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Synthetic approaches toward the reserpine

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Synthetic approaches toward the reserpine

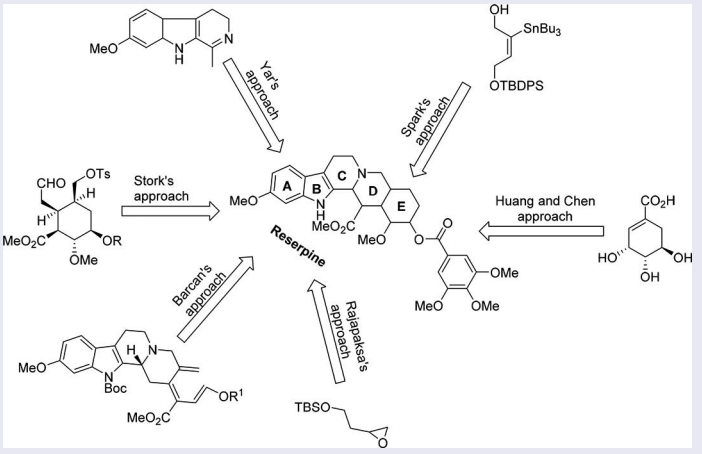
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ABSTRACT

Reserpine is an indole alkaloid, antipsychotic, and antihypertensive drug that has been used for the control of high blood pressure and for the relief of psychotic symptoms. It was first isolated in 1952 from the dried root of *Rauwolfia serpentina* whose molecular structure was established in 1953 and natural configuration was published in 1955. The first total synthesis of reserpine was reported by Woodward in 1958. This review article updates current multistep synthetic approaches toward the reserpine natural product and its analogues.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
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KEYWORDS
Enantioselective synthesis; indole-alkaloid; reserpine; stereoselective reactions; total synthesis

Introduction

Reserpine is naturally occurring alkaloid, which was first obtained from Indian snake root *Rauwolfia serpentina* by Müller et al.[1] Reserpine-distributing pentacyclic yohimbine skeleton is an indole lipid-soluble alkaloid, and their synthetic efforts are reviewed by Chen and Huang.[2] Reserpine is such a pharmacological substance which decreases neuronal or physiological activity of central nervous system. From the excitatory neurotransmitter norepinephrine, it hinders the postganglionic nerve fiber in the synaptic gap.[3] Pharmacological studies show that reserpine is a model target due to its influential antipyretic,

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tranquillizer, and antihypertensive properties.[3,4] In addition to these biological properties, reserpine is used as central nervous system hypnagogic, widely used for the treatment of melancholia and hypertension.[4–7] The correct formula for reserpine was also first proposed by the same group (Dorfman et al.[8]).

The relative configuration of reserpine was confirmed in the first magnificent total synthesis attained by Woodward et al.[9] Biosynthetic origins of reserpine were proposed on the basis of established structure and stereochemistry by Hahn and Werner,[10] Wenkert and Bringi,[11] Barger and Scholz,[12] and Woodward.[13] In 1960, Leete[14] proved that tryptamine is an indole moiety precursor of reserpine by the use of radioactive tracers. The synthesis of reserpine is antagonizing and captivating due to its pentacyclic structure which contains six bordering chiral centers and biological activity.[2] Structure–activity relationship studies of reserpine have shown that tranquillizer activity of compound is linked to the C-18 trimethoxybenzoyl group.[2]

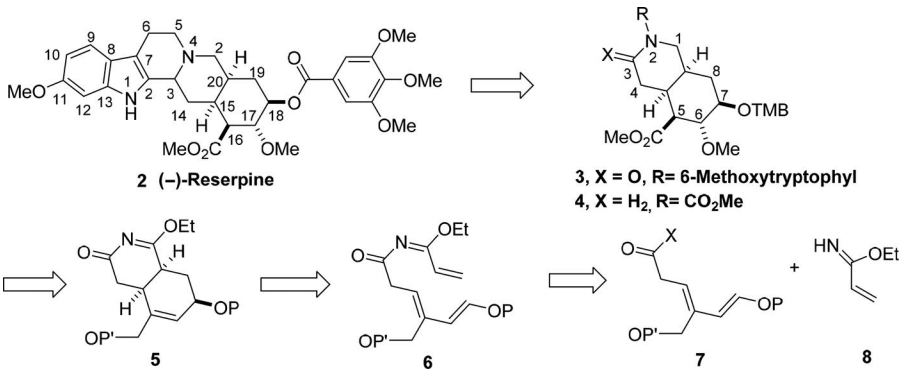
Synthetic strategies toward the synthesis of reserpine

Spark approach through intramolecular Diels–Alder reaction

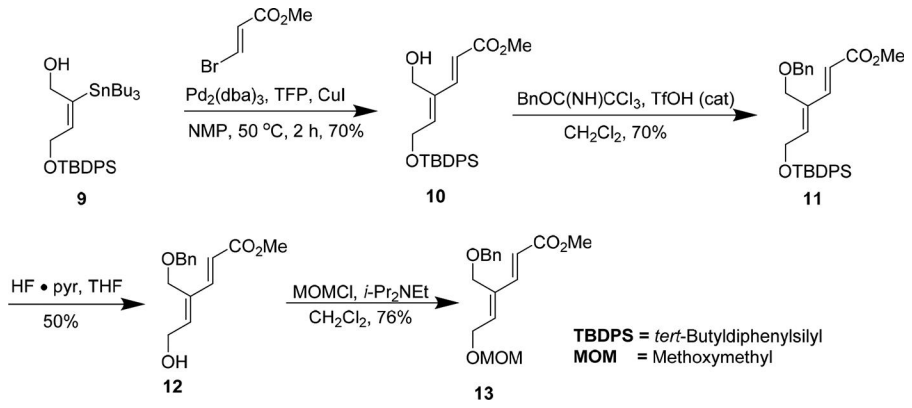
Sparks et al.[15] demonstrated stereochemically controlled intramolecular Diels–Alder reaction for the synthesis of reserpine ring system. They reported two synthetic routes for the construction of reserpine's D and E rings.

As mentioned in retrosynthetic Scheme 1, an efficient synthetic route toward Woodward intermediate **3**, which is also known as a perhydroisoquinol-3-one (rings DE of reserpine), would allow regioselective formation of C-ring of reserpine.[9,16–18]

The functional group conversion, protection/deprotection strategy, and reduction of the hexahydroisoquinolone synthon **5** would lead to the formation of perhydroisoquinolines **3** and **4**. Hexahydroisoquinolone synthon **5** could be accomplished from the intramolecular Diels–Alder cycloaddition of diene synthon **6,** where diene and dienophile are the part of same molecule. In this strategy, three of the five asymmetric centers were accessed through the tether endo mode cyclization of the diene fragment **7** where E-ring functionality is kept within diene **7**. Diels–Alder precursor **6** could be produced by coupling of hexadienoic acid synthon **7** with 1-aza-2-ethoxy-1,3-butadiene **8** (Scheme 1).



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



Scheme 2. Synthesis of 2,4-hexadienoic acid **13**.

In planning the synthesis of 3,5-hexadienoic acid synthon **7**, palladium-catalyzed vinyl halide coupling with a vinyl-organostannanes was considered to be the most convenient way. The synthesis of first-generation diene of type **7** was started using Stille coupling reaction conditions.[19,20] The standard reaction conditions to perform Stille coupling were failed to give desired coupling product **10**. Therefore, several reaction conditions for the Stille coupling were screened and only optimized reaction conditions are described in below mentioned synthetic scheme (Scheme 2).[21] A conjugated ester **10** was obtained in good yield upon treatment of organostannane **9** with methyl 3(*E*)-bromoacrylate using 2 mol% $Pd_2(dba)_3$, 16 mol% 2-trifurylphosphine, and 1.4 equiv. of copper iodide in *N*-methylpyrrolidinone at 65 °C.[22] Benzylation of the primary alcohol of conjugated ester **10** was performed using benzyl trichloroacetimidate under acidic conditions to give benzyl ether-protected diene **11** in good yield (Scheme 2).[23] To replace protecting group tert-butyldiphenylsilyl (TBDPS) in compound **11** with methoxymethyl (MOM) protecting group, TBDPS was first hydrolyzed to corresponding primary alcohol **12**, which was then protected with MOM protecting group **13**.

The silyl protecting group in diene **11** was replaced with methoxymethyl ether through silyl deprotection followed by addition of MOMCl using diisopropylethylamine as a base. Finally, kinetic deconjugation of the 2,4-hexadienoic ester **13** was performed using LDA/HMPA at −78 °C where desired 3(*Z*),5(*E*)-dienoic ester **14** was obtained in good yield (Scheme 2) and chemical structures are shown in Figure 1.

Both ^{1}H NMR and chemical studies revealed unexpected configuration of obtained deconjugated ester **14** around one of two double bonds and the given reaction conditions

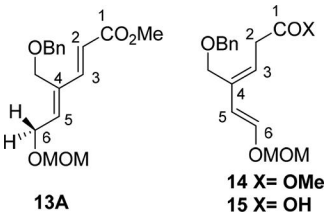


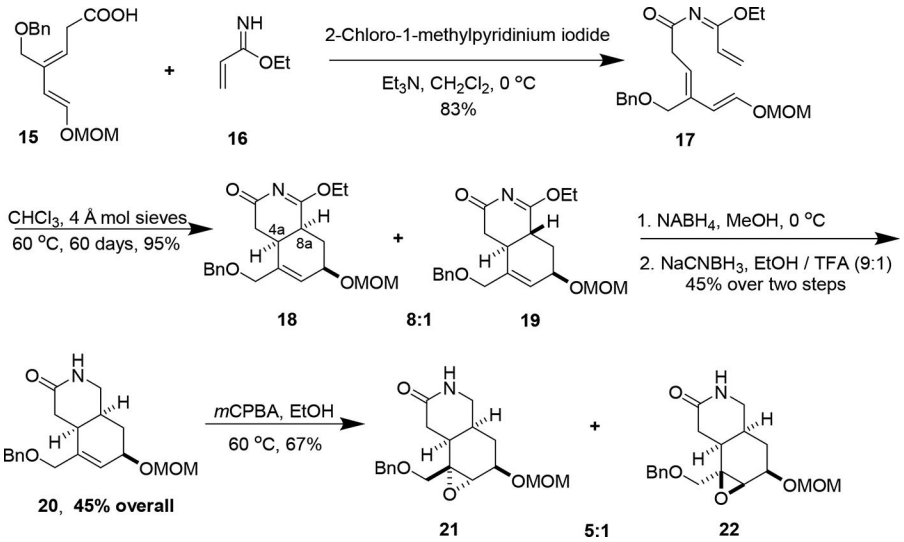
Figure 1. Structure of 2,4-hexadienoic ester **13A** and 3(*Z*),5(*E*)-dienoic ester **14**.

furnished the 3(*Z*),5(*E*)-dienoic ester **14**. Creation of 5(*E*) configuration **14** from the precursor 4(*Z*) suggests that **13A** rotamer is the only reacting species at −78 °C.

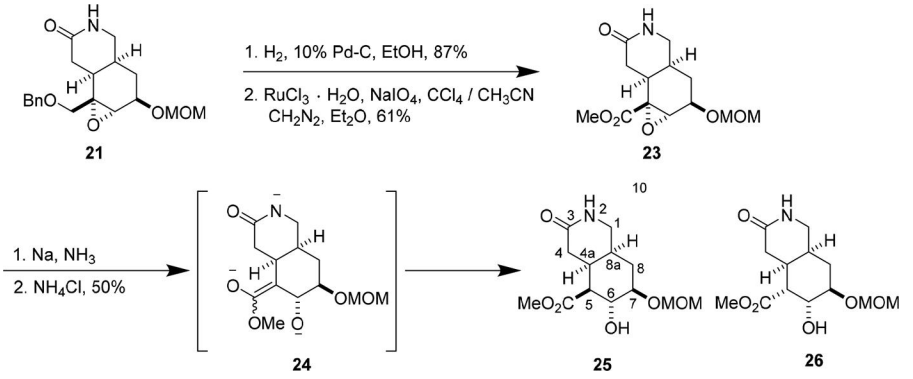
A very facile hydrolysis of ester **14** in the presence of KOH and aqueous MeOH furnished corresponding acid **15** in quantitative yield (Figure 1).

After several attempts, the synthesis of Diels–Alder precursor **17** was accomplished successfully through Mukaiyama protocol. The 2-chloro-1-methylpyridinium iodide-mediated coupling of diene acid **15** with *O*-ethylvinylimidate **16**[24] afforded Diels–Alder precursor **17** in 83% yield under Mukaiyama reaction conditions.[25] The intramolecular Diels–Alder reaction of *N*-acylvinylimidates **17** gave two cycloadducts **18** and **19** in an 8:1 ratio, respectively, in 95% yield when a dilute solution of Diels–Alder precursor **17** was heated at 60 °C for 60 days in the presence of mixture of $CHCl_3$ and 4 Å molecular sieves. The major cycloadduct **18** was obtained in low yield when mixture of cycloadduct was subjected to silica gel chromatography. However, the isomeric mixture **18** and **19** was directly used in the reduction sequence. The desired isoquinol-3-one **20** was obtained in 45% yield from isomeric mixture of **18** and **19** after successful two-step reduction of compounds **18** and **19** with $NaBH_4$ and $NaCNBH_3$. At this stage, efforts were directed toward installation of C-17 methoxy group. Regardless of the applied oxidative reaction condition, the hydroboration of the trisubstituted olefin **20** of E-ring was failed. To avoid this problem, oxygen atom at C-6 was introduced through two-step epoxidation-based fragmentation approach. The *m*CPBA-mediated epoxidation was initiated at 60 °C in the presence of protic solvent like EtOH. It should be noted that solvent capable of hydrogen bonding (EtOH) favors the formation of α-epoxide **21** in high yield as compared to β-epoxide **22** (Scheme 3).

To proceed epoxide fragmentation reaction, the benzyloxymethyl was converted to a carboxylic ester through deprotection of benzyl protecting group. The ester **23** could be obtained in number of steps through deprotection, oxidation, and esterification strategy. In fact, the 10% Pd-C-catalyzed (in the presence of H_2) deprotection of benzyl protecting group from **21** followed by ruthenium-catalyzed oxidation and diazomethane-mediated



Scheme 3. Synthesis of α-epoxide isomer **21** in high ratio.

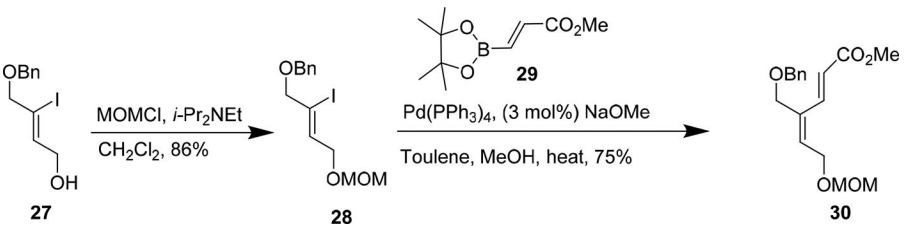


Scheme 4. Synthesis of per-hydrosoquinol-3-one **25/26**.

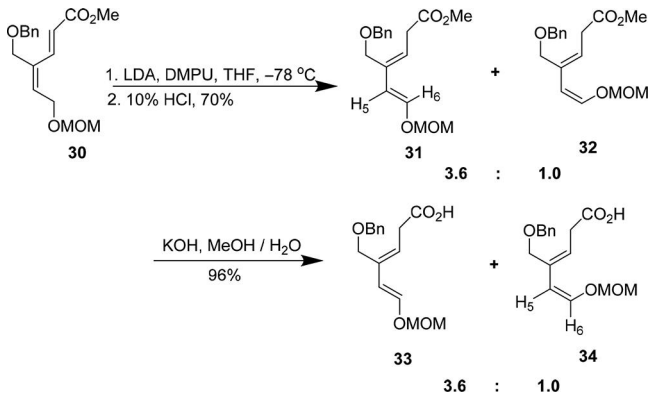
esterification furnished desired ester in 61% yield. Selective reduction of epoxy ester **23** to compound **25** could be obtained under very strong reductive condition (sodium metal in liquid ammonia at −78 °C). The compound **25** was obtained maximum in 50% yield along with recovery of compound **24** (Scheme 4). With the help of ^{1}H NMR spectroscopy, critical analysis of coupling constants of H5 at 2.68 ppm established stereochemistry of the newly created carbomethoxy functional group in the compound **25,** and small size of coupling constant of 4.6 Hz ($J_{H5\text{-}H4a}$) and large value of coupling constant 10.7 Hz ($J_{H5\text{-}H6}$) clearly indicate that the carbomethoxy group is equatorial in compound **25** (Scheme 4). The stereochemically developed DE rings of reserpine were attained by the region-selective H_2 addition across the C-O bond of epoxy with retention of configuration in the complete conversion of **23** to **25,** which cannot be achieved in the nonequatorial compound **26**.

To search for new synthetic route, a second-generation approach exploited utility of the Suzuki cross-coupling protocol for the synthesis of desired 2,4-hexadienoic ester **30**. Further deconjugation of 2,4-hexadienoic ester **30** leads to the construction of target reserpine (Scheme 5).[26] The vinyl iodide **28** with methoxymethyl protecting group was obtained upon treatment of alcohol **27** with methoxymethyl chloride under basic reaction conditions.[27] Palladium-catalyzed carbon–carbon coupling of boronic ester **29** with iodide **28** provided 2(*E*),4(*E*)-hexadienoic ester **30** in 75% yield.[28] The coupling mixture **28** and **29** was refluxed under standard Suzuki reaction conditions using $Pd(PPh_3)_4$, NaOMe, and toluene/methanol as a solvent (Scheme 5).

The kinetic deconjugation of dienoic ester **30** was required to afford Diels–Alder precursor. Regardless of some efforts, inseparable mixture of isomers **31** and **32** was



Scheme 5. Synthesis of substituted 2(*E*),4(*E*)-hexadienoic ester **30**.



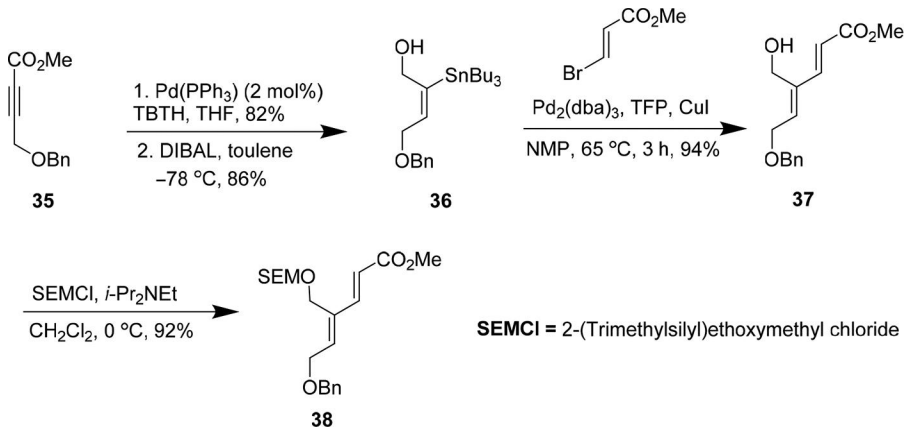
Scheme 6. Synthesis of substituted 3(*Z*),5(*E*)-hexadienoic acid.

formed upon dropwise addition of diene **30** to the solution of LDA in *N,N*-dimethylpropyleneurea (DMPU) and THF. Despite the use of various reaction conditions, no improvement in isomeric ratio 3.6 to 1 for isomer **31** and **32,** respectively, was observed. Further, isomeric ratio was determined by ^{1}H NMR. The ^{1}H NMR data of the mixture indicate that the 3(*Z*), 5(*E*) geometry is of the major isomer **31**. Extensive signal overlap in the ^{1}H NMR spectrum was observed due to inseparable mixture of isomers. On account of this reason, mixture was further saponified that allows determination of geometry of minor isomer **34**. It was found that minor isomer **34** possessed the 3(*Z*), 5(*Z*) geometry (Scheme 6).

The mixture of acid **33** and **34** could be subjected to the Diels–Alder cycloaddition. However, more selective method was anticipated for the synthesis of 3(*Z*), 5-(*E*)-hexadienoic acid **40**. For this purpose, the modified version of Stille coupling was further exploited as previously mentioned (Scheme 2).[21] Vinylstannane **36** was formed through the palladium-catalyzed hydrostannylation of alkynoate **35** in the presence of diisobutylaluminum hydride (DIBALH) and tributyltin hydride (TBTH).[29] Coupling reaction of vinylstannane **36** with bromo-substituted acrylic ester under Stille coupling was used (Scheme 2) and a longer duration and high temperature provided conjugated ester **37**. Protection of alcoholic moiety of diene **37** as a trimethylsilylethoxymethoxy ether (SEM) resulted in desired 2,4-hexadienoic ester **38** in 92% yield (Scheme 7).

The required deconjugation of 2(*E*),4(*Z*)-dienoic ester **38** was further investigated under strong basic reaction conditions. The slow addition of ester **38** to the solution of LDA and DMPU in the presence of THF followed by quenching with protic solvent gave a single product in high yield (89%). The ^{1}H NMR studies in combination with chemical analysis determined that deconjugation-based reaction offered 3(*Z*),5(*E*)-dienoic acid ester **39** as a main product. Further, lithium hydroxide-mediated saponification produced diene acid **40** in 97% yield (Scheme 8).

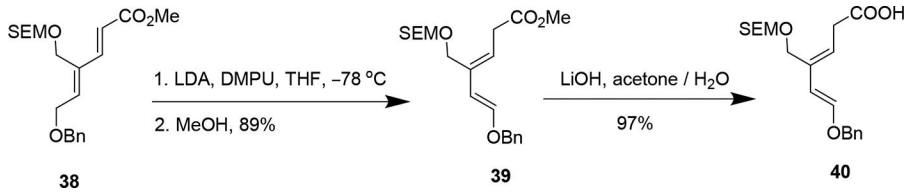
With the aim to further improve synthetic sequence, modified substrate for Diels–Alder cycloaddition reaction was prepared by treating 3,5-hexadienoic acid **40** with 1-aza-2-ethoxy-1,3-butadiene **16** in the presence of 2-chloro-1-methylpyridinium iodide.[24,25] The Mukaiyama reagent-based coupling strategy delivered *N*-acylvinylimidate **41** in 85%. Intramolecular cycloaddition occurred in the refluxing chloroform which provided two



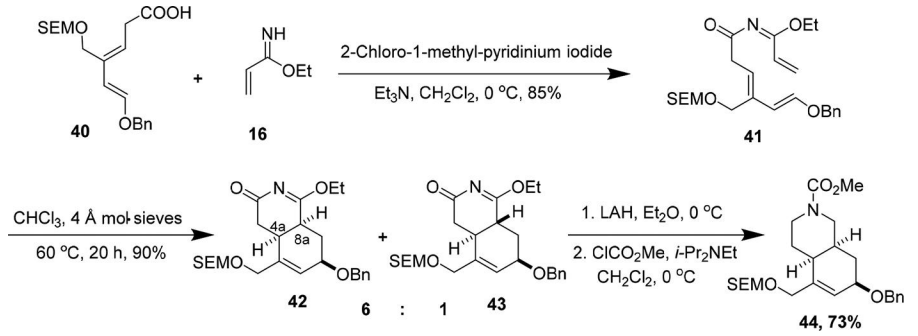
Scheme 7. Synthesis of 2(*E*),4(*Z*)-dienoic ester **38**.

cycloadducts **42** and **43** in 6:1 ratio (90% yields). The major cycloadduct **42** was labeled *cis* ring fusion on the basis of ^{1}H NMR coupling constant data ($J_{H4a\text{-}H8a}$) = 5.5 Hz) similar to that of a tether endo cycloaddition (Scheme 9). Moreover, C5–C6 double bond and *N*-acylimidate functionality (in the mixture of cycloadducts **42** and **43**) were reduced with lithium aluminum hydride and subsequently functionalized with methyl chloroformate to furnish methyl carbamate **44** in 73% yield over two steps (Scheme 9).

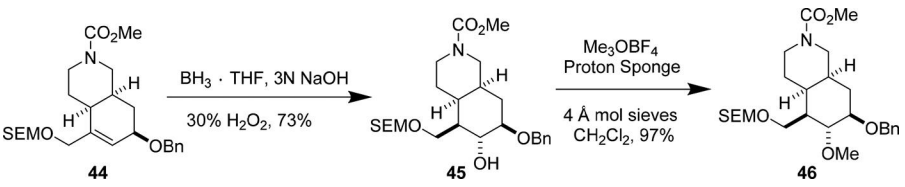
With the aim of introduction of hydroxy group at C6, hydroboration and oxidation strategy were studied. Hydroboration of olefin **44** was performed using $BH_3 \cdot THF$ complex followed by oxidation (H_2O_2, NaOH). This furnished the desired alcohol **45** in 73% yield.



Scheme 8. Synthesis of dienoic acid **40**.



Scheme 9. Synthesis of methyl carbamate **44**.



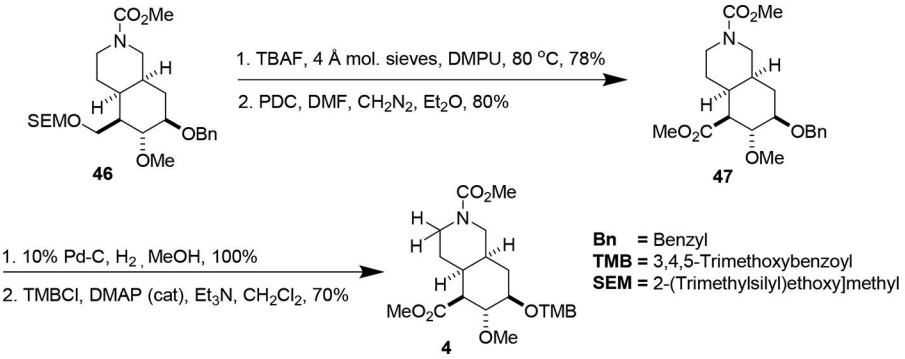
Scheme 10. Synthesis of methyl ether **46**.

Upon treatment of alcohol **45** with trimethyloxonium tetrafluoroborate in the presence of 4 Å molecular sieves in CH_2Cl_2, and Proton Sponge, the desired methyl ether **46** was obtained in 97% yield (Scheme 10).[30]

To accomplish the synthesis of perhydroisoquinoline synthon **4**, it is important to convert C-5 hydroxymethyl moiety to a corresponding methyl ester and transformation of the C-7 benzyloxy functionality to desired 3,4,5-trimethoxybenzoyl (TMB) group. Therefore, it would be necessary to remove SEM group first. The SEM protecting group was removed using TBAF in the presence of DMPU and 4 Å molecular sieves.[31] Subsequent pyridinium dichromate (PDC)-mediated oxidation of primary alcohol followed by esterification using CH_2N_2 in the presence of ether at 0 °C resulted in the formation of methyl ester **47**. The desired decahydroisoquinoline **4** requires installation of the 3,4,5-trimethoxy benzyl ester. The benzyl protecting group was removed by hydrogenolysis strategy using 10% Pd-C, H_2, and MeOH. Further esterification with 3,4,5-trimethoxybenzoyl chloride (TMBCl) afforded desired decahydroisoquinoline **4** (Scheme 11). The stereochemistry of synthetic decahydroisoquinoline **4** was confirmed by comparing ^1H and ^{13}C NMR spectra of natural compound **4** prepared from (−)-reserpine **2** (Scheme 11).[18]

Stork approach through stereoselectivity and regiospecificity

Stork et al.[32,33] described the regioselective and stereoselective synthesis of reserpine through regiospecifically formed iminium ion **49**. The iminium formation could initiate the construction of preferred arrangement at chiral C-3. It is believed that the desired regiospecificity in the compound **49** could assist efficiently in the synthesis of target reserpine. With this knowledge, it becomes possible to transform racemic and optically active fragment **48** into the desired (±) and (−)-reserpine, respectively (Figure 2).[33]



Scheme 11. Formal synthesis of (±)-reserpine (perhydroisoquinoline).

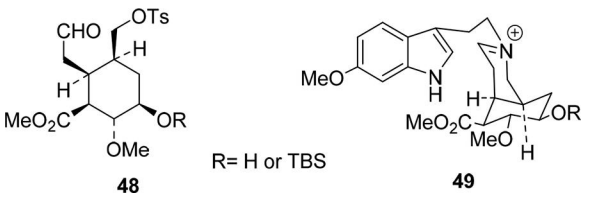
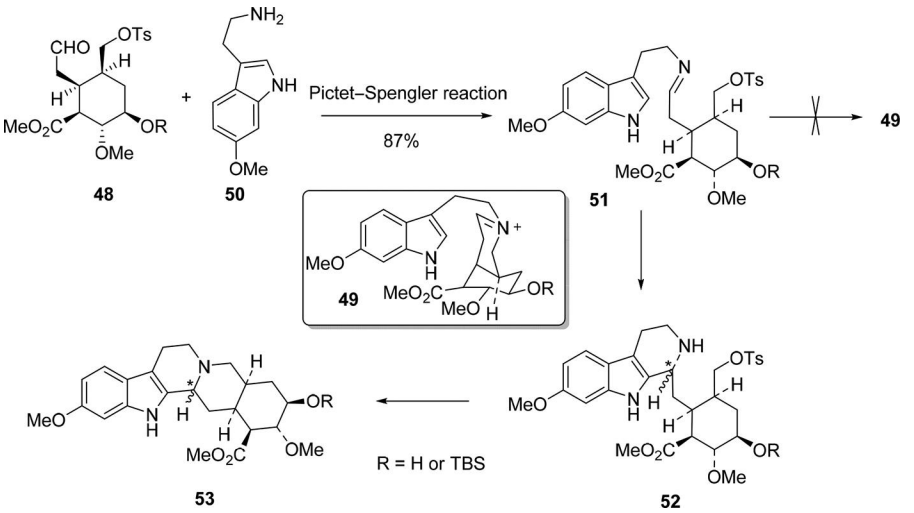


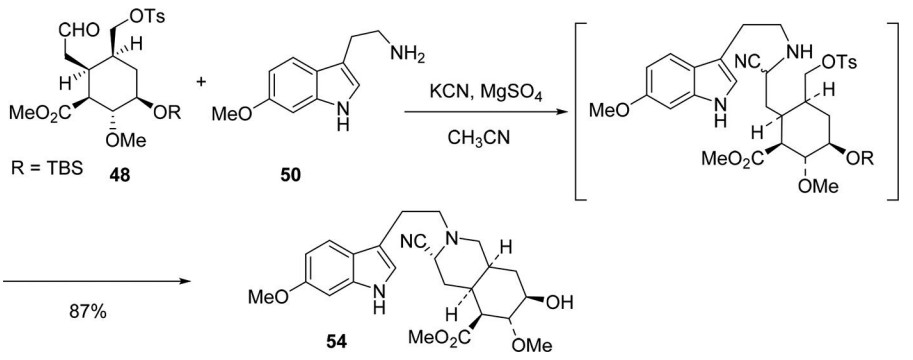
Figure 2. Structure of iminium ion **49** and aldehydotosylate **48**.

The ring C of reserpine with precise configuration at C-3 was accomplished by treating 6-methoxy-tryptamine **50** with aldehydotosylate **48** (R=H or TBS). The imine **51** can be obtained by condensing aldehyde functional group of tosylate **48** with 6-methoxy tryptamine **50**. It was initially believed that the essential iminium ion **49** could possibly be produced through intramolecular displacement of primary tosylate of the imine **51**. As expected, a pentacyclic system **53** was obtained upon reaction of **48** with **50** because by "Pictet–Spengler" reaction they had undergone more rapid cyclization with indole. To our surprise, unwanted mixture of epimers at the C-3 center in pentacyclic system was observed. Unfortunately, the undesired methyl isoreserpate **53** was formed as a major product (Scheme 12).

It seems reasonable to assume that desired iminium ion **49** is not formed and therefore iminium ion **49** has not been involved in the formation of isoreserpine mixture (Scheme 12). However, it is found that imine intermediate **51** has been immediately cyclized with the indole through "Pictet–Spengler"-type reaction instead of formation of desired iminium ion **49** through tosylate displacement. To ensure desired closure of ring D before that of ring C, the imine intermediate **51** should have been trapped by external nucleophile with leaving ability. Learning from previous observation (Scheme 12), it was realized that reaction of 6-methoxytryptamine **50** with **48** in the presence of appropriate amount of external cyanide can compete with the indole to form



Scheme 12. Stereoselective transformation of **48** to reserpine **53**.



Scheme 13. Synthesis of cyanopiperidine **54**.

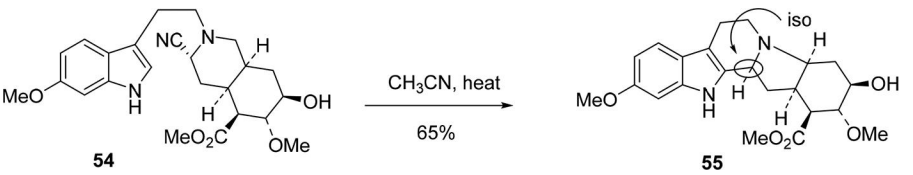
cyanopiperidine **54**. Eventually, crystalline cyanopiperidine **54** was obtained successfully as a single isomer in 87% yield using acetonitrile as a solvent and excess amount of external nucleophile (potassium cyanide) in the presence of drying agent magnesium sulfate (Scheme 13).[32,34]

Again, it was found that instead of expected reserpine, (±)-methyl isoreserpate **55** was formed from the secondary nitrile **54** under cyclization reaction condition. This happens due to the formation of a tight ion pair between the iminium and cyanide ions and addition of the indole to the iminium ion intermediate when iminium ion exists in a "boat-axial" conformation under provided experimental conditions (Scheme 14).[32]

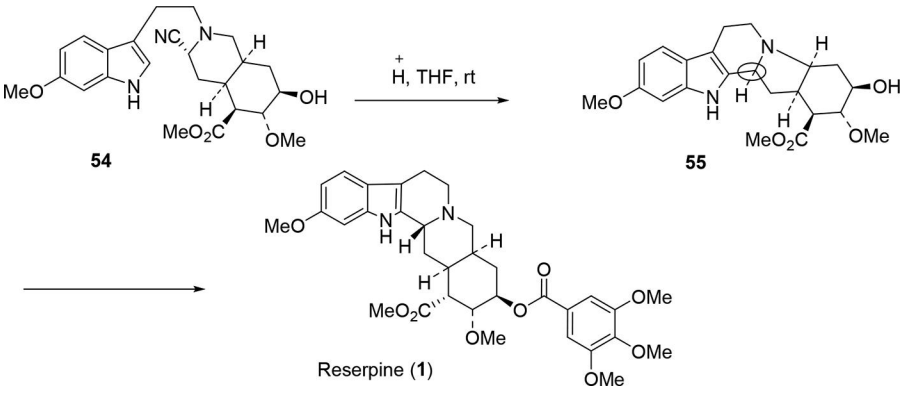
It would be possible to avoid formation of tight ion pair intermediate and induce creation of free iminium ion by enabling easy escape for cyanide ion. Free iminium ion could allow chair-axial addition and ultimately correct C-3 stereochemistry. In contrast to previous reaction conditions, which did not give desired product, desired crystalline (±)-methyl reserpate **55** was obtained in 90% yield upon treatment of **54** with dilute aqueous HCl in the presence of THF at room temperature. The desired (±)-reserpine **1** was obtained by the acylation of hydroxyl functional group of (±)-methyl reserpate **55** with 3,4,5-trimethoxybenzoyl chloride (Scheme 15).

Huang and Chen approach using (–)-shikimic acid as chiral pool

Chen and Huang[2] systematically reviewed various total syntheses of reserpine and its analogues. Huang and Chen[35] reported the effectual synthesis of octahydrobenzofuran **66** using economical (–)-shikimic acid **57** as a starting material. They proposed that the compound **66**, a correspondent of Hanessians's E-ring core, chiral hexahydrobenzofuran **56** (Figure 3), is a possible precursor for the synthesis of E-ring segment in the



Scheme 14. Synthesis of (±)-methyl isoreserpine from aminonitrile **55**.



Scheme 15. Synthesis of reserpine **1**.

(–)-reserpine. In Hanessian's approach[36], the key E-ring core **56** was easily constructed by the (–)-quinic acid (Figure 3).

In the presence of acidic cation resin and MeOH, the (–)-shikimic acid **57** was esterified to obtain corresponding ester **58**, whose hydroxyl functional groups at C-3 and C-5 positions were then protected using *tert*-$BuMe_2Si$ ether to give compound **59**. Remarkably the $BaO/Ba(OH)_2$ facilitated methylation of **59** yielded methyl ether **60** in good yield (82%). Desilylation of compound **60** at 40 °C in the presence of dilute AcOH in THF for 36 h produced diol **61**, which was then oxidized with PDC to generate α,β-unsaturated ester **62** in good yield (85%). The *tert*-$BuMe_2Si$ protecting group was smoothly introduced to the compound **62** and gave an excellent yield of 90% of compound **63**. Under *Luche's* conditions, compound **63** subsequently reduced to generate the required (3*S*) configuration of allylic alcohol **64**. Later on, the α-bromoacetal **65** was produced by the treatment of **64** with 1,2-dibromoethyl ether in the presence of *N*,*N*-dimethylaniline. The desired (3a*S*, 4*S*) configuration at position 3a, 7a in the final cyclized compound **66** was achieved by the intramolecular radical cyclization of **65** with Et_3B/Bu_3SnH (Scheme 16).

Yar approach through enamide photocyclization method

Yar et al.[37] done the total synthesis of structurally more complicated natural alkaloid, (±)-reserpine by following the en-amide photocyclization approach. The key focus of their studies is the photocyclization of en-amide **69**.

First, the photocyclization of en-amide **69** was done as an exemplar substrate. The en-amide **69** was prepared in high yield by the reaction of harmaline **67** and benzoyl chloride **68** in the triethylamine presence. In the photocyclization approach, irradiation

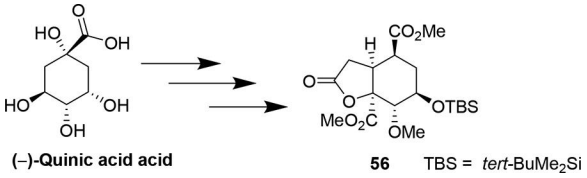
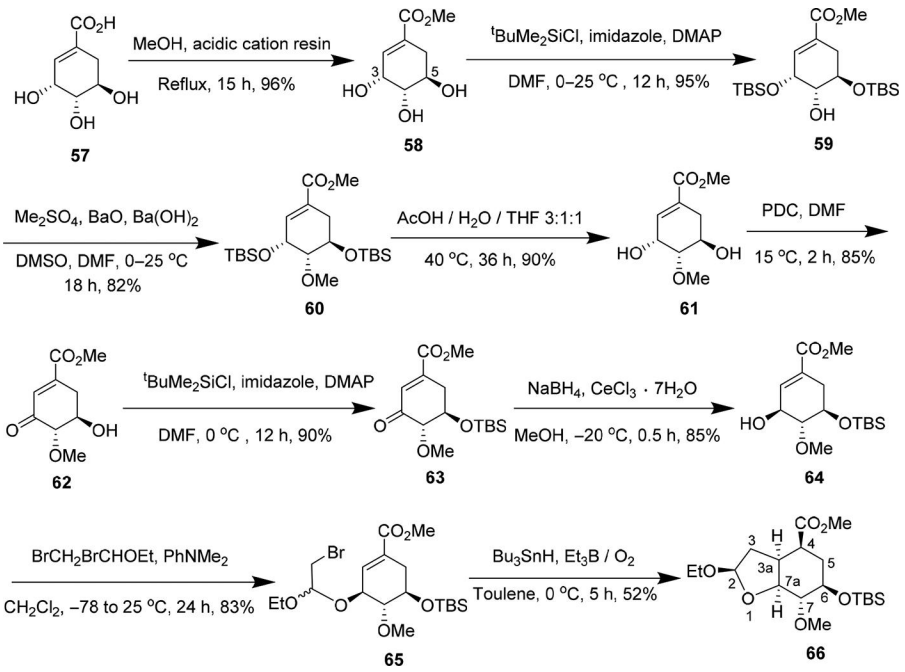
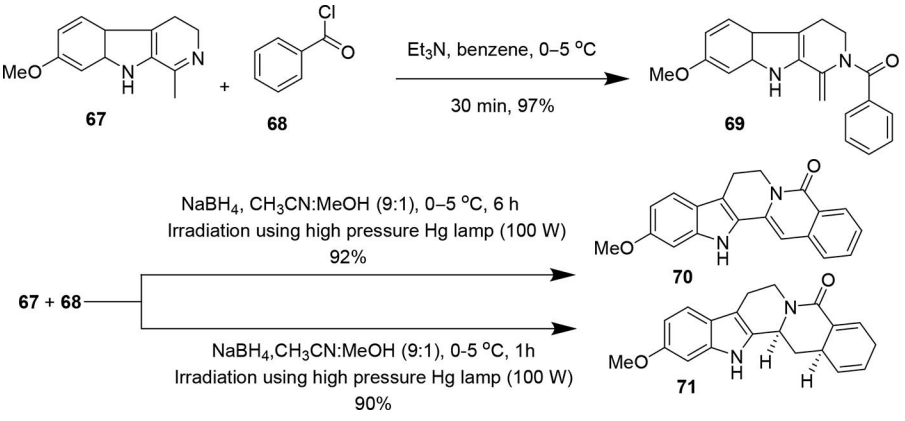


Figure 3. Conversion of (–)-quinic acid to hexahydrobenzofuran **56**.

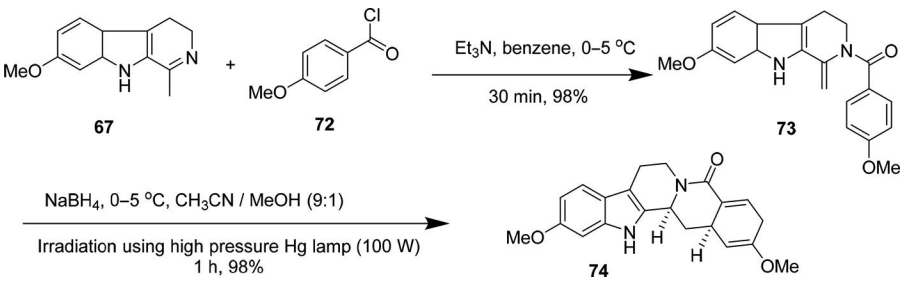


Scheme 16. Synthesis of intermediate of (–)-reserpine from (–)-shikimic acid **62**.

time duration is especially important; it was examined in different optimized conditions of photocyclization reaction. Only the unwanted lactam **70** was produced in high yield by the 6 h irradiation of en-amide **69** sodium borohydride and acetonitrile:methanol (9:1) in the occurrence of mercury lamp using high pressure. Nevertheless, the desired lactam **71** was synthesized by the en-amide **69** under the same reaction conditions except the irradiation time which was reduced to 1 h. It was examined that during the synthesis of lactam **70** or **71,** the starting material was diminished in 1 h time (Scheme 17).



Scheme 17. Synthesis of benzo[*g*]indolo[2,3-*a*]quinolizin-5-(7*H*)-one-8,13-dihydro-11-methoxy **70** and 11-methoxy-16,17,19,20-tetrahydroyohimban-21-one **71**.



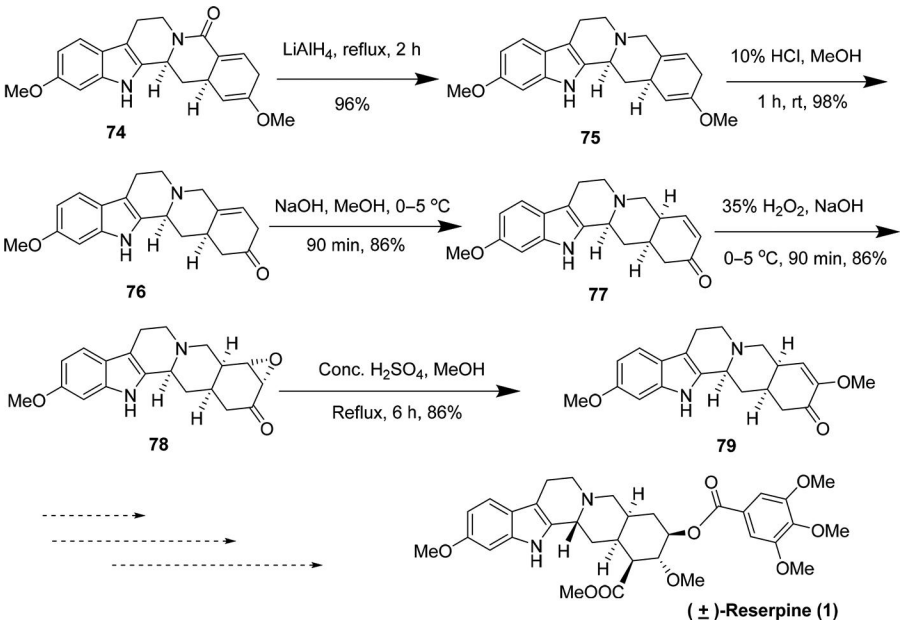
Scheme 18. Synthesis of 11,17-dimethoxy-16,17,19,20-tetrahydroxyyohimban-21-one **74**.

To achieve the objective of synthesizing lactam **74,** harmaline **67** was processed with *p*-anisoyl chloride **72** in the occurrence of benzene and triethylamine; this formed the awaited en-amide **73** in high yield (98%). Using the optimized condition of photocyclization, on the en-amide **69**, the lactam **74** was produced in good yield of 98% (Scheme 18).

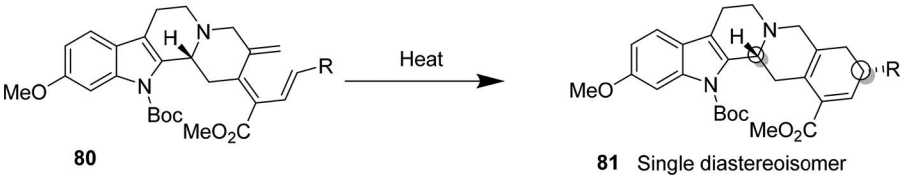
Herein the pentacyclic intermediate **79** was synthesized in several steps using naturally occurring compound harmaline **67** in approximately quantitative yield (86%).[38] This strategy was successfully applied to synthesize the key intermediate, 11,18-dimethoxy-(20α)-18, 19-didehydro-yohimban-17-one **79**, for the total synthesis of (±)-reserpine **1** (Scheme 19).

Barcan approach through torquoselective 6π electrocyclization

In 2012, Barcan et al.[39] controlled the stereochemistry relatively between C-3 and C-18 stereocenters of reserpine alkaloid (dodecahydroindolo-[2,3-*a*]-benzo[*g*]quinolizine) **81** by 6π electrocyclization of highly torque-selective thermo triene **80** (Scheme 20).



Scheme 19. Photocyclization-assisted synthesis of 11,18-dimethoxy-(20α)-18,19-didehydro-yohimban-17-one toward (±)-reserpine **1**.



Scheme 20. Torquoselective 6π electrocyclization dodecahydroindolo [2,3-*a*]benzo[*g*]quinolizine skeleton of reserpine-type alkaloids.

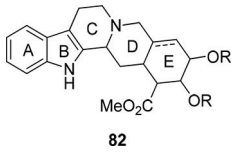


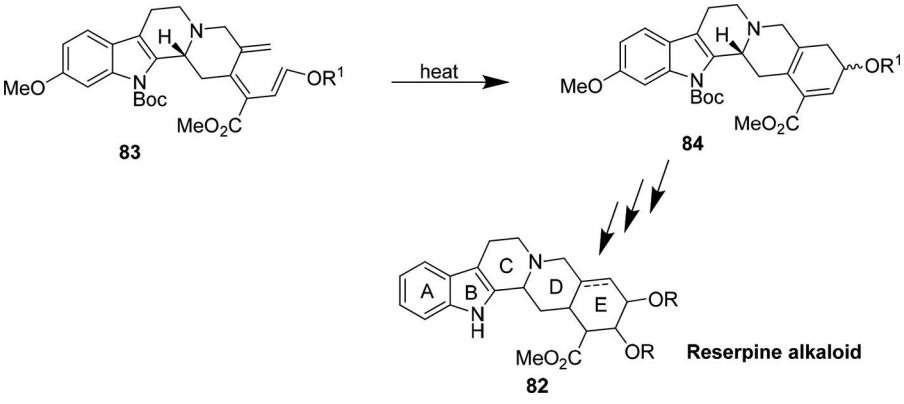
Figure 4. Skeleton of reserpine alkaloids.

Reserpine-type alkaloids possessing the skeleton of dodecahydroindolo-[2,3-*a*]-benzo[*g*] quinolizine are highly structurally complex alkaloids of indole **82** (Figure 4).

These compounds exhibit considerable activity in CNS and major constituent of herbal medicines.[1–8,40,41]

The 6π electrocyclization of trienes of all carbons is underutilized thermally, however extremely powerful reaction with the ability to engender two new stereocenters. The newly engendered stereocenters could be produced in an extremely diastereoselective manner if it started with the stereogenic center-possessed triene.[39] The presence of C3 stereocenter would let the C18 stereocenter to be molded in a stereo-controlled mode done by a torque-selective 6π electrocyclization. The triene **83** should let the stereocenter of C3 to affect the stereoselectivity of this transformation.[39,42,43] The requisite ABCDE skeleton of pentacycle **84** would be obtained by this synthetic strategy in a stereodefined manner (Scheme 21).

The planned effectual access to **83** by cross-coupling of appropriate pseudo-mental through the vinyl bromide **85** could be originated from the suitably functionalized ester



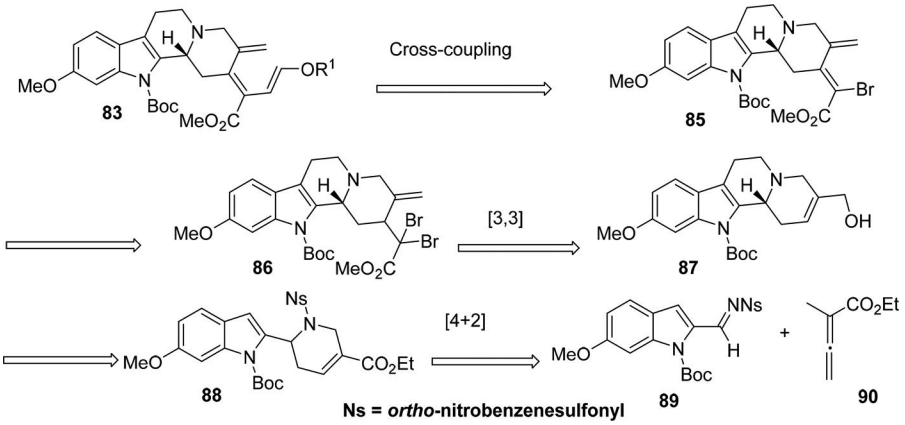
Scheme 21. Remote stereochemical induction through thermal torquoselective 6π electrocyclization.

86. By [3,3]-sigma-tropic rearrangement of the analogous di-halo-ketene acetal, they planned to engender the R,R di-halo-ester **86** from the allylic alcohol **87**. By earlier experiences, they presumed [4 + 2] annulation product **88** of the allylic alcohol **87** (Scheme 22).[44]

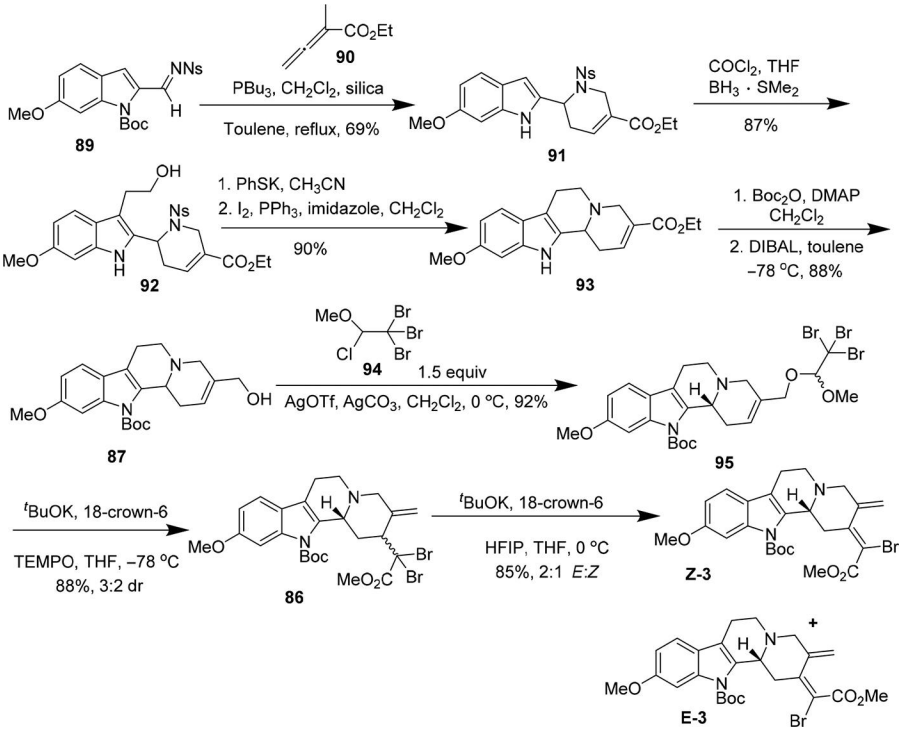
The separation of tetrahydropyridine **91** as a yellow crystalline solid was done in the occurrence of silica gel by subsequently removing the Boc group under reflux in toluene. In the occurrence of catalytic PBu_3, the [4 + 2] annulation continued uneventfully between imine **89** and butadiene **90**. They prepared tryptophol **92** by one-pot procedure. Under Fukuyama conditions, the bases are commonly used for the removal of nosyl protecting group. A variety of α halogen atom comprising dimethylorthoacetates were prepared for the synthesis of α, α-dibromoester **86** by deploying Johnson–Claisen rearrangement.[42] But [3,3] sigmatropic rearrangements were failed to affect substituted *ortho*-esters.[43] However, dehydrobromination of the acetal **95** produced dibromoketene acetal **86** through [3,3] sigma-tropic rearrangement.[45] The C-ring formation in **93** (88% yield) was done by the intramolecular alkylation of the formed secondary amine in the presence of I_2 and PPh_3. The key allylic alcohol **87** was formed by the indole N-atom protection with Boc_2O followed by the diisobutylaluminum hydride (DIBAL)-mediated ester reduction (Scheme 23).[39–45]

For the desired 6π electrocyclization, it was considered that Z-3 would be a suitable substrate to access E-triene **83** using sterospecific cross-coupling reaction conditions. The compound **84a** was obtained under optimized Suzuki cross-coupling, photochemical isomerization, and electrocyclization sequence.[39] The relative configuration of **84a** was revealed by X-ray crystallography (Scheme 24).

The dioxole **97** was recognized as a potentially appropriate candidate.[46] To undergo cross-coupling reaction, the need of 1,2-dialkoxyvinyl pseudo-metal **96** was envisioned. All the alkoxy groups were installed on the E-ring of the reserpine in a single step to overcome the difficulty of installing functionality on to **84a** by 6π electrocyclization cross-coupling (Schemes 24 and 25). In cross-coupling chemistry, acetonide compound **97** proved to be highly oxidized partner, which at optimized conditions gave the sole product **98** in 55% yields. Deprotection of acetonide **98** under optimized conditions gave



Scheme 22. Retrosynthetic analysis and synthesis of key triene **83**.

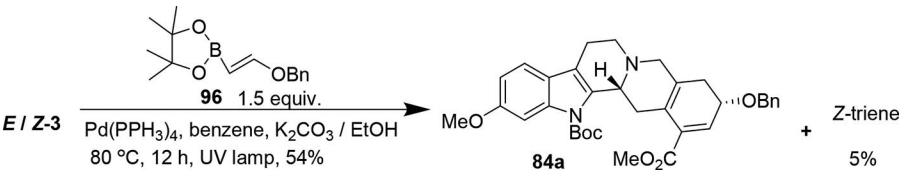


Scheme 23. Synthesis of the cross-coupling through phosphine-catalyzed [4 + 2] annulation and dibromoketene acetal Claisen rearrangement.

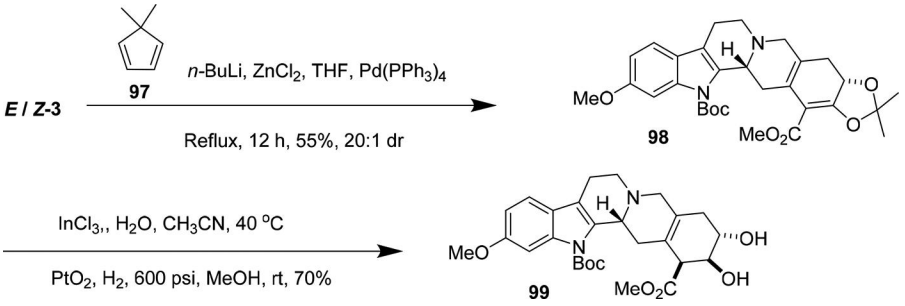
the transdiol **99** as a single diastereoisomer in 70% yield. The compound **99** is advancing to (±)-reserpine upon α-hydroxyl group-selective benzoylation (Scheme 25).

Rajapaksa approach through stereoselective formal Aza-Diels–Alder reaction

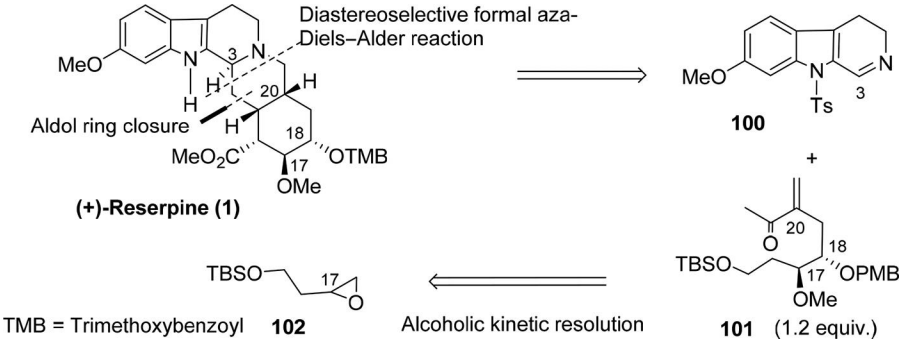
Rajapaksa et al.[47] devised the synthetic route of the (+)-reserpine enantioselectively. The synthetic route comprised of a formal aza-Diels–Alder reaction that is chiral-catalyst controlled and highly diastereoselective for the formation of main tetracyclic intermediate between an enantio-riched α-substituted enone **101** and a 6-methoxytryptamine-derived dihydro-β-carboline **100**. The kinetically controlled cyclization was utilized for the preferential C-3 configuration by 2,3-seco-derivative of aminonitrile,[32,33] the retrosynthetic analysis of (±)-reserpine **1** (Scheme 26).



Scheme 24. Torquoselective Suzuki/6π-electrocyclization.

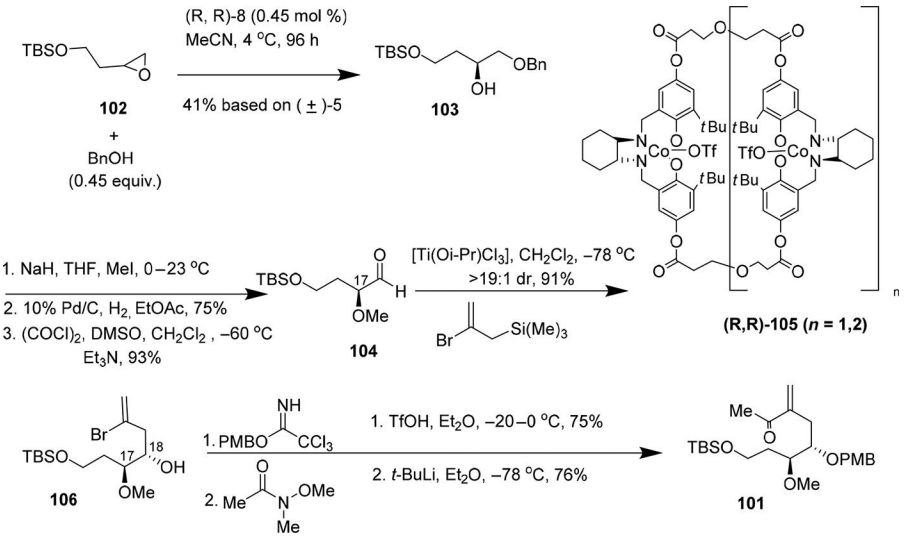


Scheme 25. Torquoselective Negishi/6π-electrocyclization.

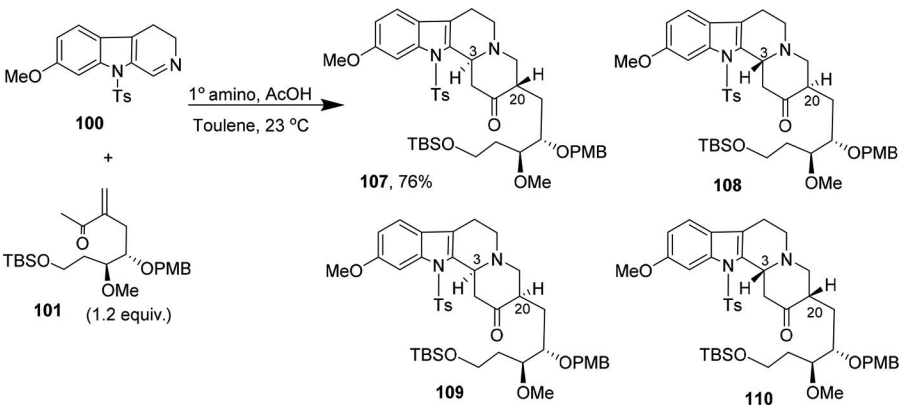


Scheme 26. Retrosynthetic analysis of (+)-reserpine (**1**).

By formal aza-Diels–Alder (FADA) reaction between two fragments **100** and **101** of analogous size, they accurately targeted the C-3 stereogenic center of reserpine framework (Scheme 27).[47]

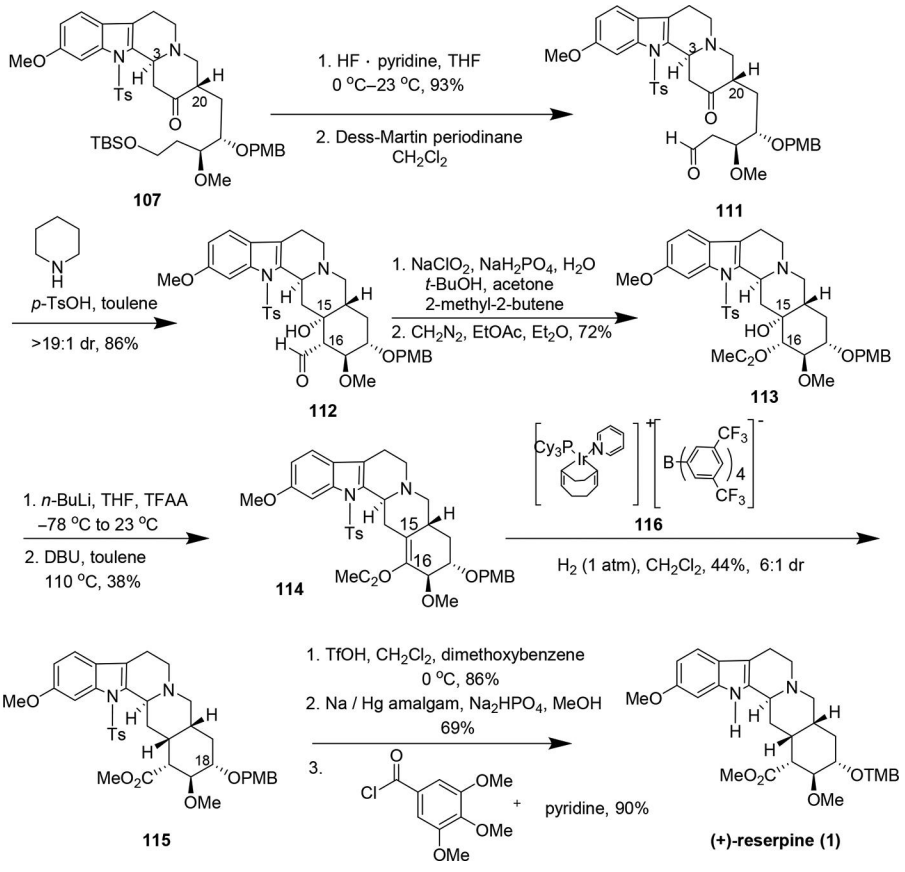


Scheme 27. Stereoselective synthesis of enone **101**.



Scheme 28. Diastereoselective thiourea-catalyzed formal aza-Diels–Alder reaction.

The stereoselective synthesis of enone composite **100** was achieved by the alcoholic kinetic resolution selectively of terminal racemic epoxide **102**. Using the salen catalyst of oligomeric cobalt **105**, obtained the masked 4-carbon triol **103**, taking benzyl alcohol as



Scheme 29. Completion of (+)-reserpine synthesis **1**.

catalyst. The conversion of masked alcohol **103** to aldehyde **104** by the sequence of three steps was done. Diastereoselective uninterrupted chelation-controlled allylation was used to the α-methoxy group of aldehyde **104**.[47] By the exchange of lithium–halogen and ensuing addition of *N*-methoxy-*N*-methylacetamide, enone **101** through C-18 alcohol protection was accomplished.

The tetracyclic ketone **107** was generated by the coupling of 6-methoxytryptamine-derived dihydro-β-carboline **100** and enone **101** (Scheme 28).[47]

Keto aldehyde **111** intramolecular reaction affected the closure of E-ring of the complete carbon framework of reserpine (Scheme 29).[47,48]

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