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Review

Mesembrine: The archetypal psycho-active *Sceletium* alkaloid

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ABSTRACT

(−)-Mesembrine is a chiral alkaloid that features an aryloctahydroindole skeleton and is most commonly found in species of the succulent genus *Sceletium*. Several *Sceletium* species are used by various ethnic groups in South Africa to manage disorders of the central nervous system. Binding assays have revealed that mesembrine is a more potent inhibitor of the serotonin transporter (SERT) than fluoxetine (Prozac) which has prompted the commercialization of mesembrine-containing consumer products. The congested all carbon quaternary stereocenter present at the bridgehead of mesembrine has rendered it a compound of interest for research in synthetic chemistry, which has assisted in the absolute configuration of the naturally occurring isomer to be assigned. Accordingly, this review will cover the recent literature pertaining to the distribution, structural elucidation, chemotaxonomy, biosynthesis, organic synthesis, as well as the biological activities of (−)-mesembrine. Recent synthetic procedures of the non-natural enantiomer as well as the racemate are also considered.

1. Introduction

The psychoactive properties of species belonging to the *Sceletium* genus (*Mesembryanthemum*) are well documented in the literature (Gericke, 2018; Gericke and Viljoen, 2008; Smith et al., 1996; Stafford et al., 2008). Historically, dried leaves of *Sceletium* have been used widely by indigenous groups native to southern Africa to elevate the mood and ease anxiety and tension and by shepherds as appetite suppressants during long journeys in dried areas (Gericke and Van Wyk, 1997). Furthermore, extracts prepared from *Sceletium* have been developed into commercial products for the treatment of central nervous system related disorders including Zembrin®, which is a standardised extract of *Sceletium*, used by patients for enhancing mood, decreasing anxiety and stress, and improving cognitive function (Dimpfel et al., 2017; Patnala and Kanfer, 2009). The psychoactive properties of *Sceletium* are attributed to the presence of structurally related alkaloids (Harvey et al., 2011) which can be classified into several skeleton types as shown in Fig. 1 including the mesembrine-type (**1**), tortuosamine-type (**2**), the joubertiamine-type (**3**), channaine (**4**) and Sceletium alkaloid A4 (**5**) (Jeffs, 1981; Veale et al., 2018). However, of these, the mesembrine-type scaffold is the most prevalent, which in addition to (**1**) includes mesembranol (**6**), mesembrenol (**7**) and mesembrenone (**8**) which all share a common *cis*-3a-aryloctahydroindole nucleus (Krstenansky, 2017).

Due in part to its relative abundance in *Sceletium*, the naturally occurring levorotatory isomer (−)-mesembrine was the first alkaloid of its group to be structurally characterized (Bodendorf and Krieger, 1957; Jeffs, 1981; Krstenansky, 2017; Popelak and Lettenbauer, 1967). Furthermore, (−)-mesembrine inhibits serotonin reuptake, and has displayed promise as a mild anti-depressant, anxiolytic, mood elevator and anti-addiction agent (Smith et al., 1996; Stafford et al., 2008). This intriguing biological utility, in addition to its quaternary stereogenic centre has resulted in this compound being intensively pursued through total synthesis (Czekelius, 2018). Accordingly, the purpose of this review is to provide a summary of the isolation, pharmacology and recent stereoselective synthesis of (−)-mesembrine.

2. Botanical distribution

There are eight recognised species of the genus *Sceletium*: *S. crassicaule* (Haw.) L. Bolus, *S. emarcidum* (Thumb.) L. Bolus ex H. J. Jaccobson, *S. exalatum* Gerbaulet, *S. expansum* (L.). Bolus [nt], *S. rigidum* L. Bolus, *S. strictum* L. Bolus, *S. tortuosum* (l.) N. E. Br. [nt] and *S. varians* (Haw.) (Gerbaulet, 1996). *S. expansum, S. strictum, S. tortuosum* (= *S. joubertii* = *S. namaquence*), *S. crassicaule*, and *S. varians* (= S. *subvelutinum*) are classified under the 'tortuosum' type sub-group. While, the rest of the species, *S. emarcidum, S. exalatum and S. rigidum* belong to the emarcidum type. The alkaloid (−)-mesembrine is known

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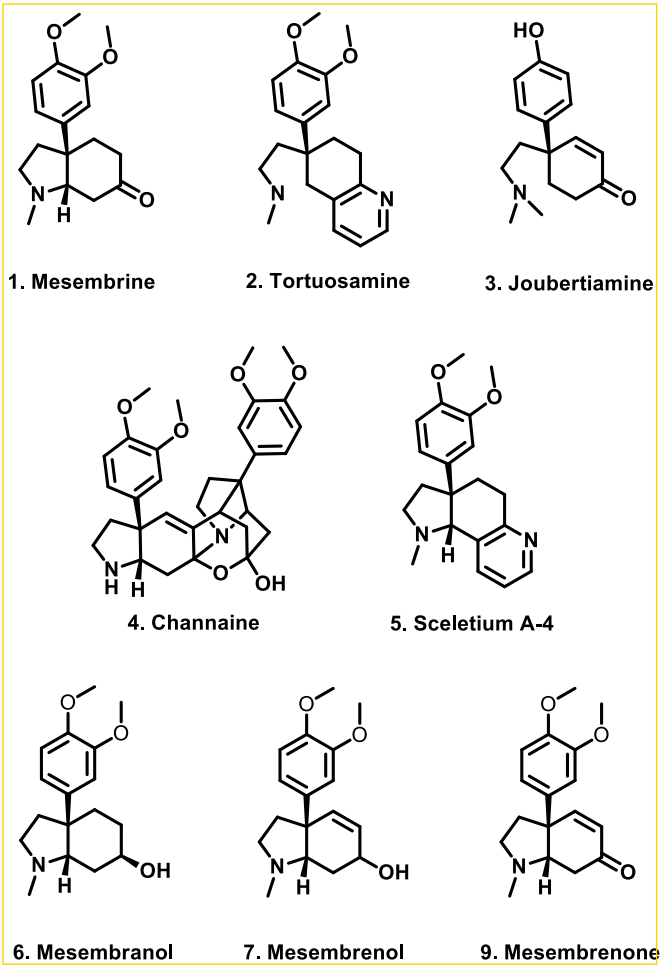


Fig. 1. Structures of selected *Sceletium* alkaloids.

to occur in at least three species of the 'tortuosum' type such as *S. tortuosum*, *S. strictrum*, and *S. expansum*. On the other hand, this alkaloid has not been detected in the 'emarcidum' type species of *Sceletium* (Patnala and Kanfer, 2013). Though (−)-mesembrine has been isolated mainly from *Sceletium* plants, gas chromatography-mass spectrometry analysis on some selected plants by Smith et al. (1998) have indicated their occurrence in other genera of the Mesembryanthemaceae family. *Apterna cordifolia*, *Delosperma pruinosum*, and *Delosperma pottsii* appeared to have some level of (−)-mesembrine. Whereas other species showed negligible or non-detectable level of (−)-mesembrine. The distribution of (−)-mesembrine in plant families is summarised in Table 1.

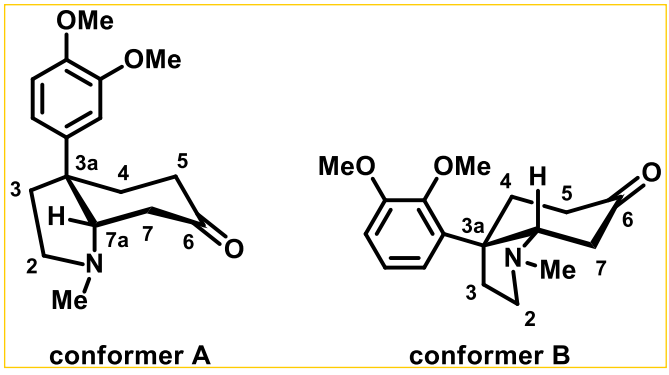


Fig. 2. The two possible conformers of (−)-mesembrine.

The concentration of (−)-mesembrine vary in *Sceletium* plants. This quantitative difference in the plant is affected by factors such as seasonal variation, growing conditions, age of plant, storing/processing (Smith et al., 1998). The content of this alkaloid is reported to be approximately 1% in *S. namaquense* and known to occur in lesser quantities in *S. strictum*. It has been isolated as a partial racemate from *S. tortuosum* (Jeffs, 1981).

3. Structure and stereochemistry

Following the initial isolation of (−)-mesembrine, Zwicky incorrectly assigned its molecular formula to be $C_{16}H_{19}NO_4$ (Zwicky, 1914). However, its molecular formula was correctly assigned as $C_{17}H_{23}NO_3$ by Rimington and Roets (1937). (−)-Mesembrine features a *cis*-fused octahydroindole unit linked to a freely rotatable aryl moiety. This octahydroindole nucleus derives from a saturated pyrrolidine ring fused to a cyclohexanone, via two bridge-head chiral carbons (C-3a and 7a), whose relative *cis* arrangement was elucidated from degradation studies and synthesis of the racemate (Popelak et al., 1960; Stevens et al., 1968). This arrangement allows for two likely conformations namely conformation A and B (Fig. 2). A lack of evidence of *trans*-diaxial coupling with the C-7a hydrogen, led to mesembrine being assigned to conformation A, which in conjunction to circular dichroism and x-ray crystallography studies of 6-epimesembrenol methiodide led the absolute configuration of (−)- mesembrine being assigned as 3a*S*, 7a*S* (Coggon et al., 1970; Jeffs et al., 1969).

4. Biosynthesis

Early proposed biosynthetic pathways for (−)-mesembrine involved a condensation between a C_6–C_2–N and a C_6 subunit (Bodendorf and Kloss, 1961). Through the incorporation of radiolabelled amino acids, into living specimens of *S. stricium*, Jeffs and co-workers proposed that

Table 1
Plant sources of mesembrine.

Plant species	Family	Detection Method	Isolation method	References
Aptenia cordifolia	Mesembryanthemaceae	GC-MS	N.A.[a]	1
Delosperma pruinosum	Mesembryanthemaceae	GC-MS	N.A.	1
Delosperma pottsii	Mesembryanthemaceae	GC- MS	N.A.	1
Narcissus pallidulus	Amaryllidaceae	GC-MS	N.A.	2
Narcissus triandrus	Amaryllidaceae	GC-MS	N.A.	3
Sceletium crassicaule	Mesembryanthemaceae	UPLC	N.A.	4
Sceletium expansum	Mesembryanthemaceae	HPLC	N.D.[b]	5, 8
Sceletium strictrum	Mesembryanthemaceae	HPLC, GLPC	CC	5, 6
Sceletium tortuosum	Mesembryanthemaceae	GC-MS, HPLC, UPLC	HSCCC, CC, PTLC	1, 4, 5, 7

1. Smith et al. (1998), 2.Berkov et al. (2014), 3.Pigni et al. (2013), 4. Shikanga et al. (2013), 5. Patnala and Kanfer (2013), 6.Jeffs et al. (1970), 7. Shikanga et al. (2011). 8. Zwicky (1914).

[a] N.A. = not available.

[b] N.D. = Not detailed.

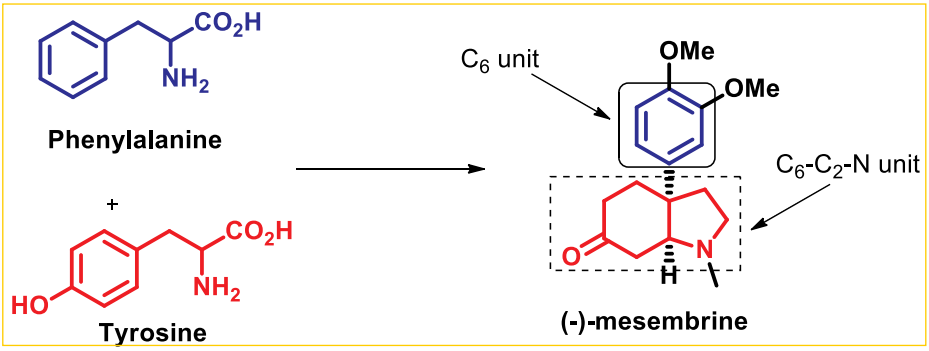


Fig. 3. Early proposed biosynthetic pathway for mesembrine.

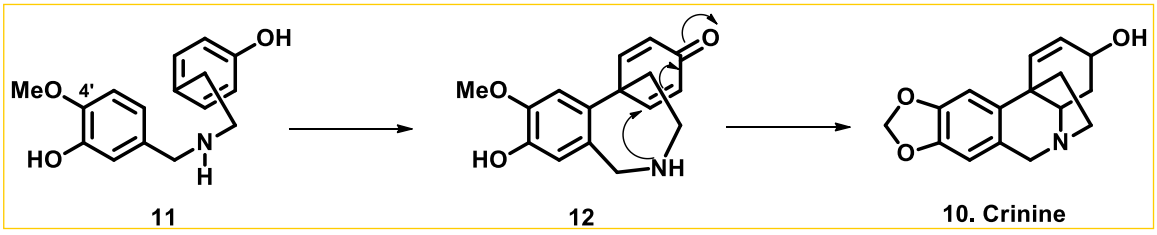


Fig. 4. Crinine biosynthetic pathway.

the octahydroindole moiety is formed through the elaboration of the C_6–C_2–N subunit, which is provided by tyrosine, while phenylalanine is source of the remaining C-6 subunit, responsible for the aryl side chain (Fig. 3). In addition, they determined that L-methionine was the source of both the *O* and *N*-methyl moieties (Jeffs et al., 1971).Jeffs et al., 1967

Biosynthetic pathways of the related Amaryllidaceae alkaloids such as crinine (**10**) have been shown (Fig. 4) to occur via the oxidative cyclisation of 4′-*O*-methyl norbelladine (**11**), which results in the formation of a dienone derivative (**12**) capable of undergoing intramolecular Michael addition, ultimately leading to the crinine skeleton (Barton et al., 1963; Battersby et al., 1964; Jeffs et al., 1974).

However, incorporation of radiolabelled norbelladine analogues into *S. strictum* suggested rather that 3′-*O*-methyl norbelladine (**13**) was the biosynthetic precursor of the mesembrines. This led Jeffs et al. (1974b) to postulate that the *bis*-spirodienone (**14**) is the intermediate in mesembrine biosynthesis (Fig. 5). However, while doubly labelled phenylalanine incorporation experiments, supported the formation of a general *bis*-spirodienone intermediate, Jeffs et al. (1974b) found that 3′-*O*-methyl norbelladine is not incorporated into mesembrine intact, thereby indicating that this specific intermediate is incorrect, thus excluding Fig. 5 as the biosynthetic pathway.

The biosynthetic pathway of mesembrine was finally resolved following the identification of sceletenone (**15**) as one of several minor mesembrine-like alkaloids (Jeffs et al., 1974b), in addition to the discovery of mono-hydroxylated joubertiamine (Arndt and Kruger, 1970). This led Jeffs et al. (1974b) to postulate a unified biosynthetic pathway for *Sceletium* alkaloids, through which sceletenone is a common precursor. As depicted in Fig. 6, the first step resembles that of the biosynthesis of colchicine (Battersby et al., 1972), in which phenylalanine derived 4′-hydroxy cinnamic acid (**16**) and *N*-functionalised tyramine (**17**), derived from tyrosine, combine to form a *bis*-spirodienone (**18**), which undergoes intramolecular Michael addition to form the sceletenone skeleton, which would then require late stage ring oxidation to form the required-oxygenated ring system of mesembrine (Jeffs et al., 1974b). A series of carefully designed radiolabelled experiments confirmed the intermediacy of cinnamic and 4′hydroxycinnamic acid in 3a-aryl octahydroindole formation (Jeffs et al., 1976) possibly via an aldehyde (Herbert and Kattah, 1989), whilst showing that formation of the octahydroindole skeleton involves a stereospecific protonation at position 7, which would need to occur after Michael addition at C-7 (Jeffs et al., 1976). Finally, it was confirmed that sceletenone is the biosynthetic precursor to the mesembrine class of alkaloids (Jeffs et al., 1978; Jeffs and Karle, 1977).

5. Synthesis

Quaternary stereogenic centres are privileged structural features which occur in numerous natural products, many of which possess

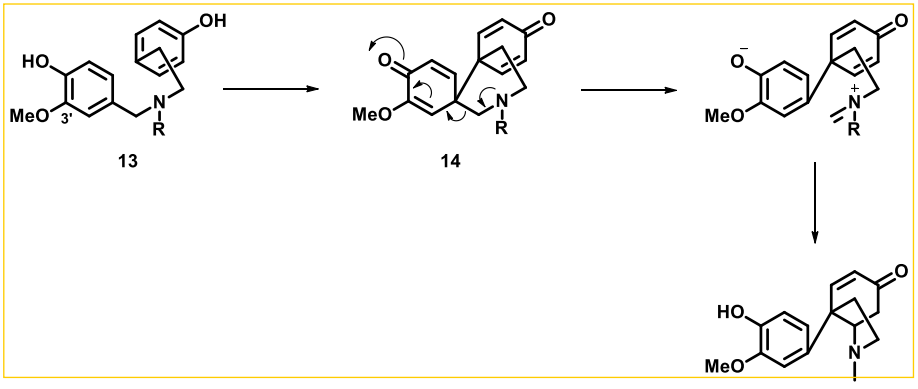


Fig. 5. Proposed biosynthesis of mesembrine alkaloids involving the *bis*-spirodienone intermediate.

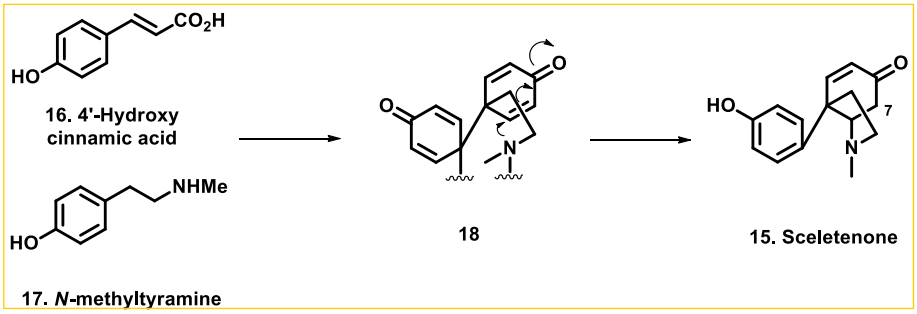
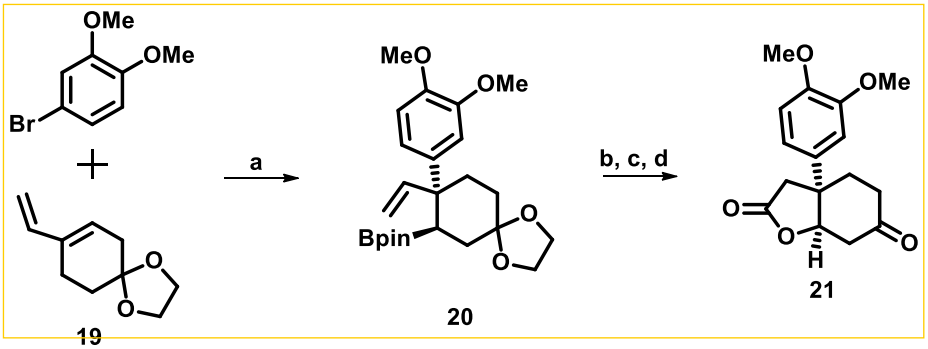


Fig. 6. Confimred biosynthetic pathway for sceletenone.



Scheme 1. a) I*t*-BuCuBr (5 mol %), Pd–P*t*-Bu$_2$CH$_2$*t*-Bu-G3 (1 mol %), DMAP (2 equiv.), (Bpin)$_2$ (2 equiv), KO*t*-Bu (1.5 equiv.), toluene, 45 °C, 12 h; **b)** (i) BH_3•SMe_2, THF, 0–22 °C; (ii) H_2O_2 NaOH; **c)** CuI (5 mol %), bipy (5 mol%), TEMPO (5 mol%), NMI (10 mol %), MeCN, air, 22 °C, 12 h; **d)** 4M HCl, THF, 22 °C, 2 h.

potent biological activities (Pandey et al., 2018). However, formation of this structural feature, particularly enantioselectively, represents a significant synthetic challenge (Christoffers and Mann, 2001; Corey and Guzman-Perez, 1998).

Accordingly, the construction of the all carbon stereocentre of mesembrine has proven to be an attractive target for total synthesis, beginning with the first synthesis of racemic mesembrine by Shamma and Rodríguez (1965). In their synthesis of (+)-mesembrine, Yamada and Otani (1971) were the first to report an asymmetric synthesis of this natural product, while Takano et al. (1981) exploited (D)-mannitol as a chiral transfer template for enantioselective synthesis of (−)-mesembrine. The synthesis of mesembrine has been expertly covered in two separate reviews (Czekelius, 2018; Du et al., 2010) which will be updated here.

Smith and Kevin Brown (2017) developed a synthetic procedure utilising cooperative Pd/Cu catalysis for the regioselective arylboration of isoprenes in order to develop useful building blocks for chemical synthesis. In the course of this study, the authors noted that the incorporation of quantitative amounts of DMAP resulted in the formation of a carbon quaternary centre. In order to demonstrate the utility of this transformation, they conducted a formal synthesis of racemic mesembrine. Applying their protocol (Scheme 1) to cyclic diene (**19**), resulted in the generation of the anti-diastereomer (**20**) from which they applied a sequential hydroboration oxidation protocol to generate lactone (**21**), a known precursor to mesembrine (Kulkarni et al., 2002).

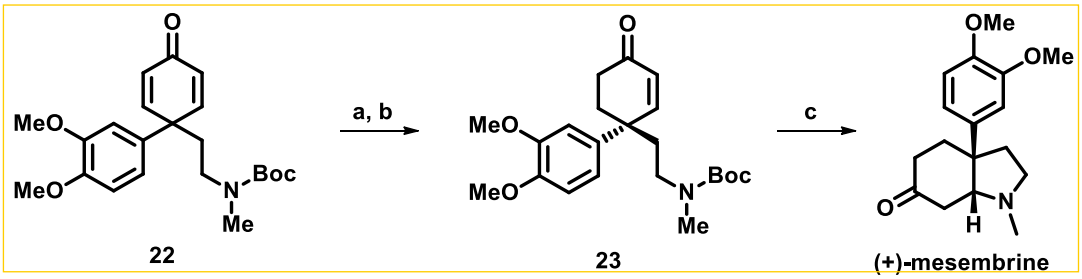
As mentioned, the primary challenge in the enantioselective synthesis of mesembrine is the construction of the all carbon quaternary centre, which several groups have sought to overcome through the desymmetrisation of γ,γ-disubstituted cyclohexadienones (Han et al., 2016; Naganawa et al., 2016). Accordingly, Bokka et al. (2018) developed related methodology where chiral cyclohexenones which feature the critical all carbon stereocenter could be generated using a copper catalyst under mild conditions (Bokka et al., 2018). Application of their method to *N*-Boc protected cyclohexadienone (**22**), resulted in enone (**23**) at an ee of 97%. Acid mediated *N*-Boc removal and subsequent conjugate addition, completed the octahydroindole ring resulting in the formation of (+)-mesembrine (Scheme 2).

Verma et al. (2018) sought to generate a common hydroindole intermediate (**24**) from which several related *Sceletium* and Amaryllidaceae alkaloids could divergently be generated. Selective nucleophilic attack of the 7-azabicyclic system (**25**) with allylmagnesium bromide, resulted in the formation of the desired isomer of (**26**). Oxidative cleavage of the double bond, followed by reductive amination resulted in the formation of (**24**). Detosylation and subsequent SeO_2 allylic oxidation delivered alcohol (**27**). Sequential olefin reduction with Raney nickel and alcohol oxidation in the presence of Dess-Martin periodinane, resulted in the formation of ketone analogue (**28**). Finally, *N*-Boc removal and methylation, delivered (+)-mesembrine (Scheme 3).

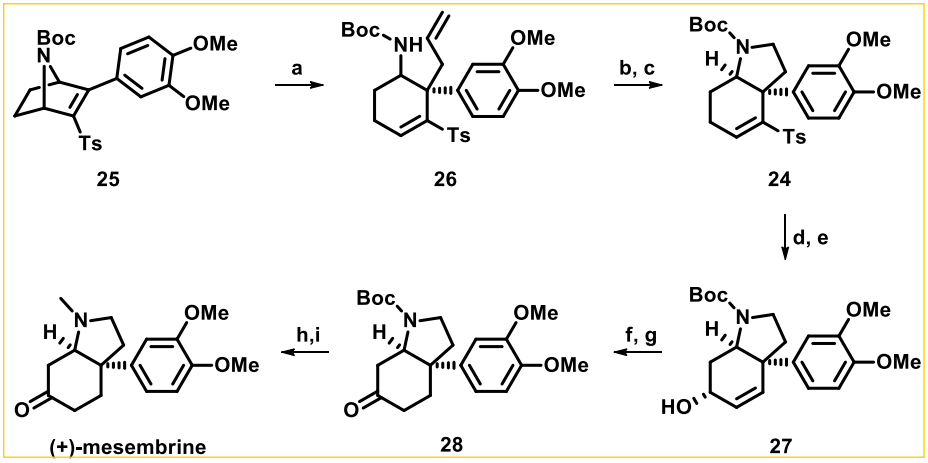
Kim et al. (2018) developed an efficient seven-step synthesis of racemic mesembrine starting from the commercially available 3-ethoxy-2-cyclohexen-1-one (**29**). Condensation of **29**, with (3,4-dimethoxyphenyl)lithium, formed the arylated cyclohexanone (**30**) which was subsequently reduced in the presence of diisobutylaluminium hydride to generate the key allyl alcohol intermediate (**31**). The pivotal Johnson-Claisen rearrangement resulted in compound (**32**) which features the critical quaternary benzylic carbon. Following oxidation with chromium trioxide to form the α,β-unsaturated ketone (**33**), treatment of the ester with methylamine, resulted in amidation and subsequent intramolecular conjugate addition to form the lactam ring (**34**). Protection of the cyclohexanone, followed by lactam reduction and acetal hydrolysis resulted in the formation of racemic mesembrine (Scheme 4).

6. Biological activity and commercial interest

The ethnopharmacological applications of *Sceletium* extracts, particularly for the treatment of disorders of the central nervous system and mood enhancing capabilities has been well described (Smith et al., 1996). Accordingly several studies have attempted to elucidate the role, if any, (−)-mesembrine may play, and which biological pathways it may interact with.



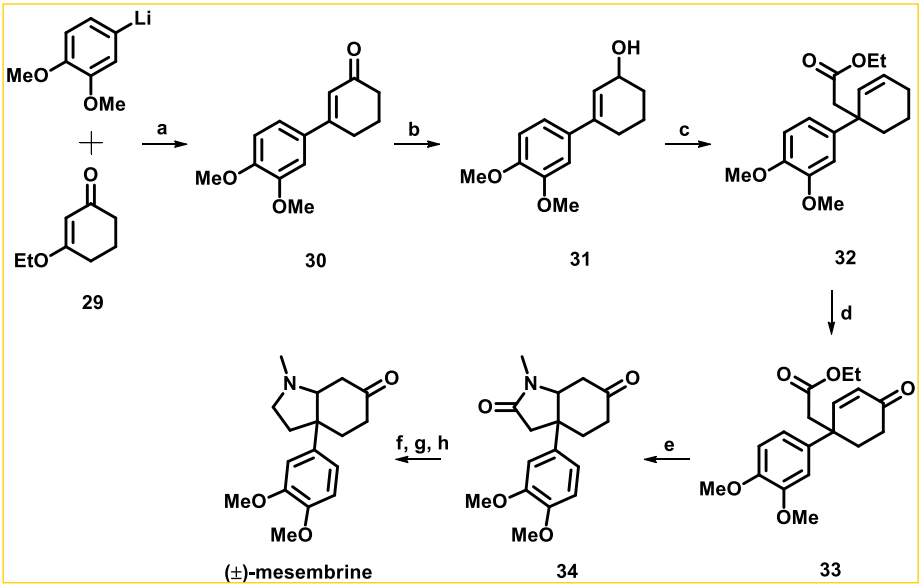
Scheme 2. a) CuCl (5 mol %). (*R,R*)-Ph-BPE (5 mol %). NaOtBu (5 mol %); **b)** PMHS (1.1 equiv), toluene, 0–22 °C; **c)** TFA, DCM, r.t.



Scheme 3. a) AllylMgBr, $Cu(OTf)_2$, 1.3-bis(2,4,6-$_{trimethylphenyl}$)imidazolium chloride, Et_2O/CH_2Cl_2, -7 °C, 10 min; **b)** OsO_4 $NaIO_4$, aetone/water (1:1); **c)** $NaCNBH_3$ THF/AcOH, 25 °C; **d)** Na–Hg. B$(OH)_3$, THF/MeOH (1:1), r.t., 2 h; **e)** SeO_2, $NaHCO_3$ dioxane, 102 °C, 16 h; **f)** Raney Ni, H_2, EtOH. 65 °C, 2 h; **g)** DMP, CH_2Cl_2. 0 °C, 8 h; **h)** TFA, CH_2Cl_2, 0 °C, 8 h; **i)** HCHO, $NaCNBH_3$ 25 °C, 25 min.

Inhibition of type 4 phosphodiesterases (PDE-4) with the mesembrine resembling compound rolipram has been shown to exert an anti-depressant effect via stimulation of both pre- and post-synaptic neurotransmission (Wachtel and Schneider, 1986). Furthermore, rolipram has been shown to have a neuroprotective effect following spinal injury (Schaal et al., 2012). Nevertheless, while standardised Sceletium extracts have shown activity as PDE-4 inhibitors, (−)-mesembrine was only found to be weak inhibitor of this target (Harvey et al., 2011). Similarly, (−)-mesembrine showed negligible activity as a choline esterase inhibitor and in a radio-ligand binding assay against the cannabinoid CB1 receptor (Harvey et al., 2011; Lubbe et al., 2010). However, the study of Harvey et al. (2011) found that (−)-mesembrine bound strongly to the serotonin transporter protein, suggesting potential as an SSRI.

In vitro and *in vivo* data together with emerging clinical evidence have resulted in several patent being filed for pharmaceutical compositions containing mesembrine for the treatment of a wide range of psychological and psychiatric disorders (www.freepatentsonline.com). The United States Patent 6,288,104 described the use of mesembrine and related compounds as potent serotonin-uptake inhibitors, and its



Scheme 4. a) −78 °C. 1 h; **b)** DIBAL-H, toluene, −78 °C, 10 min; **c)** $MeC(OEt)_3$, 2-nitrophenol, 140 °C 20 h; **d)** CrO_3 3,5-DMP, CH_2Cl_2, -10-25 °C; **e)** $MeNH_2$ EtOH, 60 °C, 3 h; **f)** Ethylene glycol, TsOH, benzene, 120 °C, 5 h; **g)** $LiAlH_4$. THF, reflux, 5h **h)** 1M HCl, THF, reflux, 4 h.

use in pharmaceutical compositions for the treatment of conditions that respond to treatment with a serotonin-uptake inhibitor, such as mild to moderate depression. Recently, the patent filed by Davies (2016) describes the use of a pharmaceutical formulation containing an extract of *Sceletium tortuosum* comprising of > 70% (w/w) stabilized mesembrine as a monoamine releasing agent (Davies, 2016). The formulation is claimed to be useful in treating mild to moderate depression, stress and anxiety, cancer, inflammation, obesity, hypertension, and obsessive-compulsive disorders. Since its identification as a potent PDE inhibitor, mesembrine has been selected by several inventors as a potential agent in combination therapy. The United States Patent 9504663 filed by (Freissmuth et al., 2016) describes the combination of prostacyclin with a known PDE4 inhibitor such as mesembrine for preventing or treating cystic fibrosis.

7. Conclusion

The ethnopharmacology of *Sceletium* species in addition to its quaternary stereocenter has rendered (−)-mesembrine a transdisciplinary molecule of interest. This has resulted in numerous synthetic, biosynthetic, pharmacological, structural and medicinal chemistry studies. However, despite the substantial interest that (−)-mesembrine has courted, numerous unanswered questions still remain, particularly pertaining to its pharmacological significance. As a molecule of interest, this brief review has sought to efficiently summarise the literature in order to give the reader a holistic overview of the current state of (−)-mesembrine research, and allow for the identification of new pertinent questions to advance our understanding of this important compound.

Acknowledgements

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