,

1728, 1659, 1601, 1513, 1451, 1386, 1350, 1255, 1219, 1132, 1108, 1027, 918; ^{1}H NMR (400 MHz, $CDCl_3$) 7.67 (1H, s, *H*-7), 7.47–7.46 (2H, m, 2C*H*Ar), 7.41–7.33 (3H, m, 3C*H*Ar), 7.33–7.29 (2H, m, 2C*H*Ar), 6.91–6.86 (2H, m, 2C*H*Ar), 6.77 (1H, s, *H*-10), 5.22–5.15 (2H, m, OCH_2Ph), 4.34 (1H, d, *J*=6.1 Hz, *H*-4a), 4.13–4.04 (1H, m, *H*-12), 4.13–4.04 (1H, m, *H*-3), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.74 (1H, d, *J*=6.1 Hz, *H*-10b), 3.64 (1H, m, *H*-12), 2.87 (1H, dd, *J*=16.6, 4.5 Hz, *H*-2), 2.64 (1H, m, *H*-11), 2.38 (1H, dd, *J*=16.6, 9.0 Hz, *H*-2), 2.23 (1H, m, *H*-11), 0.92 (9H, s, 3SiCCH_3), 0.26 (3H, s, SiCH_3), 0.23 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 205.1 (*C*-1), 162.6 (*C*-6), 159.5 (*Cq*), 152.3 (*Cq*), 148.1 (*Cq*), 136.6 (*Cq*), 136.1 (*C*HAr), 130.1 (*C*HAr), 128.5 (2*C*HAr), 127.9 (*C*HAr), 127.5 (2*C*HAr), 127.3 (*C*HAr), 121.5 (*Cq*), 121.2 (*C*HAr), 120.1 (*Cq*), 112.6 (*C*-10), 111.9 (*C*-7), 111.2 (*C*HAr), 83.0 (*C*-4), 70.8 (OCH_2Ph), 68.1 (*C*-4a), 56.1 (OCH_3), 55.7 (OCH_3), 50.9 (*C*-3), 49.1 (*C*-10b), 43.8 (*C*-12), 42.2 (*C*-2), 34.3 (*C*-11), 25.7 (3SiCCH_3), 18.2 (SiC$(CH_3)_3$), −2.4 (SiCH_3), −2.5 (SiCH_3); *m*/*z* (EI) 645 Found: M, 645.2596. $C_{36}H_{43}O_6NSSi$ requires M, 645.2580.

4.8. Amine

$LiAlH_4$ (270 mg, 7.11 mmol) was added to a stirred solution of thioether **23** (153 mg, 0.23 mmol) in THF (30 mL) at −78 °C. The reaction mixture was warmed to 20 °C and stirred for 3 h 15 min. H_2O (0.28 mL), 1 M aqueous KOH (0.28 mL) and H_2O (0.28 mL) were sequentially added (cautiously with some cooling/ice-bath) to the reaction mixture. The resulting mixture was filtered through Celite (CH_2Cl_2 as eluant), concentrated in vacuo and purified by flash column chromatography (gradient elution: 0–50% EtOAc/petroleum ether) to give the amine (100 mg, 66%) as a colourless foam. R_f=0.42 (EtOAc/petroleum ether/NEt_3; 49/49/2); ν_{max}/cm^{-1} 2928, 2856, 1608, 1576, 1515, 1467, 1317, 1255, 1125, 1080, 1016; ^{1}H NMR (400 MHz, $CDCl_3$) 7.48–7.46 (1H, dd, *J*=7.6, 1.7 Hz, C*H*Ar), 7.45–7.43 (2H, m, 2C*H*Ar), 7.38–7.34 (2H, m, 2C*H*Ar), 7.31–7.27 (2H, m, 2C*H*Ar), 6.2 (1H, dd, *J*=7.5, 1.1 Hz, C*H*Ar), 6.89 (1H, m, C*H*Ar), 6.75 (1H, s, *H*-7), 6.60 (1H, s, *H*-10), 5.11 (2H, m, OCH_2Ph), 4.78 (1H, br s, O*H*), 4.08 (1H, m, *H*-1), 4.05 (1H, d, *J*=14.3 Hz, *H*-6), 3.90 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.64 (1H, t, *J*=5.8 Hz, *H*-3), 3.46 (1H, dd, *J*=9.9, 5.9 Hz, *H*-12), 3.40 (1H, d, *J*=14.4 Hz, *H*-6), 2.93 (1H, t, *J*=3.8 Hz, *H*-10b), 2.75 (1H, d, *J*=3.0 Hz, *H*-4a), 2.58 (1H, dd, *J*=13.4, 5.7 Hz, *H*-11), 2.52 (1H, dd, *J*=13.8, 6.8 Hz, *H*-12), 2.36 (1H, td, *J*=14.7, 5.1 Hz, *H*-2), 2.23 (1H, ddd, *J*=14.9, 6.2, 3.5 Hz, *H*-2), 1.94 (1H, m, *H*-11), 0.86 (9H, s, 3SiCCH_3), 0.07 (3H, s, SiCH_3), 0.07 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 158.9 (*Cq*), 148.6 (*Cq*), 147.0 (*Cq*), 137.3 (*Cq*), 134.1 (*C*HAr), 128.8 (*C*HAr), 128.5 (2*C*HAr), 128.4 (*C*HAr), 128.4 (*Cq*), 127.7 (*C*HAr), 127.4 (*Cq*), 127.2 (2*C*HAr), 124.4 (*Cq*), 120.9 (*C*HAr), 111.8 (*C*-10), 111.4 (*C*-7), 110.9 (*C*HAr), 82.3 (*C*-4), 71.1 (OCH_2Ph), 70.3 (*C*-4a), 70.1 (*C*-1), 56.3 (*C*-6), 55.9 (OCH_3), 55.7 (OCH_3), 52.9 (*C*-12), 49.2 (*C*-3), 40.2 (*C*-10b), 35.43 (*C*-11), 35.37 (*C*-2), 25.7 (3SiCCH_3), 18.1 (SiC$(CH_3)_3$), −2.6 (SiCH_3), −2.7 (SiCH_3); *m*/*z* (EI) 633 Found: M, 633.2972. $C_{36}H_{47}O_5NSSi$ requires M, 633.2944.

4.9. Sulfone (24)

Freshly prepared dimethyldioxirane[18] (26 mL, ~0.1 M in acetone, 1.9 mmol) was added to a stirred solution of the amine and TFA (3.61 mL, 48.6 mmol) in CH_2Cl_2 (7.5 mL) at −78 °C. The reaction mixture was warmed to 0 °C and after 45 min Me_2S (1.43 mL, 19.4 mmol) was added. The mixture was concentrated in vacuo and dissolved in a mixture of EtOAc (30 mL) and 1 M aqueous KOH (30 mL). The aqueous layer was extracted with EtOAc (3×25 mL), and the combined organic extracts were dried, concentrated in vacuo and purified by column chromatography (gradient elution: 0–60% EtOAc/petroleum ether containing 2% of NEt_3) to give sulfone **24** (149 mg, 92%) as a colourless foam. R_f=0.47 (EtOAc/petroleum ether; 70%); ν_{max}/cm^{-1} 2927, 2855, 2336, 2341, 1589, 1515, 1463, 1316, 1258, 1152, 1022, 941; ^{1}H NMR (400 MHz, $CDCl_3$) 7.93 (1H, dd, *J*=7.8, 1.7 Hz, C*H*Ar), 7.57 (1H, ddd, *J*=9.1, 7.6, 1.7, C*H*Ar), 7.44–7.42 (2H, m, 2C*H*Ar), 7.38–7.35 (2H, m, 2C*H*Ar), 7.32–7.28 (1H, m, C*H*Ar), 7.10 (1H, t, *J*=7.6, Hz, C*H*Ar), 7.04 (1H, d, *J*=8.4 Hz, C*H*Ar), 6.68 (1H, s, *H*-7), 6.61 (1H, s, *H*-10), 5.10 (2H, m, OCH_2Ph), 4.03 (1H, d, *J*=14.3 Hz, *H*-6), 4.00 (1H, m, *H*-1), 3.98 (3H, s, OCH_3), 3.94 (1H, dd, *J*=12.2, 6.1 Hz, *H*-3), 3.83 (3H, s, OCH_3), 3.49 (1H, d, *J*=13.4 Hz, *H*-6), 3.29 (1H, t, *J*=7.8 Hz, *H*-12), 3.01–2.93 (1H, m, *H*-11), 2.89 (1H, m, *H*-10b), 2.86 (1H, m, *H*-4a), 2.66 (1H, td, *J*=11.0, 7.5 Hz, *H*-12), 2.31 (1H, dd, *J*=14.1, 5.5 Hz, *H*-11), 2.23 (1H, dd, *J*=15.0, 8.4 Hz, *H*-2), 2.16–2.08 (1H, m, *H*-2), 0.90 (9H, s, 3SiCCH_3), 0.19 (3H, s, SiCH_3), 0.19 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 157.1 (*Cq*), 148.6 (*Cq*), 147.2 (*Cq*), 137.1 (*Cq*), 135.2 (*C*HAr), 131.1 (*C*HAr), 128.5 (*C*HAr), 128.2 (*C*HAr), 128.0 (*Cq*), 127.8 (*C*HAr), 127.4 (*Cq*), 127.2 (*C*HAr), 125.2 (*C*HAr), 120.8 (*C*HAr), 112.4 (*C*HAr), 111.8 (*C*-10), 111.6 (*C*-7), 82.0 (*C*-4), 75.1 (*C*-4a), 71.1 (OCH_2Ph), 68.3 (*C*-1), 65.1 (*C*-3), 56.2 (OCH_3), 55.9 (OCH_3), 55.2 (*C*-6), 52.3 (*C*-12), 39.7 (*C*-10b), 34.9 (*C*-11), 33.0 (*C*-2), 26.0 (3SiCCH_3), 18.3 (SiC$(CH_3)_3$), −1.6 (SiCH_3), −1.8 (SiCH_3); *m*/*z* (EI) 665 Found: M, 665.2857. $C_{36}H_{47}O_7NSSi$ requires M, 649.2843.

4.10. Phenol (25)

Sulfone **24** (96 mg, 0.14 mmol) was dissolved in THF (7 mL) and 10% Pd/C (115 mg, 0.11 mmol) was added. The reaction mixture was placed under an atmosphere of H_2 (2×doubled balloon) and stirred for 15 h. The reaction mixture was then filtered through Celite (CH_2Cl_2 as eluant) and concentrated in vacuo to give phenol **25** (78 mg, 94%) as a pale solid. R_f=0.54(MeOH/CH_2Cl_2; 10%); ν_{max}/cm^{-1} 3049, 2982, 2684, 2306, 1782, 1424, 1262, 1154, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) 7.93 (1H, dd, *J*=7.8, 1.7, Hz, C*H*Ar), 7.57 (1H, ddd, *J*=9.1, 7.5, 1.7 Hz, C*H*Ar), 7.10 (1H, t, *J*=7.6 Hz, C*H*Ar), 7.04 (1H, d, *J*=8.4 Hz, C*H*Ar), 6.64 (1H, s, *H*-7), 6.63 (1H, s, *H*-10), 5.58 (1H, br s, O*H*), 4.06 (1H, d, *J*=14.3 Hz, *H*-6), 3.98 (3H, s, OCH_3), 3.93 (1H, dd, *J*=12.4, 6.0 Hz, *H*-3), 3.83 (3H, s, OCH_3), 3.50 (1H, d, *J*=14.0 Hz, *H*-6), 3.29 (1H, t, *J*=7.9 Hz, *H*-11), 3.00–2.92 (1H, m, *H*-12), 2.89–2.87 (1H, m, *H*-10b), 2.86 (1H, m, *H*-4a), 2.65 (1H, ddd, *J*=11.3, 8.7, 5.9 Hz, *H*-11), 2.30 (1H, dd, *J*=14.2, 5.5 Hz, *H*-12), 2.28–2.21 (1H, m, *H*-2), 2.15–2.07 (1H, m, *H*-2), 0.90 (9H, s, 3SiCCH_3), 0.18 (6H, s, 2SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 157.2 (*Cq*), 145.6 (*Cq*), 144.5 (*Cq*), 135.2 (*C*HAr), 131.2 (*C*HAr), 128.14 (*Cq*), 128.07 (*Cq*), 126.0 (*Cq*), 120.8 (*C*HAr), 112.4 (*C*HAr), 112.2 (*C*HAr), 110.3 (*C*HAr), 82.1 (*C*-4), 75.4 (*C*-4a), 68.5 (*C*-1), 65.1 (*C*-3), 56.2 (OCH_3), 55.8 (OCH_3), 55.2 (*C*-6), 52.4 (*C*-11), 39.8 (*C*-10b), 34.9 (*C*-12), 33.0 (*C*-2), 26.0 (3SiCCH_3), 18.4 (SiC$(CH_3)_3$), −1.5 (SiCH_3), −1.8 (SiCH_3); *m*/*z* (EI) 575 Found: M, 575.2416. $C_{29}H_{41}O_7NSSi$ requires M, 575.2373.

4.11. Fortucine (2)

Sodium amalgam (1.59 g, 6% Na in Hg, 4.14 mmol) was added to a stirred solution of phenol **25** (119 mg, 0.21 mmol) in refluxing MeOH (6.2 mL). After 50 min, reaction mixture was cooled and H_2O (50 mL) was added followed by 1 M aqueous KOH until pH>10. The aqueous layer was extracted with EtOAc (2×50 mL). The combined organic extracts were dried, concentrated in vacuo and purified by column chromatography (gradient elution: 0–30% MeOH/CH_2Cl_2) to give fortucine **2**[6a] (28 mg, 50%) as a colourless solid, which was recrystallised from isopropanol/hexane (1:2). R_f=0.28 (MeOH/EtOAc; 15%); mp 188 °C (dec); ν_{max}/cm^{-1} 3362, 2922, 2848, 1609, 1590, 1514, 1447, 1313, 1276, 1248, 1198, 1160, 1127, 1104, 1074, 1033; ^{1}H NMR (400 MHz, $CDCl_3$) 6.80 (1H, s, *H*-10), 6.57 (1H, s, *H*-7), 5.55 (1H, d, *J*=6.7 Hz, *H*-3), 4.30 (1H, m, *H*-1), 3.90 (1H, d, *J*=14.0 Hz, *H*-6), 3.85 (3H, s, OCH_3), 3.30 (1H, d, *J*=13.9 Hz, *H*-6), 3.30 (1H, m, *H*-12) 3.00 (1H, d, *J*=5.3 Hz, *H*-10b), 2.71 (1H, d, *J*=5.7 Hz, *H*-4a), 2.50–2.40 (2H, m, *H*-2), 2.5–2.3 (2H, m, *H*-11), 2.3 (1H, m, *H*-12); ^{13}C NMR (100 MHz, $CDCl_3$) 145.8 (*Cq*), 143.8 (*Cq*), 139.3 (*Cq*), 127.8 (*Cq*), 125.5 (*Cq*), 116.2 (*C*-3), 112.2 (*C*-7), 109.4 (*C*-10), 69.7 (*C*-1), 59.0 (*C*-4a), 55.5 (OCH_3), 55.0 (*C*-6), 51.7 (*C*-12), 40.8 (*C*-10b), 33.0 (*C*-11), 27.0 (*C*-2); *m*/*z* (CI) 274 (M+H$^+$, 100%) Found: M, 273.1367. $C_{16}H_{19}O_3N$ requires *M*, 273.1365.

4.12. Catalytic hydrogenation of fortucine (2) and authentic kirkine

Small amounts (1 mg) of fortucine **2** and natural kirkine[6b] (supplied by Prof. Bastida) were dissolved in THF (200 μL) in two separate flasks and 10% Pd/C (1 mg) was added in each. The reaction mixtures were placed under an atmosphere of H_2 (2×doubled balloons) and stirred for 2 h. The reaction mixtures were then filtered through Celite (CH_2Cl_2 as eluant) and concentrated in vacuo. The two compounds were found identical by TLC (20% MeOH/CH_2Cl_2) and by ^{1}H NMR spectroscopy ($CDCl_3$, 20 °C).

Reduced fortucine **27**: *m*/*z* (EI) 275 Found: M, 275.1519. $C_{16}H_{21}O_3N$ requires *M*, 575.1521.

Reduced kirkine **27**: *m*/*z* (EI) 275 Found: M, 275.1528. $C_{16}H_{21}O_3N$ requires *M*, 575.1521.

4.13. Pyrrolophenanthridine 36

$NaBH_4$ (1.85 g, 48.9 mmol) was added portion wise over 1 h to a stirred solution of silyl ether **6** (800 mg, 1.63 mmol) in MeOH (12 mL) and THF (12 mL) at 0 °C. The reaction mixture was heated to reflux for 30 min. After cooling, H_2O (20 mL) was added and the mixture was concentrated in vacuo to remove MeOH. The aqueous layer was then extracted with Et_2O (2×20 mL) and the combined organic extracts were washed with brine (50 mL), dried and concentrated in vacuo to give the hydrazide as yellow oil.

4-Methylbenzoyl chloride (1.08 mL, 8.15 mmol) in solution in dry CH_2Cl_2 (8 mL) was added dropwise to a stirred mixture of the above hydrazide, DMAP (40 mg, 0.33 mmol) and Et_3N (3.4 mL, 24.45 mmol) in CH_2Cl_2 (16 mL). After 24 h, H_2O (50 mL) and saturated aqueous solution of $NaHCO_3$ (50 mL) were added to the reaction mixture, and the aqueous layer was extracted with in CH_2Cl_2 (2×50 mL). The organic layer was dried, concentrated in vacuo and the crude material was triturated with ether. The mixture was filtered to remove acid anhydride, the filtrate was then concentrated in vacuo and purified by flash column chromatography (gradient elution: 0–20% EtOAc/petroleum ether) to give radical precursor **33** (843 mg, 85% over two steps) as a white foam. R_f=0.35 (EtOAc/petroleum ether; 20%).

Radical precursor **33** (843 mg, 1.375 mmol) was dissolved in chlorobenzene (14 mL) and lauroyl peroxide (DLP, 110 mg portions, 770 mg, 140%) was added into the reaction mixture at 20 min intervals for 2 h 40 min. Immediately after the first addition of DLP, the reaction mixture was heated to reflux for 7 h. After cooling, the resulting solution was concentrated in vacuo and directly purified by column chromatography (gradient elution: 0–100% EtOAc/petroleum ether) to give pentacycle **34** (321 mg, 55%) as a colorless foam. R_f=0.4 (EtOAc).

A mixture of H_2O (7.5 mL) and TFA (7.5 mL) was added to a stirred solution of pentacycle **34** (321 mg, 0.75 mmol) in THF (3.75 mL). After 2 h, the reaction mixture was diluted with EtOAc (50 mL), the organic layer was washed with H_2O (50 mL), cautiously basified by washing with saturated aqueous solution of Na_2CO_3 (3 ×50 mL), washed with brine (100 mL), dried and concentrated in vacuo to give the ketone (290 mg, 99%) as a colorless foam. R_f=0.6 (EtOAc).

This ketone (236 mg, 0.61 mmol) was dissolved in THF (6 mL) and TBAF (2.75 mL, 1 M in THF) and acetic acid (190 μL) were added. After 20 h, the resulting mixture was concentrated in vacuo and purified by column chromatography (gradient elution: 50–100% EtOAc/petroleum ether, then 1–5% MeOH/EtOAc) to give alcohol **35** (100 mg, 60%) as white crystals. R_f=0.45 (MeOH/EtOAc; 5%); *m*/*z* (CI) 272 ($M+H^+$, 100%).

$NaBH_4$ (12 mg, 0.33 mmol) was added to a stirred solution of alcohol **35** (94 mg, 0.33 mmol) in MeOH (3.2 mL) at room temperature. After 1 h, H_2O (5 mL) was added and the mixture was concentrated in vacuo to remove MeOH. The aqueous layer was then extracted with EtOAc (3×10 mL) and the combined organic extracts were washed with brine (30 mL), dried, concentrated in vacuo and redissolved in toluene (2 mL). A catalytic amount of APTS·H_2O was added and the solution was heated to reflux. After 1 h, the solution was concentrated in vacuo, and directly purified by column chromatography (100% EtOAc) to give **36** (24 mg, 30%) as a pale solid. R_f=0.5 (MeOH/EtOAc; 10%); mp 185 °C; ν_{max}/cm^{-1} 1657, 1609; ^{1}H (400 MHz, $CDCl_3$) 8.42 (1H, d, *J*=8.2 Hz), 7.97 (1H, s), 7.88 (1H, d, *J*=7.6 Hz), 7.40 (1H, dd, *J*=8.2, 1.1 Hz), 7.30 (1H, dd, *J*=7.3, 1.0 Hz), 7.19 (1H, t, *J*=7.6 Hz), 4.46 (2H, t, *J*=8.4 Hz, NCH_2), 3.41 (2H, t, *J*=8.3 Hz, NCH_2CH_2), 2.56 (3H, s, CH_3); ^{13}C (100 MHz, $CDCl_3$) 160.1 (*Cq*), 142.5 (*Cq*), 140.0 (*Cq*), 133.8 (*Cq*), 130.7 (*C*HAr), 129.2 (*C*HAr), 128.3 (*C*HAr), 125.0 (*Cq*), 124.3 (*C*HAr), 123.2 (*C*HAr), 122.2 (*C*HAr), 119.8 (*C*HAr), 116.7 (*C*q), 46.3 (NCH_2), 27.3 (CH_2), 22.0 (CH_3); *m*/*z* (CI) 236 ($M+H^+$, 100%) Found: M, 235.0997. $C_{16}H_{13}ON$ requires M, 235.0997.

4.14. X-ray crystallographic data

Single crystal X-ray diffraction was used for determining the solid-state structure of fortucine (**2**). All data were collected on a Nonius KappaCCD diffractometer at 150(1) K using Mo Kα (λ=0.71073 Å) X-ray source and a graphite monochromator. Experimental details are described in Table 1. The crystal structures were solved in SIR 97[19] and refined in SHELXL-97[20] by full-matrix least-squares using anisotropic thermal displacement parameters for all non-hydrogen atoms. All the hydrogen atoms were placed in geometrically calculated positions.

Crystal data for fortucine **2**	
Molecular formula	$C_{16}H_{19}NO_3$
Molecular weight	273.32
Crystal habit	Colourless plate
Crystal dimensions (mm)	0.12×0.12×0.05
Crystal system	Orthorhombic
Space group	*Pbca*
a (Å)	8.766(1)
b (Å)	13.240(1)
c (Å)	22.830(1)
α (°)	90.00
β (°)	90.00
γ (°)	90.00
V (Å^3)	2649.7(4)
Z	8
d (g cm^{-3})	1.370
F(000)	1168
μ (cm^{-1})	0.094
Absorption corrections	multi-scan; 0.9888 min, 0.9953 max
Diffractometer	KappaCCD
X-ray source	MoKα
λ (Å)	0.71069
Monochromator	Graphite
T (K)	150.0(1)
Scan mode	Phi and omega scans
Maximum θ	21.48
HKL ranges	−9.8; −10.13; −23.21
Reflections measured	8521
Unique data	1509
R_{int}	0.1228
Reflections used	1117
Criterion	($I>2\sigma I$)
Refinement type	Fsqd
Hydrogen atoms	Mixed
Parameters refined	184
Reflections/parameter	6
*wR*2	0.1446
*R*1	0.0645
Weights *a*, *b*	0.0657;0.8957
GoF	1.103
Difference peak/hole (e Å^{-3})	0.201(0.058)/−0.239(0.058)

Acknowledgements

We wish to thank Professor J. Bastida (Barcelona) for a sample of kirkine and Ecole Polytechnique for fellowships (to A.B. and S.H.).

References and notes

1. For a review on Amaryllidaceae alkaloids, see: Jin, Z. *Nat. Prod. Rep.* **2007**, *24*, 886.
2. Dalton, D. R. *The Alkaloids: The Fundamental Chemistry-A Biogenetic Approach*; Marcel Dekker: New York, NY, 1979.
3. Hartwell, J. L. *Lloydia* **1967**, *30*, 379.
4. (a) De Laurentis, C.; Rosato, A.; Vitali, C.; Leone, L.; Milillo, M. A. *Riv. Ital. EPPOS* **2004**, *38*, 19; (b) De Laurentis, C.; Rosato, A.; Vitali, C.; Leone, L.; Milillo, M. A. *Chem. Abstr.* **2005**, *143*, 129863; (c) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1987; Vol. 30, pp 251–376; (d) Ghosal, S.; Saini, K. S.; Razdan, S. *Phytochemistry* **1985**, *24*, 2141; (e) Mineshita, T.; Yayaguchi, K.; Takeda, K.; Kotera, K. *Ann. Rep. Shinogi Res. Lab.* **1956**, *6*, 119; (f) Chattopadhyay, U.; Chaudhuri, L.; Das, S.; Kumar, Y.; Ghosal, S. *Pharmazie* **1984**, *39*, 855; (g) Leo De, P.; Dalessandro, G.; De Santis, A.; Arigoni, O. *Plant Cell Physiol.* **1973**, *14*, 487.
5. (a) Takagi, S.; Taylor, W. I.; Uyeo, S.; Yajima, H. J. *J. Chem. Soc.* **1955**, 4003; (b) Fales, H.; Warnhoff, E. M.; Wildman, W. C. *J. Am. Chem. Soc.* **1955**, *77*, 5885.
6. (a) Tokhtabaeva, G. M.; Sheichenko, V. I.; Yartseva, I. V.; Tolkachev, O. N. N. *Khim. Prir. Soedin.* **1987**, 727; (b) Bastida, J.; Codina, C.; Peeters, P.; Rubiralta, M.; Orozco, M.; Luque, F. J.; Chharbra, S. C. *Phytochemistry* **1995**, *40*, 1291; (c) Richomme, P.; Pabuccuoglu, V.; Gozler, T.; Freyer, A. J.; Shamma, M. *J. Nat. Prod.* **1989**, *52*, 1150.
7. (a) Watt, J. M.; Breyer-Brandwijk, M. G. *Medicinal and Poisonous Plants of Southern and Eastern Africa*; E. & S. Livingstone: Edinburgh, 1962; (b) Kokwaro, J. O. *Medicinal Plants of East Africa*; East Africa Literature Bureau: Kampala, 1976.
8. Biechy, A.; Hachisu, S.; Quiclet-Sire, B.; Ricard, L.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 1436.
9. Tran-Huu-Dau, M. E.; Wartchow, R.; Winterfeldt, E.; Wong, Y. S. *Chem.—Eur. J.* **2001**, *7*, 2349.
10. Formed by the condensation of acetaldehyde with 1 (methylthio)thiocarbonyl-1-phenyl-hydrazine. See Ref. 9a.
11. (a) Callier-Dublanchet, A. C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 8791; (b) Callier-Dublanchet, A. C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 2463; (c) Depature, M.; Grimaldi, J.; Hatem, J. *Eur. J. Org. Chem.* **2001**, 941.
12. (a) Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2125; (b) Barclay, G. L.; Quiclet-Sire, B.; Sanchez-Jimenez, G. *Org. Biomol. Chem.* **2005**, *3*, 823.
13. Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588.
14. For recent synthetic studies, see: (a) Parnes, J. S.; Carter, D. S.; Kurz, L. J.; Flippin, L. A. *J. Org. Chem.* **1994**, *59*, 3497; (b) Hutchings, R. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 1004; (c) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1998**, *63*, 3986; (d) Harayama, T.; Hori, A.; Abe, H.; Takeuchi, Y. *Tetrahedron* **2004**, *60*, 1611; (e) Torres, J. C.; Pinto, A. C.; Garden, S. J. *Tetrahedron* **2004**, *60*, 9889.
15. Oxoassoanine, assoanine: (a) Llabres, J. M.; Viladomat, F.; Bastida, J.; Codina, C.; Rubiralta, M. *Phytochemistry* **1986**, *25*, 2637; Pratosine, pratorinine, pratorimine: (b) Ghosal, S.; Saini, K. S.; Frahm, A. W. *Phytochemistry* **1983**, *22*, 2305; Hippadine: (c) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1981**, *20*, 2003; (d) El Mehgazi, A. M.; Ali, A. A.; Mesbah, M. K. *Planta Med.* **1975**, *28*, 336.
16. (a) Chattopadhyay, S. C.; Chattopadhyay, U.; Marthur, P. P.; Saini, K. S.; Ghosal, S. *Planta Med.* **1983**, *49*, 252; (b) Petti, G. R.; Gaddamidi, V.; Goswani, A.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 796; (c) Ghosal, S.; Lochan, R.; Ashutosh, K.; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1985**, *24*, 1825; (d) Zee-Cheng, R. K. Y.; Yan, S. J.; Chen, C. C. *J. Med. Chem.* **1978**, *21*, 199; (e) Chen, C. C.; Zee-Cheng, R. K. Y. *Heterocycles* **1981**, *15*, 1275.
17. Jensen, K. A.; Anthoni, U.; Holm, A. *Acta Chem. Scand.* **1969**, *23*, 1916.
18. Eaton, P. E.; Wicks, G. E. *J. Org. Chem.* **1988**, *53*, 5353.
19. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. SIR97, an integrated package of computer programs for the solution and refinement of crystal structures using single crystal data.
20. Sheldrick, G. M. *SHELXL-97*; Universität Göttingen: Göttingen, Germany, 1997.