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Biomimetic approach to *Galbulimina* type I alkaloids

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Abstract—On treatment with trifluoroacetic acid the tetraene precursor **23** underwent Boc deprotection, condensation and an iminium ion accelerated intramolecular Diels–Alder cycloaddition resulting in an iminium species **12**, which was further converted into himbacine **1**, himbeline **3** and himandravine **4**, three out of four *Galbulimina* type I alkaloids thus providing strong evidence for the proposed biogenesis of this important family of alkaloids.

1. Introduction

As early as 1948 Webb discovered that the bark of relic trees belonging to the *Galbulimina baccata* genus and found in New Guinea and North Queensland (Australia) reacted strongly to alkaloid tests and this was subsequently verified by Ritchie 7 years later when he isolated nine novel alkaloids from the same bark.[1] So far 28 *Galbulimina* alkaloids have been isolated and they appear to fall into four classes based upon their structures.[2] Class I consists of four tetracyclic lactones as shown in Figure 1.

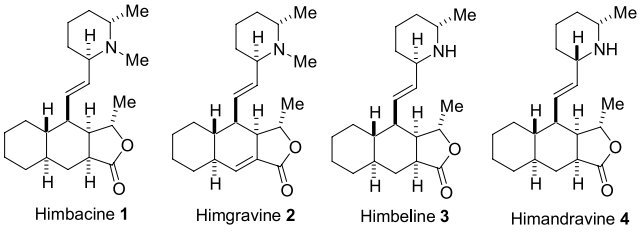
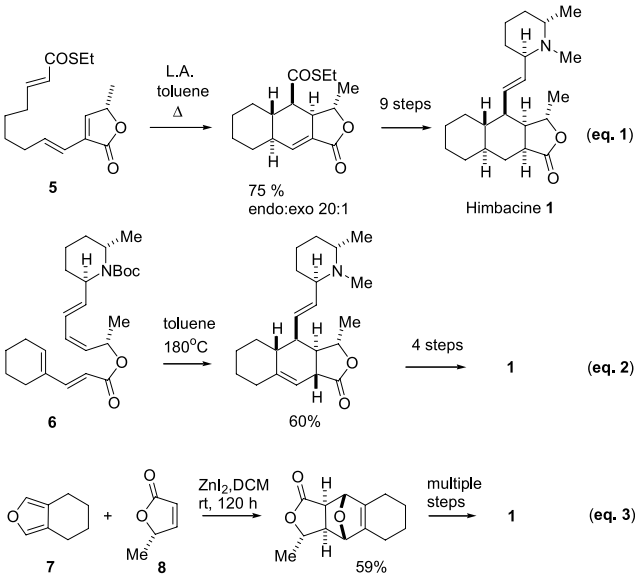


Figure 1. Class I *Galbulimina* alkaloids.

Himbacine **1**, being the major representative of the family, was the first to have it's structure identified.[3] It was originally shown to exhibit anti-spasmodic activity with low toxicity and few side effects.[4] In the 1990s though, himbacine has been shown to be a selective muscarinic antagonist and thus a potential new lead in the treatment of Alzheimer's disease.[5] Mostly due to the latter discovery himbacine has attracted significant synthetic attention.[6–9]

Three successful total syntheses of himbacine have been reported, each having similar features in common. A Diels–Alder cycloaddition was employed to construct the decalin fragment and all of the authors approached himbacine **1** via methylation of the piperidine nitrogen of himbeline **3**. Hart has synthesised the tricyclic fragment via a highly stereoselective Lewis acid catalysed cycloaddition of thioester **5** (Scheme 1, Eq. 1). Completion of the tetracycle



Scheme 1. Previous successful syntheses of himbacine **1**.

Keywords: Biomimetic synthesis; *Galbulimina* alkaloids; Himbacine; Himandravune; Himbeline.
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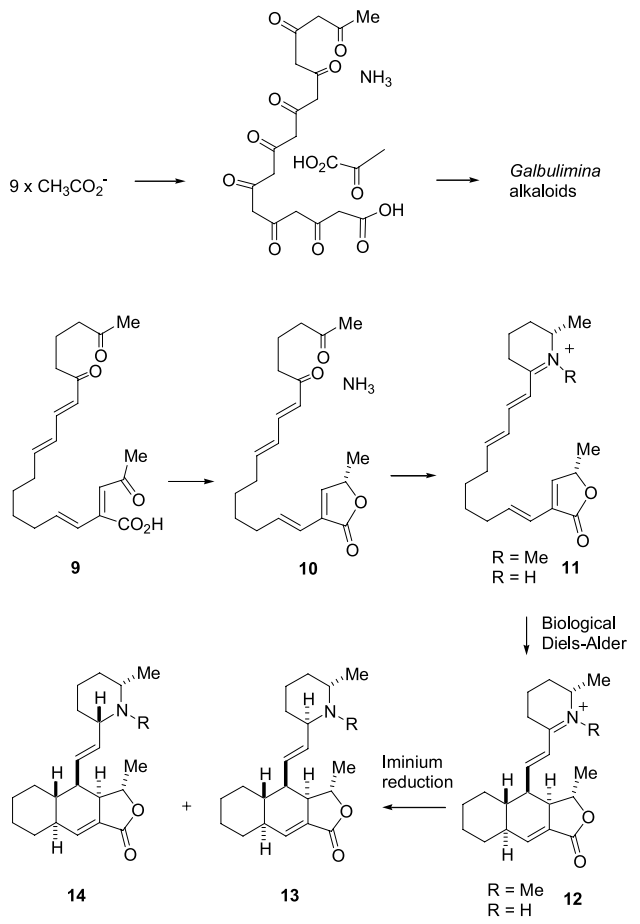
required nine extra synthetic steps[7] including a forced reduction, protection and further reoxidation of the lactone.

In what is considered as the most efficient published total synthesis of himbacine **1**, Chackalamannil performed a reverse electron demand Diels–Alder of teraene **6** (Scheme 1 Eq. 2). The *exo*-selective cycloaddition resulted in a compound with opposite stereochemistry at the centre α to the lactone to the one required for the total synthesis. Epimerization was achieved on treatment of the tetracycle with DBU in toluene and the total synthesis was accomplished in four further synthetic steps.[8] Terashima's synthesis has employed an intermolecular Diels–Alder of furan derivative **7** and butenolide **8** (Scheme 1 Eq. 3). Completion of the total synthesis required over 15 synthetic steps, although a more modular approach allowed synthesis of multiple unnatural analogues.[9] Remarkably, only Chackalamannil has synthesized himandravine **4** in a later synthetic effort.[10]

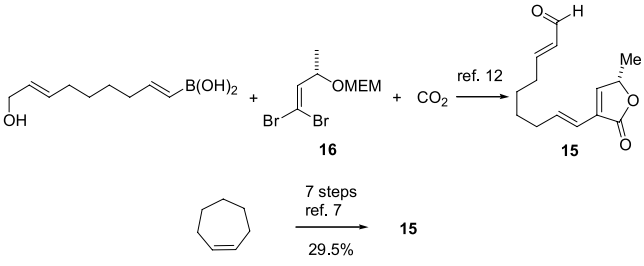
Our interest in the *Galbulimina* alkaloids dates back to the late 1980s when we decided to establish a general biomimetic approach to all members of the class I alkaloids.[11] The proposed approach should also be applicable, with modification, to the synthesis of more structurally complex class II and class III alkaloids.

2. Biomimetic approach

Ritchie speculated that nine C_2 acetate units, one C_3 pyruvate unit and a molecule of NH_3 were used to construct the alkaloids (Scheme 2),[12] without being specific on the particular biotransformations involved. Our biosynthetic pathway for the *Galbulimina* class I alkaloids[13] postulates ketide **9** formation from the same nine acetates and a pyruvate via standard polyketide biosynthesis. Reductive lactonisation would result in butenolide **10**, which on reductive amination followed by iminium ion formation via *N*-methylation or N-protonation would provide the Diels–Alder precursor **11**. Intramolecular Diels–Alder cycloaddition via an *endo* transition state would afford tetracycle **12**. Finally, hydride reduction of the iminium from either the α or β face would furnish either the himbacine (*trans*-piperidine ring) precursor **13** or the himandravine (*cis*-piperidine ring) precursor **14** (Scheme 2). Our primary goal was to establish the possibility of a biological iminium catalysed Diels–Alder reaction leading to the tricyclic lactone core of these alkaloids.



Scheme 2. Postulated biogenesis of class I alkaloids.



Scheme 3. Approaches to aldehyde **15**.

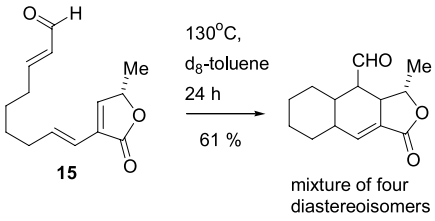
Our initial approach to aldehyde **15** is outlined in Scheme 3 and was based on a Suzuki reaction of the *trans*-bromide followed by carboxylation of the cis-position of the dibromo-alkene **16**.[13] Later, we adopted a more elegant approach by Hart[7] and accessed **15** from cycloheptene in seven synthetic steps and 29.5% overall yield.

3. Results and discussion

3.1. Gassman Diels–Alder

It was our expectation, that the Diels–Alder type reaction of butenolides like **10** would require strong activation of the dienophile. Aldehydes are known to be among the best substituents for such activation, as their LUMO energy lowering effect can be dramatically enhanced via formation of oxacarbenium species on treatment with Lewis Acids. Thus, we chose the aldehyde **15** (Scheme 3) as our initial model to study the possibility of a biological Diels–Alder.

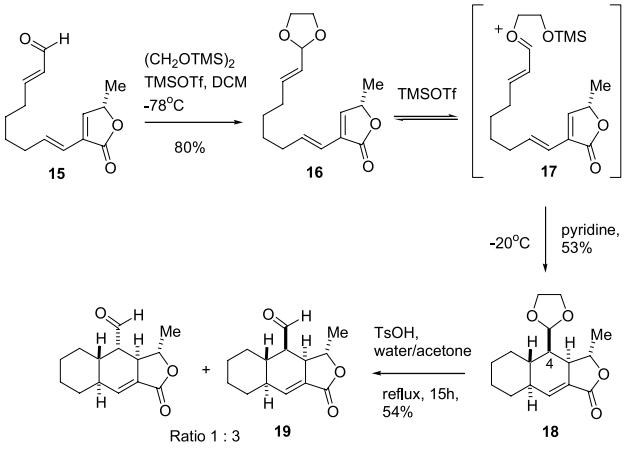
First, we attempted a thermal cycloaddition of aldehyde **15** (Scheme 4). A solution of the enal **15** in d_8-toluene was heated in the presence of 0.2 equiv of the radical inhibitor, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulphide, at 130 °C in a sealed tube for 24 h. Pleasingly an IMDA process occurred and the cycloaddition product appeared to consist of a 2.5:2.3:1.0:0.25 mixture of diastereoisomers. The isolated yield after column chromatography was a reasonable 61%, although the diastereoisomers could not be separated.



Scheme 4. Thermal cycloaddition of enal **15**.

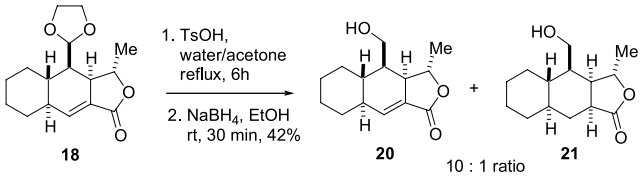
Attempts to accelerate the Diels–Alder by use of Me_2AlCl or $SnCl_4$ were unsuccessful. This was attributed to the more likely coordination of the Lewis Acids to the more basic carbonyl of the butenolide, rather then the enal.

Next, our attention was drawn to Gassman's findings indicating that acrolein acetals in the presence of Lewis or protic acids form oxonium ions, which undergo accelerated IMDA cycloadditions with a range of dienes at low temperatures.[14] At first we attempted to form a cyclic acetal of the enal **15**. The Noyori procedure involves low temperature conditions using 1,2-bis(trimethylsilyloxy)-ethane as the acetal source and TMSOTf as catalyst.[15] Application of these conditions to the enal **15** at −78 °C afforded the acetal **16**, which could be isolated if the reaction was quenched by addition of pyridine. However, if the reaction was allowed to warm to −20 °C, the presence of TMSOTf, acting as a Lewis Acid, promoted a Gassman intramolecular Diels–Alder reaction presumably via the formation of an oxonium ion intermediate **17**. Pleasingly, tricyclic acetal **18** was isolated in a 53% yield with a 40:1 ratio of diastereomers (Scheme 5).



Scheme 5. Gassman Diels–Alder.

At first we expected the minor cycloadduct to be an *exo*-pathway product, but our first attempt to hydrolyse the acetal **18** led to isolation of the aldehyde **19** as a 3:1 mixture of epimers. Epimerisation under the hydrolysis conditions could only have occurred at C4 and this suggested that the Gassman Diels–Alder produced only *endo*-cycloaddition product with some minor epimerization at C4 position occurring under the reaction conditions. Our next aim was to obtain unambiguous proof of the stereochemistry of the cycloadduct. A briefer aqueous hydrolysis and an in situ $NaBH_4$ reduction of the aldehyde **19** avoided epimerization at C4 position in the alcohol **20**. Quite unexpectedly 1,4-addition of the hydride was competitive under the same conditions resulting in formation of a minor saturated tricycle **21** (Scheme 6).



Scheme 6. Synthesis of alcohol **20**.

The alcohol **20** is a white crystalline solid and we expected to obtain crystals of the major component on attempted crystallization of the mixture of **20** and **21**. To our surprise the single crystal that was chosen for X-ray analysis contained the minor component **21**. Gratifyingly, the diffraction analysis data[16] (Fig. 2) confirmed that the stereochemistry of the tricyclic core of **21** is the same as that of himbacine **1**.

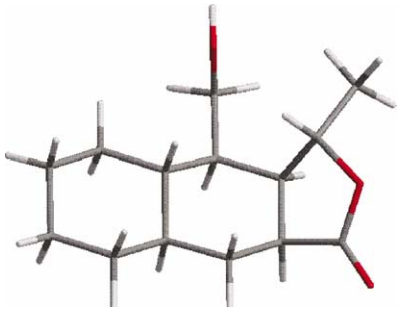


Figure 2. Chem 3D plot of the X-ray of **21**.

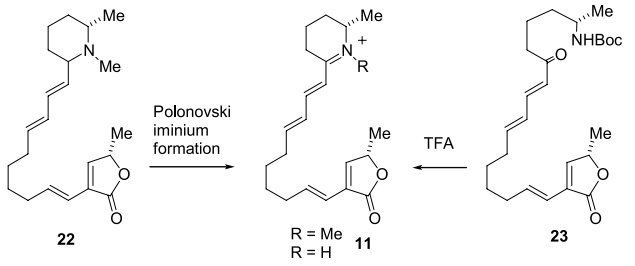
Having obtained proof that with sufficient dienophile activation, the intramolecular Diels–Alder reaction of a butenolide like **15** gives *endo*-cyclisation products with high level of stereocontrol, we moved on to investigate the proposed biomimetic cycloaddition of iminium species like **11**.

3.2. Biomimetic Diels–Alder reaction

Two possible synthetic pathways towards the iminium **11** were investigated. The first one centered on a Polonovski[17] generation of **11** (R=Me) from the piperidine species **22**. The second envisaged formation of the iminium species **11** (R=H) on acid catalysed cleavage of the *N*-Boc protecting group and condensation of the tethered amine in an open chain precursor **23** (Scheme 7).

Our multiple attempts to synthesise himgravine **2** type adducts in Polonovski-type oxidations of the piperidine compound **21** were unsuccessful[18] and will not be discussed further in this publication. On the other hand, positive results were obtained in the investigation of the alternative condensation pathway.

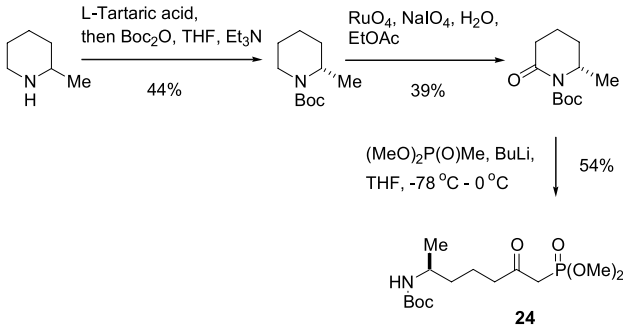
It was expected that the cyclisation precursor **23** would be accessed via a Wittig type olefination of aldehyde **15** and phosphonate **24**.



Scheme 7. Approaches to iminium species **11**.

The synthesis of the chiral phosphonate **24** was accomplished in three steps. 2-Methyl piperidine was resolved via crystallization with L-tartaric acid,[19] which was followed by Boc protection and oxidation.[20] Treatment of the piperidinone with a small excess of the lithiated dimethyl methylphosphonate produced the desired Horner–Emmons reagent **24** in 54% yield after column chromatography (Scheme 8).

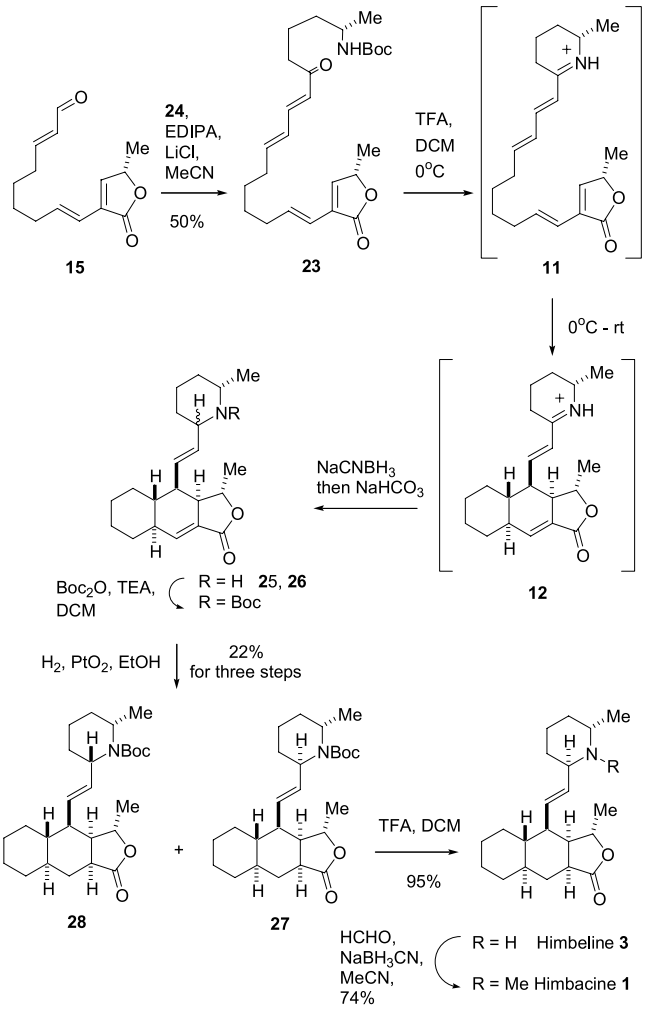
Reaction of the phosphonate **24** with the aldehyde **15**



Scheme 8. Synthesis of phosphonate **23**.

employing the modified Masamune–Roush conditions[21] produced the tetraene **23**, which was treated with trifluoroacetic acid at 0 °C in dichloromethane effecting Boc cleavage and condensation to the desired iminium species **11**. The reaction mixture was then allowed to warm up slowly to room temperature and stirred for an additional hour then quenched by addition of an excess of sodium cyanoborohydride almost immediately followed by addition of saturated aqueous sodium bicarbonate. At this point ^{1}H NMR analysis of the crude reaction mixture showed complete disappearance of resonances corresponding to the starting material along with the appearance of two characteristic peaks at δ 6.62 and 6.69 ppm, corresponding to the resonances of the protons of the α,β unsaturated double bond of two epimeric products **25** and **26** derived from consecutive *N*-Boc deprotection, condensation, IMDA cycloaddition and iminium ion reduction (Scheme 9). The reduction proved to be non-facial selective and both β-hydrogen peaks had identical integration in the 500 MHz ^{1}H NMR.

We found that direct separation of the diastereomeric mixture of **25** and **26** from the complex crude reaction mixture was impossible and required *N*-Boc protection

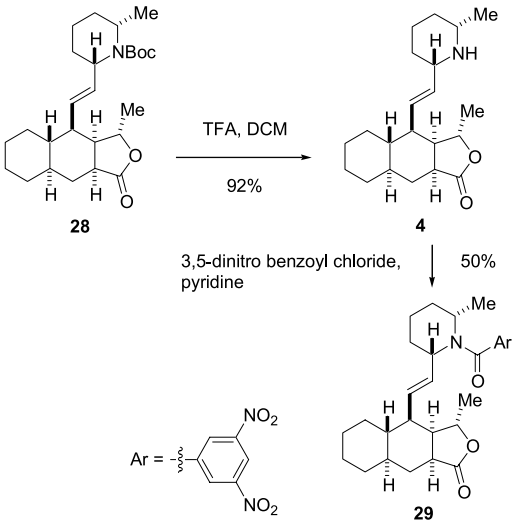


Scheme 9. Completeion of synthesis.

followed by a highly selective hydrogeneation of the trisubstituted double bond over Adam's catalyst[3] in order to separate the *N*-Boc protected himbeline **27** and himandravine **28** derivatives. Boc deprotection of **27** yielded synthetic himbeline **3**, which was *N*-methylated following literature method[7] to give synthetic himbacine **1**, whose structure was confirmed via ^{1}H NMR in a doping experiment with an authentic sample of the natural product.[22]

N-Boc deprotection of **28** led to isolation of synthetic himandravine **4** (Scheme 10). In absence of a natural product sample to run a doping experiment, it was decided to establish the structure via X-ray analysis. Thus, **4** was converted into a dinitro-benzoate derivative **29**. The results of the single crystal X-ray analysis of **29** are presented in Figure 3.

In summary, we have demonstrated a single step biomimetic transformation of **23** into a tetracyclic iminium species **12**, which was further transformed into himbeline **3**, himbacine **1** and himandravine **4**. We believe this proceeds via a consecutive *N*-Boc deprotection, condensation and iminium ion activated intramolecular Diels–Alder cycloaddition process. This provides strong support for our proposed biogenesis of these class 1 *Galbulimina* alkaloids.



Scheme 10. Synthesis of himandravine derivative **29**.

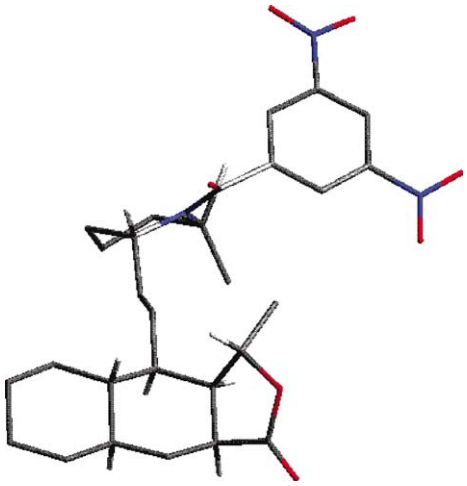


Figure 3. Chem 3D plot of the X-ray structure of **29**.

3.3. A new hypothesis

It was our original intent to propose a more complete biogenetic pathway analysis, which would be applicable not only to the class I but to other classes of *Galbulimina* alkaloids as well. Himbosine **30** is a representative of the highly oxygenated hexacyclic class II alkaloids. Similarities between alkaloids of the two classes is indicated by numbering in Figure 4.

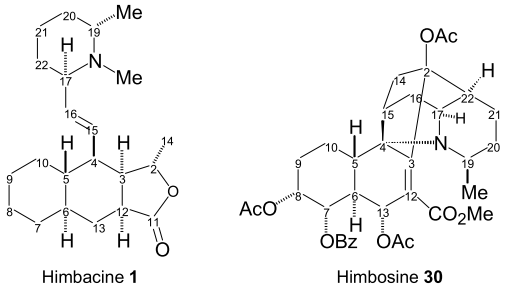
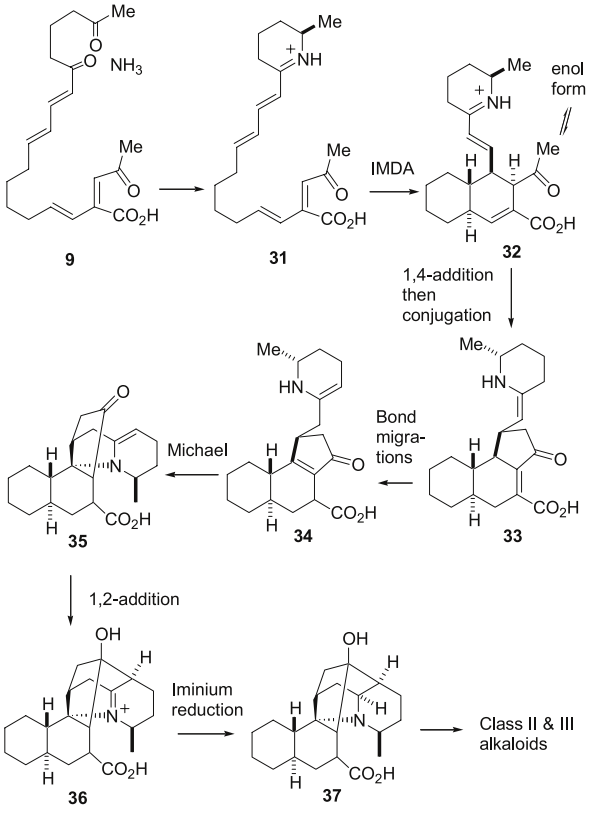


Figure 4. Class I and II *Galbulimina* alkaloids.

Analysis of both structures shows that the class II alkaloids have extra carbon–carbon bonds between C22 and C2, C14 and C15 and that the piperidine nitrogen becomes connected to C4. Extra oxygenation of C8, C7, and C13 of the decalin unit could be attributed to later metabolic oxidation steps.

Our successful biomimetic synthesis of the class I alkaloids (notably both major alkaloids himbacine **1** and himandravine **2** were synthesized in the same synthetic route) employing an iminium ion activated intramolecular Diels–Alder reaction allows us to postulate that similar chemistry would be involved in the biosynthesis of the class II and III alkaloids. Our proposed biosynthetic pathway is presented in Scheme 11. The scheme starts with the same polyketide **9**, which would not undergo a reductive lactonisation, but would directly give the iminium **31** on condensation with ammonia. **31** is set for an iminium ion activated intramolecular Diels–Alder reaction producing the tricyclic **32**. The iminium activates the exocyclic double bond as an acceptor and the tautomerised enolic form of the ketone would add in a conjugate fashion to give the C14–C15 carbon–carbon bond. Further tautomerisation of the enamine **33** accompanied by double bond migration into **34** would be followed by Michael addition to give the *N*–C4 connectivity in **35**. 1,2-Addition of the enamine would accomplish the C2–C22 bond in polycycle **36**, which on iminium reduction would give **37**, a possible intermediate in the biosynthesis of class II and III *Galbulimina* alkaloids.



Scheme 11. Postulated biogenesis of class II and III alkaloids.

4. Experimental

4.1. General

4.1.1. Preparation of ketal 18. To a solution of enal[7] **15** (88.9 mg, 0.38 mmol) in dichloromethane (6 ml) cooled to −78 °C under an atmosphere of argon was added 1,2-bis-(trimethylsiloxy)-ethane (235 mg, 1.14 mmol). This solution was stirred at −78 °C for 15 min at which stage trimethylsilyltrifluoromethylsulphonate (84.4 mg, 0.38 mmol) was added dropwise. The resultant bright yellow solution was stirred at −78 °C for a further 3 h, at which stage the temperature of the reaction mixture was rapidly increased to −20 °C. The reaction mixture was stirred for 2 h between −30 and −20 °C during which time the colour of the reaction mixture darkened considerably. Excess pyridine (0.5 ml) was added discharging the dark colour. The reaction mixture was then warmed to room temperature, diluted with dichloromethane (20 ml) and poured into saturated sodium hydrogen carbonate (30 ml). The layers were separated and the aqueous layer extracted with dichloromethane (2×20 ml). The organics were combined, dried over magnesium sulphate, filtered and volatiles removed in vacuo. The obtained yellow oil was purified by flash chromatography (diethyl ether/pet. ether 4:7) to yield the product **18** as a colourless oil (56 mg, 53%); $[\alpha]_D^{22}$ +54.3 (*c* 1, $CHCl_3$); *m/z* (CI^+) found 279.1596, $C_{16}H_{22}O_4+H^+$ requires 279.1596; ν_{max}/cm^{-1} (film) 2854 (m), 1757 (s), 1683 (m), 1408 (m), 1226 (m), 979 (m); δ_H (500 MHz, $CDCl_3$) 1.12 (1H, m), 1.16 (1H, m), 1.26–1.46 (3H, m), 1.47 (3H, d, *J*=6.0 Hz), 1.72 (1H, m), 1.75–1.80 (2H, m), 2.05–2.11 (2H, m), 2.15 (1H, ddd, *J*=9.5, 7.5, 4.0 Hz), 2.61 (1H, ddd, *J*=9.5, 7.5, 3.0 Hz), 3.81–3.83 (2H, m), 3.94–3.96 (2H, m), 4.78 (1H, d, *J*=4.0 Hz), 4.94 (1H, dq, *J*=7.5, 6.0 Hz), 6.71 (1H, dd, *J*=3.5, 3.0 Hz); δ_c (125 MHz, $CDCl_3$) 21.84, 26.12, 26.58, 32.24, 33.86, 41.28, 41.35, 43.51, 44.31, 64.37, 64.62, 77.47, 105.1, 131.4, 141.2, 169.3.

4.1.2. Preparation of alcohol 20. To a solution of ketal **18** (56 mg, 0.2 mmol) in acetone–water (2/1, 9 ml) was added *para*-toluenesulfonic acid (114 mg, 0.6 mmol). The solution was brought to a gentle reflux which was maintained for 6 h. The reaction mixture was then cooled, diluted with dichloromethane (50 ml) and washed with water (25 ml). The aqueous portion was extracted with dichloromethane (25 ml), the organics combined, dried over magnesium sulphate, filtered and the volatiles removed in vacuo. The crude mixture was dissolved in ethanol (7 ml) and the solution was cooled to 0 °C. To this rapidly stirred solution was added sodium borohydride (15 mg, 0.4 mmol). The reaction mixture was then stirred at room temperature for 20 min at which stage excess sodium borohydride (30 mg, 0.8 mmol) was added and the reaction mixture was stirred for a further 10 min. The reaction was quenched by careful addition of acetone (6 ml) over a period of 2 min and then poured into water (20 ml) and diluted with dichloromethane (20 ml). Dilute hydrochloric acid (1 M, 3 ml) was added to the biphasic mixture, the layers were separated and the aqueous portion was extracted with dichloromethane (20 ml). The organics were combined, dried over magnesium sulphate, filtered and the volatiles removed in vacuo. The obtained yellow oil was purified by flash chromatography (diethyl ether/pet. ether 2:3) giving the product **20** as a white crystalline solid (20 mg, 42%); mp 149–151.5 °C; $[\alpha]_D^{22}$ +52.5 (*c* 0.4, $CHCl_3$); *m/z* (CI^+) found 254.1756, $C_{14}H_{20}O_3+NH_4^+$ requires 254.1756; ν_{max}/cm^{-1} (KBr) 3435 (br s), 2839 (s), 1735 (s), 1630 (m), 1442 (m), 1380 (m); δ_H (500 MHz, $CDCl_3$) 0.87 (1H, m), 1.13 (1H, m), 1.25–1.39 (3H, m), 1.56 (3H, d, *J*=6.0 Hz), 1.76–1.84 (3H, m), 1.90 (1H, ddt, *J*=9.5, 7.0, 6.5 Hz), 1.97 (1H, m), 2.07 (1H, m), 2.70 (1H, ddd, *J*=12.5, 7.0, 3.5 Hz), 3.73 (2H, d, *J*=6.5 Hz) 4.80 (1H, dq, *J*=12.5, 6.0 Hz), 6.65 (1H, dd, *J*=3.5, 3.0 Hz); δ_c (125 MHz, $CDCl_3$) 21.62, 26.04, 26.44, 31.79, 32.43, 40.56, 40.83, 42.99, 45.76, 61.68, 78.28, 131.4, 140.9, 169.5.

4.1.3. Preparation of phosphonate 24. To a stirred solution of dimethyl methylphosphonate (1.86 g, 15 mmol) in THF (50 ml) was added *n*-butyl lithium (1.6 M solution in hexanes, 10 ml) dropwise at −78 °C. The reaction mixture was stirred for an hour and (2*S*)-methyl-*N*-Boc-piperidinone[20] (2.13 g, 10 mmol) was added. Reaction mixture was allowed to warm to room temperature and stiring was continued for an additional hour. Water (20 ml) was added and the resulting mixture was poured into a separating funnel containing ethyl acetate (100 ml) and water (100 ml). Layers were separated and the aqueous layer was extracted with ethyl acetate (2×25 ml). Combined organics were dried ($MgSO_4$), filtered and volatiles removed in vacuo. Flash chromatography (short column, EtOAc with 2.5% MeOH) yielded the title compound as a colourless oil (1.86 g, 54%); $[\alpha]_D^{22}$ −2.9 (*c* 1.0, $CHCl_3$); *m/z* (CI^+) found 337.1661, $C_{14}H_{28}NO_6P+H^+$ requires 337.1654; ν_{max}/cm^{-1} (film) 3318 (br m), 2972 (s), 1710 (s), 1690 (s), 1253 (m), 1174 (m), 1033 (s); δ_P (125 MHz, $CDCl_3$) 23.91; δ_H (500 MHz, $CDCl_3$) 1.09 (3H, d, *J*=6.5 Hz), 1.31–1.46 (2H, m), 1.39 (9H, s), 1.59 (2H, m), 2.62 (2H, m), 3.07 (2H, d, *J*=22.5 Hz), 3.59 (1H, m), 3.73 (3H, s), 3.79 (3H, s), 4.39 (1H, br s); δ_c (125 MHz, $CDCl_3$) 19.63, 21.08, 26.28, 36.11, 40.63, 41.66, 43.59, 45.98, 52.85, 78.85, 155.29, 201.48.

4.1.4. Preparation of tetraene 23. A mixture of aldehyde **15** (270 mg, 1.15 mmol), phosphonate **24** (656 mg, 1.94 mmol), lithium chloride (210 mg, 5 mmol) and diisopropyl ethyl amine (246 mg, 2 mmol) in acetonitrile (10 ml) was stirred for 12 h. Water (10 ml) and diethyl ether (10 ml) were added and layers were separated. Aqueous layer was extracted with diethyl ether (2×10 ml), combined organics dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (petrol ether/ethyl acetate 6:1) gave the title compound **23** as a colourless oil (256 mg, 50%); $[\alpha]_D^{22}$ +48.1 (*c* 1.0, $CHCl_3$); *m/z* (CI^+) found 446.2898, $C_{26}H_{39}NO_5+H^+$ requires 446.2906; ν_{max}/cm^{-1} (film) 3320 (br m), 2971 (s), 1735 (s), 1710 (s), 1650 (s), 1630 (m), 1525 (m), 1253 (s), 1033 (m); δ_H (500 MHz, $CDCl_3$) 1.10 (3H, d, *J*=5.5 Hz), 1.36–158 (8H, m), 1.40 (9H, s), 1.43 (3H, d, *J*=6.0 Hz), 1.62 (2H, m), 2.12–2.30 (2H, m), 2.54 (2H, m), 3.62 (1H, m), 4.40 (1H, br s), 5.10 (1H, dq, *J*=2.5, 6.0 Hz), 5.84 (1H, m), 5.90 (1H, m), 6.06–6.11 (2H, m), 6.81 (1H, dt, *J*=16.0, 5.5 Hz), 7.07 (1H, m), 7.16 (1H, d, *J*=2.5 Hz); δ_c (125 MHz, $CDCl_3$) 17.9, 19.1, 20.3, 21.1, 27.6, 28.3, 28.5, 29.3, 32.0, 36.5, 39.5, 46.0, 77.4, 116.8, 122.2, 128.4, 130.3, 138.9, 146.7, 146.9, 148.9, 171.0, 172.9, 200.3.

4.1.5. Preparation of *N*-Boc-himbeline 27 and *N*-Boc-himandravine 28. To a stirred solution of tetraene **23** (120 mg, 0.27 mmol) in DCM (5 ml) at 0 °C was added trifluoroacetic acid (100 μl, 1.34 mmol), the reaction mixture was stirred for 30 min and allowed to warm to room temperature. Stirring was continued for an additional hour, when ethanol (5 ml) and sodium cyanoborohydride (100 mg, 1.6 mmol) were added. The reaction was stirred for 30 s and quenched by addition of saturated aqueous sodium bicarbonate solution (10 ml). The resulting mixture was poured into a separating funnel and diluted with ethyl acetate (20 ml). Layers were separated and the aqueous phase was extracted with ethyl acetate (2×10 ml). Combined organics were dried (Na_2SO_4), filtered and concentrated to give crude cycloaddition products as a yellow oil, which was diluted with dichloromethane (10 ml). Triethylamine (30 mg, 0.3 mmol) and di-*tert*-butyl-dicarbonate (65 mg, 0.3 mmol) were added and the resulting solution was stirred for 14 h. The volatiles were removed in vacuo and the residue was dissolved in ethanol (20 ml). To the solution was added platinum (IV) oxide (10 mg, cat.) and the resulting mixture was stirred under atmosphere of hydrogen for 12 h. Filtration through a plug of Celite, which was washed with ethyl acetate (10 ml), and concentration in vacuo afforded the crude products as a brown oil, which was purified by flash chromatography (petrol ether/ethyl acetate 6:1).

N-Boc-himbeline **27**. A colourless oil (12.4 mg, 11%); $[\alpha]_D^{22}$ +58.2 (*c* 0.5, $CHCl_3$); lit.[7] +60.6 (*c* 0.55, $CHCl_3$); *m/z* (CI^+) found 432.3111, $C_{26}H_{41}NO_4+H^+$ requires 432.3114; ν_{max}/cm^{-1} (film) 3055 (s), 1765 (s), 1670 (m); δ_H (500 MHz, $CDCl_3$) 0.69 (1H, m), 0.97 (3H, m), 1.08–1.36 (3H, m), 1.22 (3H, d, *J*=8.0 Hz), 1.40 (3H, d, *J*=6.0 Hz), 1.43 (9H, s), 1.45–2.10 (12H, m), 2.23 (1H, m), 2.61 (1H, dt, *J*=6.5, 12.5 Hz), 4.00 (1H, m), 4.42 (1H, m), 4.62 (1H, dq, *J*=10.0, 6.0 Hz), 5.21 (1H, dd, *J*=15.0, 10.0 Hz), 5.52 (1H, dd, *J*=15.0, 6.0 Hz); δ_c (125 MHz, $CDCl_3$) 13.05, 20.66, 21.92, 25.19, 25.86, 25.95, 26.10, 28.22, 30.95, 31.75, 33.40, 39.78, 41.30, 42.0, 45.41, 46.76, 48.47, 51.95, 78.85, 131.05, 133.89, 154.74, 178.21.

N-Boc-himandravine **28**. A colourless oil (12.2 mg, 11%); $[\alpha]_D^{22}$ +62.1 (*c* 0.6, $CHCl_3$); *m/z* (CI^+) found 432.3118, $C_{26}H_{41}NO_4+H^+$ requires 432.3114; ν_{max}/cm^{-1} (film) 3055 (s), 1765 (s), 1670 (m); δ_H (500 MHz, $CDCl_3$) 0.72 (1H, m), 0.99 (2H, m), 1.11 (3H, d, *J*=6.0 Hz), 1.11–1.29 (4H, m), 1.29 (3H, d, *J*=6.5 Hz), 1.43 (9H, s), 1.45–1.90 (11H, m), 2.08 (1H, m), 2.21 (1H, m), 2.60 (1H, dt, *J*=6.0, 13.0 Hz), 4.30 (1H, m), 4.61 (1H, dq, *J*=10.0, 6.0 Hz), 4.73 (1H, m), 5.31 (1H, dd, *J*=15.0, 10.5 Hz), 5.53 (1H, dd, *J*=15.0, 7.5 Hz); δ_c (125 MHz, $CDCl_3$) 14.48, 20.48, 22.25, 26.14, 26.45, 28.28, 28.50, 30.10, 31.39, 32.04, 33.60, 40.04, 41.76, 42.32, 45.65, 46.08, 48.98, 50.22, 77.05, 79.28, 131.73, 134.32, 154.82, 178.34.

4.1.6. Preparation of himbeline 3. To a solution of *N*-Boc-himbeline **27** (12.4 mg, 0.027 mmol) in dichloromethane (3 ml) was added TFA (0.3 ml) and the reaction mixture was stirred for 1 h. The volatiles were removed in vacuo and the residual oil dissolved in dichloromethane (10 ml). The solution was washed with saturated aqueous sodium bicarbonate solution (2×5 ml). The aqueous phase was extracted with dichloromethane (2×5 ml) and the combined organic phase was dried (K_2CO_3), filtered and evaporated to give the title compound **3** as an oil (9.3 mg, 95%) which required no further purification. $[\alpha]_D^{22}$ +17.5 (*c* 0.95, $CHCl_3$); lit.[3] +19 (2.4% in $CHCl_3$); *m/z* (FAB) found 332.2595, $C_{21}H_{33}NO_2+H^+$ requires 332.2590; ν_{max}/cm^{-1} (film) 3055 (s), 1765 (s), 1670 (m); δ_H (500 MHz, $CDCl_3$) 0.72 (1H, m), 1.00 (3H, m), 1.08 (3H, d, *J*=6.5 Hz), 1.10–1.30 (4H, m), 1.40 (3H, d, *J*=6.0 Hz), 1.42 (1H, m), 1.45–1.80 (10H, m), 2.09 (1H, m), 2.23 (1H, dt, *J*=10.0, 6.5 Hz), 2.62 (1H, dt, *J*=13.0, 6.0 Hz), 3.09 (1H, m), 3.53 (1H, m), 4.64 (1H, dq, *J*=10.5, 6.0 Hz), 5.24 (1H, dd, *J*=15.5, 10.5 Hz), 5.70 (1H, dd, *J*=15.5, 6.5 Hz); δ_c (125 MHz, $CDCl_3$) 19.62, 21.31, 22.22, 26.07, 26.37, 30.96, 31.27, 31.93, 32.51, 33.58, 39.88, 41.42, 42.22, 45.50, 46.28, 48.96, 53.01, 76.80, 131.46, 135.00, 178.32.

4.1.7. Preparation of himbacine 1.[7] Synthetic himbeline **3** (6.5 mg, 0.02 mmol) in acetonitrile (4 ml) was added sodium cyanoborohydride (6.5 mg, 0.1 mmol) and 37% aqueous formaldehyde solution (25 mg, 0.03 mmol). The reaction mixture was stirred at room temperature for 1 h and neutralized (pH 7) by dropwise addition of glacial acetic acid and allowed to stir for an additional 2 h. The solvents were removed in vacuo and the residue was dissolved in dichloromethane (10 ml). The solution was washed with saturated aqueous sodium bicarbonate solution (10 ml), the aqueous phase was extracted with dichloromethane (4×5 ml) and the combined organics were dried over potassium carbonate, filtered and evaporated. The crude product was purified by flash chromatography on basic alumina (petrol ether/ethyl acetate 5:1) to give the title compound **1** as an oil[23] (5.0 mg, 74%); $[\alpha]_D^{22}$ +47.5 (*c* 0.25, $CHCl_3$); lit.[7] +51.4 (*c* 1.01, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.74 (1H, m), 1.00 (3H, d, *J*=6.5 Hz), 0.91–1.08 (3H, m), 1.10–1.30 (3H, m), 1.40 (3H, d, *J*=6.0 Hz), 1.37–1.48 (2H, m), 1.50–1.58 (2H, m), 1.63–1.80 (6H, m), 1.87 (1H, m), 2.10 (1H, m), 2.20–2.27 (1H, m), 2.22 (3H, s), 2.62 (1H, dt, *J*=12.5, 6.5 Hz), 2.84 (1H, m), 3.02 (1H, m), 4.63 (1H, dq, *J*=10.5, 6.0 Hz), 5.26 (1H, dd, *J*=15.0, 10.0 Hz), 5.57 (1H, dd, *J*=15.0, 9.0 Hz); δ_c (125 MHz, $CDCl_3$) 13.95, 18.91, 22.19, 26.06, 26.43, 31.41, 31.98, 32.57, 33.21, 33.54, 39.83, 41.15, 41.49, 42.18, 45.67, 49.09, 53.35, 61.29, 76.77, 133.30, 133.48, 178.32.

4.1.8. Preparation of himandravine 4. To a solutiom of *N*-Boc-himandravine **28** (11.2 mg, 0.026 mmol) in dichloromethane (3 ml) was added TFA (0.3 ml) and the reaction mixture was stirred for 1 h. The volatiles were removed in vacuo and the residual oil dissolved in dichloromethane (10 ml). The solution was washed with saturated aqueous sodium bicarbonate solution (2×5 ml). The aqueous phase was extracted with dichloromethane (2×5 ml) and the combined organic phase was dried (K_2CO_3), filtered and evaporated to give the title compound **4** as an oil (7.9 mg, 92%) which required no further purification. $[\alpha]_D^{22}$ +20.5 (*c* 0.25, $CHCl_3$); lit.[3] +23 (1.9% in $CHCl_3$); *m/z* (FAB) found 332.2595, $C_{21}H_{33}NO_2+H^+$ requires 332.2590; ν_{max}/cm^{-1} (film) 3055 (s), 1765 (s), 1670 (m); δ_H (500 MHz, $CDCl_3$) 0.69 (1H, m), 0.92–1.43 (8H, m), 1.07 (3H, d, *J*=6.5 Hz), 1.42 (3H, d, *J*=6.0 Hz), 1.53–1.89 (9H, m), 2.03 (1H, m), 2.21 (1H, m), 2.59 (1H, dt, *J*=13.0, 6.5 Hz), 2.69 (1H, m), 3.11 (1H, m), 4.61 (1H, dq,

$J=10.0$, 6.0 Hz), 5.28 (1H, dd, $J=15.0$, 10.5 Hz), 5.51 (1H, dd, $J=15.0$, 6.5 Hz); δ_c (125 MHz, $CDCl_3$) 19.79, 22.52, 23.11, 24.67, 26.25, 26.55, 31.32, 32.13, 32.46, 33.79, 40.02, 41.53, 42.36, 45.40, 48.83, 52.45, 59.46, 77.50, 131.40, 136.04, 178.47.

4.1.9. Preparation of benzoate 29. To a stirred solution of 3,5-dinitro benzoyl chloride (30 mg, 0.13 mmol) in dichloromethane (5 ml) was added solution of himandravine **4** (22.3 mg, 0.067 mmol) in pyridine (5 ml) dropwise over 10 min. The resulting mixture was stirred at room temperature for 6 h and poured into water (20 ml). Organics were extracted with ethyl acetate (3×10 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give a brown oil. Flash chromatography (petrol ether/ethyl acetate 2:1) gave the product as an oil (19.3 mg, 50%). The product was obtained as white prisms on slow evaporation of a diethyl ether solution. $[\alpha]_D^{22}$ +29.9 (*c* 0.83, $CHCl_3$); mp 166–167 °C; ν_{max}/cm^{-1} (film) 2930 (m), 1772 (s), 1756 (s), 1629 (s), 1544 (s), 1418 (m), 1344 (s); δ_H (500 MHz, $CDCl_3$) 0.76 (1H, m), 0.98–1.12 (2H, m), 1.06 (3H, d, $J=$ 7.0 Hz), 1.15–1.30 (3H, m), 1.28 (3H, d, $J=6.0$ Hz), 1.34–1.47 (2H, m), 1.58–1.94 (11H, m), 2.02 (1H, m), 2.20 (1H, m), 2.27 (1H, m), 2.66 (1H, dt, $J=13.0$, 6.5 Hz), 4.66 (1H, dq, $J=10.0$, 6.0 Hz), 5.50 (1H, dd, $J=15.5$, 10.0 Hz), 5.78 (1H, dd, $J=15.5$, 5.5 Hz), 8.52 (2H, d, $J=2.0$ Hz), 9.08 (1H, t, $J=2.0$ Hz); δ_c (125 MHz, $CDCl_3$) (one carbon not identified due to peak broadening) 14.40, 20.90, 21.93, 25.89, 26.26, 27.66, 30.22, 31.42, 31.80, 33.37, 39.84, 41.56, 42.08, 45.81, 48.87, 76.36, 77.09, 119.05, 126.33, 132.31, 133.59, 140.30, 148.47, 166.04, 177.77.

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