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Synthetic Approaches to α-, β-, γ-, and δ-lycoranes

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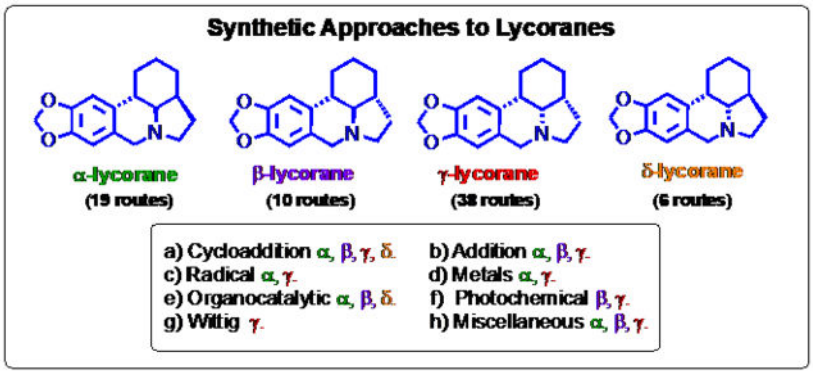
Abstract

Lycorane is a pentacyclic core presented in alkaloids isolated from the *Amaryllidaceae* family of herbaceous flowering plants. Members of this class of natural products have shown to display important biological properties including analgesic, antiviral, and antiproliferative activities. This review presents the known synthetic routes toward α-, β-, γ-, and δ-lycoranes. α-(19 routes), β-(10 routes), γ-(38 routes), and δ-(6 routes).

Graphiocal Abstract



This review compiles the current synthetic approaches toward lycoranes. Particularly, all those synthetic approaches gave access to α-lycorane (19 routes), β-lycorane (10 routes), γ-lycorane (38 routes), and δ-lycorane (6 routes), with 15 different routes reporting asymmetric total synthesis (mainly taking advantage of organocatalysts and transition metals).

Keywords

α-lycoranes; β-lycoranes; γ-lycoranes; δ-lycoranes; synthesis

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1. INTRODUCTION

Plants from the Amaryllidaceae family have produced various structurally diverse alkaloids. Those isolated compounds have shown important biological properties such as antiproliferative, antiviral, analgesic, antineoplastic, antifungal, and anti-inflammatory properties.[1–7] Historically, the first discovered alkaloid from this family was the natural product named lycorine (Figure 1), which was isolated in 1877.[8] Since then, various other alkaloids have been identified and classified as lycoranes, which consist of five fused rings. Despite the pentacyclic core, this type of alkaloid has been classified as a tetracyclic system consisting of rings A, B, C, and D. (Figure 1). Some alkaloids that have the lycorane scaffold are lycorine, zephyranthine, fortucine, and siculinine (Figure 1), whereas the first attempt to synthesize lycorane found in literature is a semi-synthesis reported by Kotera *et al.* in 1960.[9] Although there are additional reports for the synthesis of the alkaloids mentioned above, this review focus on all α-, β-, γ-, and δ-lycoranes, while a recently review covered only total syntheses of γ-lycoranes.[10]

The impact of lycoranes can be seeing by looking into the following SciFinder database chart (Figure 2), which demonstrate the high number of publications in the period of 1960–2023. A total of 138 lycorane mentions were found, from which, α-lycorane (19 routes), β-lycorane (10 routes), γ-lycorane (38 routes), and δ-lycorane (6 routes). These synthetic approaches are summarized in the following sections.

2. Cycloaddition approaches

Within the ring system found in the lycorane family, there are three adjacent six-membered rings, thus it is reasonable to consider cycloaddition reactions to construct the backbone structure of such natural products. In this regard, Hill *et al.*[11] carried out the synthesis of (±)-β-lycorane, starting with a Diels-Alder reaction between nitrostyrene **1** and butadiene **2**,[12] which afforded trisubstituted cyclohexene **3** in modest yield (35%), but with the expected stereochemistry (Scheme 1). Subsequently, the nitro group on **3** was reduced to amine under Raney Nickel conditions. During this step, the acetyl group migrated to the newly formed amine to generate an amide in 67% yield. The exposed allylic alcohol intermediate was then oxidized to ketone **4** using Sarett's reagent. Then, adduct **4** was subjected to a Wittig reaction with carbetoxymethylenetriphenylphosphoran[13] **5** to produce α,β-unsaturated ester **6** in 31% yield. Hydrogenation of **6** in presence of Adam's catalyst, created a saturated carboxylic acid derivative in quantitative yield. NMR analysis demonstrated that the stereochemistry of the hydrogens was equatorial. Further reduction with lithium aluminum hydride ($LiAH_4$) in THF provided amino alcohol **7**. Important to note that using ether as solvent the *N*-acetyl group was not reduced. The creation of the lycorane ring B was achieved with a Pictet-Spengler cyclization in the presence of paraformaldehyde. Alcohol tosylation produced intermediate **8**, which underwent an *in situ* intramolecular cyclization to deliver quaternary ammonium salt **9**. Finally, elimination of the *N*-ethyl group from **10** under Hoffman degradation conditions resulted in (±)-β-lycorane (Scheme 1).

The same group took advantage of the prior (±)-β-lycorane synthesis to access (±)-α-lycorane in fewer steps. Initially, the same dienophile **1** was used, but this time hexa-3,5-dienoate **12** was employed as the diene (Scheme 2). Diels-Alder reaction produced the expected nitro-ester **13** with the expected stereochemistry and similar yield (31%).[14] The following steps relied on intramolecular reduction-cyclization reactions. Hydrogenation of **13** was carried out using Pd/C as catalyst, with a 72% yield for the synthesis of lactam **14a**. Reduction of this lactam with $LiAH_4$ in THF proceeded in 70% yield. Finally, amine **15** was subjected to a Pictet-Spengler reaction to produce the desired adduct **(±)-11a** [(±)-α-lycorane] in a 43% yield. Hence, completing the synthesis in only 4 total synthetic steps (Scheme 2).

Martin *et al.* [15] reported the syntheses of (±)-α-, β- and δ-lycoranes, also taking advantage of cycloaddition reactions[16,17] but employing azatrienes as key intermediates (Schemes 3 & 4). Their syntheses started by the condensation between piperonal **16** and benzylamine **17** to produce an imine that in a second step was reacted with acyl chloride **18** to generate enamide **19** in 48% yield after the two synthetic steps. Heating **19** in toluene promoted a Ramberg-Bäcklund rearrangement[18] yielding diene **20** in 97% yield. Next, an intramolecular [4+2] cyclization was performed, which resulted in formation of lactams **21a-c** in 1:1.5:1.4 ratio, respectively and a 43% overall yield (Scheme 3).

Once the three lactams (**21a-c**) were identified and separated, they were reacted as follows: Reduction with $LiAH_4$ gave rise to tertiary amines **22a-c**. Then, hydrogenation using Pd/C and H_2 (balloon) was performed to deprotect the benzyl group and to hydrogenate the double bond, producing octahydroindoles **15a-c**. The creation of ring B was achieved using Bischler-Napieralsky reaction conditions[19], from previously prepared carbamates **24a-c**, which in turn were synthesized from reacting intermediates **15a-c** with methyl chloroformate followed by cyclization with phosphoryl chloride that generated lactams **25a-c**. These lactams were reduced with $LiAH_4$ to finish the synthesis of **(±)-11a-b** and **11d** [(±)-α-, β- and δ-lycorane, respectively] (Scheme 4).

Taking advantage of the versatility that 1,3-dipolar cycloadditions offer, Pearson and co-workers [20] developed the synthesis of γ-lycorane (Schemes 5 & 6). The synthesis began by treating bromopiperonal **26** with *n*-BuLi to produce the corresponding lithiated compound that was added to cyclohexenone **27**, forming adduct **28** in 65% yield (Scheme 5). The present primary alcohol was selectively protected with *tert*-butyldimethylsilyl chloride (*t*BuMe$_2$SiCl, TBSCl), affording adduct **29** in 89% yield. The addition-elimination reaction between TBS enolate **30** and intermediate **29** was promoted with lithium perchlorate, obtaining ester **31** in 74% yield.[21,22] Then, reduction of this ester with $LiAH_4$ produced alcohol **32** in 97% yield. Subsequent mesylation with methanesulfonyl chloride (MsCl) and substitution using tetrabutylammonium azide (*n*-Bu_4NN_3) created azide **33** in 84% yield. The primary alcohol was then deprotected using tetrabutylammonium fluoride (TBAF), followed by mesylation and nucleophilic substitution using lithium chloride, which produced chloro-azide **34**. (Scheme 5).

Chloro-azide **34** was heated at 140 °C to promote a 1,3-dipolar cycloaddition reaction, forming pentacyclic intermediate **35**, which fragmented into zwitterion **36**. Then, after loss

of N_2, imine **37** was produced. From here, imine **37** underwent a 6-exo-tet cyclization to deliver iminium **38**.[23–25] Finally, reduction with $NaBH_4$ afforded the expected (±)-γ-lycorane **(±)-11c** (Scheme 6).

The synthesis of (±)-α-lycorane reported by Rigby *et al.* [26] started from commercially available α,β-unsaturated carboxylic acid **39** (Scheme 7). This acid was reacted with diphenylphosphoryl azide (DPPA) to form its corresponding acyl azide. This azide underwent a Curtius rearrangement[27–29] to produce cyclohexene 1-isocyanate *in situ*. Then, it was reacted with cyclohexyl isocyanide **40** to form ring D via [1+4] cycloaddition reaction and product **41** in 61% yield. Selective *N*-alkylation of amide **41** with alkyl bromide **42** in the presence of NaH as base, provided the expected *N*-alkylated adduct **43** in 74% yield. Hydrolysis of the enamine with oxalic acid produced a ketolactam, which after reduction with $NaBH_4$ gave rise to the α-hydroxylactam **44**, in 35% yield. Treatment with tributyltin hydride (*n*-Bu_3SnH) formed ring B via radical cyclization generating tetracycle **45**.[30] The next step was a Barton-McCombie deoxygenation.[31] In this, the hydroxyl group in **45** was first treated with phenyl chlorothionoformate, followed by deoxygenation with *n*-Bu_3Sn to form product **46a** in 61% yield. Finally, reduction with $LiAH_4$ completed the synthesis of (±)-α-lycorane **11a** in 84% yield.

Padwa and his group[32] developed a clever synthetic route in which an intramolecular Diels-Alders reaction was evoked (Scheme 8). Starting material **47** was heated to activate the furan ring,[33–36] which formed intermediate **48** in 87% yield. The *N*-Boc was deprotected with trifluoroacetic acid and the released amine was reacted with acyl chloride **49** producing amide **50** in 78% yield. To obtain ring B, a palladium-catalyzed cyclization was performed using Jeffrey's catalyst,[37] obtaining pentacycle **51** in 68% yield. Next, the ketone group was reacted with ethylene mercaptan **52** to form its corresponding thioacetal and then reduced with Raney-Nickel to obtain the deoxygenated compound **53** in 79% yield. The ester group on **53** was hydrolyzed followed by a Barton decarboxylation[38–40] to afford **54**. Reduction of amide **54** was carried out in two-steps; first $LiAH_4$, produced iminium **38** and second $NaBH_3CN$ reduced the iminium to produce the expected (±)-γ-lycorane **(±)-11d** in 74% yield (Scheme 8).

In 2013, Cho *et al.* [41] reported the synthesis of α-lycorane using also a Diels-Alder reaction as a key synthetic step (Scheme 9). This pathway began with the reaction between diene **55** and dienophile **56**, obtaining bicyclic lactone **57**; with an *endo*/*exo* product ratio of 10:1 and a 76% yield.[42–46] A Zn-mediated reduction provided dehalogenated lactone **58** in 82% yield. **59** was achieved by methanolysis of lactone **58** in acidic media. The new alcohol on **59** was reacted with dimethylacetamide dimethylacetal **60** using microwave irradiation to produce adduct **61** *via* an Eschenmoser-Claisen rearrangement[47,48] in 91% yield. Basic hydrolysis of the methyl ester followed by addition of diphenylphosporyl azide (DPPA) produced an acyl azide that after Curtius rearrangement[49] generated isocyanate **62**. Treatment of isocyanate **62** with LiOH and then with HCl gave rise to an amine. Then, an *in-situ* cyclization via 5-exo-trig produced lactam **63a** in 84% yield. This new lactam was used in a Pictet-Spengler reaction[50] to form tetracycle **64a** in 23% yield. Finally, reduction

of the isolated double bond and the carbonyl group afforded (±)-α-lycorane **11a** in 75% yield (Scheme 9).

Stork *et al.* [51] reported a formal synthesis of α-lycorane using a [4+2] cycloaddition. Appel reaction[52] between acid **65** and 3-pyrrolidinol **66** generated amide **67** in 93% yield. The alcohol in **67** was oxidized to ketone **68** using Parikh-Doering conditions[53] in 79% yield. Following this, a Horner-Wadsworth-Emmons olefination delivered ester **70** in 57% yield. This ester was reduced to its respective alcohol using $LiBH_4$ and then substituted with 2-nitrophenyl selenocyanate to provide seleno-compound **71** in 55% for both steps. In the next step, Grieco elimination[54] was performed to create triene **72** in 94% yield; this triene was heating to reflux with chlorobenzene for 24 hours, promoting a Diels-Alder cycloaddition in 51% yield. Lastly, the double bond in **73** was reduced by catalytic hydrogenation using Pd/C, affording **25a**, an intermediate that has been reported previously in the synthesis of α-lycorane (Scheme 10).

Wang *et al.*[55] developed a short synthesis of α-lycorane through [3+2] cycloadditions of iminium ylide-olefins (Scheme 11). Starting with alkylation of **74** with 5-bromo-1-pentene **75** provided **76** in 67% yield. The nitrile presented in **76** was reduced with DIBAL to form aldehyde **77** in good yield. [3+2] cycloaddition[56] was achieved using *N*-benzylglycine **78** and hexamethyldisilazane to produce **79** with a modest yield. Finally, hydrogenolysis of amine and Pictet-Spengler reaction created α-lycorane **11a,** with 40% yield.

Vollhardt *et al.* [57] reported a formal synthesis of γ-lycorane through [2+2+2]-cycloaddition of alkynes to enamines mediated by cobalt (Scheme 12). The synthesis of intermediate **86** is described as follows: treatment of carboxylic acid **80** with thionyl chloride provided acyl chloride **81**, which was then reacted with 4-aminobutanal diethyl acetal **82** generating amide **83** in 97% yield. Alkynylation using palladium as the catalyst afforded **84** in good yield. Treatment of **84** in acid media promoted a cyclization that generated pyrrolidinol **85**. Elimination of the alcohol and trimethylsilyl groups provided **86** in good yield. With intermediate **86** on hand, a [2+2+2]-cycloaddition with alkyne **87** and cyclopentadienylcobalt dicarbonyl formed tetracycle **88** in 65% yield.[58,59] Regioselective removal of a silyl group with tetrabutylammonium fluoride and oxidative demetallation produced **89** in 90% yield. The second silyl group was removed with trifluoroacetic acid to form diene **90** in 67% yield. Finally, Hydrogenation with Adams catalyst afforded a mixture of **91**, **92**, and **11c** with 1:2:1 ratio and 60% yield.

3. Conjugate addition approaches

Besides cycloaddition approaches, other groups have taken advantage of conjugated additions to prepare both racemic and asymmetric lycoranes.[60,61] For instance, the synthesis of (±)-γ-lycorane was reported by Tu (Scheme 13).[62] He took advantage of the kinetic enolate of **93**, which was subjected to a Michael reaction with nitro alkene **94** to form compound **95**. The creation of imine **96** was carried out by reduction of the nitro group using Raney-Nickel; imine **96** was subjected to a second reduction with $NaBH_3CN$ to produce **15d**, which was protected with CbzCl, providing carbamate **97**. A Bischler-Napieralsky

reaction generated lactam **25c**, which by reduction with $LiAH_4$, afforded (±)**11c** in 85% yield.

Tomioka *et al.*[63,64] commenced the synthesis of (±)-lycorane **11b** by means of a chemoselective conjugated addition of organolithium **98** to nitroalkene **99**, forming **100** in 94% of yield[56],[65] (Scheme 14). Subsequently, a cyclization step employing a nitro Michael reaction was carried out with 2 equivalents of CsF as base and 0.1 equivalents of myristyltrimethylammonium bromide as catalyst.[66] This step created diastereoisomers **101b** and **101d** in 94% yield. It should be noted that only diastereoisomer **101b** was obtained pure after recrystallization in 43% yield. The remaining 51% was a mixture of diastereoisomers in a ratio of 3:1 with **101d** as the major diastereoisomer. Then, pure **101b** was used to generate (±)-β-lycorane as follows: the nitro group was reduced to its corresponding amine **102b** with Zn and HCl in quantitative yield. Lactam **14b** was formed by treating aminoester **102b** with NaOMe in MeOH. Octahydroindole **15b** was produced by reduction of **14b** with $LiAH_4$ that, upon treatment with methyl chloroformate, produced carbamate **24b**. Ring B was created by treatment of **24b** with $POCl_3$. Lastly, the reduction of **25b** with $LiAH_4$ created **(±)-11b**.

To synthesize **(±)-11a**, Tomioka employed the 1:3 diastereomeric mixture of **101b** and **101d**. This mixture was subjected to a reduction of the nitro group, forming the amino ester **102d** in 77% of yield. This was then treated with sodium methoxide in methanol to afford lactam **14a** in 88% yield (Scheme 15). **14a** was then reduced with $LiAH_4$ in 94% yield, giving rise to the octahydroindole **15a.** Finally, a modified Pictet-Spengler reaction with Eschenmoser salt **103** provided **(±)-11a**.

An asymmetric synthesis reported by Tomioka *et al.*[67] was carried out by a conjugated addition process using chiral ligand **106**, diene **105**, and organolithium **104**; followed by cyclization *via* Michael addition, producing substituted cyclohexanes **107a** and **107b**, in 18% and 68% yield, respectively. Because cyclohexane **107b** was obtained in higher yield and better enantiomeric excesses (99% *ee*), it was used for the synthesis of (+)-β-lycorane. Therefore, **107b** was treated in acid medium (HCl), which promoted removal of *t*-BuO groups and a fisher esterification on the less hindered acid. The formation of lactam **109** was achieved by Curtius rearrangement of acid **108** from an intermediate isocyanate created by Bischler-Napieralsky cyclization using polyphosphoric acid. To finish the reduction of amide **109**, lactamization and reduction (a domino reaction with borane-dimethyl sulphide complex was performed), delivered (+)-β-lycorane **11b** (Scheme 16) in 70% yield.

4. Radical reactions approaches

It is well known that radical reactions are powerful chemical reactions that allow chemical diversity and opens the door to new chemical transformations. In this regards, Bialy *et al.*[68] reported a radical reaction to synthesize (−)-γ-lycorane (Scheme 17). The first step was the condensation of 1,2-cyclohexadione **110** with (*S*)-1-phenylethylamine **111**[69–70] to form enamine **112**; followed by *in-situ* treatment with chloroacetyl chloride **113** to produce amide **114**. A Finkelstein reaction with sodium iodide generated iodine compound **115**. The radical stage created ring D from the reaction of iodine compound **115** with Bu_3SnH, obtaining

116a and **116b** in 84% yield. Both products were reacted with $NaBH_4$, giving rise to alcohols **117a** and **117b** in 26% and 46%, respectively. Dehydration with Martiń s reagent[71] generated alkene **118**. *N*-debenzylation was carried out under Birch conditions obtaining **119** in 83%, which was then *N*-alkylated with alkyl chloride **120** to produce product **121a**. A second radical cyclization with Bu_3SnH formed ring B of lactam **46b**. $LiAH_4$ reduction gave **(−)-11c** in 64% yield.

Cordero *et al.*[72] have also reported the synthesis of (±)-γ-lycorane. They began with the preparation of cyclohexanone **93**, which was obtained by reacting organolithium **98** (Scheme 14) and cyclohexene oxide **122** to acquire alcohol **123** that was then oxidized under Swern conditions to provide ketone **93.** This was then reacted with lithium diisopropylamide to produce its enolate that was trapped with acetic anhydride affording enol acetate **124** in 85% yield.[73] The next step was the radical reaction between iodoacetonitrile **125** and the enol acetate **124**, forming ketonitrile **126** in 84% yield and a 27:1 diastereomeric ratio, favoring the *cis* configuration. The reduction of nitrile under Adam's catalyst caused a 5-exo-trig cyclization, giving rise to the secondary amine **15c** in 90% yield. To complete the synthesis, Pictet-Spengler reaction conditions were used, which afforded (±)-γ-lycorane in 56% yield (Scheme 18).

Zamir Zard *et al.*[74] reported a formal synthesis of (±)-γ-lycorane using a radical reaction, beginning with the condensation between aldehyde **127** and thiosemicarbazide **128**,[75] forming hydrazone **129**, which was reduced *in-situ* with sodium borohydride providing hydrazide **130** in 76% yield. The hydrazide previously afforded was acylated with piperonyl chloride **131** affording **132** in 79% yield. The radical cyclization using tributyltin hydride led to both products **25c** and **134**. Reducing both compounds with $LiAH_4$, plus HPLC separation produced (±)-**11c** (Scheme 19).

In a second report, Zard *et al.*[76] synthesized (±)-γ-lycorane by means of a radical-ionic sequence. The first step was the condensation of amine **135** with cyclohexanone **136**. This imine reacted in a one-pot process with trichloroacetyl chloride **137,** producing trichloroacetamide **138** in 73% for both steps. The ionic radical reaction was then carried out using Ni-AcOH, achieving the 5-endo radical cycling that led to the product **139** in 60% yield (Scheme 20). A second radical reaction was carried out with Bu_3SnH in a 6-endo process that created lycorane's ring B in product **140**; reduction of the double bond with sodium cyanoborohydride gave the *cis* product **46c** as the sole isomer. Reduction of **46c** with $LiAH_4$ formed (±)-γ-lycorane in 88%.

Zard *et al.*[77] also developed another radical approach to (±)-α-lycorane, this time using xanthates[78–80] as a source of free radicals (Scheme 21). The synthesis began with condensation of benzylamine derivate **135** with cyclohexanone **136**, generating its corresponding imine, which was acylated with chloroacetyl chloride **141**, providing amide **142**. Substitution with potassium salt **143** led to the formation of xanthate **144** in 95% yield. The key radical stage was carried out by heating to reflux **144** in dichloroethane and Lauroyl Peroxide, producing the cyclization products **145** in 19% and **146** in 53%. Enamide **146** underwent a second radical cyclization with *n*Bu_3SnH to form lactam **46a** and the last ring of lycorane. As usual, reduction of **46a** with $LiAH_4$ provided (±)-α-lycorane.

Regains *et al.*[81] developed the synthesis of (±)-γ-lycorane by means of selenofunctionalization of alkenes using LED light.[82] The synthesis was initiated by the reaction between primary amine **148** and carboxylic acid **147** forming amide **149** in 54% yield. By treating the double bond present in **149** with diphenyl diphenylide, carbon tetrabromide and LED light provided **150** in 85% yield. Trimethylsilysilane-mediated radical reaction of **150** gave reduction product **151** and cyclization product **152** in nearly equal ratio. Reaction of **152** with $LiAH_4$ performed amide reduction, while removal of the TMS group was completed using TFA, with a yield of 68% for both steps, to deliver (±)-γ-lycorane **11c** (Scheme 22).

The synthesis reported by Cossy *et al.*[83] also used a radical approach for the formation of ring C of (±)-γ-lycorane. Reductive amination between **153** and **127** yielded the secondary amine **154**, which created chloramine **155** in 95% yield when treated with *tert*-butyl hypochlorite. The radical cyclization via aminyl was carried out using the $CuCl/CuCl_2$ system,[84] achieving the 5-exo-trig cyclization in 70% yield, and produced both isomers **156a** and **156b**. The mixture was subjected to different elimination methods, which were inconclusive. Instead, the depicted selective halogen exchange was completed, generating iodinated compound **157** in 50% yield. This was subjected to elimination with DBU, affording alkene **158** in 50% yield. When **158** was subjected to radical conditions with tributyltin hydride, (±)-γ-lycorane **11c** was obtained in 30%, together with reduction product **159** in 25% (Scheme 23).

Miranda *et al.*[85] reported a formal synthesis of γ-lycorane using xanthates. The first reaction was the transformation of cinnamic acid **160** into isocyanate **161** by Curtius rearrangement. Isoquinolone **162** was obtained by thermal sigmatropic rearrangement[86,87] of **161** in 77% yield, and *N*-alkylation of quinolone **162** with 4-bromo-1-butene was achieved in 80% yield. The reaction between xanthate **164** and the double bonds present in **163** promoted formation of tricycle **165** in 55% yield.[88,89] Hydrolysis of ester in basic media and cyclization of acid **166** with HCl afforded **167** in modest yields (Scheme 24).

5. Mediated by transition metals

Transition metals have also been used by several research groups towards the synthesis of lycoranes.[90–93] One of the first reports was documented by Mori *et al.*[94] for the synthesis of (+)-γ-lycorane. They reacted substituted cyclohexene **168** with amide **169** using palladium as a catalyst with (*S*)-BINAPO as ligand.[49],[95–97] The subsequent alkylation provided **170** in 66% yield and 40% *ee*. It is important to note that the initial configuration of the cyclohexene was preserved, then **170** was cyclized intramolecularly using palladium coupling, which produced tricycle **171** in 81% yield. Subsequent decarboxylation created amide **121c** (87%). Intramolecular cyclization of **121c** under Heck conditions gave access to ring B of **172**. Catalytic hydrogenation (99%) and reduction with $LiAH_4$ (95%) formed (+)-γ-lycorane **11c** (Scheme 25).

Another asymmetric synthesis of (+)-γ-lycorane was developed by Gong *et al.*[98,99] They constructed rings A and B by the reaction between aryl boronic acid **173** and nitroalkene **174** in the presence of catalytic rhodium complex and (*S*)-BINAP,[100],[101] obtaining **175** with

98% *ee* and 65% yield. Addition to nitroalkene **175** with methyl acetate **176** and LDA at −78 °C produced nitroester **177**, and reduction of the nitro group with Raney-Ni and subsequent cyclization formed lactam **14c.** Ring B closure was carried out with a Pictet-Spengler reaction using paraformaldehyde and trifluoroacetic acid,[102] producing **46c** that was then treated with $LiAH_4$ to form **(+)-11c** (Scheme 26).

Shao *et al.*[103] reported an asymmetric syntheses of (+)-α-lycorane using a Nickel complex. Addition to nitroalkene **178** using ditertbutyl malonate **179,** stereo controlled by the complex provided between chiral amine **180** and $NiBr_2$,[104,105] provided the adduct **181** with 91% yield and 93% *ee*. Afterwards, hydration-hydrolysis-decarboxylation provided a ketoacid **182** in 82% yield. Ester creation using thionyl chloride was carried out producing **183** in 82% yield. 6-endo-trig cyclization using tetramethylguanidine formed the substituted cyclohexanone **184** in 60% yield, 93% *ee* and diastereomeric ratio 6:1. Protection of the carbonyl was be carried out with 1,2-ethanedithiol **52** in 77% yield, and reduction of the nitro group followed by 5-exo-trig cyclization created amide **186** in 70% yield. $LiAH_4$-mediated reduction followed by carbamate formation using ethyl chloroformate produced**187** in a 53% yield for both steps. Then, carbamate **187** was treated under Bischler-Napieralsky reaction conditions to form cyclization product **188** in 85% yield. Treatment of thioketal in **188** with hydrogen and Raney-Nickel provided adduct **25a** and reduction of the amide with $LiAH_4$ afforded the expected (+)-α-lycorane **11a** in 80% yield (Scheme 27).

Ojaima *et al.*[106,107] carried out the asymmetric synthesis of (+)-γ-lycorane, following the synthesis reported by Mori in 1995 as reference. Ojaima used palladium accompanied by chiral ligand **189**, the substituted cyclohexane **168** was reacted with anion **190** previously generated with LDA. Product **170** was obtained with 99.4% *ee* and 83% yield. With these new conditions, Ojaima improved the reaction reported by Mori obtaining higher ee. Then, **170** was converted to pentacyclic oxolycorane **191** in 61% yield through a one-pot, tandem allylic amination-intramolecular Heck reaction. Then, **191** was subjected to sequential demethoxycarbonylation, hydrogenation, and $LiAH_4$ reduction to give the desired (+)-γ-lycorane **11c** (Scheme 28).

Zhou *et al.*[108,109] reported the synthesis of (−)-α-lycorane by dynamic kinetic resolution of arylcyclohexanone **192** mediated by ruthenium catalyst **193**,[110–112] giving rise to cyclohexanol **194** with 96% *ee*. Treated under Mitsunobu conditions to afford the corresponding azide, follow by reduction to its corresponding amine produced **195** in 75% yield. The primary amine underwent a Pictet-Spengler reaction generating **196** in 95% yield. This now a secondary amine was transformed to amide using bromoacetyl chloride. This was followed by hydrolysis of the acetal in acid medium to produce adduct **197** in 89% yield for both steps. The formation of the five-membered ring was achieved in 67% yield by creating the carbanion using potassium *tert*-butoxide followed by 5-exo-tet cyclization to deliver **198a**. The ketone reduction was achieved by a Wolff-Kishner reaction[113] followed by amide reduction with $LiAH_4$ as usual. The final product was (−)-α-lycorane **11a** (Scheme 29).

The synthesis of (±)-γ-lycorane reported by Baudoin *et al.*[114] consisted in four reaction stages involving a double arylation via CH activation mediated with Pd.[115–117] It began

with *N*-alkylation of acetamide **199** using sodium hydride and alkyl halide **42,** providing *N*-alkylated product **200** in quantitative yield. This intermediate was a key compound for the palladium-mediated double arylation, producing tetracycle **201** in 81% yield. Having this intermediate, selective hydrogenation of the C ring was achieved by using Rh/C under six atmospheres of pressure, which formed adduct **46c** in 61%. Finally, amide **46c** was reduced to (±)-γ-lycorane with $LiAH_4$ (Scheme 30).

The synthesis reported by Sun *et al.*[118] for the synthesis of (−)-α-lycorane started with the reaction between allyl acetate **203** and brominated compound **202** by a Heck reaction, generating vinyl acetate **204** in 68% yield (Scheme 31). The chiral sulfinylimine **205** previously prepared from 1,4-butanediol was reacted with acetate **204** in a modified palladium-mediated Barbier-type reaction[119–122] followed by an intramolecular cyclization with the ester present in the aromatic ring, affording **206** in 53% yield and a diastereomeric ratio of 20:1. Treatment of **206** with HCl removed both the *tert*-butyl silyl and *tert*-butyl sulfinyl groups, providing **207** in 96% yield. The previously formed alcohol was then treated with methanesulfonic anhydride, producing mesylate **208** in 96% yield. Metathesis with cyclohexene was catalyzed by a second generation Hoveyda-Grubb's catalyst, which produced **209** in 93% yield. The next step was a 5-exo-tet cyclization; for this purpose, **209** was treated with potassium *tert*-butoxide, affording amide **210a** in 93% yield. The last two reaction steps were hydrogenation of the double bond and reduction of the carbonyl group to yield (−)-α-lycorane **11a**.

The synthesis route reported by Bäckvall *et al.*[123] used palladium chloroamidation. The alcohol **211** was subjected to a Mitsunobu reaction using phthalamide **212**, producing **213** in 98% yield. Removal of the phthalamide was achieved using hydrazine hydrochloride, providing amine hydrochloride **214** in 98% yield. Carbamate **216** was generated quantitatively using benzyl chloroformate **215**, while chloroamidation was carried out with palladium acetate[124] forming bicycle **217** with high yield and stereoselectivity (> 98% for *cis isomer*). The next synthetic step was an S_N2' to the allyl chloride moiety using Grignard reagent **218** and CuCN; however, attempts for Grignard addition resulted in poor yields. Nonetheless, when $LiCuCl_4$ was utilized[125] an acceptable yield was observed (77%). The stereochemistry of the reaction showed that the substitution was *anti*, which formed tricycle **219** (Scheme 32).

The last two stages involved a hydrogenation and a Bischler-Napieralsky reaction. When the hydrogenation was done first, followed by the Bischler-Napieralsky reaction, it was possible to obtain (±)-α-lycorane **11a** without configuration change in the stereogenic centers. However, when the Bischler-Napieralsky reaction was first carried out starting from **219**, the isomerization of the product was observed, forming **210c**. This was convenient, as following with hydrogenation and reduction using $LiAH_4$ produced (±)-γ-lycorane **11c** (Scheme 33).

The synthesis reported by Chuang *et al.*[126] has as a key step, an aza-Wacker-Heck process. This pathway began by reacting carboxylic acid **80** with thionyl chloride to form acyl chloride **81.** This was reacted in a *one-pot* process with amine **148**, giving rise to amide **221** in 76% yield. This intermediate underwent an aza-Walcker-Heck process catalyzed by

palladium acetate to form rings B and D, accessing compounds **210b** and **222** in 71% and 5% yield, respectively. Two reductions were performed, first a catalytic hydrogenation and the second with $LiAH_4$, which provided (±)-γ-lycorane **11c** in 72% yield overall (Scheme 34).

Huang *et al.*[127] reported the synthesis of (±)-γ-lycorane in three reaction steps with a key step being a palladium-mediated C–H activation. Beginning with a reductive amination between aldehyde **127** and amine **223**, the imine was then treated with sodium borohydride, producing amine **224** in 84% yield. The next step consisted of an iodocyclization process using iodine and potassium carbonate, affording iodocompound **225** in 90% yield. The cyclization step through aromatic C–H activation was carried out using $Pd(Ph_3)_4$, but unfortunately, the cyclization could not be regio-controlled and afforded products **11c** and **226** in a 1:1 ratio with a 90% yield (Scheme 35).

The synthesis of (−)-γ-lycorane reported by Donohoe et al.[90a] started by aziridination reaction using 2-cyclohexen-1-one **27** and benzyl (tosyloxy) carbamate **227,** affording azidirine **228** in 64% yield and 98:2 e.r. **228** was then treated with sodium borohydride to generate alcohol **229** in 77% yield and 2.3:1 d.r. Carbamate deprotection was achieved smoothly using potassium carbonate, and in a second step, the amine was reacted with alkyl bromide **230** to produce **231** in 75% yield (two steps). Hydrogen borrowing alkylation between **231** and acetophenone **232** mediated by iridium generated **233** in moderate yield (53%). Treatment of **233** with Br_2 promoted *5-exo-trig* cyclization and provided dibromated compound **234** in 40% yield. Elimination mediated by potassium *tert*-butoxide and intramolecular Heck reaction produced **46c** in good yields. Finally, double bond reduction using Pd/C and H_2 followed by $LiAH_4$ provided (−)-γ**11c** lycorane (Scheme 36).

Yang *et al.*[93] developed a methodology to synthetize (+)-α-, (+)-β-, (+)-γ-, and (−)-δ-lycorane. The synthetic route to obtain all α, β, γ, δ lycoranes was similar and therefore, in Scheme 37 just one example is presented. Nonetheless, it is important to note that this is the first approach that can give access to all members of the lycorine asymmetrically. The first reaction was Ir/amine catalytic alkylation to obtain aldehyde **236** in 80% yield. Sakurai allylation of the aldehyde provided homoallylic alcohol **237** in good yields (80%), Ring closing metathesis mediated with Grubbs II produced substituted cyclohexane **238** in 80% yield. Double bond reduction with Pd/C and H_2 afforted **239** in 90% yield and oxidation using Dess Martin periodinane afforded ketone **240** in good yield (85%). Horner-Wadsworth-Emmons reaction afforded α-β unsaturated compound **241** in 81% yield, followed by reduction using H_2 and Pd/C produced **242** in 90% yield. Ester reduction with $NaBH_4$ afforded alcohol **243** in 75% yield and intramolecular Mitsunobu reaction promoted 5-*exo*-tet cyclization, which produced tricyclic **15a** in 70% yield. Finally, Pictet-Spengler cyclization using Eschenmoser's salt provided (+)-α-lycorane **11a** in 75% yield.

Zhang *et al.* reported (−)-α-lycorane synthesis in 3 steps.[91] The first reaction was a Heck/Tsuji–Trost reaction between sulfonamide **244** and iodo compound **245** to produce tricycle **246** in 87% yield. Double bond reduction using Pd/C and H_2 and remotion of the tosyl group mediated by Mg followed by Pictet-Spengler reaction afforded the (−)-α-lycorane in moderate yield (Scheme 38).

Cai *et al.* reported the synthesis of (−)-α-lycorane starting with a reaction between pyrone **248** and pyrrolidine **249**, which provided **250** in 91% yield and 91% ee.[92] This intermediate was heating to reflux in chlorobenzene to promote a retro Diels-Alder, giving access to **251** in 92% yield. The double bonds in **251** were then reduced first using $Pd(OH)_2/C$ and then using Mg, which afforded **252** in 90% yield. Hydrolysis of the ester in **252** with LiOH, followed by treatment with TCNHPI provided **253** in moderate yield (62%). **253** was then reacted with **254** in a cross-coupling catalyzed by nickel to produce **24** in 71% yield. Amine deprotection was achieved using TMSOTf and 2,6-lutidine to produce **15** in 98% yield. Finally, Pictet-Spengler reaction afforded the expected (−)-α-lycorane in 63% yield (Scheme 39).

6. Organocatalytic approaches

Not only transition metals have been used to synthesize lycoranes, but organocatalyst as well. In regard to organocatalyst approaches, Hong *et al.*[128] developed the synthesis of molecules that had been intermediates for the synthesis of (−)-α-lycorane and (−)-β-lycorane using an organocatalyzed double Michael reaction. Using the Hayashi-Jørgensen organocatalyst[129,130] **256** for the Michael addition between nitrostyrene **1** and aldehyde **255** to generate intermediate **257**, which in one-pot, underwent an intramolecular cyclization process by means of a second Michael addition with CsF and nBu_4NBr produced tetrasubstituted cyclohexane **258**. This was converted to the carboxylic acid **259** via a Pinnick-type oxidation followed by treatment with oxalyl chloride and DMF that provided the corresponding acyl chloride. Following this, the acyl chloride was then reacted with the 2-mercaptopyridine *N*-oxide (Barton's reagent) to carry out a Barton-McCombie decarboxylation reaction using Bu_3SnH to access **101b** (Scheme 40). This molecule has already been reported by Tomioka *et al.*[63,64] for the synthesis of β-lycorane.

Employing thiourea organocatalyst **261**, Xu *et al.*[131] reported a formal synthesis of α-lycorane *via* a double Michael addition for the generation of the C ring. The double cascade Michael addition[132] of **260** with **1** using organocatalyst **261** created a substituted cyclohexane **262** in 90% *ee* and 12:1 diastereomeric ratio. Reduction of the nitro group with $NiCl_2•6H_2O$-$NaBH_4$ led to 70% intramolecular lactamization, forming the D ring on **263** which, after carrying out a modified Pictet-Spengler reaction, provided **264** in 95% yield. Hydrolysis and decarboxylation of **264** produced ester **265,** followed by reduction with $LiBH_4$, gave rise to alcohol **266**, which was oxidized under Dess-Martin conditions to form aldehyde **267**. Decarbonylation in the presence of $Rh(PPh_3)_3Cl$ gave amide **46a** in 82% yield, which can be converted to **11a** (Scheme 41).

A second asymmetric approach to the synthesis of (+)-α-lycorane was reported by Shao.[133] This time an addition of acetaldehyde **268** to nitroenyne **178** using Jorgenses catalyst **256**. Michaels adduct **269** was reacted under Pinnick oxidation[134] conditions to form carboxylic acid **270.** This acid was treated with TsOH to promote hydration of the alkyne, creating α-β unsaturated compound **182** in 41% yield after three steps. Intermediate **182** was treated with thionyl chloride and ethanol to provide ester **183**, which then underwent cyclization with tetramethylguanidine (TMG). Then, protection of the carbonyl, as previously reported, formed **185**. Raney-Nickel reduction-cyclization afforded amide **14a**

in 73% yield. As typical, a Pictet-Spengler cyclization followed by reduction of amide provided (+)-α-lycorane **11a** (Scheme 42).

Zhao *et al.*[135] and his research group developed asymmetric syntheses of (−)-α-lycorane and (−)-β-lycorane using modular designed organocatalyst (MDO's)[136,137] as a synthetic tool to obtain highly substituted cyclohexanes. Nitrostyrene **1** and dicarbonyl compound **271** with thiurea QDT **272 (**derived from quinidine and *L*-proline as MDO's) mediated a Michael/Michael tandem process, generating cyclohexane **273** (*ee* >99% and d.r. 96:4). Reduction of this aldehyde with sodium borohydride followed by protection of the alcohol with *tert*-butyldimethylsilane chloride (TBDMSCl) provided **274a** in 91% yield. The reaction of the ketone under Baeyer-Villiger oxidation conditions formed ester **274b** in 96% yield. Then, amide **274c** was prepared by reduction-cyclization using $NaBH_4/NiCl_2$ system in 89% yield. Pictet-Spengler reaction and deprotection of the alcohol was carried out using paraformaldehyde in an acid medium, obtaining pentacycle **266** in 84% yield. The oxidation of alcohol **266** to aldehyde **267** was conducted using pyridinium chlorochromate (75%), while the decarbonylation was carried out using the same conditions described previously by Xu *et al.* [131] This was followed by standard reduction with $LiAH_4$. With this methodology, the got access to both (−)-α-lycorane and (−)-β-lycorane using different thioureas to obtain the desired stereoisomer (Scheme 43).

Furthermore, Wei *et al.*[138] reported the asymmetric synthesis of (−)-δ-lycorane that consisted of a double Michael additions catalyzed by squaramide **277** (Scheme 44). The start of the synthesis was carried out between the double addition of the β-ketoester **275** and nitroalkene **276**. The reaction proceeded with 92% *ee* and 88% yield of the substituted cyclohexane **278**. Deprotection of the alcohol, hydrolysis of the ester and decarboxylation of the formed acid was achieved with sulfuric acid in DMSO at 120 °C affording **279** in 92% yield. Treatment of alcohol **279** with MsCl and triethylamine created **280** in 95% of yield. Reduction of the nitro group with zinc and acetic acid afforded cyclic amine **281**in 94% yield, while protection of the amine with ethyl chloroformate led to carbamate **282** in 90% yield. Bischler-Napieralsky cyclization was carried out using triflic anhydride and dimethylaminopyridine, gave rise to cyclic lactam and triflic enolate **283** in 87% yield. Treatment of **283** with Pd/C/hydrogen and $LiAH_4$ provided (−)-δ-lycorane **11d** in 78% yield (Scheme 44).

7. Photochemical approaches

The power of photochemistry has also been evoked to access lycoranes. The synthesis reported by Iida *et al.*[139] followed an intramolecular cyclization, mediated by light, of an enaminoketone as the key step. Intramolecular cyclization of **284** using phenylithium formed a benzyne intermediate which by a nucleophilic attack off the amino group, produced 6-methoxyindoline **285**. This product was reduced under Birch condition to afford diene **286** quantitatively. Then, it was reacted with **131** to obtain enaminoketone **287** The product of the cyclization **167** mediated by ultraviolet light[140] was obtained in 70% of yield. To finalize the synthesis, two reductions were carried out: the first with $LiAH_4$ to reduce both carbonyls, affording **288** with a yield of 32%, followed by hydrogenation of the olefin using Adams' catalyst, which delivered (±)-γ-lycorane **11c** with a 47% yield (Scheme 45).

Also, Booker-Milburn *et al.*[141] developed the synthesis of (±)-γ-lycorane by intramolecular [2+2] cycloaddition of pyrrole **289** followed by [1,5] Sigmatropic rearrangement to provide tricycle **290**.[142–144] This tricycle was heated to 100 ° C to open the azidirine ring, accessing imine **291** in 86% yield for both steps. This imine was subjected to a reductive amination after being treated with 6-iodopiperonal **292**, creating tertiary amine **293** in 64% yield; cyclization via Heck reaction generated intermediate **294** in 87% yield (Scheme 46). This pentacycle was submitted to catalytic hydrogenation, giving rise to **295** in 82% of yield. Removal of the *tert*-butyl ester was achieved by treatment of **295** with trifluoroacetic acid, creating the corresponding carboxylic acid. The resulting crude acid was decarboxylated using oxalyl chloride followed by reduction of the intermediate iminium ion with sodium borohydride, affording (±)-γ-lycorane **11c**.

Similarly, the protocol to obtain (±)-β-lycorane was achieved by condensing cyclohexanone **296** with benzylamine to create imine **297**. This imine was reacted with piperonyl chloride **131**, generating enamide **298,** which was irradiated with a 400 W pyrex lamp, affording tetracycle **299** in 43% yield. Amide **299** was reduced with $LiAH_4$ to produce amine **300** in 97% yield. The hydrogenolysis of the benzyl groups was achieved using hydrogen and Pd/C, while a second step (mesylation) of **301** was conducted to favor a 5-exo-tet cyclization, afford the expected lycorane (Scheme 47).[141]

8. Wittig rearrangement

Tomooka *et al.*[145] developed the enantioselective synthesis of (+)-γ-lycorane from building block **302** that had planar chirality.[146] Hemiaminal **302** was reacted with phosphonate **303** under a Horner-Wardsworth-Emmons conditions to provide α,β- unsaturated ester **304** in 89% yield. The reduction of this ester with DIBAL delivered alcohol **305** in quantitative yield. This alcohol was used for an intramolecular Mitsunobu reaction to form nonacyclo **306** in 90% yield. It should be noted that this compound presents planar chirality, and it was possible to isolate with 98% *ee*. This nonacyclo was treated with *n*-butyllithium to promote an aza-[2,3]-Wittig rearrangement, creating cyclohexene **307** in 94% yield, >98% *ee*. After, a selective hydroboration with disiamyl borane led to alcohol **308** in 98% yield. This alcohol served for an intramolecular Mitsunobu reaction providing octahydroindole **309** in 96% yield. **309** was subjected to reductive detosylation with lithium naphthalide, creating ammonium salt **310** in 84% yield. **311** was generated by the coupling between carboxylic acid **80** and the amine **310,** obtaining in 96% yield. Coupling via Heck reaction allowed access to tetracycle **210c** in 84% of yield. Lastly, catalytic hydrogenation and reduction with $LiAH_4$ gave (+)-γ-lycorane **11c** (Scheme 48).

Li *et al.*[147] and his group also developed a methodology towards γ-benzylbutenolides[148] **313** that was used for the synthesis of (±)-γ-lycorane. Wittig-rearrangement[149,150] of vinylogous urethane **312** promoted by lithium diisopropyl amide yielded α,β-unsaturated lactone **313** in 62% yield and diastereomeric ratio of 5:1. Reduction of enamine with sodium cyanoborohydride followed by rection with *m*CPBA provided lactone **314** in 82% yield for both steps. This lactone reacted with vinylmagnesium bromide **315** and copper chloride, creating Michael adduct **316** in 88% yield. Metathesis of **316** mediated by second-generation Grubbs catalyst afforded cyclohexene **317** in 92% yield. Once the fused bicycle

was synthesized, the lactone was treated with $LiAH_4$ to deliver diol in 96% yield, which was treated with mesyl chloride, producing the corresponding mesylated adduct in 92% yield. Then, reaction with benzylamine formed cyclic amine **22c** in 62% yield. *N*-debenzylation using Pd/C and hydrogen delivered amine **15c.** Finally, a Pictet-Spengler reaction provided (±)-γ-lycorane **11c** (Scheme 49).

9. Miscellaneous

Besides all the synthetic approaches reviewed above, many other researchers have reported miscellaneous syntheses that are described below. For instance, Liu *et al.*[151] reported the synthesis of (±)-γ-lycorane based on a cyclopropyl ring opening to provide an advanced intermediate (Scheme 46). They began with a condensation between amine **318** and aldehyde **319**, this new imine was reduced to its amine using $NaBH_4$. In a third step, in the presence of HCl, the enol ether decomposed to ketone **320**. With **320** in hand, an electrophilic addition to the double bond was carried out using Br_2, followed by a 5-exo-tet cyclization. This was next treated with K_2CO_3 to provide cyclopropyl ring product **321** in 82% of yield for both steps.[152] Ring B generation was formed by palladium coupling, [153] which provided **322** in 82% yield. The ketone moiety was reduced to alcohol **323** in 95% yield, followed by PBr_3 mediated bimolecular nucleophilic substitution, to providing brominated product **324** in 95% yield. Next, the cyclopropyl ring was opened[154–156] in 77% yield, producing halogenated compound **325**. Elimination with sodium *tert*-butoxide formed diene **326** in 81% yield and when subjected to hydrogenation created (±)-γ-lycorane **11c** (Scheme 50).

Kibayashi *et al.*[157] developed a formal synthesis of (±)-γ-lycorane using iminoenol **327** and 2-bromo-4,5-methylenedioxybenzyl chloride **120** that produced enaminone **328**. This enaminone was treated with lithium dimethyl amide **329** to create benzyne intermediate **330** that quickly cyclized[158] producing adduct **331**. Oxidation using KOH/O_2 created compound **167**, which had already been reported by Iida *et al.*, thus concluding the formal synthesis of (±)-γ-lycorane **11d** (Scheme 51).

A synthesis reported by Ueda *et al.*[159] was completed in six synthetic steps (Scheme 48). First, nucleophilic substitution between the primary amine **318** and alkyl halide **42** provided secondary amine **332** with good yield. The second step involved deprotection of the enol ether in acidic medium to afford ketone **320** in 69% yield. Then, the next step was the formation of octahydroindole, achieved by heating to reflux **320** under HCl, which isomerized the double bond to the most stable α,β-unsaturated system. This allowed a 1,4-addition to form octahydroindole **333** in 82% yield. Product's stereochemistry revealed that the octahydroindole hydrogens were *cis*, coinciding with the most stable product, and ring closure.[160] The next stage was achieved using lithium piperidine **334** that led to the construction of the last ring in 40% of yield. Reduction of ketone **335** was achieved through synthesis of thioketal using 1,2-ethanedithiol **52**, followed by Raney-nickel reduction, leading to the synthesis of (±)-γ-lycorane **11c** (Scheme 52).

Angle *et al.*[161,162] developed a formal synthesis of (±)-γ-lycorane starting from *N*-triisopropylsilyl pyrrole **336** This product was subjected to a Friedel-Crafts reaction with

succinic anhydride **337**, giving rise to its corresponding keto-acid, then two reductions using sodium borohydride and catalytic hydrogenation created carboxylic acid **338** in 95% yield. Formation of Weinreb amide using **339** followed by deprotection of pyrrole with TBAF and protection with Boc anhydride produced amide **340** in 84% yield. Treatment of Weinreb amide with Grignard reagent **218** generated ketone **341** in 71% yield. Then, reduction with $NaBH_4$ afforded alcohol **342**. Creation of ring C was achieved by intramolecular Friedel-Crafts cyclization using $Sn(OTf)_2$.[163] Product **343** was obtained quantitatively, while the hydrogenation with PtO_2 gave rise a sole *cis*-octahydroindole product **344** in 97% yield. Treatment of **344** under standard Bischler-Napieralsky conditions were ineffective; due to this, *N-tert*-butyloxycarbonyl group was change to ethyloxycarbonyl, which provided **345** in 88% yield. Bischler-Napieralsky with $POCl_3$ afforded (±)-γ-lycorane **11c** in 71% yield (Scheme 53).

Ganem *et al.*[164] reported the synthesis of (±)-γ-lycorane by aldol condensation of dicarbonyl compound **353**. This was prepared as depicted in scheme 54. The reaction between methylenedioxyphthalic anhydride **346** and 3-pyrrolidinone acetal **347** followed by reduction of the resulting carboxylic acid with $LiAH_4$ provided alcohol **348**. Oxidation of this to aldehyde **349** permitted the addition of the previously prepared propargyl aluminum complex **350**, forming propargyl alcohol **351**. Then, deprotection of ketone in an acid medium followed by hydration of the alkyne formed the desired dicarbonyl compound **353**.

Treatment of dicarbonyl compound **353** with potassium carbonate promoted an intramolecular Michael addition followed by an aldol condensation (Robinson annulation) [165] forming adduct **354**. TsOH mediated dehydration created α,β-unsaturated compound **355**. This compound was hydrogenated to make ketone **356**. Reduction of the carbonyl by tosylhydrazide followed addition of $NaCNBH_3$ created (±)-γ-lycorane **11c** (Scheme 55).

Umezawa *et al.*[166] reported the synthesis of both (±)-α-lycorane and (±)-γ-lycorane using ketoacid **361**. Alkene **357** was synthesized in 2 steps by addition of Grignard reagent **218** to cyclohexanone **136** followed by HCl treatment produced the adduct in 88% yield. Following this, hydroboration-oxidation of the double bond delivered alcohol **123** in 75% yield. This was then subjected to Jones oxidation conditions producing cyclohexanone **93**. Then, this cyclohexanone **93** was reacted with pyrrolidine **358** to form enamine **359**, which was later reacted with methyl bromoacetate **335**, followed by acid treatment to form 1,4-dicarbonyl compound **361** in 81% yield (Scheme 56).

Once compound **361** was produced, it was reacted with hydroxylamine hydrochloride, generating oxime **362** in 75% yield. Reduction with Zn/AcOH produced intermediate **363**, which underwent intramolecular cyclization providing a mixture of lactams **364**, **365**, and **366** with yields of 7.8%, 15% and 10.5%, respectively (Scheme 57).

Coupling constants were used to determine the configuration of the lactams. It was confirmed that hydrogens on **366** were *trans* with $J = 10$ Hz. Hydrogenation using Adams' catalyst gave lactam **14a** in quantitative yields. NMR analysis revealed its actual stereochemistry ($J = 10$ and 7 Hz). This intermediate has been reported by Hill *et al.* [14] towards the formal synthesis of α-lycorane. On the other hand, the synthesis of γ-lycorane

was obtained via hydrogenation of lactam **365** to produce known intermediate **14c**. The latter was subjected to a reduction followed by a cyclization via Pictet-Spengler, generating (±)-**11c** in a 56% yield. (Scheme 58).

The work documented by Funk *et al.*[167] began with Peterson olefination using aldehyde **367** and Grignard **368** to make alkene **369** in 79% yield. Treatment of **369** with *n*-BuLi and trimethyl tin chloride formed organotin **370** in 84% yield.[168] Stille coupling between **370** and **371** produced diene **372** in 73% yield. Taking advantage of the diene present in the molecule, the adduct was heating to reflux in toluene to promote a 6π electro-cyclization[169] in good yield (92%), creating adduct **373**. Diene reduction was achieved by catalytic hydrogenation at 500 psi forming octahydroindole **344** in 64% yield. The primary amine was deprotected by treating carbamate **344** with lutidine and TMSOTf, affording **15c** in 82% yield. Lastly, **15c** underwent a Pictet-Spengler reaction with formalin and hydrochloric acid to give rise to (±)-γ-lycorane **11c** (Scheme 59).

Kikuchi *et al.*[170] reported a Michael addition between homophthalimide **374** and methylvinyl ketone **375** that provided adduct **376** in 65% yield. Reduction of the imide was achieved after protecting the ketone moiety with ethylene glycol, followed by treatment with $NaBH_3CN$ and HCl, which delivered enamide **378** in 80% yield. Protection of ketone in **378** with ethylene glycol provided ketal **379**, and reduction with $LiAH_4$ followed by addition of HCl promoted a 6-endo-trig cyclization. This product **380** presented *cis* configuration. Benzyl removal using H_2 and $PdCl_2$ was achieved in 90% yield, while acylation of secondary amine **381** produced chloramide **382** (using chloroacetyl chloride **113**). The product of this last reaction underwent 5-exo-tet cyclization to form pentacycle **198c** in 85% yield. Reduction of both carbonyls first tosylhydrazide and then with $LiAH_4$ formed (±)-γ-lycorane **11c** in 70% yield (Scheme 60).

Oppolzer *et al.*[171] have also reported a synthesis of (±)-α-lycorane. They initiated their synthesis with the addition of organolithium reagent **98** to cyclohexenone **27** forming allylic alcohol **383** in 87% yield. Lithium perchlorate mediated the substitution between **383** and acetal **30**, affording ester **384** in 86% yield. Then, the reduction of the previously created ester with DIBAL produced aldehyde **385**. Condensing the product with hydroxylamine and reduction with $NaBH_3CN$ afforted hydroxylamine **386**. A retro-Cope[125] was carried out at 140 °C provided octahydroindole **387** in 83% yield. By an *N, O*-hydrogenolysis followed by a modified Pictet-Spengler reaction using Eschemonser salt **103**,[172] (±)-α-lycorane **11a** was generated in 74% yield (Scheme 61).

The synthetic route by Banwell *et al.*[173] towards (±)-γ-lycorane started by reacting allyl acetate **388** with bromoform in sodium hydroxide, generating bromocyclopropane **389** in 81% yield. Hydrolysis of the acetate in basic medium (potassium hydroxide) formed alcohol **390** in 96% yield, which was followed by oxidation with PCC delivered ketone **391** in good yield. This ketone was then submitted to Wittig-Horner conditions to produce adduct **393** in quantitative yield. Hydrogenation reduced the nitrile to amine, which was then protected to carbamate **394** using methyl chloroformate. Propane ring opening followed by π-cyclization created bicycle **395** in 95% yield. Suzuki reaction with boronic acid **173** created **396** in 92% yield. Hydrogenation in the presence of Pd/C, followed by Bischler-Napieralsky

reaction generated the known tetracyclic amide **25c. 25c** was ultimately reduced with $LiAH_4$ providing **(±)11c** (Scheme 62).

Fujioka *et al.*[174] reported an elegant asymmetric synthesis of (−)-γ-lycorane. They initiated the synthesis by reacting aldehyde **397** with 1,2-(4-methoxyphenyl)-1,2-diamine **398**. [175],[176] then, this adduct was treated with *N*-bromosuccinimide to promote bromonium ion generation and 5-exo cyclization, with a tandem aminal oxidation forming molecule **399** in a 57% yield, of a single isomer. The reduction of the double bond was carried out using Pearlman catalyst [$Pd(OH)_2$] producing **400**, which was then transformed into a methyl ammonium salt. Lactam **401** was created by basic hydrolysis of the prior ammonium salt. This lactam was hydrolyzed under an acidic medium amide to deliver **402**. Alkylation of this intermediated with **403** afforced adduct **404**. An intramolecular Friedel-Crafts reaction of **404** mediated with $AgBF_4$, produced **46c**, which was as usual reduced with $LiAH_4$ to form (–)-γ-lycorane (Scheme 63).

Hilton *et al.*[177] developed a methodology for the generation of dihydroindolones, which was used for the synthesis of (±)-γ-lycorane. They commenced their synthesis by bromination of 3,4- (methylenedioxy) benzylamine **223** to form adduct **135** in 80% yield. Condensation between amine and cyclohexanone **136** produced imine **405**. This imine was reacted “without purification” with diacetoxyacetyl chloride **406** to form amide **407** in 72% for two-steps. This key intermediate allowed formation of dihydroindolone core, by reacting **407** with boron trifluoride in a microwave for 15 min, generated dihydroindolone **139** in 87% yield. Coupling using Heck reaction conditions gave intermediate **408** in 74% yield. Hydrogenation of the both double bonds to access amide **46c** was achieved using an H-Cube reactor. Finally, reduction with $LiAH_4$ led to (±) -γ-lycorane (Scheme 64).

Amat *et al.*[178] developed an enantioselective pathway to form (+)-α-lycorane using (*R*)-phenylglycinol **410** as the chiral source.[179],[180] They first reacted **410** with 1,4-dicarbonyl **409** to create imine **411**. Intramolecular cyclization of imine **411** afforded oxazolidine **412**, which underwent lactamization to form adduct **413** in 54% of yield. Treatment of **413** with $LiAH_4$ led to oxazolidine ring opening and amide reduction, forming amine **414**. This adduct was treated directly with hydrogen and Boc anhydride to perform a protecting group exchange, forming**344** in 66% yield. Lastly, Pictet-Spengler cyclization with formalin in acid medium produced (+)-α-lycorane 97% (Scheme 65).

Kibayashi *et al.*[181] documented a formal synthesis of (±)-γ-lycorane through intramolecular cyclization of enaminones. This synthesis began with condensation of bromo-piperonal **319** and ethanolamine **415**. Then, this new imine was reduced with $NaBH_4$, affording **416** in 89% yield. Amino alcohol **416** was reacted with 1,3-cyclohexanodione **417**, producing enaminone **418** in 75% yield. The alcohol present in **418** was exchanged to bromo **419** using PBr_3 in 75% yield, while the 5-exo-tet cyclization in γ position was promoted by LDA, affording oxoindole **328** (20%) and elimination of product **420** in modest yield (28%) (Scheme 66). This oxoindole has been reported by the same group as an intermediary for the synthesis of γ-lycorane.[157]

Liu *et al.*[182] also reported a synthesis of β-lycorane through Michael addition-elimination reactions. Reaction between **421** and nitroolefin **174** in basic conditions produced **422** in 91% yield. Treatment with LDA and AcOEt in a second Michael addition provided ester **423** and subjecting **423** to Zn and AcOH promoted reduction of nitro group, ketal deprotection, and 6-exo-trig cyclization affording **424** in 86% yield. Reacting **424** with NaOMe fostered formation of a lactam, and in a second step $LiAH_4$ reduction generated β-lycorane (Scheme 67).

Zhang *et al.*[183] reported a formal synthesis of (±)-γ-lycorane in five steps. Initial condensation of amine **318** and aldehyde **319** formed an imine that was reduced to amine **332** with sodium borohydride. Subjecting **332** to hydrochloric acid produced α,β-unsaturated ketone **425**, and further treatment with K_2CO_3 promoted a Michael addition that provided adduct **332** in 80% yield. Ring B closure was achieved by $Pd_2(dba)_3$ affording **335** in 81% yield (Scheme 68).

Prasad *et al.*[184] documented a synthetic method for the synthesis of (+)-γ-lycorane taking advantage of Overman rearrangement.[185,186] Construction of **427** was achieved from phosphonate **426** in eight steps (not shown). Treatment of the allylic alcohol present in **427** with trichloroacetonitrile provided its corresponding allylic trichloroacetimidate that, in a second step, was reacted in a microwave to form allylic trichloroacetamide **428** in 56% yield. Ring closing metathesis with a second-generation Grubbs catalyst produced cyclohexene **429** in 83% yield. Following this, deprotection of alcohol with pyridinium *p*-toluenesulfonate and DMP oxidation formed enone **431**. Selective reduction generated alcohol **432** in 88% yields. Alcohol **432** was then treated with triethyl orthoacetate to promote Claisen rearrangement,[187,188] affording ester **433** in 61% yield. For the last steps, amide formation was possible with cesium carbonate, giving **63c** in 76% yield. Lastly, Pictet-Spengler cyclization, hydrogenation, and $LiAH_4$ reduction created (+)-γ-lycorane in good yield (Scheme 69).

10 Conclusions

Amaryllidaceae alkaloids have been remarkable natural products since their discovery due to their inherited biological activities. For this reason, different synthetic strategies have been developed to access the known lycorine backbones. For instance, a recent review regarding the total synthesis of γ-lycorane has clearly articulated and discussed approaches and challenges towards this important family of natural products. This review compiled all known synthetic approaches aimed at the synthesis of the lycorane backbone. In principle, the synthetic methodologies presented in this review will contribute to the synthesis of other relevant small molecules and/or natural products.

In this review, eight general synthetic routes for the synthesis of lycorane were documented, including; 10 cycloaddition approaches, 4 conjugate addition approaches, 8 radical reaction approaches, 10 mediated by transition metals, 5 Organocatalytic approaches, 3 photochemical approaches, 2 Wittig rearrangement, and 17 miscellaneous routes. Specifically, all those synthetic approaches allowed the synthesis of α-lycorane (19 routes), β-lycorane (10 routes), γ-lycorane (38 routes), and δ-lycorane (6 routes), with 15 different

routes reporting asymmetric total synthesis (mainly taking advantage of organocatalysts and transition metals). Undoubtedly, this field will continue its expansion with the discovery of new catalysts and the use of other technologies, such as mechanochemistry and electrochemistry that are gaining popularity.

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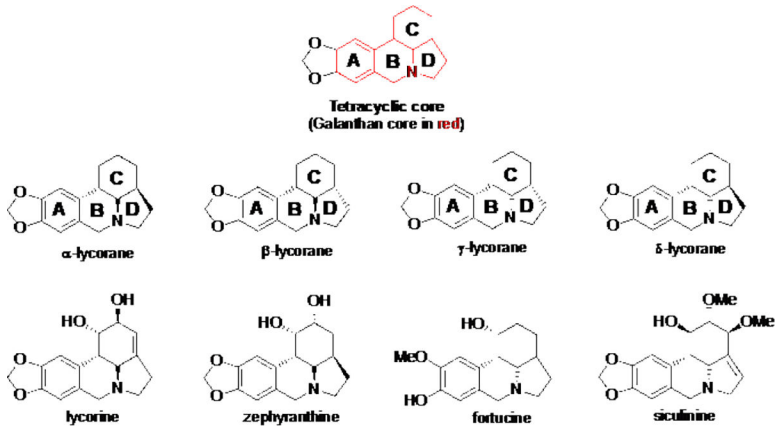


Figure 1.
Lycoranes and representative natural products.

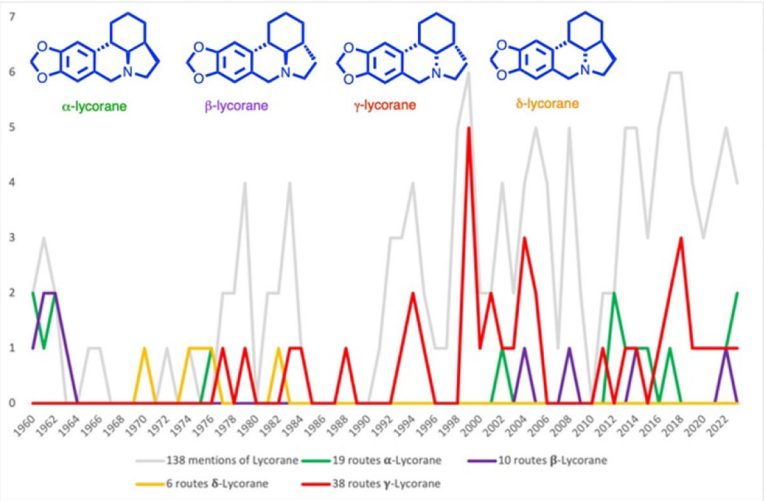
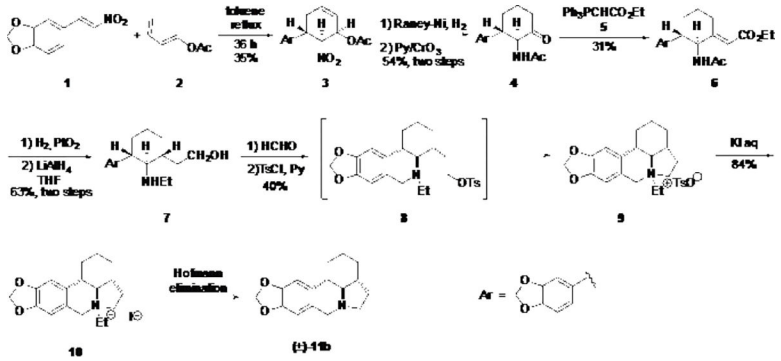
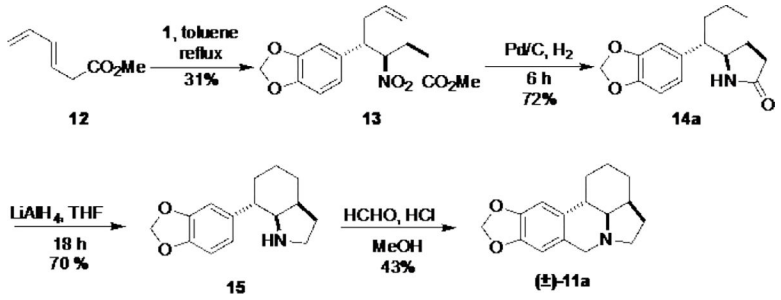


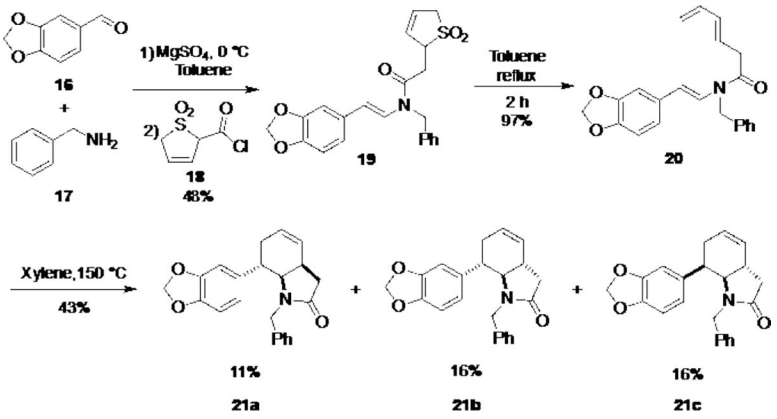
Figure 2.
Lycoranes in the literature.



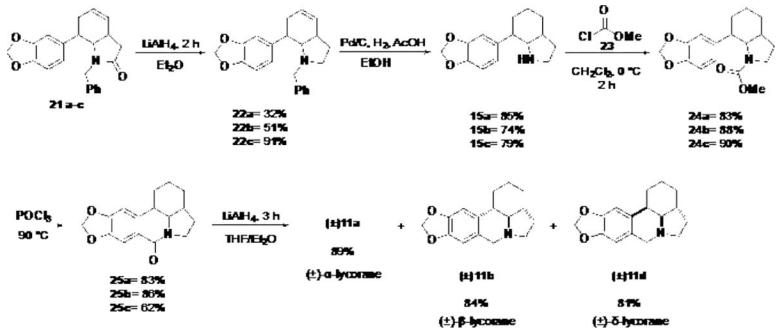
Scheme 1.
Hill's synthesis of (±)-β-lycorane.



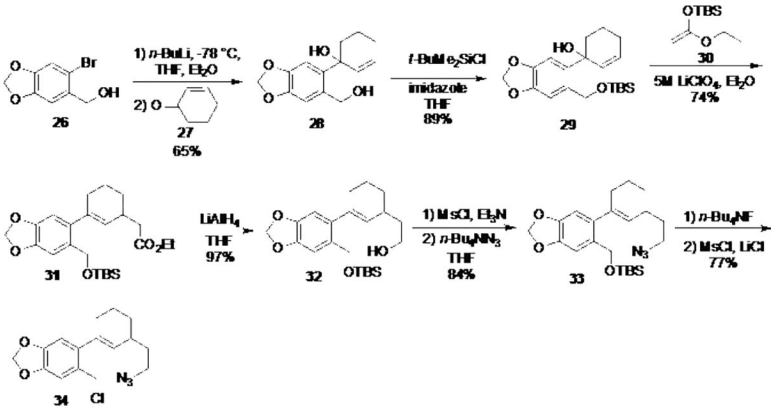
Scheme 2.
Hill's synthesis of (±)-α-lycorane.



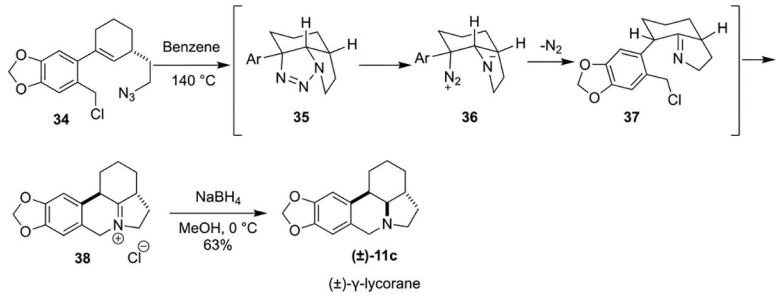
Scheme 3.
Preparation of intermediates **21a-c.**



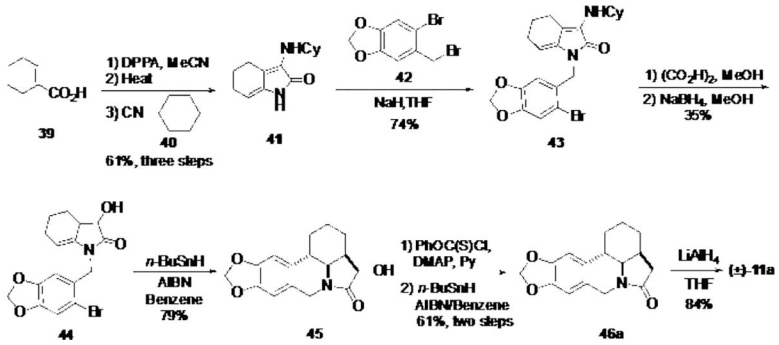
Scheme 4.
Martin's synthesis of (±)-α, β, and δ-lycorane.



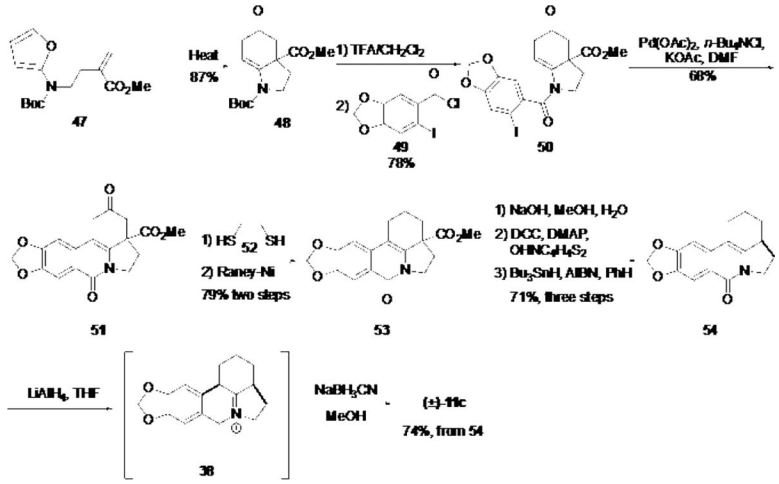
Scheme 5.
Synthesis of intermediate **34.**



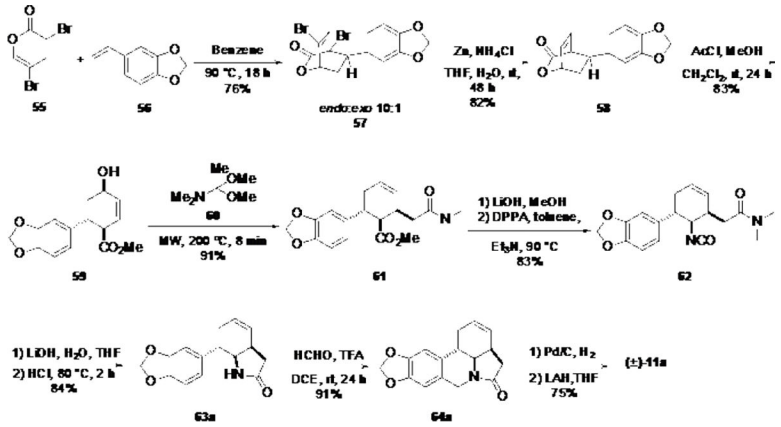
Scheme 6.
Pearson's synthesis of (±)-γ-lycorane.



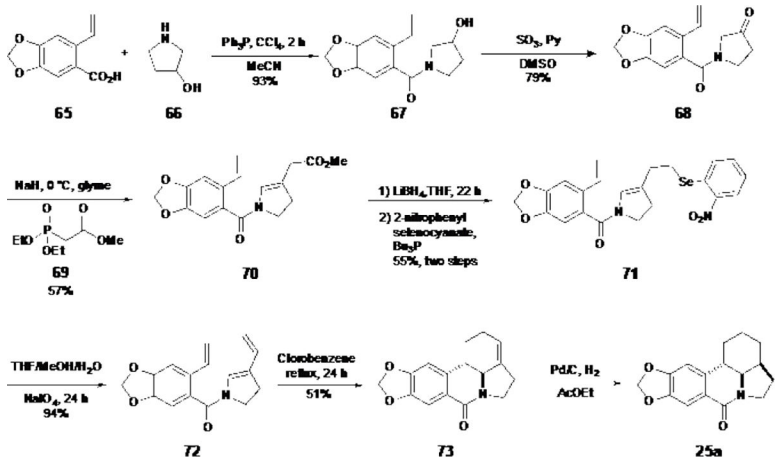
Scheme 7.
Rigby's synthesis of (±)-α-lycorane.



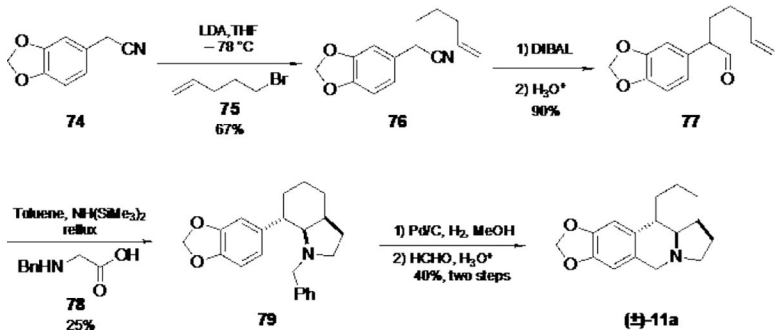
Scheme 8.
Padwa's synthesis of (±)-γ-lycorane.



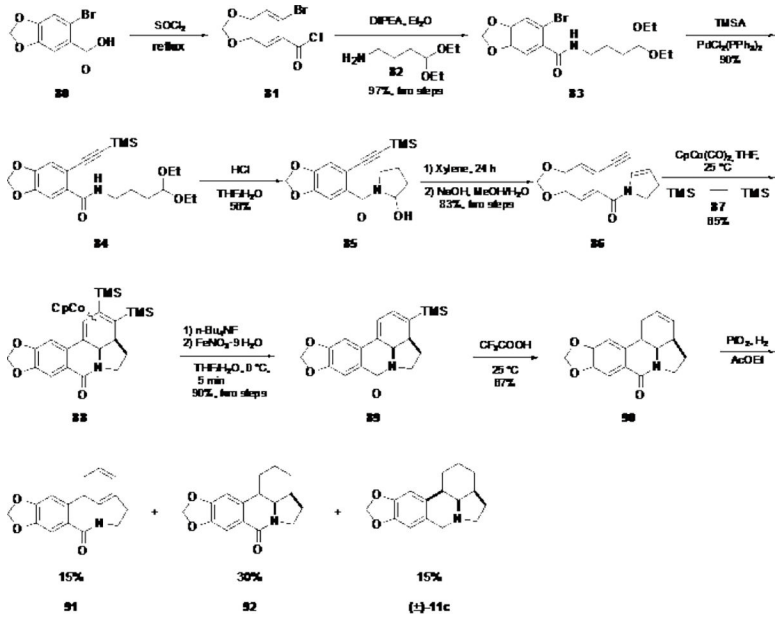
Scheme 9.
Cho's synthesis of (±)-α-lycorane.



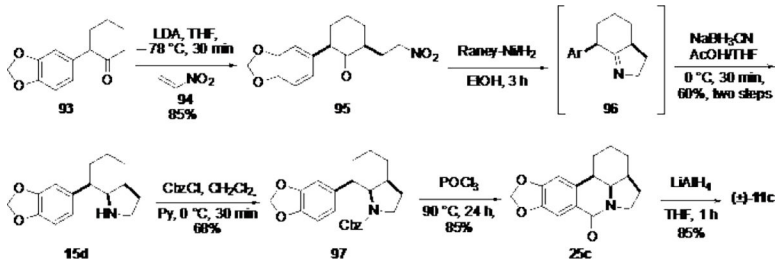
Scheme 10.
Stork's formal synthesis of (±)-α -lycorane.



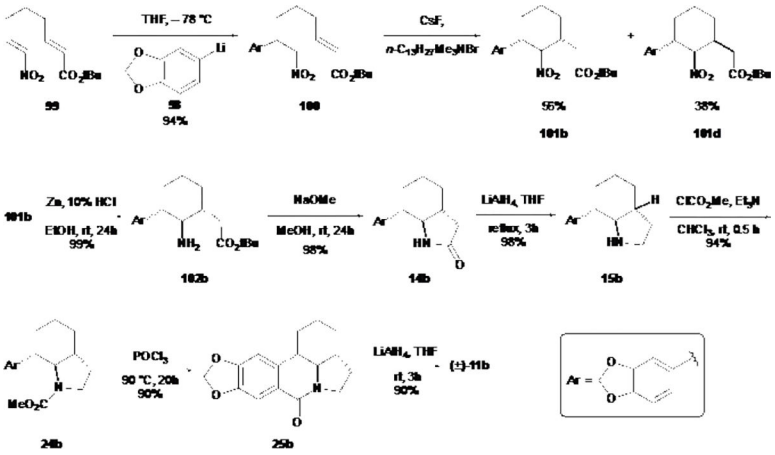
Scheme 11.
Wang's synthesis of (±)-α-lycorane.



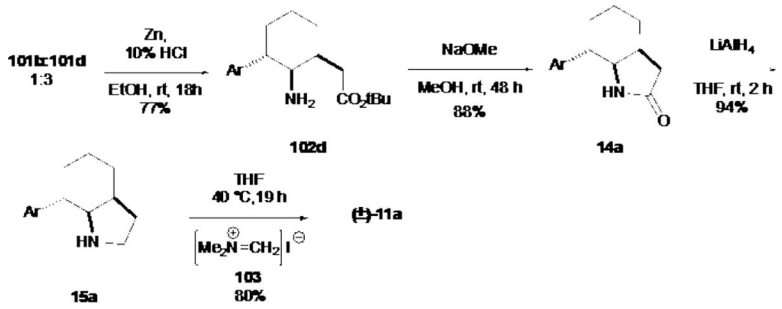
Scheme 12.
Vollhardt's formal synthesis of (±)-γ-lycorane.



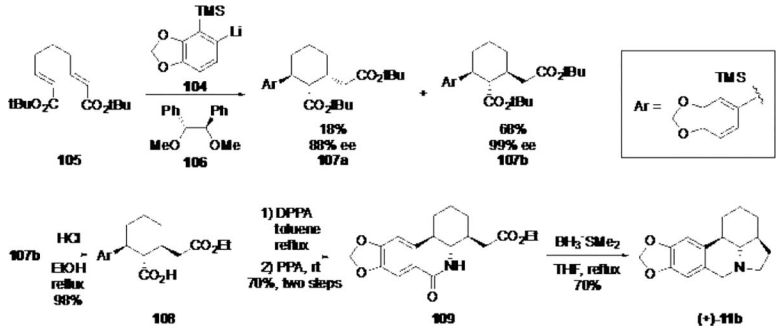
Scheme 13.
Tu's synthesis of (±)-γ-lycorane.



Scheme 14.
Tomioka synthesis of (±)-β-lycorane.

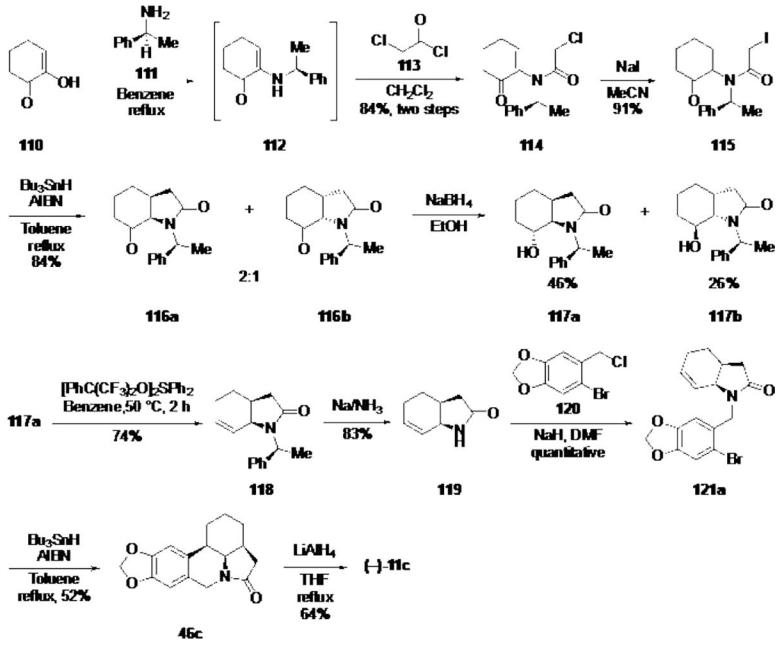


Scheme 15.
Tomioka's synthesis of (±)-α-lycorane.



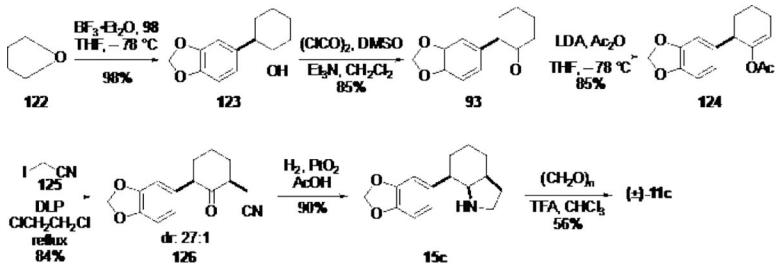
Scheme 16.

Tomioka's asymmetric synthesis of (+)-β-lycorane.



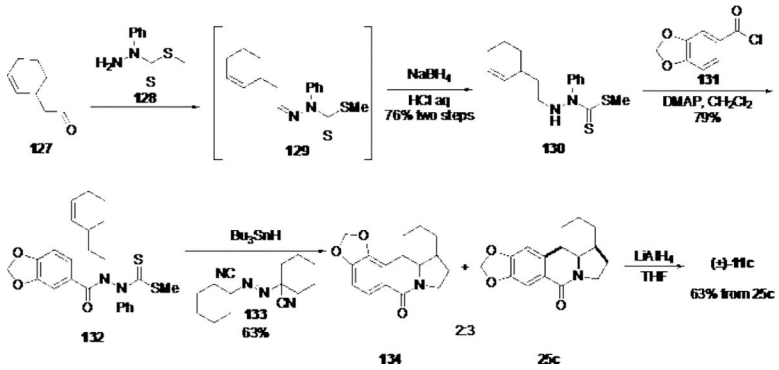
Scheme 17.

Bialy's synthesis of (−)-γ-lycorane.



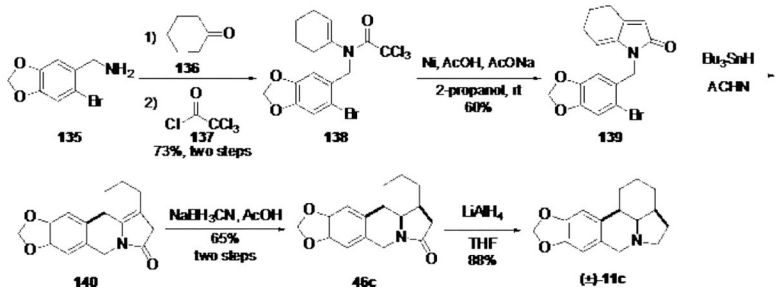
Scheme 18.

Cordero's synthesis of (±)-γ-lycorane.

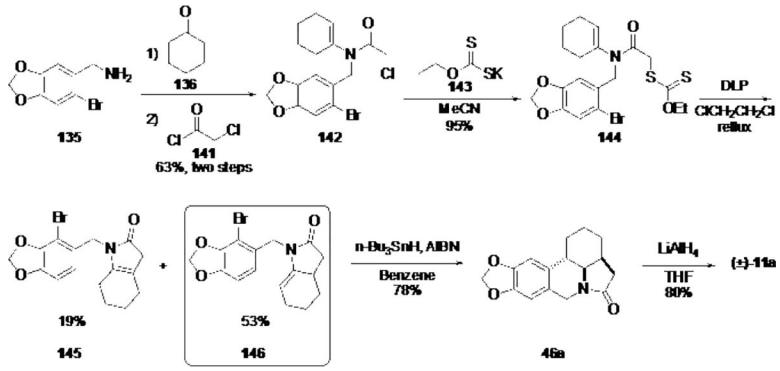


Scheme 19.

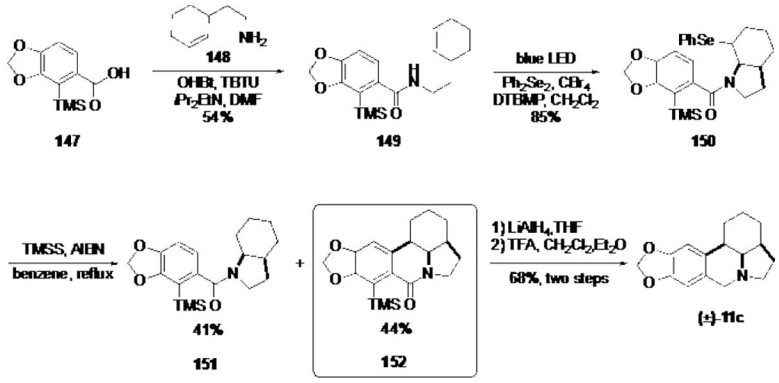
Zard's formal synthesis of (±)-γ-lycorane.



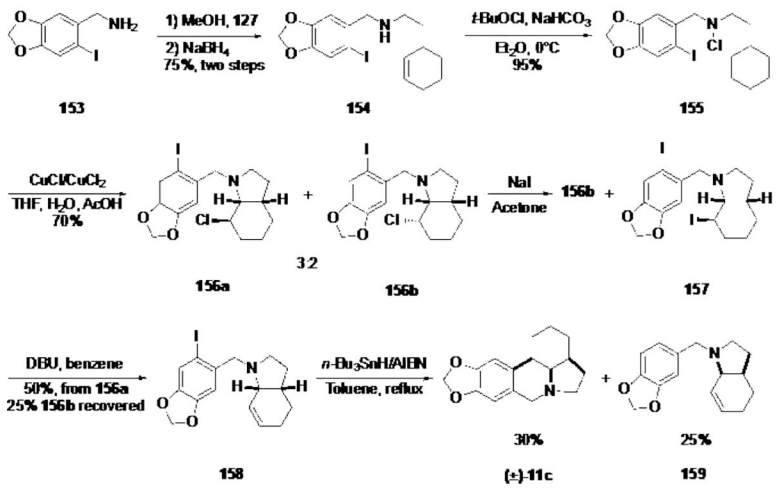
Scheme 20.
Zard's second synthesis of (±)-γ-lycorane.



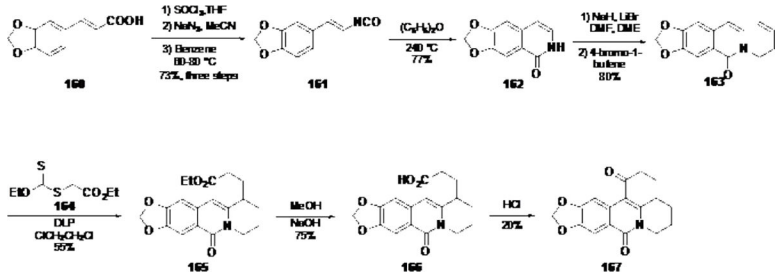
Scheme 21.
Zard's synthesis of (±)-α-lycorane.



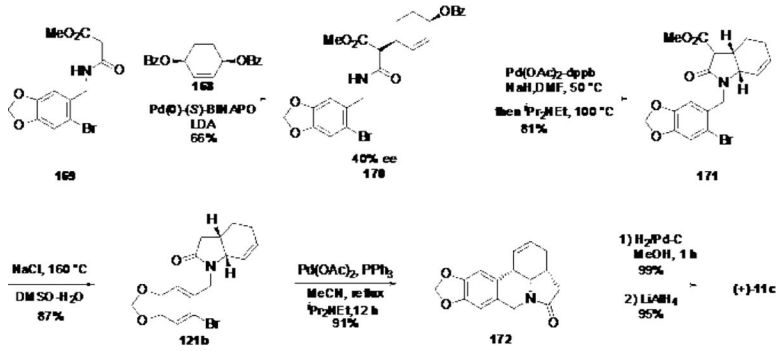
Scheme 22.
Regains's synthesis of (±)-γ -lycorane.



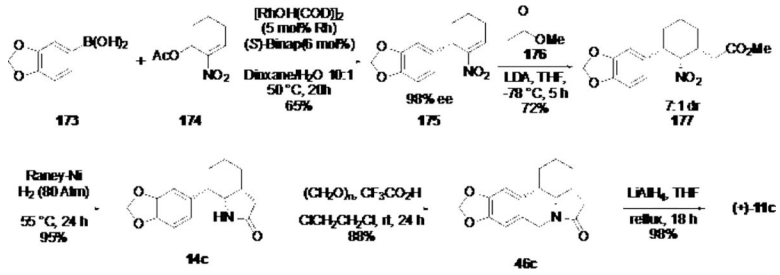
Scheme 23.
Cossy synthesis of (±)-γ -lycorane.



Scheme 24.
Miranda's formal synthesis of (±)-γ -lycorane.

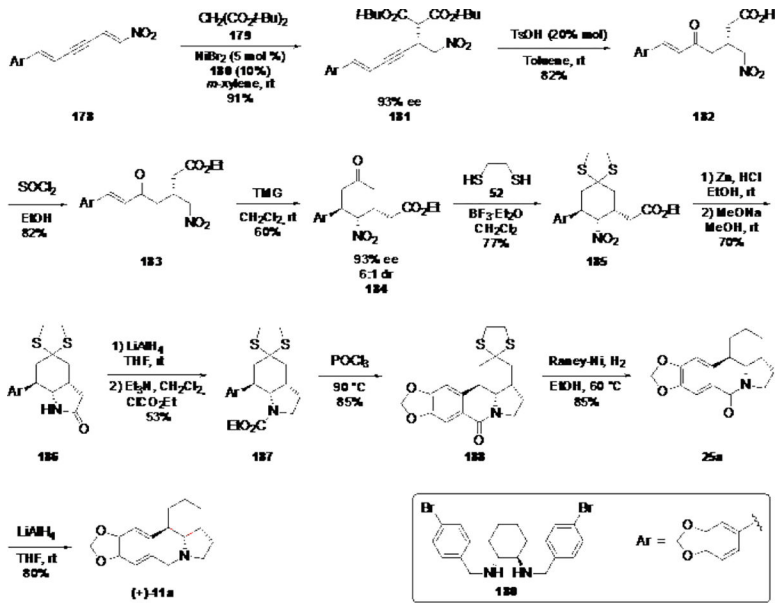


Scheme 25.
Mori's synthesis of (+)-γ-lycorane.

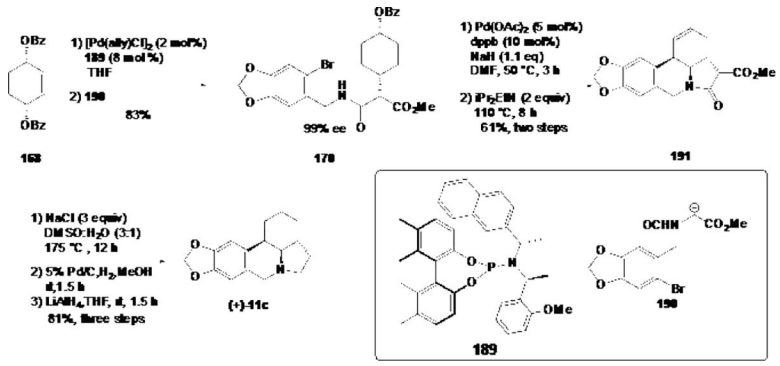


Scheme 26.

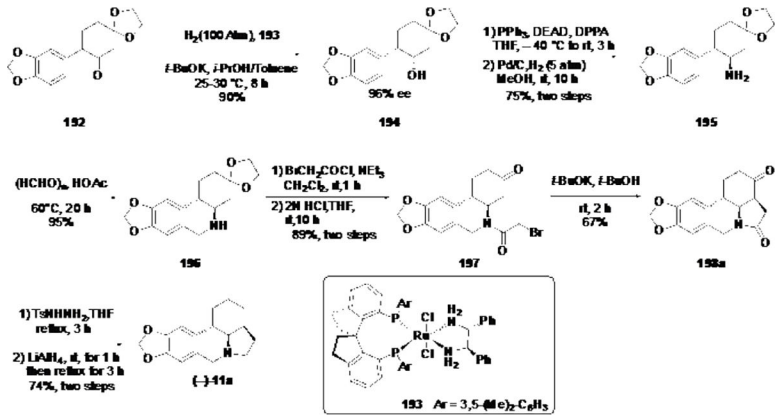
Gong's asymmetric synthesis of (+)-γ-lycorane.



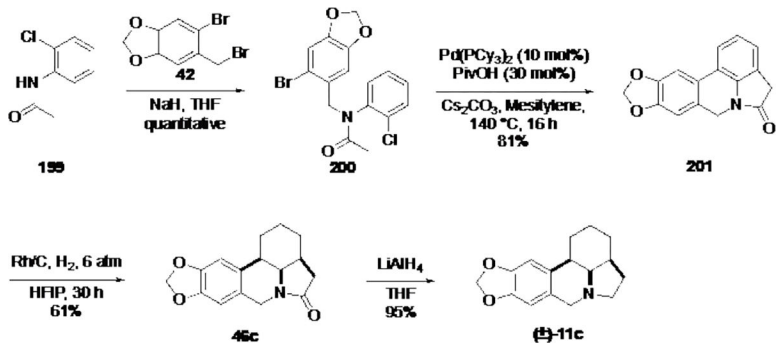
Scheme 27.
Shao’s asymmetric synthesis of (+)-α-lycorane.



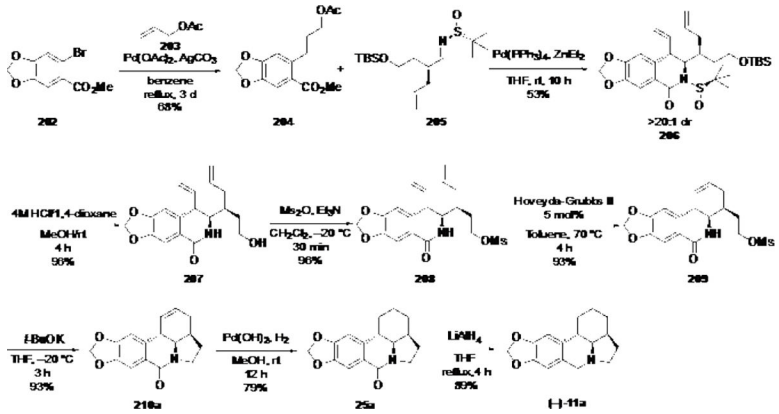
Scheme 28.
Ojaima's synthesis of (+)-γ-lycorane.



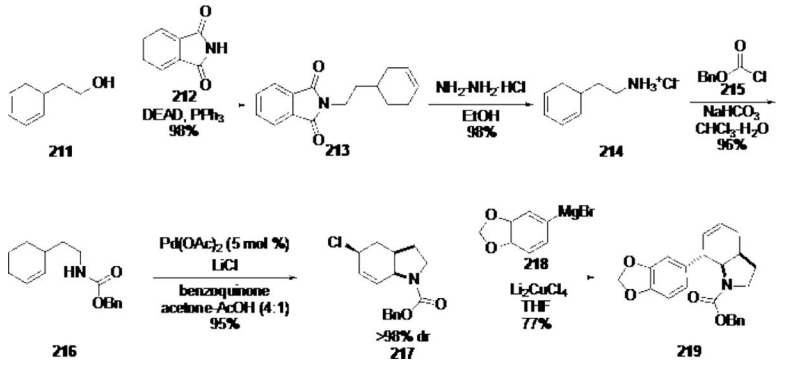
Scheme 29.
Zhou's Synthesis of (−)-α -lycorane.



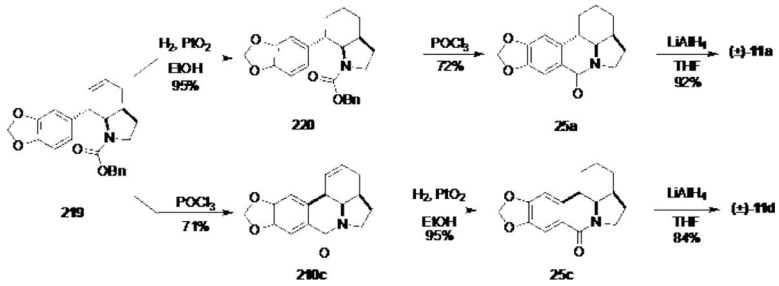
Scheme 30.
Baudoin's synthesis of (±)-γ-lycorane.



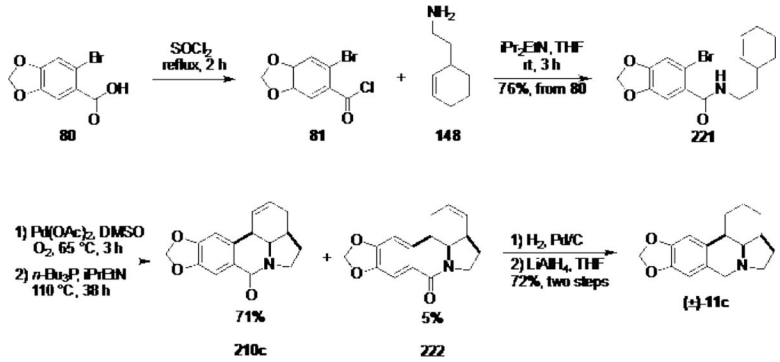
Scheme 31.
Sun's synthesis of (−)-α-lycorane.



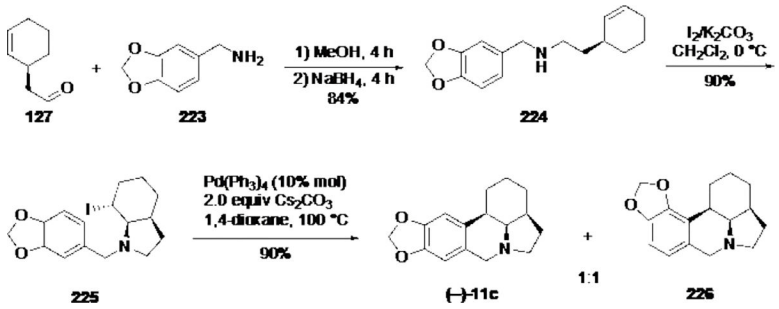
Scheme 32.
Synthesis of intermediate **219.**



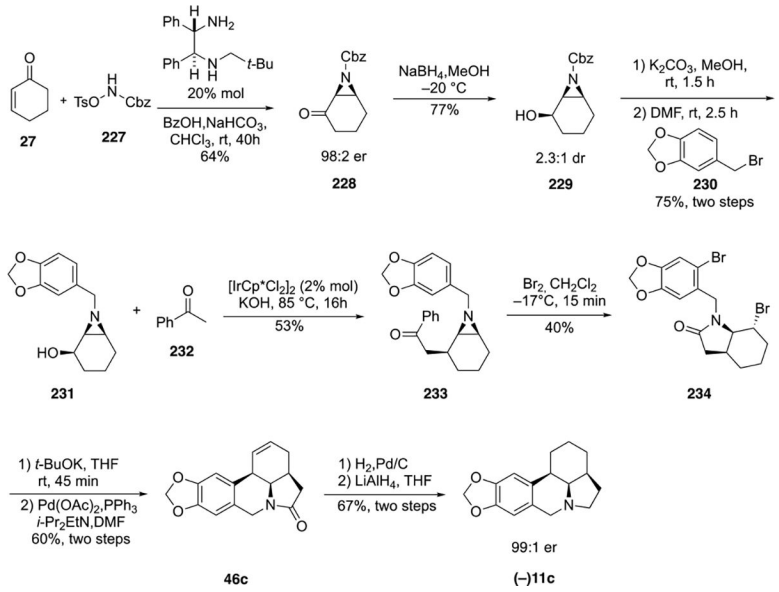
Scheme 33.
Bäckvall synthesis of (±)-α, γ -lycorane.



Scheme 34.
Chuang's synthesis of (±)-γ -lycorane.

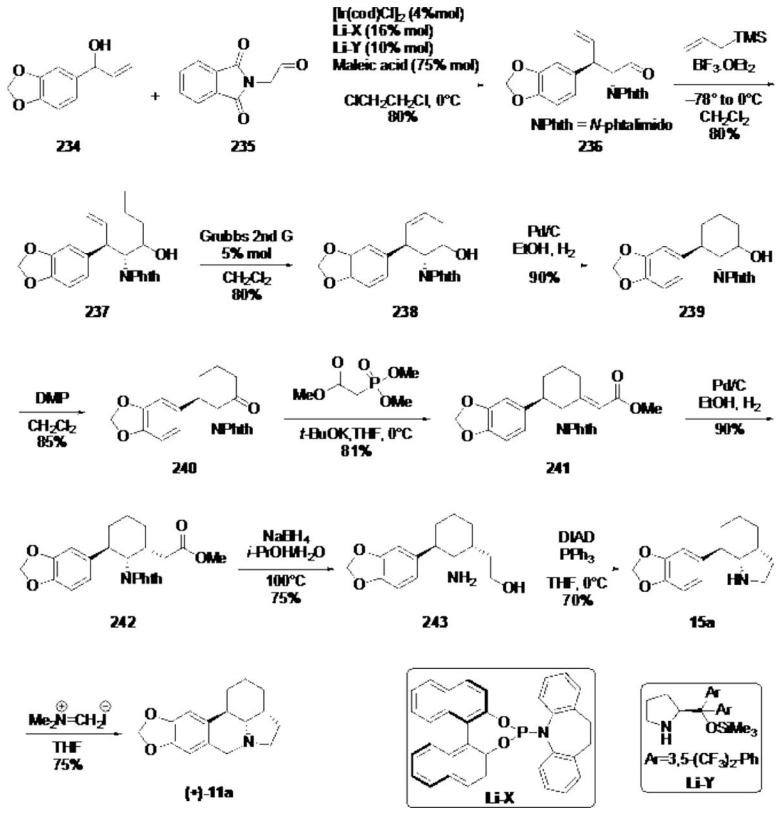


Scheme 35.
Huang's synthesis of (–)-γ-lycorane.



Scheme 36.

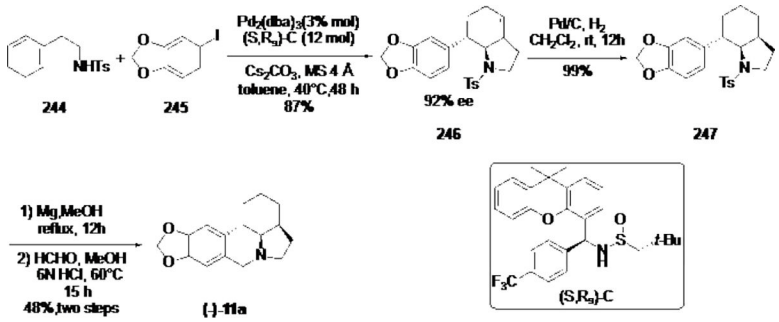
Donohoe's synthesis of (−)-γ -lycorane.



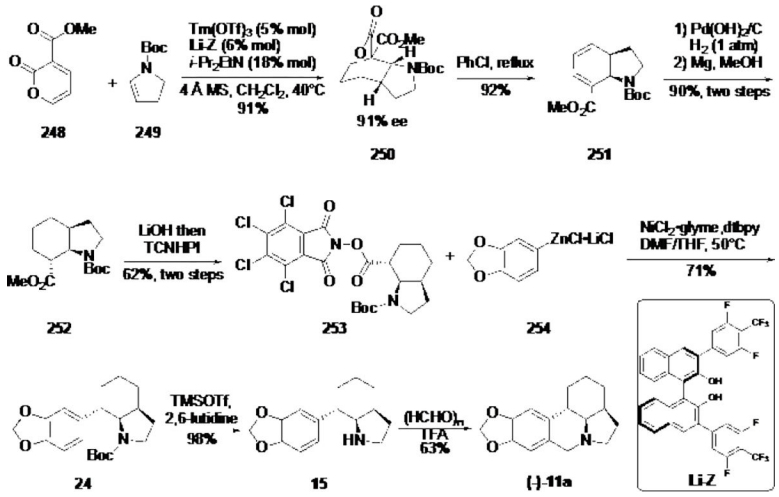
234 235 236 237 238 239 240 241 242 243 15a (+)-11a

Scheme 37.

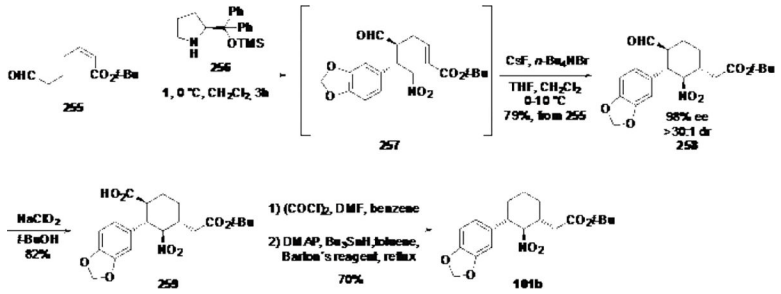
Yang's synthesis of (+)-α, (+)-β, (+)-γ, (−)δ -lycorane.



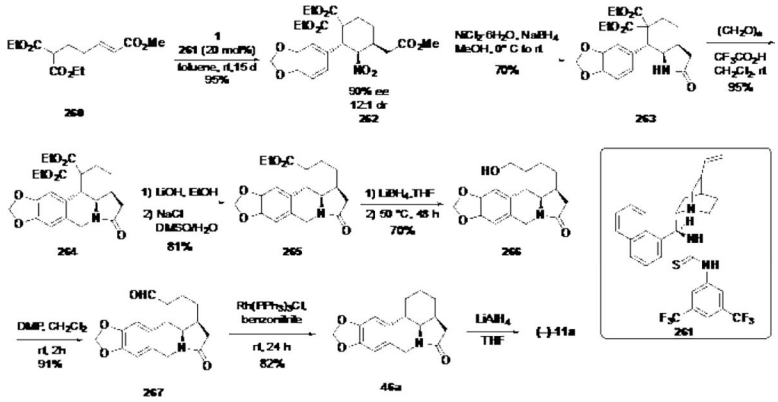
Scheme 38.
Zhang synthesis of (−)-α-lycorane.



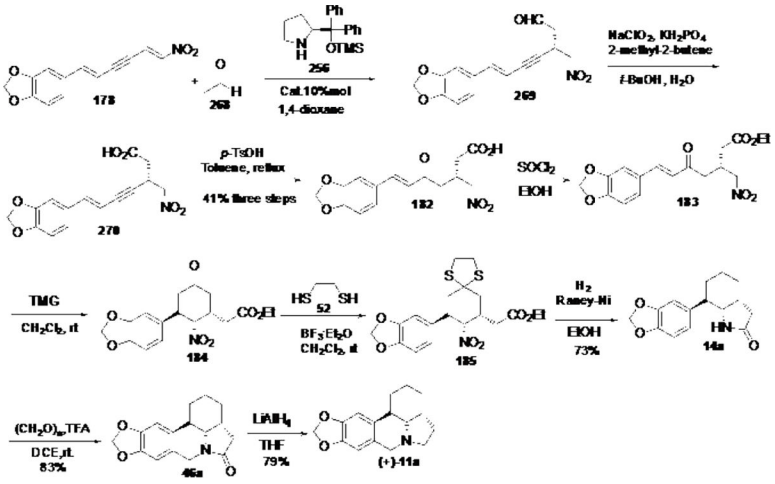
Scheme 39.
Cai's synthesis of (−)-α-lycorane.



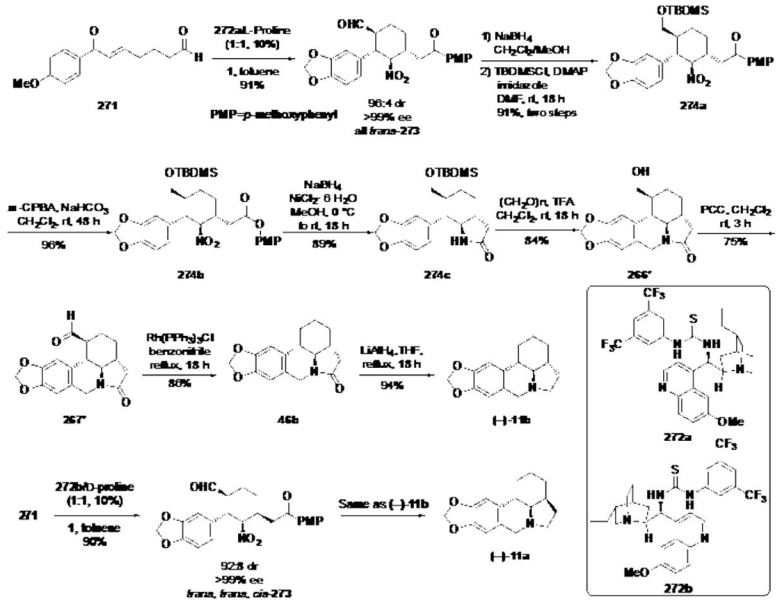
Scheme 40.
Hong's formal synthesis of (−)-β-lycorane.



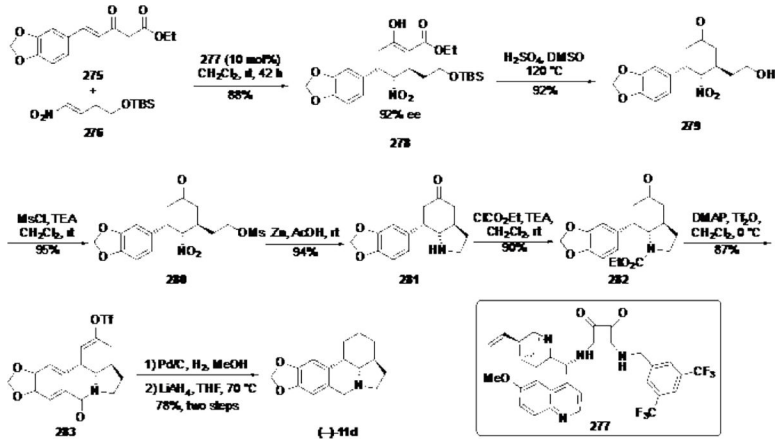
Scheme 41.
Xu’s formal synthesis of (−)-α-lycorane.



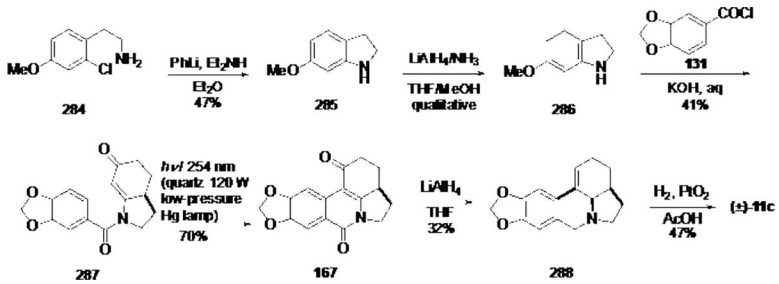
Scheme 42.
Shao's asymmetric synthesis of (+)-α-lycorane.



Scheme 43.
Zhao's asymmetric synthesis of (–)-α- and β(–)-lycorane.

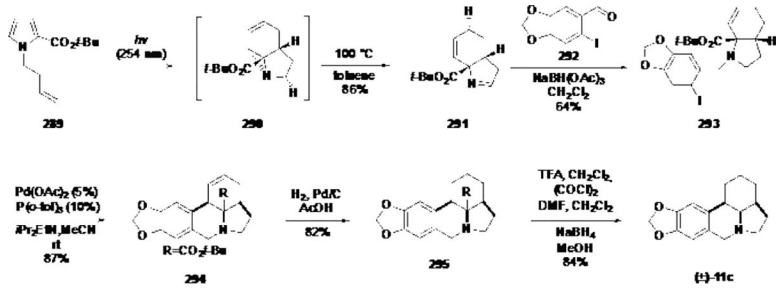


Scheme 44.
Wei's asymmetric synthesis of (−)-δ-lycorane.

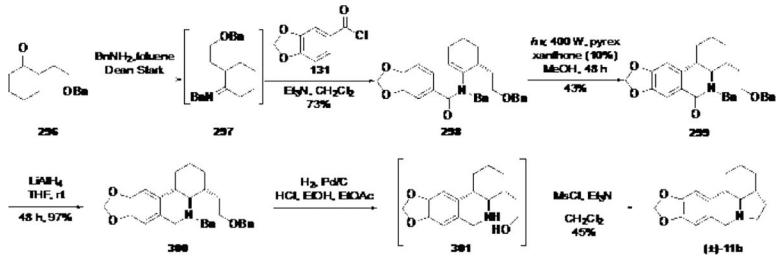


Scheme 45.

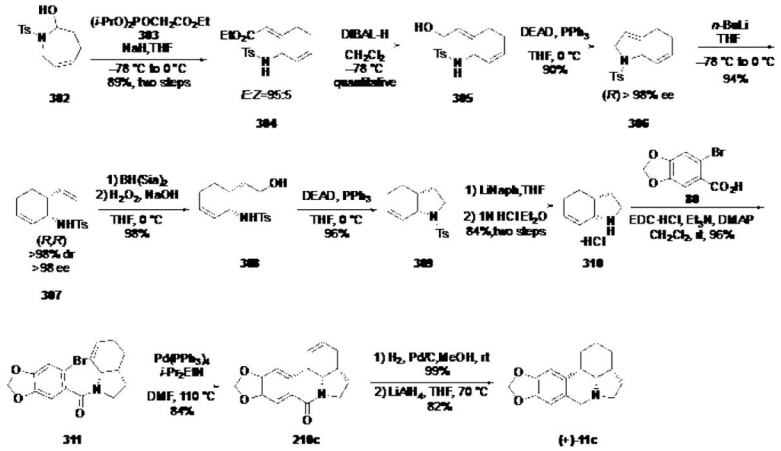
Lida's synthesis of (±)-γ-lycorane.



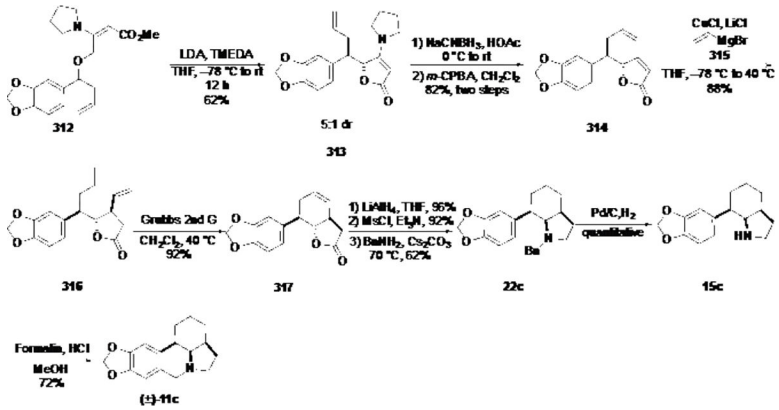
Scheme 46.
Booker-Milburn's synthesis of (±)-γ-lycorane.



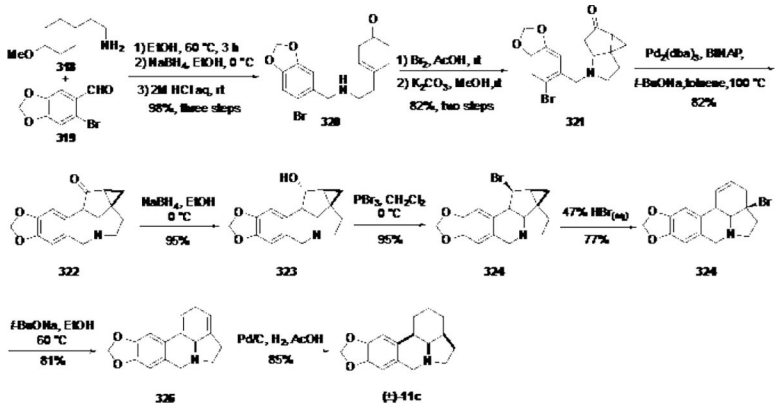
Scheme 47.
Booker-Milburn's synthesis of (±)-β-lycorane.



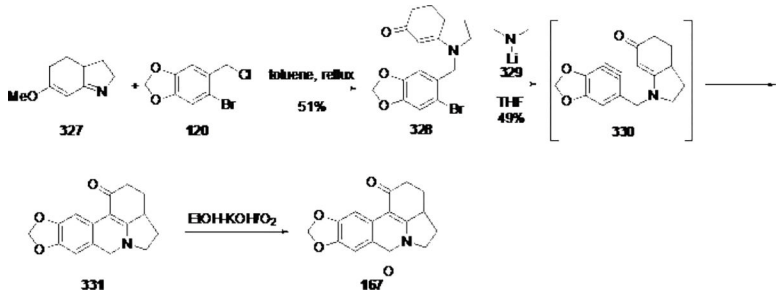
Scheme 48.
Tomooka's synthesis of (+)-γ-lycorane.



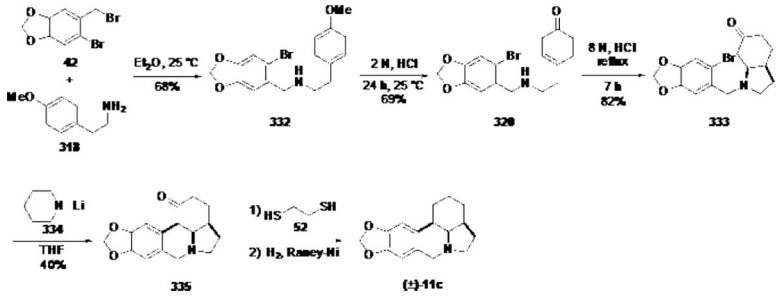
Scheme 49.
Li's synthesis of (±)-γ-lycorane.



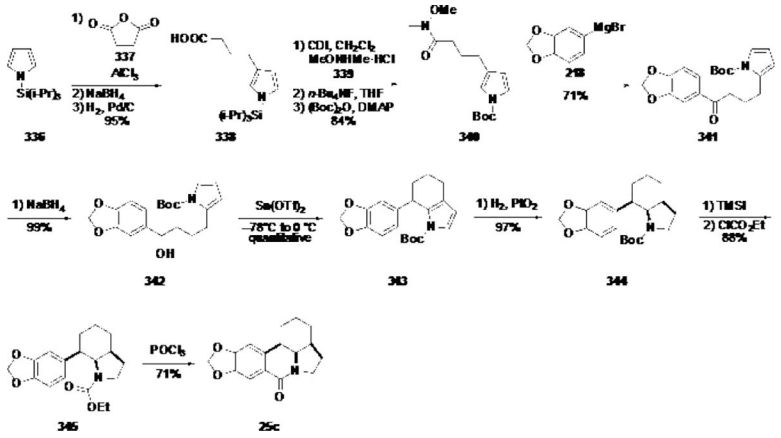
Scheme 50.
Liu's synthesis of (±)-γ -lycorane.



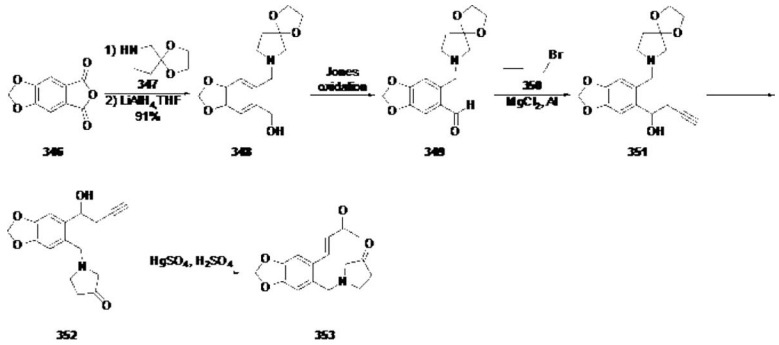
Scheme 51.
Kibayashi's formal synthesis of (±)-γ-lycorane.



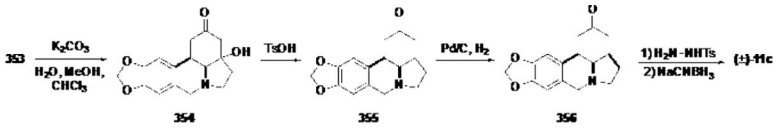
Scheme 52.
Ueda's synthesis of (±)-γ-lycorane.



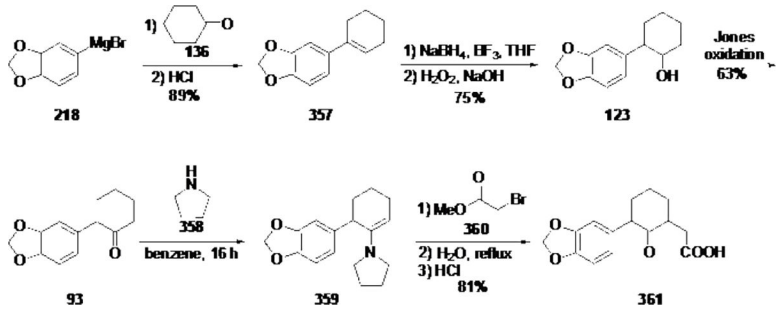
Scheme 53.
Angle formal synthesis of (±)-γ -lycorane.



Scheme 54.
Ganem's synthesis of intermediate **353.**

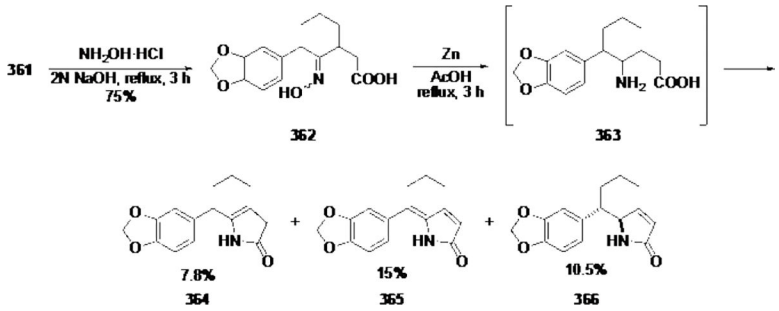


Scheme 55.
Ganem's synthesis of (±)-γ-lycorane.

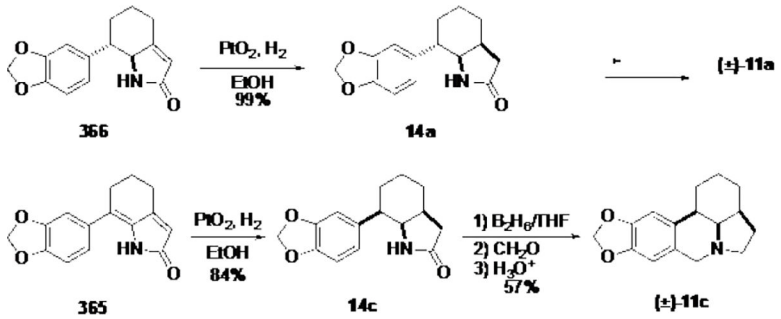


Scheme 56.

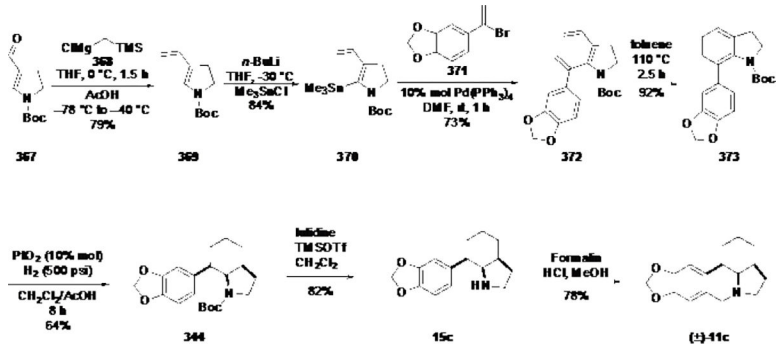
Umezawa's synthesis of intermediate **361.**



Scheme 57.
Umezawa's synthesis of intermediates **364–366.**

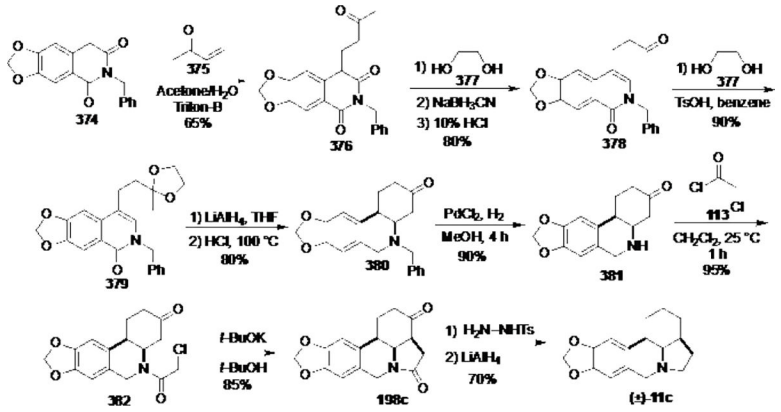


Scheme 58.
Umezawa's syntheses of (±)-α and (±) γ-lycorane.

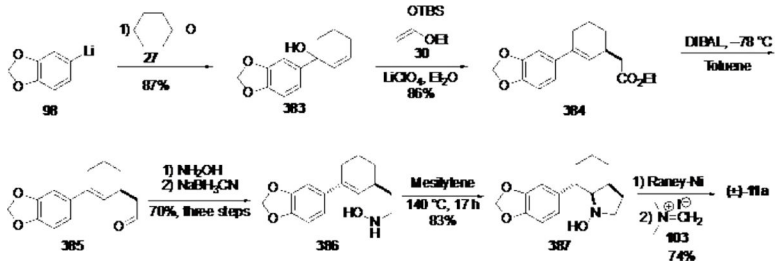


Scheme 59.

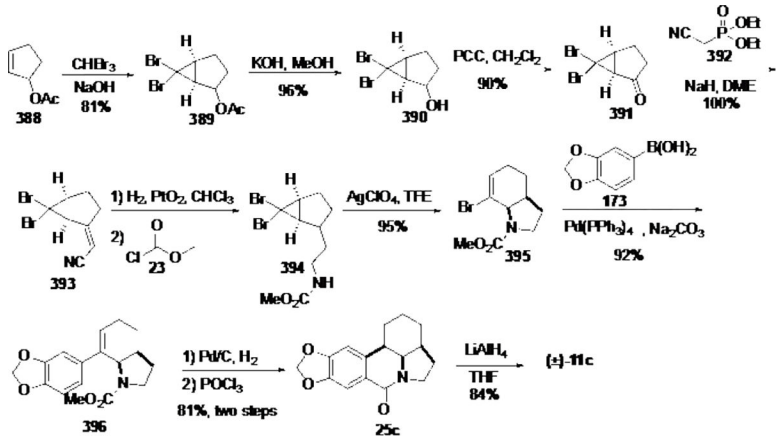
Funk's synthesis of (±)-γ-lycorane.



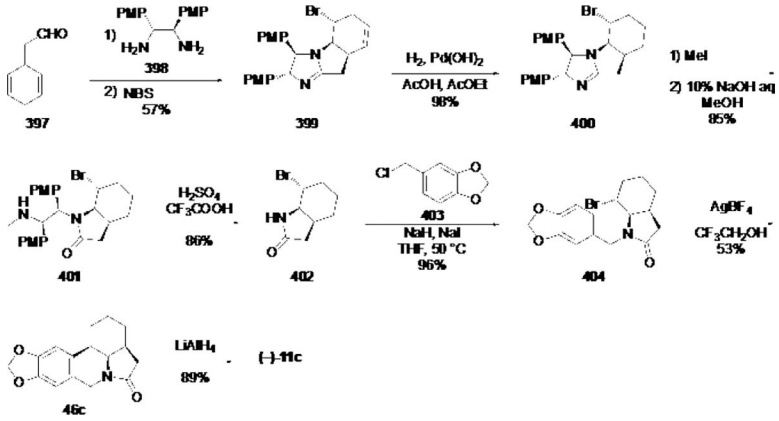
Scheme 60.
Kikuchi's synthesis of (±)-γ-lycorane.



Scheme 61.
Oppolzer's synthesis of (±)-α-lycorane.

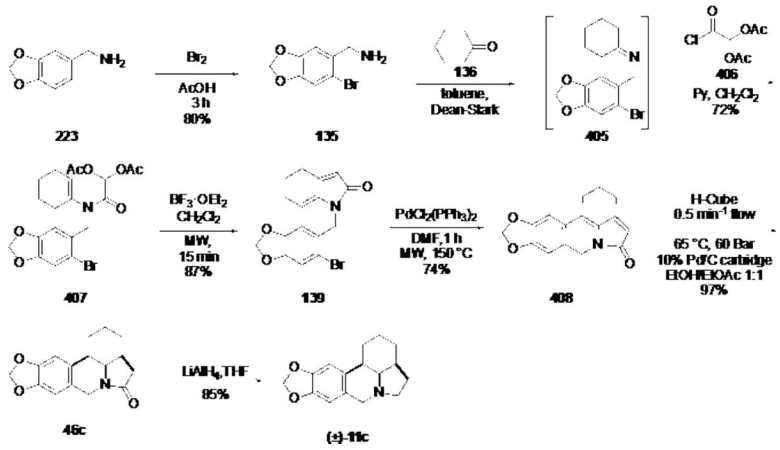


Scheme 62.
Banwell's synthesis of (±)-γ-lycorane.

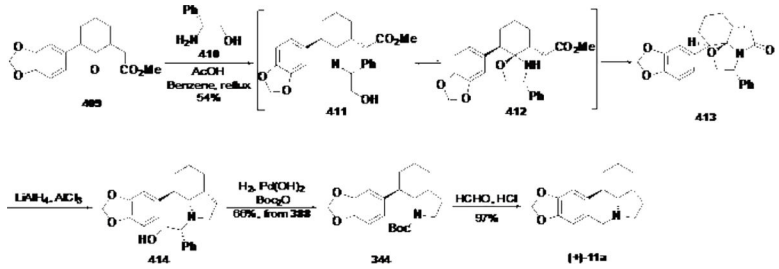


Scheme 63.

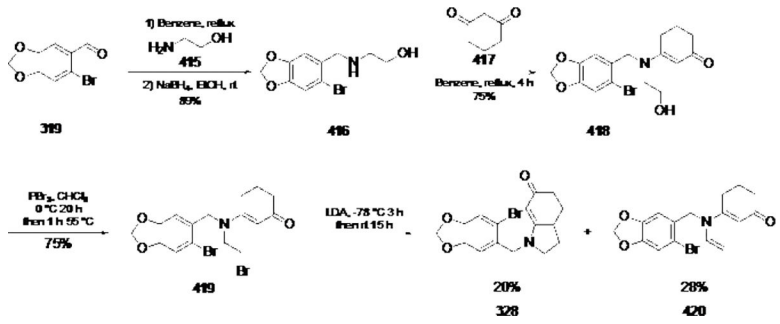
Fujioka's asymmetric synthesis of (−)-γ-lycorane.



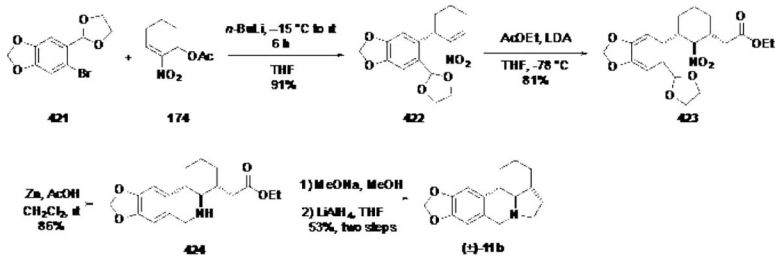
Scheme 64.
Hilton's synthesis of (±)-γ-lycorane.



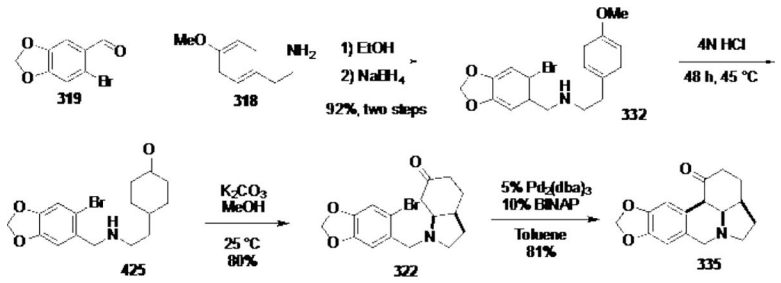
Scheme 65.
Amat's synthesis of (+)-α-lycorane.



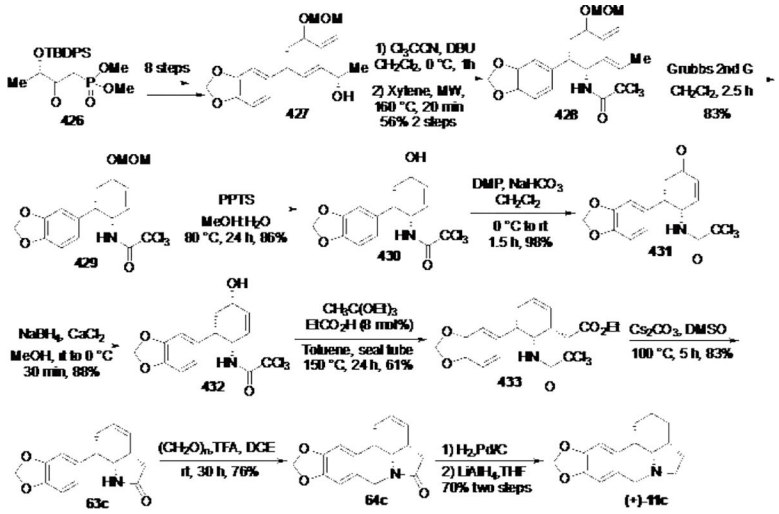
Scheme 66.
Kibayashi's formal synthesis of (±)-γ-lycorane.



Scheme 67.
Liu's synthesis of (±)-β-lycorane.



Scheme 68.
Zhang's formal synthesis of (±)-γ-lycorane.



Scheme 69.
Prasad's synthesis of (+)-γ-lycorane.