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Synthesis of Lobeline, Lobelane and their Analogues. A Review

Guangrong Zheng and Peter A. Crooks

Department of Pharmaceutical Sciences, College of Pharmacy University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

Introduction

(–)-Lobeline (**1**) (2*R*, 6*S*, 10*S*-, Fig. 1) is the major alkaloidal constituent of *Lobelia inflata*, a plant native to North America with a long history of use as a natural remedy. The plant is also called Indian tobacco because Native Americans smoked the dried leaves as a substitute for tobacco.¹ The remarkable pharmacological profile of lobeline has been demonstrated in numerous studies, especially in the research areas of substance abuse and neurological disorders.^{2–5} Neurochemical and behavioral studies from our laboratories have suggested that the effect of lobeline on psychostimulant abuse is through inhibition of the vesicular monoamine transporter 2 (VMAT2).² In neuropharmacological studies, lobelane (**2**, Fig. 1), a “des-oxygen” derivative of lobeline, has been demonstrated to be a more specific VMAT2 inhibitor compared to lobeline.^{6,7} Lobelane is also behaviorally active in decreasing methamphetamine self-administration in rats,⁸ validating VMAT2 as a therapeutic target for the treatment of methamphetamine abuse. A number of lobeline/lobelane analogues have been designed and synthesized and the structure-activity relationships (SAR) of these analogues has been reviewed recently.⁵ The present review summarizes (2005–2014) the synthesis of lobeline, lobelane and structurally related analogues.

I. Lobeline

The history of the use, biology and chemistry of alkaloids from *Lobelia inflata*, with a focus on lobeline, has been reviewed in 2004.³ The present survey focuses on the recent advances in the synthesis of lobeline for the years 2005–2014.

1. Epimerization of Lobeline

One of the most important chemical properties of lobeline is that it readily undergoes a pH-dependent epimerization at C2 of the piperidine ring *via* the transient retro-aza Michael addition product **3**, yielding a mixture of 2*R*,6*R*-*cis*-lobeline (**1**) and its 2*S*,6*S*-*trans*-isomer **4** (Fig. 2).^{9–13}

2. Synthesis of Lobeline

Three elegant asymmetric syntheses of (–)-lobeline (**1**) have been discussed in previous reviews.^{3,9} However, those synthetic routes might not be suitable for large scale preparations as they are fairly lengthy and of low efficiency. Klingler and Sobotta¹⁴ have

disclosed an efficient asymmetric hydrogenation process for the preparation of (–)-lobeline (**1**) from 2,6-*cis*-lobelanine (**5**) on an industrial scale (Scheme 1). The process involves a catalyst system consisting of dichloro-*bis*-[(cycloocta-1,5-diene)rhodium (I)] ([RhCl(COD)]₂) and (2*R*,4*R*)-4-(dicyclohexyl-phosphino)-2-(diphenylphosphinomethyl)-*N*-methylaminocarbonyl pyrrolidine (**6**).¹⁵ Good yields in good optical purity were obtained utilizing this catalyst system. Lobelanine (**5**), a chemical precursor for the biosynthesis of lobeline,¹⁶ can be easily obtained by reaction of 3-oxo-3-phenylpropionic acid, glutaric dialdehyde, and methylamine hydrochloride in acetone and citrate buffer (Scheme 1).¹⁷

Birman *et al.*¹² have reported an asymmetric synthesis of (–)-lobeline (**1**) *via* desymmetrization of lobelanidine (**7**) with the use of a non-enzymatic, enantioselective acyl transfer catalyst, (*S*)-benzotetra-misole (BTM, **8**), forming monoester **9**, followed by oxidation with Jones' reagent and removal of the acyl group under acid condition to avoid epimerization (Scheme 2). Lobelanidine (**7**), a minor alkaloid from *Lobelia inflata*, was synthesized by NaBH₄ reduction of lobelanine (**5**) to afford an 85/15 mixture of diastereomeric diols in favor of **7**, followed by recrystallization (Scheme 2).¹² Lobelanine hydrochloride was obtained as an 85/15 mixture of *cis/trans* isomers using the same method described in Scheme 1.¹⁷

A Pd-catalyzed, aerobic oxidative, kinetic resolution method, developed by Stoltz group (Scheme 3),^{18,19} was used for selective oxidation of one of the two hydroxy groups in lobelanidine (**7**) to afford a 1:1 mixture of *cis/trans* equilibrating diastereomers of lobeline in high ee% (99%) (Scheme 4).¹³ Using a dynamic crystallization procedure by first converting the mixture of the *cis/trans* diastereomers into their hydrochloride salts, followed by heating in *i*-PrOH and slow cooling, the *cis*-isomer of lobeline was selectively precipitated out (Scheme 4).¹³ The lobelanidine (**7**) used in this procedure was synthesized *via* a novel multi-step route starting from aldehyde **11** (Scheme 4).¹³

Chênevert and Morin²⁰ have reported the synthesis of (–)-lobeline (**1**) *via* enzymatic desymmetrization of lobelanidine (**7**). Acylation of **7** with vinyl acetate as both the acylation reagent and solvent in the presence of *Candida antarctica* lipase B (CAL-B) at 50 °C for 18 h afforded monoester **18** in 70% yield and high ee% (> 98%). Jones oxidation of the hydroxy group in **18**, followed by removal of the acetyl group under acidic condition afforded (–)-lobeline (**1**) (Scheme 5).

II. Synthesis of Lobeline Derivatives

Using (–)-lobeline (**1**) as the starting material, a number of derivatives have been synthesized and utilized in biological screening assays. (–)-Sedamine (**20**), which can be considered as a “partial” analogue of lobeline, was synthesized by Zheng *et al.* utilizing the intramolecular retro-aza Michael addition reaction of (–)-lobeline (Scheme 6).¹⁰

A series of carboxylic acid esters (**24**) and sulfonic acid esters (**25**) of (–)-lobeline (**1**) has been reported by Hojahmat *et al.*²¹ These lobeline derivatives were synthesized by reacting **1** with various acyl chlorides and sulfonyl chlorides (Scheme 7). To minimize the epimerization of the products, the acylation and sulfonylation reactions were conducted in

the absence of base. Wieland *et al.*²² and Flammia *et al.*²³ treated (–)-lobeline (**1**) with PCl₃ or SOCl₂, respectively, to afford chloro analogue **26** (Scheme 7).

Jones' oxidation of the 10-hydroxy group of lobeline by Wieland and E. Dane²⁴ affords lobelanine (**5**). Flammia *et al.*²³ and Ebnöther²⁵ both used 85% H₃PO₄ as a dehydration reagent to convert lobeline (**1**) to compound **27** (Scheme 8). As reported by Ebnöther,²⁵ the carbonyl functional group of lobeline can be stereoselectively reduced to lobelanidine (**7**) using either NaBH₄ or LAH. Such stereoselectivity for the reduction of ketone was also reported by Birman *et al.*¹² However, no mechanism has been proposed. Based on the crystal structure of lobelanidine,²⁶ there is a three-centered intramolecular hydrogen bond between the nitrogen atom and the two oxygen atoms in lobelanidine. Such structural feature is probably the driving force for the stereoselectivity. Or maybe the starting material, lobeline, forms similar type of intramolecular H bond thus resulted in face selectivity.

Flammia *et al.*²³ reported the synthesis of compound **28a** *via* Clemmensen reduction of lobeline (Scheme 8).²³

Stereoisomers of compound **28a**, i.e. compounds **28b**, **28c**, and **28d**, have been synthesized using **28a** and **27** as starting materials (Scheme 9) by Zheng *et al.*²⁷ Conversion of **28a** to compound **29** under Jones' oxidation conditions, followed by NaBH₄ reduction, gave a mixture of **28a** and **28b**, in a ratio of 9:20, from which **28a** was isolated by fractional recrystallization of the isomeric mixture; **28b** was obtained by purification *via* silica gel chromatography from the mother liquors. Similarly, reduction of compound **27** with NaBH₄ afforded **28c** and its diastereomer **28d**, which were isolated in a manner similar to **28a** and **28b**. The structures of **28c** and **28d** were characterized by comparing NMR with their corresponding enantiomers **28a** and **28b**, respectively. Hydrogenation of **28a**, **28b**, **28c**, and **28d** afforded the corresponding saturated compounds **30a**, **30b**, **30c**, and **30d**, respectively (Scheme 9).²⁷

Further de-functionalization of lobeline resulted into a series of “des-oxygenated” analogues (Scheme 10), as reported by Zheng *et al.*⁶ Epimerization of *cis*-lobeline (**1**) at C-2 under basic condition in methanol for 48 h at room temperature afforded a 1:1 mixture of the two C-2 epimers, which were reduced to product **31**, consisting a mixture of the four possible diastereomers. Dehydration of **31** with 85% H₃PO₄ yielded a mixture of *cis*- and *trans*-distyryl compounds **32a** (*cis*-) and **32b** [(–)-2*S*,6*S-trans*], which could be readily separated by silica gel column chromatography. The structural of **32a** and **32b** were further confirmed by X-ray crystallography.^{28,29} Hydrogenation of **32a** and **32b** afforded lobelane (**2**) and its (–)-2*S*,6*S-trans* isomer, respectively. Similarly, epimerization of **29**, followed by reduction and dehydration, yielded **32a** and its (+)-2*R*,6*R-trans* epimer (**32c**). Hydrogenation of **32c** afforded (+)-2*R*,6*R-trans*-lobelane. Simultaneous reduction of the double bond and the carbonyl group of *cis/trans* **29** by Pd/C catalyzed hydrogenation in 10% HOAc/MeOH afforded **34a**. Dehydration of **34a** yielded **35a** and **35b**. Similarly, compounds **35c** and **35d**, enantiomers of **35a** and **35b**, respectively, were obtained from **27** by following the same procedure for the synthesis of **35a** and **35b** from **29**. Separation of **35a** from **35b** and **35c** from **35b** was accomplished by silica gel chromatography.

III. Synthesis of Lobelane Analogues

All the lobelane analogues synthesized in Section II were evaluated for their interaction with VMAT.^{6,7} Lobelane (**2**) appears to be the most selective and potent VMAT2 inhibitor.⁷ Systematic structural modifications have been carried out on the lobelane molecule in searching for analogues with increased potency/selectivity and improved drug proprieties (Figure 3).

1. Analogues with Modifications on the Phenyl Rings

Lobelane can also be synthesized *via* a three-step procedure,³⁰ initial condensation of 2,6-lutidine with benzaldehyde, forming the conjugated product **36** (Ar = Ph), followed by hydrogenation in the presence of Adams' catalyst, to give *nor*-lobelane **37** (Ar = Ph), and *N*-methylation using NaCNBH₃/(CH₂O)_n (Scheme 11). Utilizing the same approach, a series of lobelane and *nor*-lobelane analogues, **37** and **38**, in which the two phenyl rings are replaced by two naphthalenyl rings or substituted phenyl rings, has been synthesized (Scheme 11).^{6,31}

The synthesis of azaaromatic ring containing lobelane analogues, on the other hand, had to be carried out utilizing an alternative approach, since side-chain azaaromatic moieties are also susceptible to hydrogenation under Adams' catalyst. Vartak *et al.*³² have employed *N*-methylated 2,6-lutidine (**39**) as a condensation partner with various azaaromatic aldehydes to form compound **40**,³³ which was then hydrogenated to afford the desired product **41**. Interestingly, each type of heterocyclic moiety requires different reaction conditions for both condensation (method A) and hydrogenation (method B) steps (Scheme 12).

Ding *et al.*³⁴ have reported an efficient synthesis of an azaaromatic analogue of *nor*-lobelane, *cis*-2,6-di-(2-quinolyl)piperidine (**42**), featuring a Wittig reaction between dialdehyde **45** and phosphonium intermediate **46**. Compound **45** was synthesized *via* Swern oxidation of dihydroxy **44**, derived from pyridine-2,6-dicarboxylic acid (**43**). Compound **46** was synthesized *via* a four-step procedure by initial SeO₂ oxidation of 2-methylquinoline (**49**), followed by reduction, bromination, and phosphonium intermediate formation (Scheme 13).

Conversion of **47** to **42** was achieved by deprotection of the Cbz group using 6 N HCl at reflux followed by catalytic hydrogenation to reduce the double bonds (Scheme 13). Attempts to convert **47** into **42** in one step, *via* simultaneous removal of the Cbz group and reduction of the double bonds by hydrogenation were not successful, possibly due to hydrogenolytic ring opening of the piperidine ring under these conditions. The method should be applicable to the synthesis of other heterocyclic analogues.³⁴

2. Analogues with Modifications on the Ethylene Linkers of Lobelane

In a series of lobelane homologues, the two ethylene groups connecting the two phenyl rings to the C-2 and C-6 positions of the piperidine ring in lobelane have been replaced by linkers of 0–3 carbons (Figure 4).³⁵

Analogue **51**, in which two phenyl rings are attached directly to C-2 and C-6 of the central piperidine ring, was synthesized by initial *N*-methylation of 2,6-biphenylpyridine (**60**), followed by exhaustive reduction of the pyridinium moiety in **61** with sequential NaBH₄ reduction and catalytic hydrogenation (Scheme 14).

Analogue **52a** was obtained by catalytic hydrogenation of **65**, which was synthesized *via* Suzuki coupling of 2-chloro-6-benzylpyridine (**64**) with phenylboronic acid using [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-IPr) as a catalyst and *t*-BuOK as a base in *i*-PrOH.³⁶ Compound **64** was synthesized by Kumada coupling of 2-bromo-6-methoxypyridine (**62**) with benzylmagnesium chloride, followed by treatment of the coupling product **63** with POCl₃ in DMF. Analogue **52a** was converted to **52b** by *N*-methylation, as described in Scheme 11 (Scheme 15).

Analogues **53a/53b** and **54a/54b** were synthesized from compounds **68** and **69**, respectively, in a similar manner as described above for the synthesis of **52a/52b** from **65**. Compound **67**, the common intermediate for **68** and **69**, was synthesized by Suzuki coupling of 2-bromo-6-methylpyridine (**66**) with phenylboronic acid. Condensation of **67** with benzaldehyde, or deprotonation of the 2-methyl group of **67** followed by an S_N2 reaction with 2-iodoethylbenzene afforded **68** and **69**, respectively (Scheme 16).

Similarly, analogues **55a/55b**, **56a/56b**, and **57a/57b**, which contain a single methylene linker at C-6 and a methylene, an ethylene or a propylene linker at C-2 of the piperidine ring, were prepared from their corresponding pyridinyl precursors, **71**, **72**, and **73**, respectively (Scheme 17 and 18). Compound **71** was obtained *via* Kumada coupling of 2,6-dibromopyridine (**70**) with benzylmagnesium chloride (Scheme 17). Compounds **72** and **73** were synthesized *via* Negishi coupling of **64** with 2-phenyl-1-ethylzinc iodide or 3-phenyl-1-propylzinc iodide, respectively, using PEPPSI-IPr as a catalyst and LiBr as an additive in THF/DMF (Scheme 18).³⁷

Analogues **58a** and **58b**, in which the two phenyl rings are linked to the central piperidine ring by an ethylene moiety at C-6 and a propylene moiety at C-2, were synthesized by initial mono-condensation of 2,6-lutidine with benzaldehyde, yielding the conjugated product **74**, followed by a similar procedure to that described in Scheme 16 for the synthesis of **54a** and **54b** (Scheme 19).

Analogues **59a/59b** were synthesized using a similar procedure to that described for the synthesis of **55a/55b** (Scheme 20).

It is important to note that analogues **52a/52b**, **53a/53b**, **54a/54b**, **56a/56b**, **57a/57b**, and **58a/58b**, synthesized as described in Schemes 15, 16, 18, and 19, all are in racemic forms. Racemic mixtures are acceptable for initial pharmacological assays; however, chiral pure compounds should be used for further studies. Thus, enantioselective synthetic methods need to be developed, should any of these analogues selected for further development.

3. Isomerized Lobelane Analogues

A series of isomerized lobelane analogues in which the C2, C6 phenethyl groups of lobelane are repositioned to the N1, C2 (**77a**); N1, C3 (**77b**); N1, C4 (**77c**); C2, C4 (**78a/78b**); or C3, C5 (**79a/79b**) positions of the piperidine ring, has been synthesized (Figure 5).³¹

The syntheses of these analogues were initiated from the condensation reaction of 2-, 3-, 4-picoline, 2,4-, or 3,5-lutidine with benzaldehyde or *N*-benzylidene-4-chloroaniline (for 3-picoline and 3,5-lutidine) to form conjugated products **80** or **82**. Due to the low activity of the pyridinyl 3-methyl group, *N*-benzylidene-4-chloroaniline was used as an activated form of benzaldehyde in the condensation reactions. Transformation of **80** and **82** to their corresponding final products was achieved by utilizing a similar procedure to that used for the synthesis of **37** and **38** in Scheme 11 (Scheme 21 and 22).

Compounds **83a** and **83b**, which are isomerized and unsaturated lobelane analogues containing a linker unit that is one carbon shorter between the piperidine and the phenyl rings than compound **79a/79b**, were synthesized starting from *N*-methyl-4-piperidone (**84**).³⁸ Condensation of **84** with an aromatic aldehyde afforded compound **85**, which was treated with a pre-equilibrated 1:4 (mol/mol) mixture of sodium borohydride and trifluoroacetic acid in a 1:1 (v/v) mixture of DCM and ACN to yield two separable geometrical isomers **83a** and **83b** (Scheme 23).

4. Analogues with Modifications on the Piperidine Ring

The piperidine ring of lobelane has been replaced by a piperazine, quinuclidine, tropane, pyrrolidine, or azetidine ring, for a variety of SAR studies.

a) Analogues Containing a Piperazine Ring—The synthesis of piperazine ring-containing analogues, **86a** and **86b**, was achieved by employment of a similar approach to that described in Scheme 11 for the synthesis of **37** and **38**, using 2,6-dimethylpyrazine (**87**) as a starting material (Scheme 24).³¹

b) Analogues Containing a Conformational Restricted Heterocyclic Ring—The quinuclidine ring represents a conformationally restricted form of the piperidine ring. Quinuclidine ring-containing compounds **89a** and **89b** have been designed to mimic the stereochemistry of the spatially confined axial/axial conformer or the fully extended equatorial/equatorial conformer of lobelane, respectively. Both compounds were synthesized *via* an S_N2-type cyclization of intermediates **92** and **93**, respectively.³⁹ Utilizing a dissolving metal reduction procedure developed by Watson et al.,^{40,41} 2,4-*trans*-isomer **92** was obtained from its precursor **90** with high stereoselectivity (16:1, *trans*:*cis*). The Troc group was also removed during the reaction. Under similar reaction conditions, 2,4-*cis*-isomer **93** was obtained from compound **91**, a des-Troc product of **90** (Scheme 25).

Compound **90** was synthesized *via* Horner-Wadsworth-Emmons olefination of piperidinone intermediate **94** with triethyl phosphonoacetate. Two synthetic routes were used for the synthesis of **94**. The first route starts with the condensation of 2,6-dimethyl-4-hydroxypyridine (**95**) with benzaldehyde, followed by catalytic hydrogenation to form

compound **96**. *O*-Benzylation of **96** with BnBr in the presence of K₂CO₃ in DMF, followed by *N*-benzylation by treatment with excess BnBr (20 equivalent) in ACN afforded the quaternary ammonium product **97**. Reduction of **97** with NaBH₄ followed by the treatment with TFA in DCM/H₂O furnished piperidinone **98**. Replacement of the *N*-benzyl group in **94** with an *N*-Troc group afforded the desired intermediate **94** (Scheme 26).³⁹

The second synthetic route for the preparation of compound **94**, a more efficient method compared to the one above, is based on a strategy developed by the Comins' group,^{42–45} involving sequential stereoselective addition of Grignard reagent phenethylmagnesium chloride to the *N*-Troc pyridinium salt of 4-methoxypyridine (**99**) (Scheme 27).³⁹

The tropane ring represents another conformationally restricted form of the piperidine ring. Analogues **101** and **102**, in which a trop-2-ene or tropane ring is substituted for the piperidine ring in lobelane, were synthesized.⁴⁶ Clemmensen reduction of compound **103** afforded **101**, which was converted to **102** by catalytic hydrogenation. Compound **103** was obtained by aldol condensation of tropinone with benzaldehyde or a substituted benzaldehyde (Scheme 28).

c) Analogues Containing a Smaller Sized Pyrrolidine or Azetidine Ring—

Pyrrolidine-containing lobelane analogues, **105a**, **105b**, **106a**, **106b**, have been prepared by initial nucleophilic addition of phenethylmagnesium chloride to Katritzky's bicyclic hemiaminal **108**, forming a pair of separable diastereomers **109a** and **109b** in a 2:1 ratio.⁴⁷ Hydrogenolysis of **109a** and **109b** by a catalytic hydrogen transfer reaction with Pd(OH)₂ on carbon as a catalyst and ammonium formate as a hydrogen source afforded the *meso* isomer **105a** and the (+)-*trans*-2*R*,5*R* isomer **106a**, respectively, which were then treated with paraformaldehyde and NaBH(OAc)₃ to form their corresponding *N*-methylated products **105b** and **106b** (Scheme 29).⁴⁸ Starting from *D*-phenylglycinol (**110**) in place of *L*-phenylglycinol (**107**) in the above synthetic route, the (–)-*trans*-2*S*,5*S* isomer **111a** and its *N*-methylation product **111b** were also obtained (Scheme 29).⁴⁸ Utilizing this synthetic strategy, a series of homologues of **105a/105b**, including **112a/112b** and **113a/113b**,⁴⁸ and phenyl ring substituted analogues of **105a**, i.e. compounds **114**,⁴⁹ has been synthesized (Figure 6).

A series of *cis-meso* and *trans-racemic* azetidine-containing lobelane analogues, **115** and **116**, respectively, has been synthesized from *cis*- (**118**) and *trans*-dibenzyl 1-benzylazetidine-2,4-dicarboxylate (**119**), respectively (Scheme 30).⁵⁰ The synthetic approach is similar to the synthesis of **42** described in Scheme 13. Isomers **118** and **119** were obtained as a separable (by silica gel column) 2:1 mixture, *via* a reported four-step sequence starting from glutaric anhydride (**117**).^{51,52} Treatment of **118** with NaBH₄ afforded diol **120**, which was then converted into compound **121** *via* hydrogenolysis of the benzyl group followed by protection of the exposed NH with a Cbz group. Swern oxidation of alcohol **121**, followed by *in situ* Wittig olefination with an appropriate phosphonium salt afforded compound **122**. Hydrogenation of the alkene moieties in **122** with simultaneous hydrogenolysis of *N*-Cbz group under Pd/C or Pd(OH)₂ catalyzed hydrogenation resulted in a complex mixture. Instead, **122** was hydrogenated in the presence of Wilkinson's reagent to

afford compound **123**, followed by removal of the Cbz group *via* hydrogenolysis over Pd/C to yield **115**. Utilizing the same procedure, *trans* isomer **116** was obtained from **119** (Scheme 30).⁵⁰

5. Analogues with Modifications on the N-Methyl Group

Replacement of the N-methyl group in lobelane with a more polar *N*-substituent, i.e. carboxylic ester, nitrile, hydroxy, hydrazine, amine, and guanidine, has been carried out.⁵³ These analogues were designed to have improved water solubility. *N*-Alkylation of nor-lobelane with methyl bromoacetate or chloroacetonitrile afforded analogues **124** and **125**, respectively. Treatment of **124** and **125** with DIBAL-H furnished the corresponding amino alcohol analogue **126** and the diamino analogue **127**. *N*-Methylation of **127** afforded **128**. Reaction of **127** with *N,N'*-di-(*tert*-butoxycarbonyl)thiourea, followed by treatment with CF₃COOH afforded the guanidino analogue **129**. Conversion of nor-lobelane to the corresponding hydrazino analogue **130** was accomplished by initial *N*-nitrosation followed by LAH reduction. *N*-Methylation of **130** afforded dimethyl derivative **131** (Scheme 31).

Analogues **132a** and **132b**, which contain an *N*-1,2(*R*)-dihydroxypropyl and *N*-1,2(*S*)-dihydroxypropyl group, respectively, were prepared by reacting phenyl ring substituted nor-lobelane analogue **37** with *S*-glycidol or *R*-glycidol, respectively (Scheme 32).⁵³ Similarly, Penthala *et al.*⁴⁹ has synthesized a series of *N*-1,2(*R*)-dihydroxypropyl derivatives of **105a** and **114** (Scheme 33).

Conclusion

This review has summarized the progress on the synthesis of lobeline, lobelane, and their analogues. Significant progress has been made over the last 10 years on the development of efficient methods for the total synthesis of lobeline and on extensive structural modifications of lobelane. With the continued interest in finding treatments for psychostimulant abuse, drug discovery effort based on structural modification of the lobeline and lobelane molecules is likely to continue. The authors hope that this review will generate more interest in future SAR expansion on these molecules.

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Figure 1.

Figure 2.

Figure 3.

51 $R = \text{CH}_3$, $m = n = 0$

52a $R = \text{H}$, $m = 0$, $n = 1$

52b $R = \text{CH}_3$, $m = 0$, $n = 1$

53a $R = \text{H}$, $m = 0$, $n = 2$

53b $R = \text{CH}_3$, $m = 0$, $n = 2$

54a $R = \text{H}$, $m = 0$, $n = 3$

54b $R = \text{CH}_3$, $m = 0$, $n = 3$

55a $R = \text{H}$, $m = n = 1$

55b $R = \text{CH}_3$, $m = n = 1$

56a $R = \text{H}$, $m = 1$, $n = 2$

56b $R = \text{CH}_3$, $m = 1$, $n = 2$

57a $R = \text{H}$, $m = 1$, $n = 3$

57b $R = \text{CH}_3$, $m = 1$, $n = 3$

58a $R = \text{H}$, $m = 2$, $n = 3$

58b $R = \text{CH}_3$, $m = 2$, $n = 3$

59a $R = \text{H}$, $m = n = 3$

59b $R = \text{CH}_3$, $m = n = 3$

Figure 4.

Figure 5.

Figure 6.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.

Scheme 9.

Scheme 10.

Scheme 11.

method A

Ar = 3-Pyridyl NaOH (2 equiv), H₂O, 5 min 100%
 4-Pyridyl NaOH (2 equiv), H₂O, 5 min 63%
 2-Quinolyl NaOH (2 equiv), 50% EtOH, 8 h 90%
 4-Quinolyl DIPEA, 50% EtOH, 40 °C, 12 h 47%
 3-Indolyl DIPEA, EtOH, reflux, 8 h 80%

method B

Pd-C, EtOAc, 4 h, 50 psi 43%
 Pd-C, EtOAc, 24 h, 50 psi 80%
 Pt sponge, AcOH (2 equiv), EtOH, 12 h, 30 psi 35%
 Pd-C, AcOH (2 equiv), EtOH, 72 h, 50 psi 52%
 Pd-C, NaOH (2 equiv), EtOH, 72 h, 50 psi 18%

Scheme 12.

Scheme 13.

Scheme 14.

Scheme 15.

Scheme 16.

Scheme 17.

Scheme 18.

Scheme 19.

Scheme 20.

Scheme 21.

Scheme 22.

Scheme 23.

Scheme 24.

Scheme 25.

Scheme 26.

Scheme 27.

Scheme 28.

Scheme 29.

Scheme 30.

Scheme 31.

Scheme 32.

Scheme 33.