Reserpine: A Challenge for Total Synthesis of Natural Products

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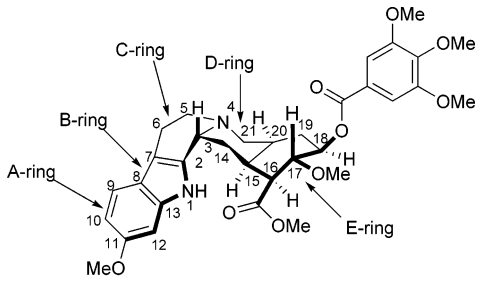
1. Introduction

Reserpine (**1**) is one of the lipid-soluble indole alkaloids sharing the yohimbine pentacyclic skeleton. Pharmacological studies have revealed that reserpine is a central nervous system depressant. It blocks the post-ganglionic nerve fiber from the excitatory neurotransmitter norepinephrine in the synaptic gap[1] and depletes all of the biogenic monoamines, serotonin, and the catecholamines by inhibiting their accumulation in storage granules in the brain, intestine, platelets, and other organs. Because of its remarkable antihypertensive and sedative properties, it is still used today for treatment of hypertension and psychiatric disorders.[2]



1 (-)-Reserpine

The main sources of reserpine are various *Rauwolfia* species (Table 1);[3] *R. serpentina*, *R. canescens*, and *R. vomitoria* are especially rich in reserpine and have been investigated in detail. Reserpine has also been isolated from other closely related apocynaceous plants, viz., *Tonduzia longifolia* Markgraf, *Alstonia constricta* F. Muell., *Vinca (Lochnera) rosea* L., *Vallesia dichotoma* Ruiz et Pavon, *Excavatia coccinea* Markgraf, *Vinca minor* L., and *Ochrosia poweri* Baily.

Reserpine was first isolated by Schlittler and coworkers from India snake root *R. serpentina* Benth. in 1952.[4] The same group also first proposed the correct formula for this alkaloid.[5] The relative configuration of reserpine was provided via chemical means by Aldrich, Diassi, Dickel, Dylion, Hance, Huebner, Korzun, Kuehne, Liu, MacPhillamy, Robb, Roychaudhuri, Schlittler, St. André, van Tamelen, Weisenborn, Wenkert, and Wintersteiner[6] and confirmed in the first brilliant total synthesis achieved by Woodward.[7] The relative configuration of reserpine was also confirmed later by Karle via X-ray crystallographic analysis.[8] The absolute stereochemistry of reserpine was proposed by Schlittler[9] and Diassi[10] by the use of Klyne's extension of Hudson's lactone rule to the molecular rotation difference between reserpic and reserpic lactone[6,11] and later confirmed by Ban[12] using a chemical method.

With the structure and stereochemistry of reserpine established, its biosynthetic origins were proposed by Barger,[13] Hahn,[14] Woodward,[15] Wenkert,[16] and others. In 1960 Leete used radioactive tracers

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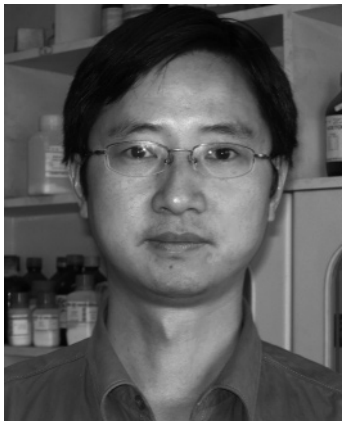


Jian Huang was born in 1974 in Sichuan, China. He received his B.S. and Master's degrees in Chemistry from Sichuan University in 1996 and 1999, respectively. From 1999 to 2004 he worked as an engineer at the R&D center of Jiangsu Chia Tai-Tianqing Pharmaceutical Co., Ltd. Currently, he is in the second year of his Ph.D. studies on the total synthesis of the pentacyclic indole alkaloid, L-reserpine, under the supervision of Professor Fen-Er Chen.

to prove that tryptamine is the precursor to the indole moiety of reserpine.[17] It is now believed that the initial steps in the biogenetic pathway of reserpine involve the oxidative cleavage of loganin to provide secologanin. Secologanin, upon coupling with 6-methoxytryptamine, yields the indole alkaloid skeletal type that provides a vincoside derivative with the correct reserpine $C_3\beta$-H stereochemistry. Next, the vincoside derivative is converted, via a series of reactive intermediates **5**−**8**, into reserpine by D- and E-ring closure (Scheme 1).[18]

Structure−activity relationship studies have shown that while the C-18 trimethoxybenzoyl group is necessary for the sedative activity of reserpine, the C-17 methoxy group is not. In addition, steric factors must play a role in its mode of action because 3-epireserpine is totally biologically inactive. This clue provides the synthetic chemist a starting point for modifying the skeleton of reserpine in a search for a more efficient antihypertensive agent that has fewer side effects.

Degradation of reserpine can be achieved by four approaches (Scheme 2). In the first approach[19] reserpine was heated in formic acid in the presence of formamide; the C2−C3 bond was cleaved, resulting in 2,3-secoreserpine **9**. After treatment with methyl chloroformate, *cis*-hydroisoquinoline **10** was produced. In the second approach[20] reserpine was subjected to hydrolysis with 0.75 N methanolic sodium hydroxide, resulting in reserpic acid **11** and trimethoxybenzoic acid. In the third approach[21] reserpine was oxidized by nitrous acid to produce 3,4-dehydroreserpine **12**. This oxidation forms the basis of the official USP reserpine assay procedure.[22] In the fourth approach reserpine was autoxidated into dioxyreserpine **13** by exposure to air and light.[23]

Reserpine ranks as one of the most complex natural products of its size, inasmuch as it incorporates six contiguous chiral centers (five of which are in the core cyclohexane E-ring), and contains a mere 21 skeletal atoms compactly arranged in five rings. Since its full structure was elaborated the stereochemical complexity and biological significance of reserpine have made it a fascinating target for total synthesis, providing a test case for evaluation of new strategies that are conceived upon emergence of new synthetic methods. Thus, the total synthesis of this alkaloid has been considered one of the historic yardsticks in the annals of natural product synthesis.[24] In this regard, the first total synthesis of reserpine by Woodward[7,25] in 1956 represented a milestone in the field of organic synthesis. Since then, considerable efforts have been made in the development of the asymmetric total synthesis of this alkaloid.

Historically, two fundamental synthetic strategies have provided successful access to this yohimbine alkaloid, and these entries are depicted in a retrosynthetic format in Scheme 3 for illustrative purposes. The more widely employed E-ring strategy (Scheme 3, entry a), following the original concept of Woodward's reserpine synthesis, focuses on the primary synthesis of the E-ring portion of the molecule followed by elaboration of the D-, C-, B-, and A-rings in "ascending order". An alternative, efficient DE-ring strategy highlighted by Wender[26] (Scheme 3, entry b) targets the chiral *cis*-fused DE-ring as a unit for synthesis, succeeded by construction of the rest of the molecule in "ascending order."

To date, several outstanding reviews of the chemistry and synthesis of yohimbine alkaloids (including reserpine and other yohimbine alkaloids) have been published,[3,27] covering the period up until 1996. The present review focuses on the total synthesis of reserpine, commences discussion with report of the first successful total synthesis by Woodward in 1956,

Table 1. *Rauwolfia* Species Containing Reserpine[a]

code	name	code	name
af	*R. affinis* Muell.-Arg. (*grandiflora*)	mo	*R. mombasiana* Stapf
a	*R. amsoniaefolia* (Miq.) A. DC.	na	*R. nana* E. A. Bruce
bh	*R. Bahiensis* A. DC.	n	*R. natalensis* Sond. (caffra)
bo	*R. boliviana* Mgf. (*schueli*)	ni	*R. nitida* Jacq.
cf	*R. caffra* Sond.	o	*R. obscura* K. Sch.
ca.	*R. cambodiana* Pierre ex Pitard	pa	*R. paraensis* Ducke
c	*R. canescens* L. (*tetraphylla*)	pe	*R. pentaphylla* Ducke
cb	*R. cubana* A. DC.	p	*R. perakensis* King et Gamble
cu	*R. cumminsii* Stapf	r	*R. rosea* K. Sch.
di	R. discolor	sl	*R. salicifolia* Griseb.
d	*R. densiflora* Benth. ex Hook. f.	sd	*R. sandwicensis* A. DC.
g	*R. grandiflora* Mart. ex A. DC.	sa	*R. sarapiquensis* Woods
h	*R. heterophylla* Roem. et Schult. (*tetraphylla*)	sc	*R. schueli* Speg.
ht	*R. hirsute* Jacq. (*tetraphylla*)	sw	*R. sellowii* Muell.-Arg.
i	*R. indecora* Woods. (*ligustrina*)	s	*R. serpentine* (L.) Benth. ex Kurz
j	*R. javanica* Koord et Val.	sp	*R. sprucei* Muell.-Arg.
l	*R. lamarckii* A. DC. (*viridis* Roem. et Schult.)	su	*R. sumatrana* (Miq.) Jack
lg	*R. ligustrina* Roem. et Schult.	tr	*R. ternifolia* HBK. (*ligustrina*)
lt	*R. littoralis* Rusby	t	*R. tetraphylla* L.
mp	*R. macrophylla* Stapf	vi	*R. viridis* (Muell.-Arg.) Guillaumin
mn	*R. mannii* Stapf	v	*R. vomitoria* Afz.
m	*R. micrantha* Hook. F.		

[a] Reprinted with permission from ref 3. Copyright 1965 Elsevier.

and includes contributions to the literature from then to the end of 2004. With this review we give an account of the research performed in the total synthesis of reserpine, especially regarding the strategies involved in constructing the structurally complicated E-ring or DE-ring subunit, and demonstrate the potential for future development of efficient reserpine synthesis.

This review is divided into three main parts according to the specific precursor strategy. Therefore, the first and largest part (section 2) comprises seven approaches to reserpine using the stereochemically and functionally rich E-ring as the key building block. In the following part (section 3) three methodologies leading to a *cis*-fused DE-ring and, thus, to the synthesis of reserpine are shown. The first two parts are directed at synthetic chemists interested in reserpine. In the third part the strategies and tactics in constructing the functionally abundant E-ring or DE-ring are given in detail with an attempt to put them in perspective (section 4). This part targets organic chemists with an interest in the development of novel synthetic methodologies for the total synthesis of naturally occurring compounds.

2. Syntheses Using the E-Ring Core as a Precursor

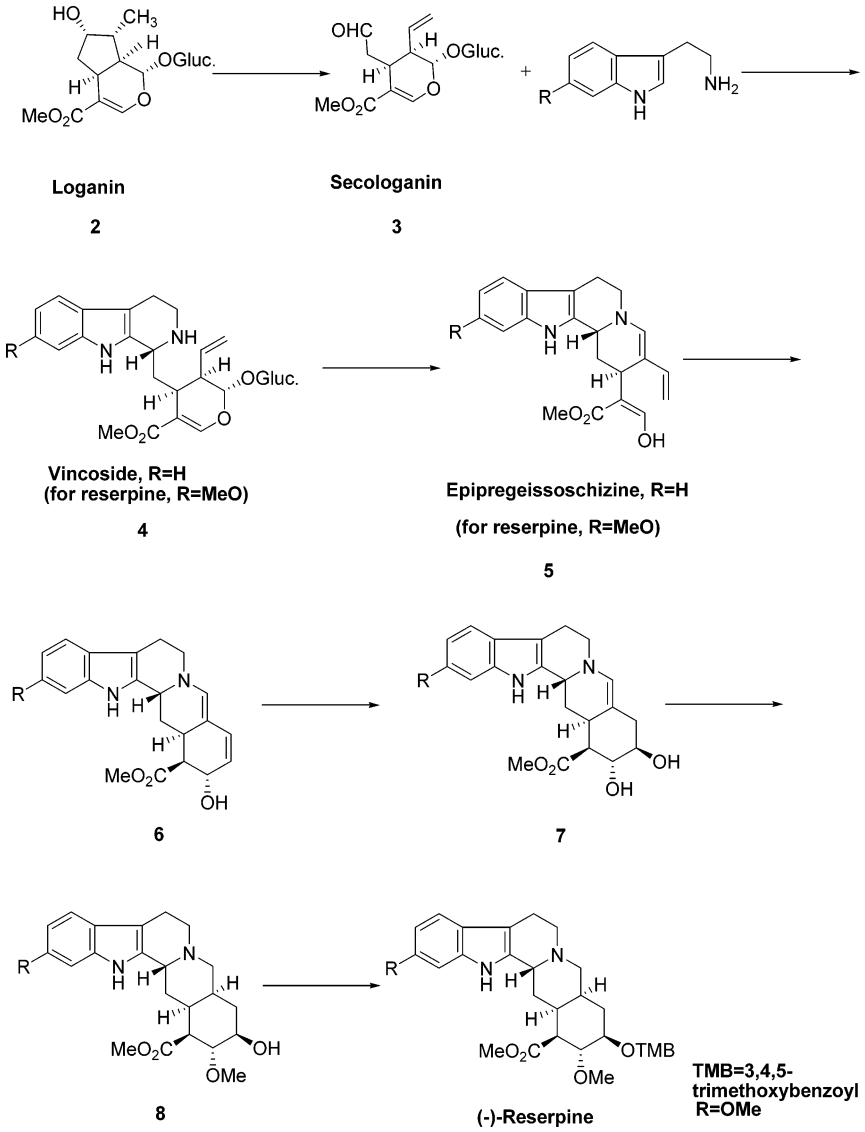
2.1. Woodward Approach via Diels–Alder Condensation

The first total synthesis of reserpine was achieved by Woodward and co-workers[7,25] only a year after the elucidation of its structure. This seminal synthesis began with a brilliant stereoselective construction of the stereochemically and functionally rich E-ring followed by condensation with the tryptophyl subunit and subsequent C-ring closure to elaborate the pentacyclic reserpine framework; it concluded with a cleverly executed epimerization at C-3 to create the correct 3β-H stereochemistry of reserpine. Woodward's work laid a foundation for many future syntheses of reserpine because the synthesis of many of the intermediates developed in their approach have been attempted by different groups.

Woodward's synthesis, outlined in Scheme 4, commenced with an intermolecular Diels–Alder reaction between 1,4-benzoquinone and vinylacrylic acid via the endo transition state. This reaction resulted in the early establishment of the *cis*-D/E-ring fusion containing three chiral centers in proper orientation for reserpine along with an E-ring double bond positioned for further functionalization. The conformation of the *cis*-decalin adduct **14** was then used to establish the remaining two stereocenters in the desired configuration (having the convex face more accessible than the concave face). Regioselective reduction with sodium borohydride of the carbonyl group at C-5 in **14** led to the dihydroadduct **15**, which was attacked by perbenzoic acid on the convex face at the Δ^2 double bond to give rise to oxide **16**. Lactonization was effected by sodium acetate and acetic anhydride; subsequent Meerwein–Ponndorf–Verley reduction[28] established the five-membered lactone and formation of the 3,5-oxide bridge via a selective epoxide opening. This step provided the unsaturated ether **18** with the desired C-3***R*** configuration. Methylation of the resulting **18** with sodium methoxide furnished the highly oxygenated bicyclo[4.4.0]decane **19** with the desired C-2***R*** stereochemistry. Thus, the five stereocenters in the E-ring of reserpine are properly oriented.

With **19** in hand, the next pivotal step was to elaborate the precursor E-ring for reserpine synthesis. Bromination of **19** with NBS resulted in the formation of bromohydrin **20**. In this process bromonium ion formation on the convex side of a conformer placed the D-ring in a pseudochair conformation, followed by trans-antiperiplanar attack of a molecule of water to give the target molecule. The bromohydrin **20** was oxidized by chromium trioxide to the corre-

Scheme 1. Biosynthesis of Reserpine

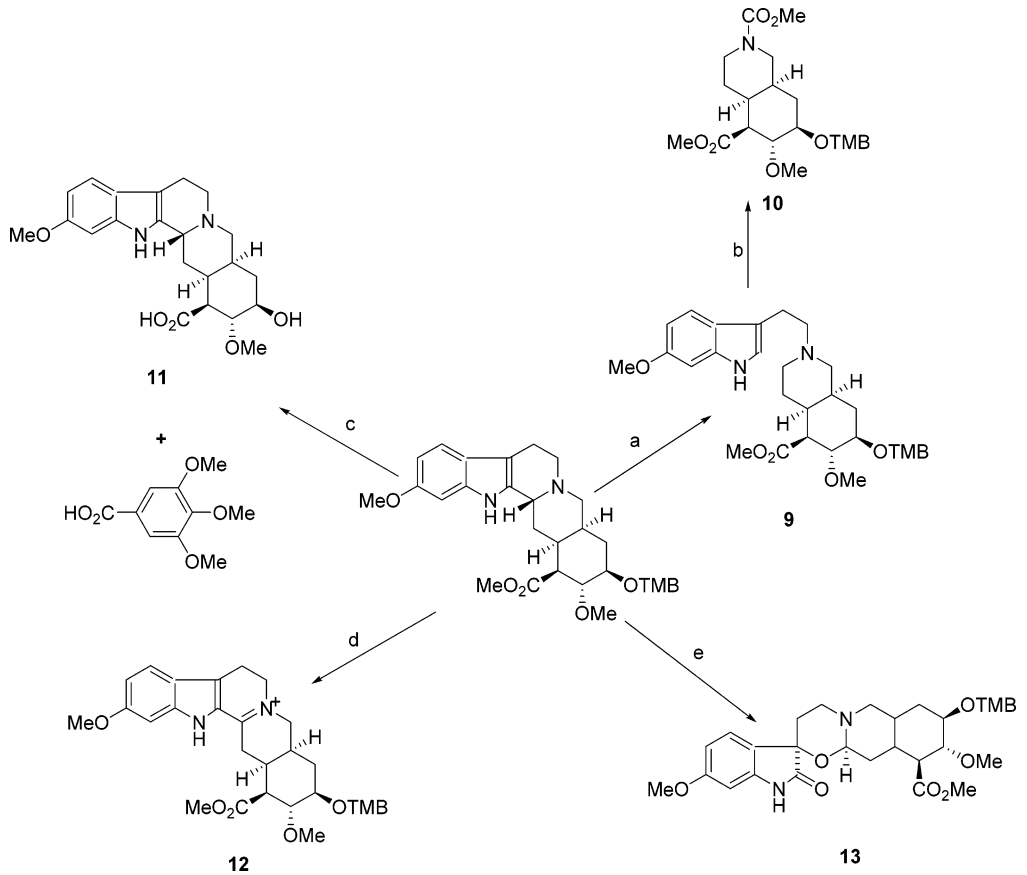


sponding α-bromo ketone **21**. Next, a short and straightforward access to the unsaturated keto acid **22** was accomplished by an in-situ C-8 carbon−oxygen bond cleavage/debromination/3,5-ether bridge elimination in the presence of zinc in glacial acetic acid. Subsequent esterification, acylation, and oxidation with aqueous osmium tetroxide resulted in the *cis*-diol **23**, which, following a periodate cleavage and esterification, provided the aldehyde ester **24**. Thus, the E-ring was constructed with five properly disposed stereocenters and proper functionality. D-Ring assembly was executed by condensation of **24** with 6-methoxytryptamine **25**[29] to give the lactam **26**, which was subjected to a Bischler−Napieralski cyclization[30] to complete the closure of the C-ring. In subsequent reduction with sodium borohydride, the hydrogen ion attacked the cyclic iminium ion **27** from the more accessible convex face of the ring system to produce the thermodynamically stable methyl-*O*-acetyl-isoreserpate **28** with the opposite $C_3\alpha$−H stereochemistry.

Thus, the final step in Woodward's synthesis of reserpine was epimerization of the C-3 center of **28**. Woodward designed a clever solution to obtain the desired C-3 epimer by constraining the pentacyclic intermediate **28** into an unfavorable conformation using intramolecular tethering. Thus, the E-ring substituents in the 3-*iso*-lactone **29** molecule were axially placed via sequential hydrolysis and lactonization of **28**. Epimerization at C-3 on exposure to pivalic acid in refluxing xylene would follow to furnish 3-normal lactone **30** with correct $C_3\beta$−H stereochemistry resulting from the strain engendered by the axial bulky moiety. Finally, after methanolysis and esterification with 3,4,5-trimethoxybenzoyl chloride, **30** was transformed into (±)-reserpine, which was resolved by D-camphor-10-sulfonic acid to give (−)-reserpine, identical in all respects to natural reserpine.

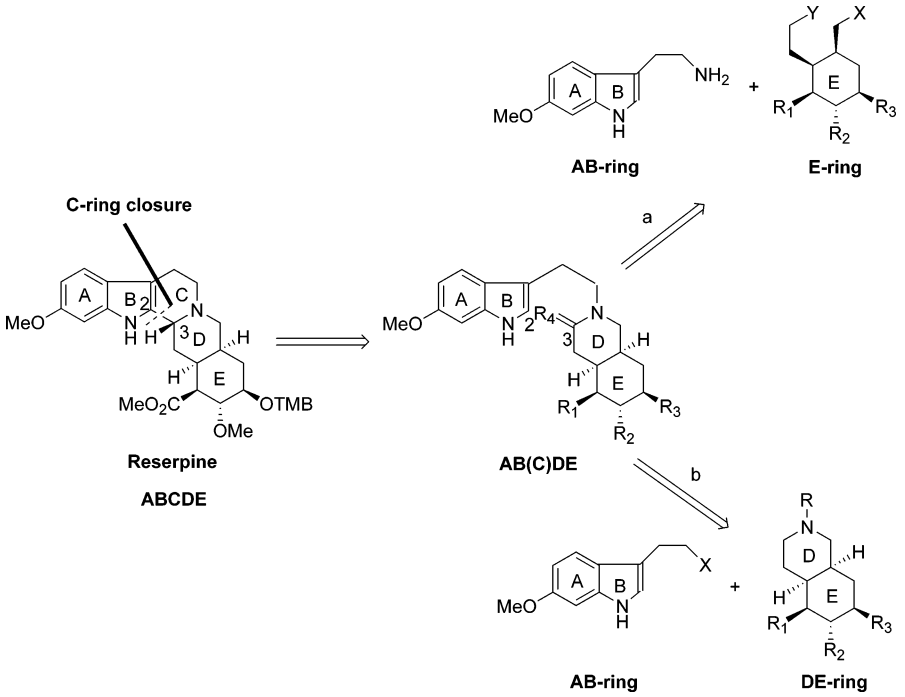
A few later contributions have focused on developing alternative ways to target synthesis of Woodward's intermediates, as in Scheme 5. In 1956 an improved and efficient route to **19**, developed by Woodward and co-workers,[31] was accomplished in a four-step sequence comprising bimolecular Diels−Alder reaction between 1,4-benzoquinone and methyl vinylacrylate, Meerwein−Ponndorf−Verley reduction of the *cis*-decalin adduct **31**, bromination of the

Scheme 2. Degradation of Reserpine[a]



[a] Conditions: (a) $HCONH_2$, HCO_2H, Δ; (b) $ClCO_2Me$, C_6H_6, Δ; (c) MeOH, NaOH; (d) HNO_3; (e) air, *hv*.

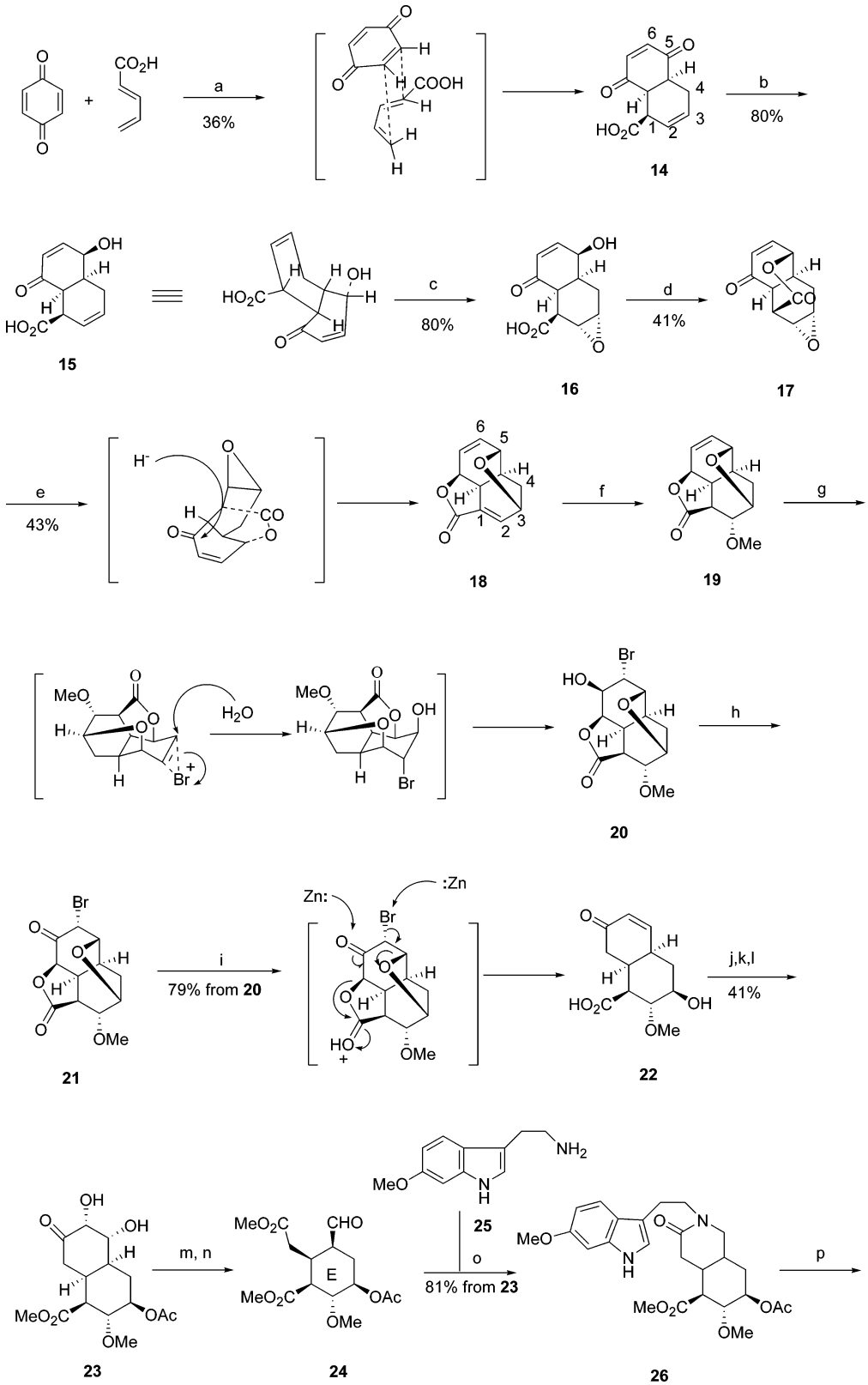
Scheme 3. Retrosynthetic Analysis of Reserpine



resulting tricyclic lactone **33**, and methanolysis of the bromo lactone **34**. Very recently we developed a highly regioselective and high-yielding protocol for the reduction of **32** into **33**.[32] Instead of aluminum isopropoxide, we used zinc borohydride generated in situ from potassium borohydride and zinc chloride, thus avoiding the formation of aromatic isomer of **32** from the original Woodward's synthesis.

The remarkable feature of Woodward's synthesis was the straightforward way in which the five adjacent stereocenters in the E-ring unit were built into the key building block, the aldehyde ester **24**.

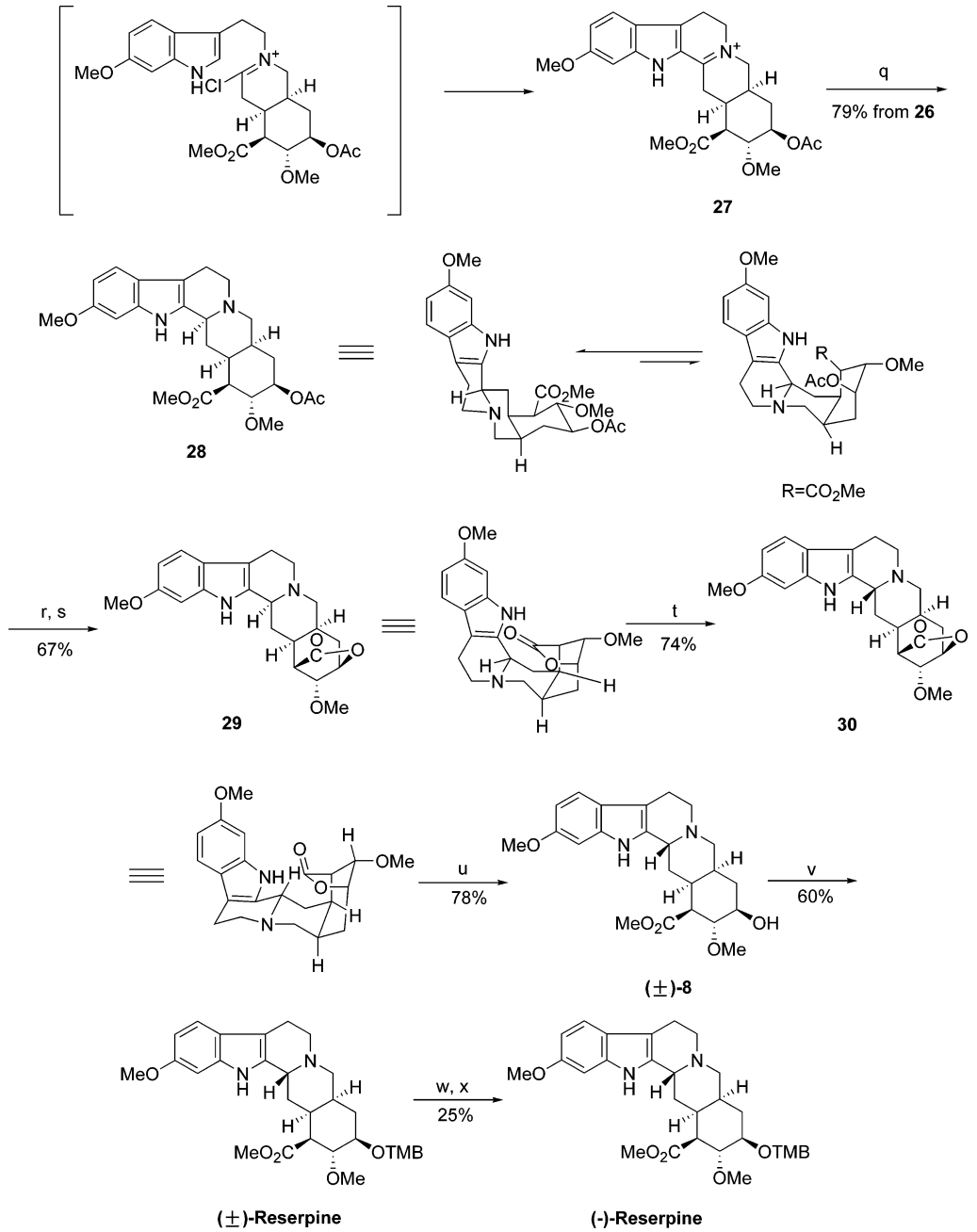
Scheme 4. Woodward's Synthesis of Reserpine[a]



Preparation of this intermediate has opened up the possibility of a general synthesis of reserpine and other yohimbine alkaloids. Considering the structural complexity of the reserpine molecule and the limited number of reagents available to carry out nontrivial structural transformation, it is admirable that Woodward was able to undertake, let alone satisfactorily complete, its total synthesis with the resources at his disposal.

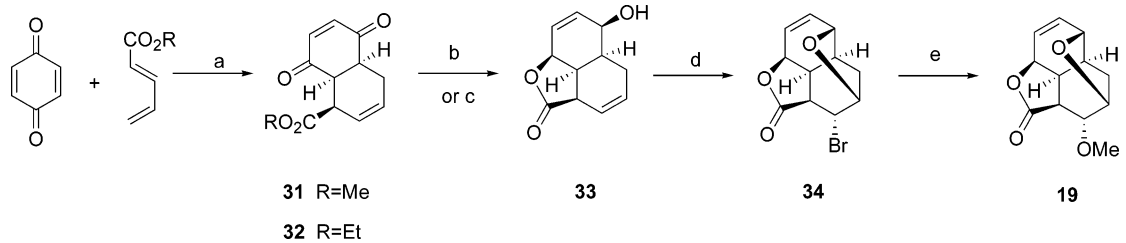
Despite the elegance of his work, three problems still remained in Woodward's original synthesis: (1) conversion of the 3-*iso*-lactone into the 3-normal lactone, (2) replacement of the 18-*O*-acetate by a trimethoxybenzoyloxy group, and (3) resolution of the

Scheme 4 (Continued)



[a] Conditions: (a) benzene, reflux; (b) $NaBH_4$; (c) $C_6H_5CO_3H$; (d) NaOAc, Ac_2O; (e) Al(*i*-PrO)$_3$, *i*-PrOH; (f) NaOMe, MeOH; (g) NBS, aq H_2SO_4; (h) CrO_3, aq AcOH; (i) Zn, AcOH; (j) CH_2N_2; (k) Ac_2O; (l) OsO_4; (m) HIO_4; (n) CH_2N_2; (o) $NaBH_4$, MeOH; (p) $POCl_3$; (q) $NaBH_4$; (r) KOH, MeOH; (s) DCC, pyridine; (t) *t*-$BuCO_2H$, reflux; (u) NaOMe, MeOH; (v) 3,4,5-trimethoxybenzoyl chloride; (w) *d*-camphor-10-sulfonic acid, MeOH, $CHCl_3$; (x) 1 N NaOH.

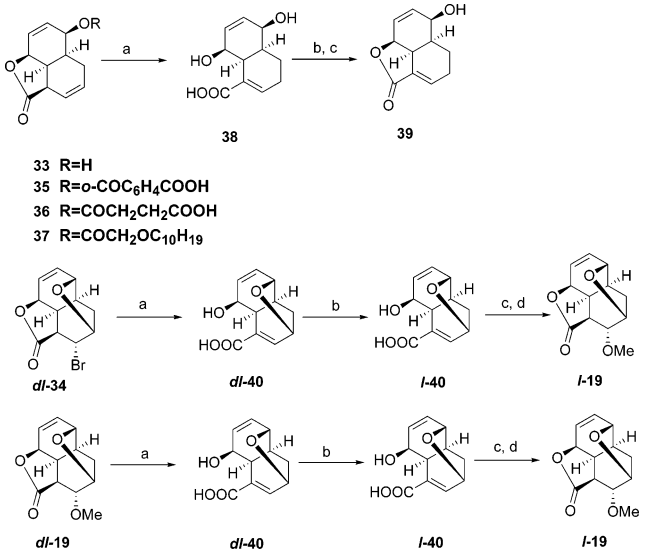
Scheme 5. Improved Route to Bicyclo[4.4.0]decane 19[a]



[a] Conditions: (a) benzene, reflux; (b) Al(*i*-PrO)$_3$, *i*-PrOH; (c) $Zn(BH_4)_2$, THF (Chen's procedure); (d) Br_2, MeOH; (e) MeONa, MeOH.

racemic alkaloid with respect to technical preparation—it is not preferable to place the resolution at the end of a long synthesis. Not surprisingly, a few later modifications with an eye toward commercial exploitation have been made to avoid these problems. These modifications involved (1) resolution of Wood-

Scheme 6. Resolution of Reserpine Intermediate[a]

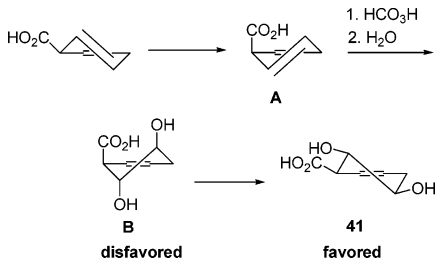


[a] Conditions: (a) alkaline hydrolysis; (b) brucine resolution; (c) DCC; (d) MeOH, MeONa.

ward's intermediates at an early stage, (2) introduction of the trimethoxybenzoyl radical into the potential C-18 position earlier to eliminate the need to hydrolyze the 18-acetyl group to the free hydroxyl and re-esterification,[33] and (3) reduction of the Δ^3 compound **27** directly to the normal series to avoid the necessity to prepare and isomerize the C-3 isolactone. Along the broad lines of Woodward's synthesis, Velluz's modification[34] focused on resolution in the stage of dihydroadduct **15** using brucine or ephedrine as the resolving agent, ozonization cleavage of unsaturated keto acid **22** to furnish the chiral aldehyde ester **24**, and, most important, reduction of the corresponding Δ^3 compound with zinc and perchloric acid to result in (−)-reserpine exclusively. In an analogous Novak's modification[35] (Scheme 6) resolution was achieved at the stages of tricyclic lactone **33**, bromo lactone **34**, and bicyclo[4.4.0]decane **19** formation. Attempts to resolve the acid phthalate **35**, succinate **36**, or menthoxyacetate **37** of tricyclic lactone **33** were unsuccessful because of the formation of complicated and noncrystallizing mixtures in the transformation of these optical active esters back to the corresponding hydroxyl lactones.

The resulting dihydroxy acid **38** by alkaline hydrolysis of **33** was resolved, however, by its conversion into diastereomeric brucine salts, which are readily separated by a simple fractional crystallization with the double bond shifting into conjugation. Alkaline hydrolysis of bromo lactone **34** or bicyclo-[4.4.0]decane **19** gave the unsaturated acid **40**, which was resolved into optical isomers via a classic resolution of diastereomeric salts with the help of brucine. Subsequent lactonization and methoxylation provided optically pure enantiomer **19**. Woodward and co-workers patented a resolution of the pentacyclic intermediate **28** in which L-dibenzoyltartaric acid was employed as the resolving agent.[36] Also, Muller and co-workers reported an efficient procedure for resolution of dihydroadduct **15** by means of quinine, brucine, cinchonine, and levorotatory ephedrine.[37]

Chart 1. Formation of Diol 41



2.2. Pearlman Approach via de Mayo Reaction

Nearly 20 years after Woodward's pioneering work, the second synthesis of reserpine, reported by Pearlman[38] in 1979, utilized a novel de Mayo reaction[39] with an equivalent of formyl acetic ester to place vicinal carboxaldehyde and acetic ester appendages onto the double bond to build up a more highly substituted E-ring precursor of reserpine (Scheme 7).

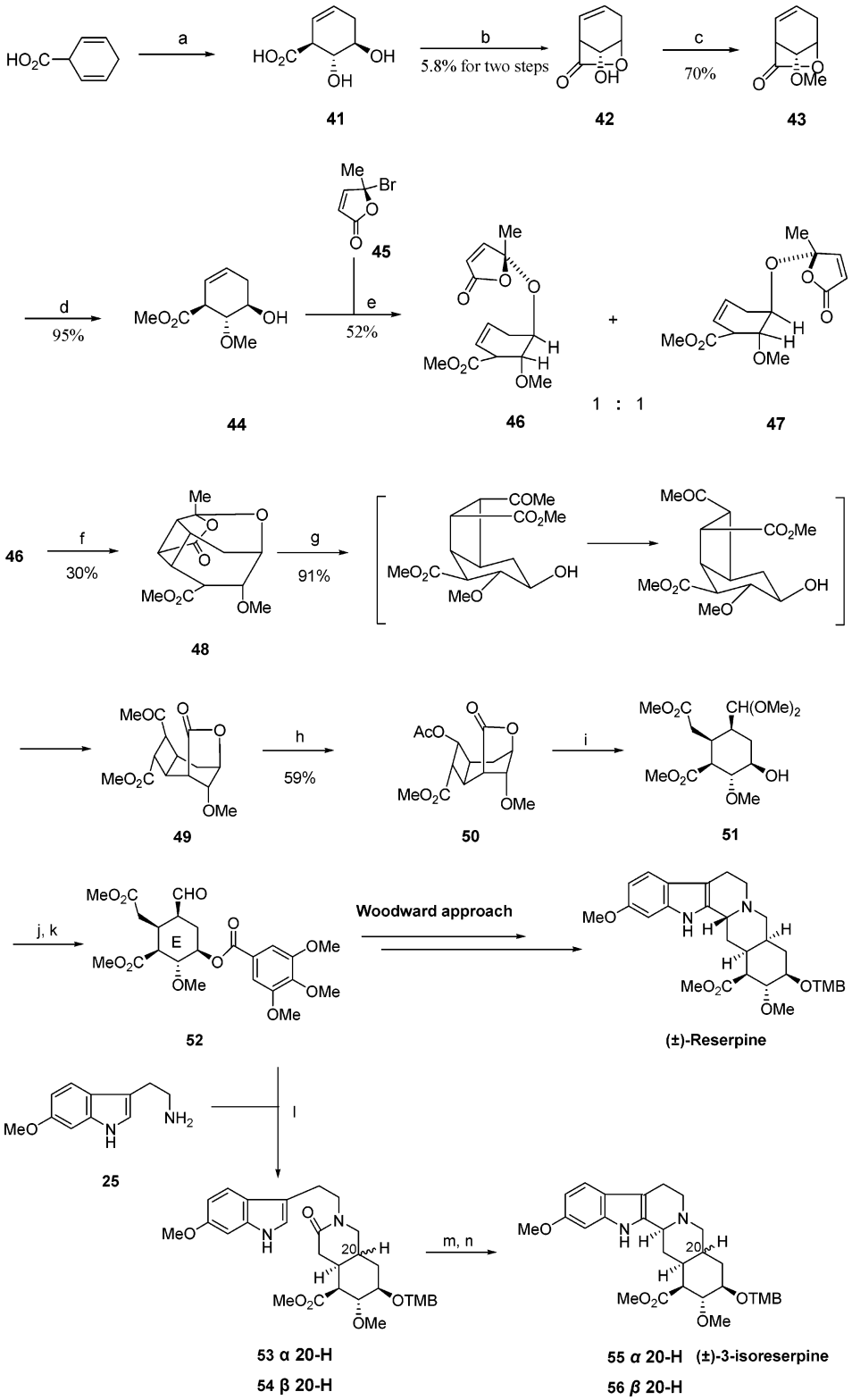
On the basis of a prior methodology[40] developed in their laboratories, Pearlman's synthesis began with 1,4-dihydrobenzoic acid, prepared by a Birch reduction of benzoic acid using lithium as the reducing agent.[41] Epoxidation of 1,4-dihydrobenzoic acid with performic acid followed by boiling in water produced a sufficiently high yield of the diol **41** with the desired "diequatorial" conformation.

A plausible explanation for the stereochemical course of the selective epoxidation−opening process arises from consideration of the inversion of the half-chair conformation of 1,4-dihydrobenzoic acid shown in Chart 1.

In this case, 1,4-dihydrobenzoic acid is first flipped into its axial conformer **A**, which is converted into the axial conformer **B** of **41** via *trans*-diaxial dihydroxylation of the double bond. Finally, the more stable diequatorial diol **41** was formed preferentially via a ring reversal. The process of this topomerization can be detected and the barrier to inversion measured by means of dynamic (variable-temperature) NMR.[42]

Thermolysis of **41** at 180 °C followed by selective methyl etherification with MeI in the presence of Ag_2O and crushed $CaSO_4$ produced the desired lactone **43**. It is interesting to note that attempts to effect methyl etherification of **42** employing NaH and MeI resulted in its decomposition into benzoic acid as a result of base-catalyzed aromatization. Methanolysis of the lactone **43** with acidic methanol afforded the desired hydroxyl−ester **44** in essentially quantitative yield. Reaction of **44** with a pseudo-acid bromide of *cis*-β-acetylacrylic acid[43] in the presence of Ag_2O and crushed $CaSO_4$ generated a 1:1 mixture of the ketal **46** and its diastereomer **47**, which can be separated by routine chromatography. Irradiation of **46** in 0.003 M acetone induced an intramolecular [2 + 2] photocycloaddition to produce the adduct **48**. The undesired isomer **47** was converted back to **44** in quantitative yield by acid methanolysis. Refluxing of **48** in methanolic sulfuric acid caused disconnection of the ketal bridge, epimerization of the liberated acetyl group from the endo to the more stable exo configuration,[44] and intramolecular lactonization between the carbomethoxyl substituent of the cyclo-

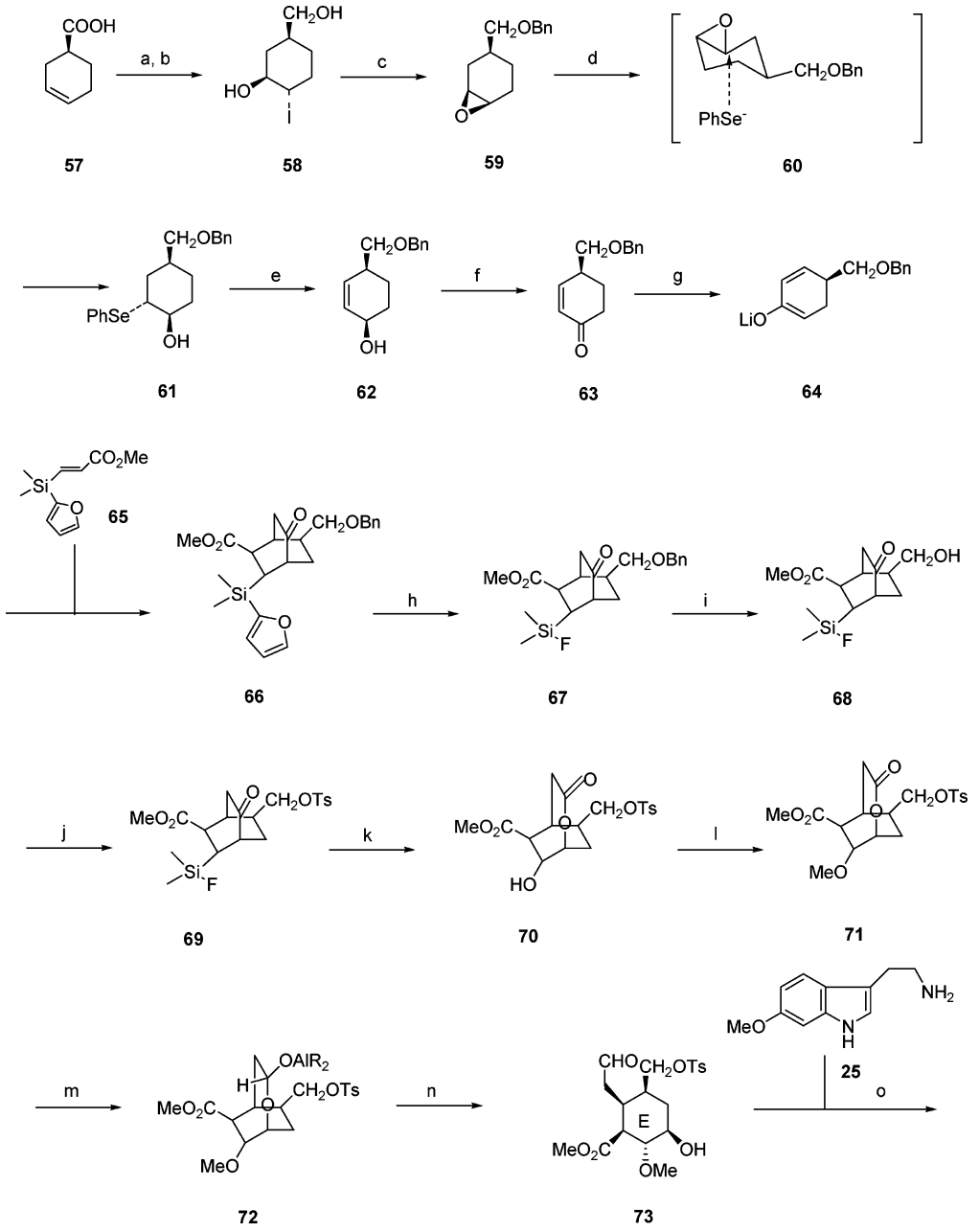
Scheme 7. Pearlman's Synthesis of Reserpine[a]



[a] Conditions: (a) HCO_3H, H_2O; (b) 183 °C; (c) MeI, $CaSO_4$, Ag_2O; (d) MeOH, H_2SO_4; (e) $CaSO_4$, Ag_2O; (f) *hν*, acetone; (g) MeOH, H_2SO_4; (h) F_3CCO_3H; (i) MeOH, H_2SO_4, reflux; (j) 3,4,5-trimethoxybenzoic anhydride, DMAP; (k) 50% aq AcOH; (l) $NaBH_4$; (m) $POCl_3$; (n) $NaBH_3CN$.

hexane ring and the liberated hydroxyl group; the methyl ketone **49** was obtained in excellent yield. Baeyer−Villager oxidation of **49** by trifluoroperacetic acid[45] in the presence of Na_2HPO_4 in dichloromethane furnished the corresponding β-acetoxycyclobutane ester **50** with a 91% yield, which upon treatment with acidic methanol introduced the five contiguous chiral centers in dimethyl acetal **51** via an in-situ retro-aldolization−lactone ring opening. Esterification of **51** with subsequent acidic hydrolysis resulted in aldehyde **52**, which is closely related to Woodward's reserpine aldehyde ester **24**. This key intermediate

Scheme 8. Stork's Synthesis of Reserpine[a]



in the Pearlman reserpine approach can undergo the same series of reactions given for **24**, thus completing the total synthesis of reserpine.

To prove the identity of **52**, it was converted into isoreserpine by initial conversion to lactams **53** and **54**. Subsequent Bischler−Napieralski cyclization resulted exclusively in **55** and **56** having the isoreserpine stereochemistry at C-3. That no reserpine was generated under this condition is in accord with Woodward's earlier observations and underscores the need for his solution to the problem of generating the correct stereochemistry at C-3 of the target.

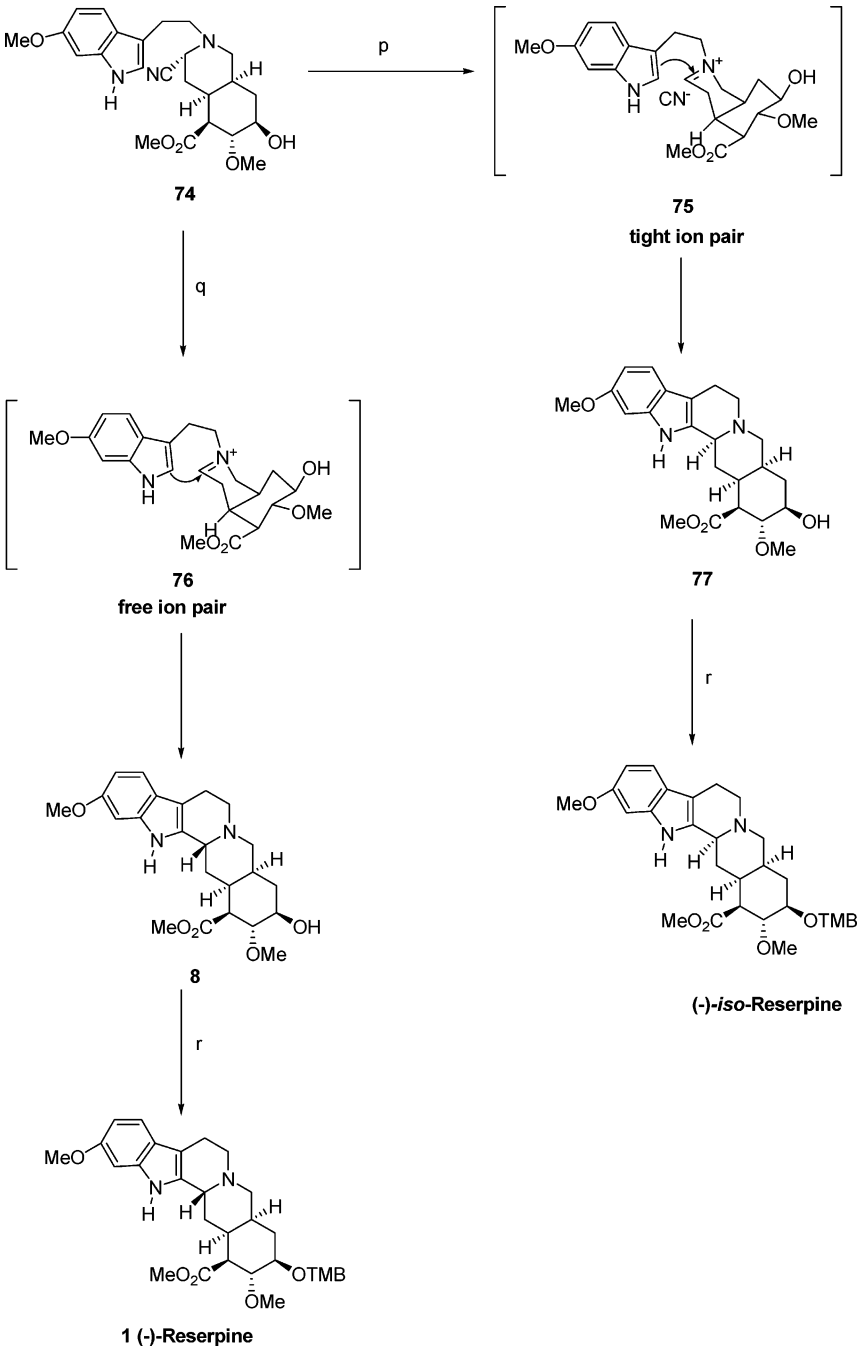
Although the overall yield of **52** was less than 1%, this was actually high enough for practical purposes for two reasons. First, the monetary expense of the lost starting material (benzoic acid) and reagents (lithium and 30% hydrogen peroxide) is negligible. Also, the procedure is reasonably convenient to carry out because of the easy separation of undesired byproducts. Thus, this approach is actually practical from the standpoint of both expenses and convenience, albeit with low yield.

2.3. Stork Approach via Double Michael Addition

The first enantiospecific synthesis of (−)-reserpine, accomplished by Stork,[46] successfully employed the versatile double Michael reaction[47] as a key step in constructing the E-ring unit of reserpine (as outlined in Scheme 8). The most important aspect of this elegant synthesis is its solution of the stereochemical problem of producing the correct configuration at C-3 of the reserpine molecule. This problem was resolved by introduction of α-amino nitrile via a Strecker reaction[48] as a masked iminium ion to complete C-ring closure.

The synthesis started with the readily available enantiopure (*S*)-3-cyclohexenecarboxylic acid (**57**),[50]

Scheme 8 (Continued)



[a] Conditions:[49] (a) I_2, KI, $NaHCO_3$, $CH_2Cl_2-H_2O$(1:1 v/v), 0 °C; (b) DIBALH, THF, −78 °C; (c) NaH, BnBr, DMF; (d) $(PhSe)_2$, $NaBH_4$, EtOH; (e) 30% H_2O_2, THF, 0 °C to room temperature; reflux, THF; (f) *p*-nitrobenzoic acid, Ph_3P, DEAD, THF; (g) $LiN(SiMe_3)_2$; (h) Bu_4NF, THF; (i) hydrogenolysis; (j) tosylation; (k) peracid treatment; (l) methylation; (m) DIBALH; (n) hydrolysis; (o) NaCN, AcOH, H^+; (p) MeCN, Δ; (q) $AgBF_4$ or H^+, THF; (r) 3,4,5-trimethoxybenzoyl chloride.

which was converted into 4-benzyloxymethylcyclohexenone (**63**), the substrate for the crucial double Michael addition step. The sequence for preparation of **63** involved conversion of **57** to the iodohydrin **58**, which was then converted via epoxide **59** and selenide **61** to the required **63**. The main point of interest here lies in the fact that the benzyloxymethyl group in **59** is sufficient to define a particular chair conformation in **60**, which then leads to the correct regiochemistry of **63** via the anticipated axial opening. Double Michael addition of the lithium enolate of **63** with β-furyldimethylsilyl methyl acrylate (**65**) generated the desired bicyclic ketone **66** with all five stereocenters of the reserpine E-ring subunit in the correct arrangement. The silylfuran group in **66** was smoothly transformed into the corresponding fluorosilane functionality in **67** upon treatment with tetrabutylammonium fluoride in THF. Cleavage of the benzyl group of **67** followed by tosylation of the hydroxy group of the resulting **68** under basic conditions led to the tosylate **69**. Tosylate **69** was then subjected to peracid treatment to elicit not only the Baeyer−Villager oxidation but also the Tamao−Kumada[51] reaction to transform the silicon substituent into the desired hydroxy group of bicyclic lactone **70** via an oxidative removal process. Methylation of

the secondary hydroxy group in **70** yielded the ether **71**, which, after a one-pot lactone ring opening and reduction, provided the enantiopure hydroxyl aldehyde **73** bearing an analogy to Woodward's reserpine aldehyde ester **24**.

Having the key precursor **73** in hand sets the stage for elaboration of reserpine. Connection of the primary carbinol tosylate in **73** to the nitrogen of tryptamine **25** was followed by closure of the D-ring via a Strecker reaction, leading to the α-amino nitrile **74**, with the axial orientation for the cyano group. C-Ring closure took place by simply heating **74** in acetonitrile, leading to the wrong C-3 epimer isoreserpine alcohol **77**; however, this result is unexpected because it was anticipated that an axial indole attack on the cyclic iminium cation **76** would result in formation of the corresponding reserpine alcohol **8** with 3β-H stereochemistry. This result was rationalized by the suggestion that upon thermolysis the amino nitrile **74** decomposes to give a tight ion pair. The cyanide anion occupies the axial position of the iminium ion **75** and thus blocks the nucleophilic attack from that face. The indole nucleophile would have to approach from an equatorial direction, the result being the formation of **77** with an equatorially connected indole ring at C-3. In light of this, addition of either silver fluoroborate or dilute hydrochloric acid had the effect of breaking up the tight ion pair to generate the free iminium ion **76**.[52] C-Ring closure subsequently occurred with nucleophilic attack of the indole system from the most stereoelectronically favored face of **76** to give reserpine alcohol **8** bearing the configuration at C-3 corresponding to (−)-reserpine. Trimethoxybenzoylation of **8** then completed this interesting synthesis of (−)-reserpine.

Thus, Stork contributed a concise, stereoselective synthesis of (−)-reserpine in which the C-ring closure was effected at a lower oxidation state at C-3; this approach differs from the postring closure reduction of Woodward to resolve the long-standing problem of the stereoselectivity of the C-ring-forming cyclization reaction.

2.4. Fraser-Reid Approach via a Serial 5-Exo/6-Exo Radical Cyclization

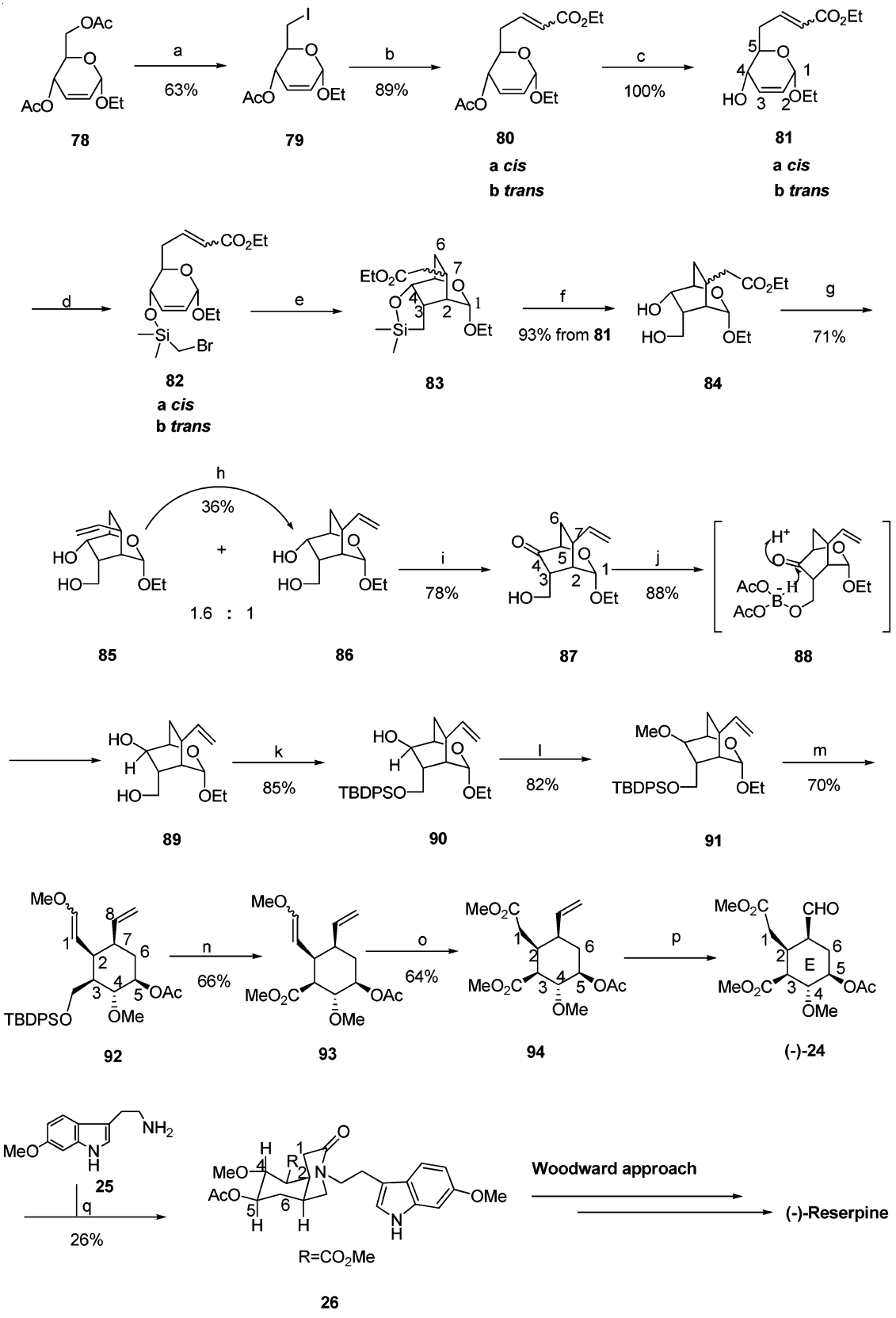
In 1994 the Fraser-Reid group reported a novel asymmetric synthetic strategy[53] for elaboration of the chiral, richly functionalized E-ring subunit based on a serial radical 5-exo/6-exo cyclization of pyranose-derived dienes as the key transformation, as shown in Scheme 9.

The starting material for this synthesis was the ethyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside **78**,[54] which was readily prepared in multigram amounts from commercially available tri-*O*-acetyl-D-glucal. Conversion of **78** into the corresponding iodide **79** was achieved in a 63% overall yield by successive hydrolysis, tosylation, and iodization. Free-radical coupling of **79** with tin acrylate was conducted following the modified procedure[55] of Russell[56] and Baldwin[57] to afford a mixture of the *trans*- and *cis*-olefinic ester **80** in 89% total yield, which was subjected to base hydrolysis in the presence of Et_3N in aqueous methanol to give the alcohol **81** quantitatively.

Following the tactic popularized by Nishiyama[58] and Stork,[59] Fraser-Reid and co-workers incorporated the silicon tether into the C-4 position of **81** to act as a synthetic equivalent for the one-carbon branch required at C-3 of **24** by reaction of **81** with (bromomethyl)dimethylsilyl chloride, leading to the *trans*- and *cis*-silylmethylene ethers **82**. The radical cyclization−trapping process was triggered by refluxing of both *trans*- and *cis*-**82** in the presence of Bu_3SnCl, AIBN, and $NaCNBH_3$ in tert-butyl alcohol;[60] this process furnished the desired cage molecule **83** in a complete regio- and stereocontrolled manner in which three correct stereocenters needed for the E-ring of reserpine were established. Here two radical cyclizations are involved. The first 5-*exo* radical cyclization occurs with Δ^2 unsaturation to introduce a carbon branch at C-3 of **82** as well as generate an additional radical at C-2 in **82** for further cyclization. The second 6-*exo* radical cyclization, which is favored by the presence of an electron-withdrawing substituent at the terminus of **82** at C-7, befalls onto the Δ^7 unsaturation to complete construction of the polysubstituted cyclohexane ring.

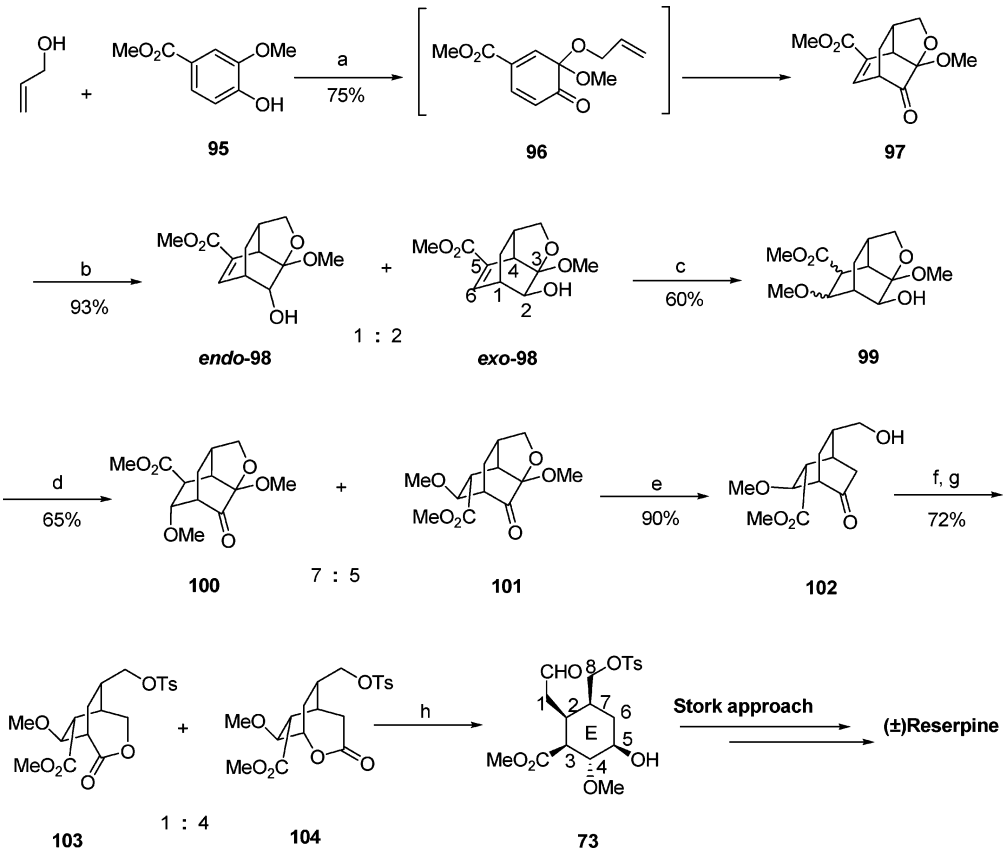
The next crucial step in the synthetic pathway was establishment of the remaining two stereocenters. Desilylation of **83** was effected directly by Tamao's oxidation (H_2O_2/$KHCO_3$/KF),[51] leading to diol **84** as a C-7 epimeric mixture in which the carbethoxymethyl group at C-7 was a latent synthon for the formyl group in target molecule **24**. The observation that the cis/trans ratio of **82** was of no consequence with respect to the epimeric composition of **84** was explained by Fraser-Reid's suggestion that before the radical cyclizations occurred *cis*-**82** had undergone isomerization through a course of addition/elimination of Bu_3Sn to give the corresponding thermodynamically more stable trans isomer. Elaboration of the vinyl group at C-7 in **86** was accomplished by a five-step procedure comprising silylation protection, LAH reduction, mesylation, selenoxide elimination, and desilylation, giving a 1.6:1 mixture of diol **85** and **86**, which could be separated by routine column chromatography. The undesired diol **85** with the wrong configuration at C-7 could be converted into the desired correct conformer **86** in a 50% yield by ozonolysis, epimerization, and methylenation. With the aim of correcting the wrong C-4 configuration, the diol **86** was oxidized into the ketone **87** regioselectively by treatment with Bu_2SnO in toluene followed by NBS in chloroform according to David's procedure.[61] Reduction of **87** with $NaBH(OAc)_3$[62] in EtOAc was executed to ensure hydrogen delivery from "below", as in **88**, increasing the yield of the target **89** with the desired C-4 orientation to 88%. Thus, the five stereocenters of Woodward's aldehyde ester **24** in the Fraser-Reid group's reserpine approach were established in the correct stereochemical array. The primary and secondary hydroxy groups of **89** were subjected to silylation and methylation, respectively, to generate the ether **91**, which was converted into the enol ether **92** via bridged ether cleavage, Wittig olefination, and acetylation with Levine's procedure.[63] Through a straightforward multistep sequence of functional-group modifications

Scheme 9. Fraser-Reid's Synthesis of Reserpine[a]



[a] Conditions: (a) (i) MeONa, MeOH, (ii) TsCl, pyridine, (iii) NaI, Ac_2O, 60 °C; (b) $Bu_3SnCH{=}CHCO_2Et$, AIBN, PhMe; (c) MeOH−Et_3N−H_2O (8:2:1); (d) $ClSiMe_2CH_2Br$, Et_3N, CH_2Cl_2; (e) Bu_3SnCl, $NaCNBH_3$, AIBN; (f) H_2O_2, $KHCO_3$, KF; (g) (i) TBSCl, imidazole, DMF, (ii) LAH, Et_2O, (iii) MsCl, Et_3N, CH_2Cl_2; (iv) PhSeSePh, $NaBH_4$, H_2O_2, reflux, (v) *n*-Bu_4NF, THF; (h) (i) O_3, MeOH, Me_2S, (ii) K_2CO_3, MeOH, (iii) $Ph_3P^+MeCl^-$, KHMDS; (i) Bu_2SnO, NBS; (j) $NaBH(OAc)_3$, EA; (k) TBDPSCl, Et_3N, DMAP; (l) MeI, Ag_2O; (m) (i) AcOH−THF−H_2O (4:2:1), 90 °C, (ii) $Ph_3P^+CH_2OMeCl^-$, BuLi, THF, (iii) Ac_2O, pyridine; (n) (i) *n*-Bu_4NF, THF, (ii) PDC, DMF, (iii) TMS−CHN_2; (o) (i) AcOH, THF, (ii) PDC, DMF, (iii) TMS−CHN_2; (p) O_3, MeOH, −78 °C then Me_2S; (q) (i) $NaBH_4$, CH_3OH, Δ, (ii) TMS−CHN_2, (iii) Ac_2O, pyridine.

Scheme 10. Liao's Synthesis of Reserpine[a]



[a] Conditions: (a) $PhI(OAc)_2$, CH_2Cl_2; (b) $NaBH_4$, MeOH; (c) MeOH, K_2CO_3, reflux; (d) $(COCl)_2$, Me_2SO, NEt_3, CH_2Cl_2, −78 °C; (e) SmI_2, MeOH, THF; (f) TsCl, pyridine, CH_2Cl_2; (g) *m*-CPBA, CH_2Cl_2; (h) DIBALH, −78 °C.

involving desilylation, oxidation,[64] and esterification[65] the enol ether **92** was transformed into the ester **93** with a 66% yield. Acidic hydrolysis of the enol ether in **93** followed by oxidation and esterification provided the diester **94**, which by ozonolysis led to Woodward aldehyde ester **24**.[66] At this point Fraser-Reid had essentially achieved a formal synthesis of reserpine.

Thus, the Fraser-Reid group explored a unique enantiospecific synthesis of the (−)-reserpine E-ring subunit by employing D-glucose as the chiral pool in which the enantiomerically pure Woodward intermediate **24** was accomplished in 27 steps. The efforts of the Fraser-Reid group illustrate how serial radical cyclizations of tethered pyranosyl-derived dienes can be used to construct complex, functionality-rich cyclohexane systems with a high degree of stereochemical control.

2.5. Liao Approach via Intramolecular Diels–Alder Reaction

In 1996 Liao and co-workers described a new synthetic route using intramolecular [4 + 2] cycloaddition chemistry to synthesize (±)-reserpine.[67] This strategy permitted preparation of the bicyclo[2.2.2]-oct-5-en-2-one derivative, which serves as a convenient substrate for synthesis of the more highly functionalized Stork aldehyde **73** (Scheme 10).

At the outset of Liao's method an intramolecular Diels–Alder reaction[68] of the masked *o*-benzoquinone **96**—formed in situ from methyl vanillate **95** and allyl alcohol[69] in the presence of $PhI(OAc)_2$[70] via an oxidative coupling reaction[71]—produced the bicyclic ketone **97** with a double bond to allow for further manipulation of functional groups. In addition, it introduced the desired three stereocenters at C-5, C-2, and C-7 of Stork aldehyde **73**. Reduction of **97** with $NaBH_4$ resulted in alcohols *endo*- and *exo*-**98** as a separable 1:2 epimeric mixture. The undesired alcohol *endo*-**98** could be transformed into **97** via a Swern oxidation. Treatment of *exo*-**98** with refluxing methanolic K_2CO_3 resulted in the introduction of a methoxyl group at C-6 via a Michael addition to provide a 5:7 mixture of the trans adduct **99**. Liao and co-workers found that when **97** and *endo*-**98** were treated with refluxing methanolic K_2CO_3 independently, none of the Michael addition products were formed. The crude **99** was oxidized into ketones **100** and **101** as a 7:5 mixture following Swern's technique. Application of SmI_2 [72] allowed for the selective reduction of **101** purified by column chromatography into alcohol **102** in excellent yield. After tosylation followed by Baeyer–Villiger oxidation, alcohol **102** produced two isomeric lactones **103** and **104** in a ratio of 1:4 with a 72% yield. Reduction of **104** with DIBALH in toluene provided the well-known pentasubstituted aldehyde **73**, a key building block that has previously been transformed into reserpine by Stork.[46]

Although the work of Liao's group was not easily amenable to large-scale preparations of reserpine, this protocol illustrates that the intramolecular Diels–Alder cyclization of the masked *ortho*-benzo-

quinone derivatives, available from polysubstituted phenol via a one-step oxidation−coupling induced by $PhI(OAc)_2$, can be used effectively to generate a bicyclo[2.2.2]oct-5-en-2-one scaffold to deliver the desired stereochemistry of the E-ring precursor for the yohimbine alkaloid synthesis.

2.6. Hanessian Approach Utilizing (−)-Quinic Acid as Chiral Pool

In 1997 Hanessian and co-workers published a stereocontrolled total synthesis of (−)-reserpine using readily available (−)-quinic acid as a chiral template[73] to construct the chiral E-ring subunit of reserpine.[74] In this (−)-reserpine synthetic route (Scheme 11) the acid-catalyzed lactonization of (−)-quinic acid in a mixed solvent of benzene and DMF furnished a known[75] bicyclic lactone **105**. The equatorial hydroxyl group at C-3 of **105** was regioselectively benzylated by Moffatt's procedure[76] via the *cis*-*O*-stannylene acetal intermediate to give lactone **107**.[77] This intermediate was eventually transformed into the conjugated ester **111** through a straightforward multistep sequence of functional-group modifications involving protection of the C-1 and C-4 hydroxyl groups, catalytic debenzylation by Pearlman's catalyst ($Pd(OH)_2$/C),[78] sodium periodate and ruthenium dioxide-mediated oxidation of the resulting alcohol into the corresponding ketone, and methanolysis and β-elimination. Silylation of the hydroxyl group at C-5 to ether **112** and a subsequent Grignard reaction with vinylmagnesium bromide in THF gave the C-3 vinyl carbinol **113** in 90% yield as the major product. The formation of **113** is nicely rationalized by a cyclic transition state in which the nucleophile is added to the less-hindered face of a chelated carbonyl.[79] The versatility and feasibility of highly stereocontrolled intramolecular cyclizations of α,β- and β,γ-unsaturated α-halo-acetates were demonstrated by Hanessian's group[80] in their substituted lactones synthesis, which has also permitted easy access to lactone **115**. Esterification of **113** with chloroacetate followed by an exchange with sodium iodide conveniently led to the α-iodoacetate ester **114**, which was treated with Ph_3SnH in the presence of AIBN[81] in refluxing benzene to produce a 2.3:1 mixture of isomers, favoring the desired lactone **115**. The unwanted isomer **116** could be transformed into a mixture of **115** and **116** in a ratio of 2.3:1 by treatment with DBU. Oxidative cleavage of **115** with ozone, followed by transformation to the corresponding acid and esterification, led to the ester **117** in a 24% overall yield from quinic acid in which four (C-15, C-17, C-18, and C-20) of the five contiguous chiral centers of reserpine are in place.

With the key precursor **117** representing the E-ring of reserpine in hand the next crucial issue to be addressed was assembly of the pentacyclic ring skeleton and the fate of the stereochemistry at C-3 of reserpine. Regioselective reduction of the carbonyl group of the lactone in **117** with Sia_2BH (disamylborane) in THF[82] occurred smoothly, producing the corresponding hemiacetal **118**. The C/D-ring closure was achieved by refluxing **118** with 6-methoxytryptamine in toluene to furnish a mixture of lactam **119** and **120** as C-3β and C-3α isomers. The ratio of the two isomers was found to be dependent on the acids employed with a maximum yield of **119** (53%) obtained in the presence of pivalic acid. Several attempts were made to perform the C/D-ring closure using many different acids, but all were unsuccessful in improving the isomer ratio. Hanessian and co-workers suggested a possible mechanism for C/D-ring closure beginning with an attack of the indole moiety on a half-chairlike imine or immonium ion intermediate via pseudoaxial (Chart 2, a) or pseudoequatorial (Chart 2, b) approaches to transient intermediates **119a** and **120a**, respectively. This step was followed by spontaneous elimination of methanol and lactam formation. Also, Hanessian and co-workers rationalized the prevalence of the desired isomer **119** over **120** by suggesting that the putative initially formed iminium ion may undergo a competing attack by the excess anion (Cl^-, carboxylate, or sulfonate) to give a transient α-substituted amine; this amine spontaneously loses methanol to give a lactam and then the intermediate **123a**. The resulting extended conjugated immonium lactam system (**123a** ↔ **123b**) could benefit from a pseudoaxial approach en route to the desired **119**.

By protecting the tertiary carbinol at C-16 in **119** as the TMS ether and subsequently reducing it using diborane the amine **121** was produced, which by desilylation and SmI_2-mediated deoxygenation provided the ester **122** and introduced the C_{16} stereocenter. Finally, removal of the TBDMS protecting group at C-18 and esterification with 3,4,5-trimethoxybenzoyl chloride completed the enantiospecific total synthesis of (−)-reserpine.

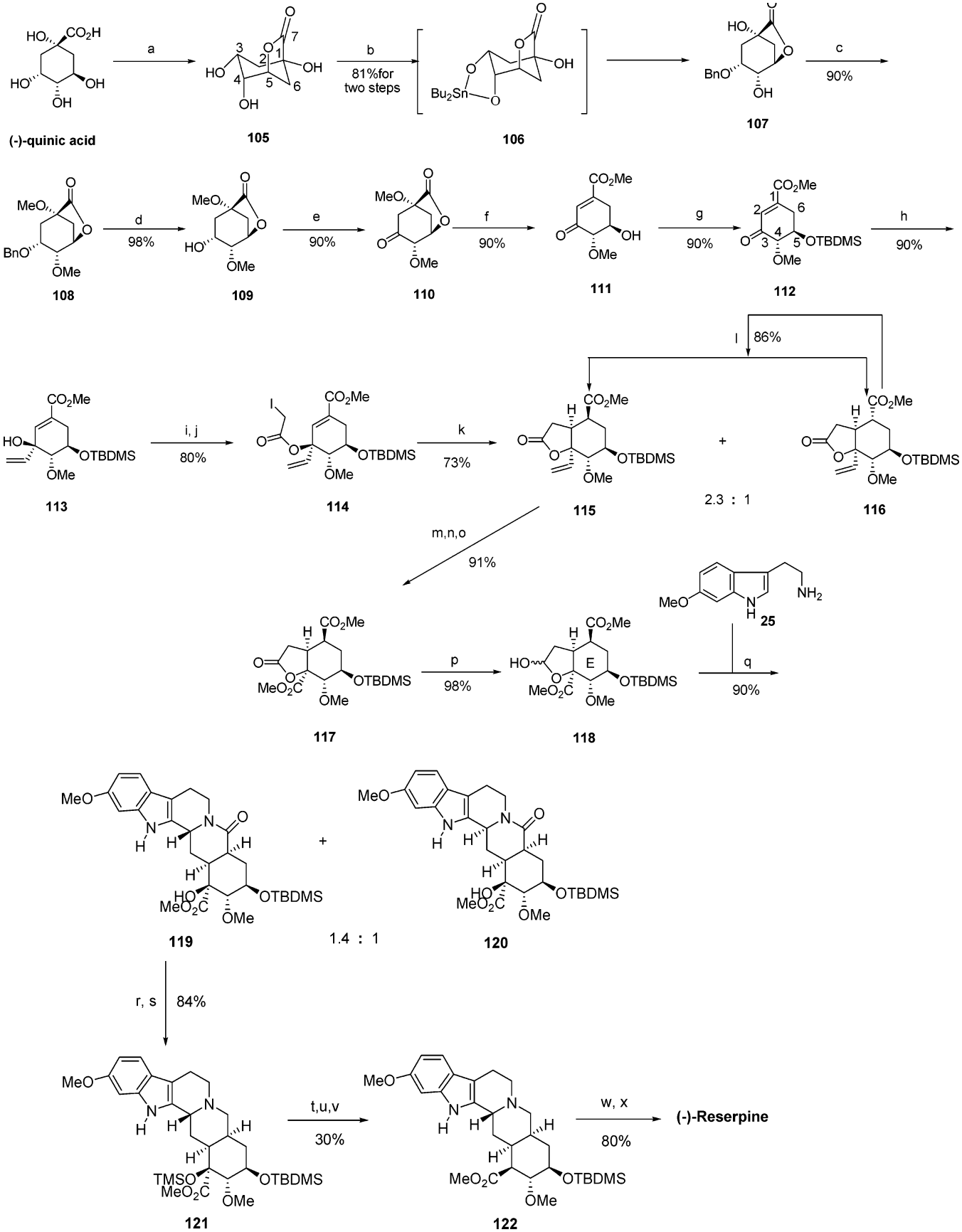
All in all, Hanessian and co-workers accomplished an elegant and enantiospecific synthesis of (−)-reserpine from (−)-quinic acid in 20 steps and with a 2.6% overall yield. The key feature of this synthesis is the closure of C/D-ring from the imine intermediate using a Pictet−Spengler-type condensation.[83] The efforts of Hanessian's group demonstrate the utility of (−)-quinic acid as a chiral pool in the total synthesis of yohimbine alkaloids.

2.7. Mehta Approach via Intermolecular Diels−Alder Reaction

Reserpine was the subject of intensive synthetic investigation for many years by Mehta's group,[84] who developed general and versatile strategies for the synthesis of densely functionalized *cis*-hydrindanes based on the use of tricyclo[$5.2.1.0^{2,6}$]decane derivatives as synthetic intermediates. These studies culminated in a stereoselective synthesis of (±)-reserpine in 2000[85] in which the topology of the readily accessible *endo*-tricyclo[$5.2.1.0^{2,6}$]decane and *cis*-hydrindane system was exploited successfully to generate the desired stereochemical pattern present in Woodward's reserpine aldehyde ester **24**. The synthetic route for the preparation of **24** is outlined in Scheme 12.

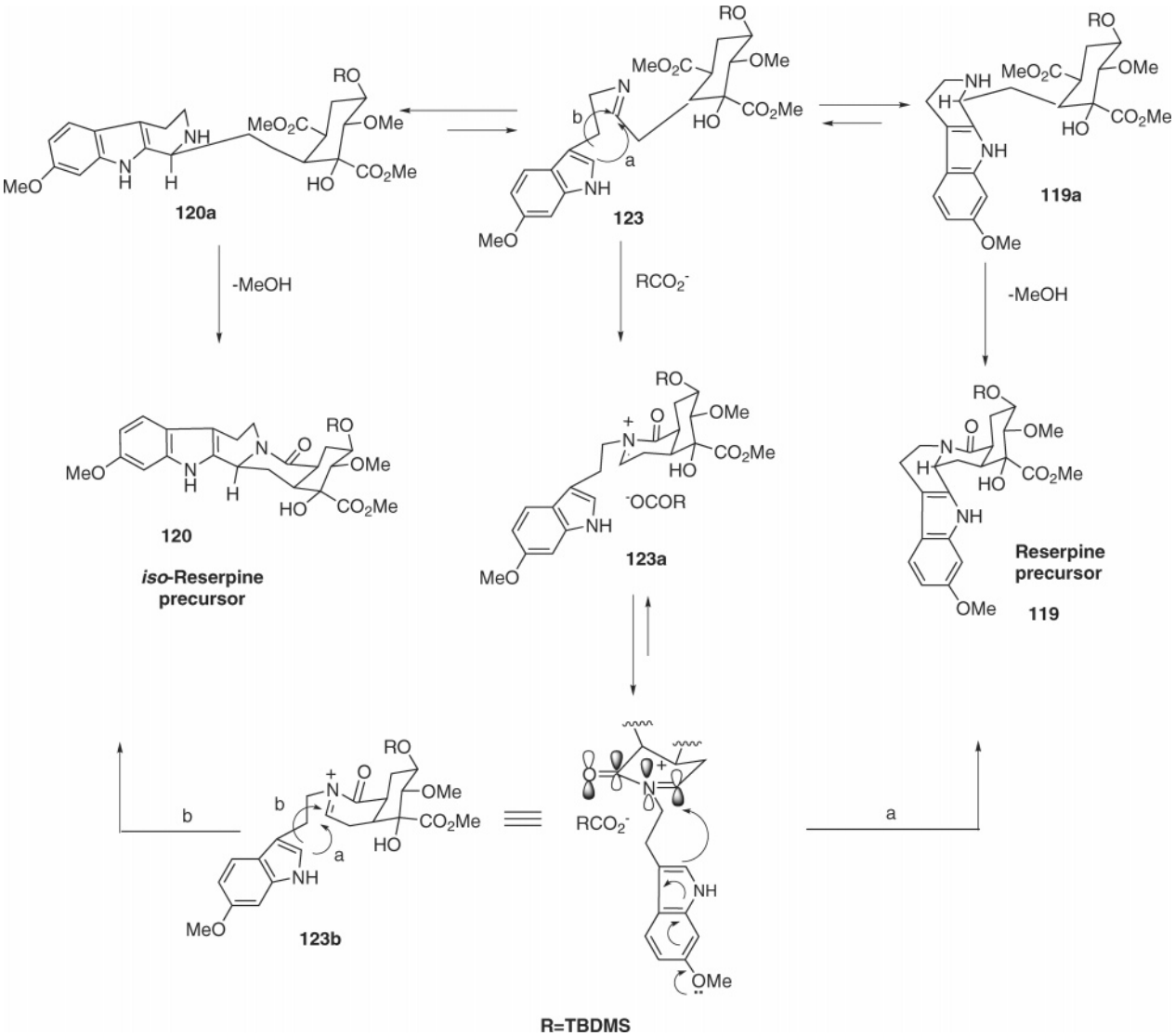
Formation of the desired keto−acetonide **127** was accomplished by a four-step sequence beginning with a Diels−Alder reaction of cyclopenta-1,3-diene and 5,5-dimethoxytetrachlorocyclopentadiene,[86] regiose-

Scheme 11. Hanessian's Synthesis of Reserpine[a]



[a] Conditions: (a) TsOH, DMF, benzene; (b) Bu_2SnO, BnBr; (c) KH, MeI, THF; (d) H_2, $Pd(OH)_2$/C, MeOH; (e) $NaIO_4$, $RuO_2 \cdot xH_2O$; (f) $KHCO_3$, MeOH; (g) TBDMSOTf, 2,6-lutidine; (h) THF, CH_2=$CHMgBr$; (i) DCC, $ClCH_2CO_2H$, DMAP, CH_2Cl_2; (j) MeCN, NaI; (k) Ph_3SnH, AIBN, C_6H_6; (l) DBU; (m) O_3 then DMS; (n) $NaClO_2$, *t*-BuOH, 2-methyl-2-butene, NaH_2PO_4, H_2O; (o) Et_2O, CH_2N_2; (p) Sia_2BH, THF; (q) PhMe, Me_3CCO_2H; (r) 2,6-lutidine, TMSOTf, CH_2Cl_2; (s) B_2H_6, THF, HMPA, $HO(CH_2)_2OH$; (t) MeCN, HF; (u) CH_2Cl_2, 2,6-lutidine, TBDMSOTf; (v) SmI_2, HMPA, $HO(CH_2)_2OH$, THF; (w) HF, MeCN; (x) 3,4,5-trimethoxybenzoyl chloride, Et_3N.

Chart 2. Possible Mechanism for Formation of 119 and 120

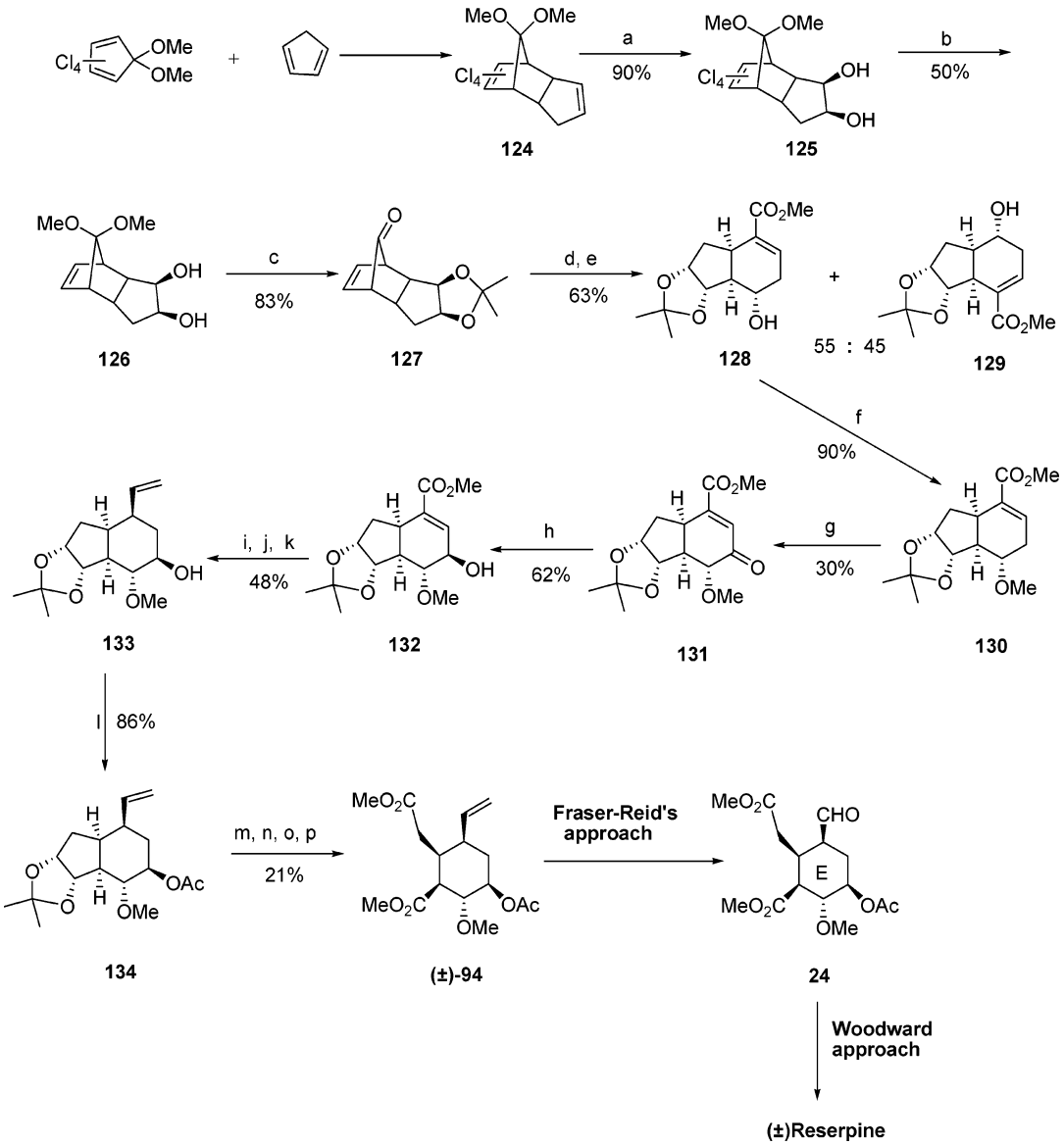


lective catalytic *cis*-dihydroxylation, reduction dehalogenation in metal−ammonia solution, and a one-pot protection−deprotection in acetone in the presence of Amberlyst-15. Extraction of the *cis*-hydrindane framework was conducted by Baeyer−Villiger oxidation of **127** and methanolysis of the resulting conjugated lactone to lead to the readily separable regioisomeric hydroxyl esters **128** and **129** in a ratio of 55:45. From the conjugated ester **128**, a compound incorporating three stereogenic centers and aldehyde functionality in a latent form, the synthesis of reserpine was straightforward. Methylation of **128** with CH_3I under solvent-free conditions[87] furnished the methoxy ester **130** in 90% yield, which was subjected to PDC oxidation and Luche reduction ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) of the resulting enone carbonyl in **131** to give the enol ester **132** in a regioselective and stereoselective manner. Mehta proposed that the reduction proceeded via a hydride addition to the carbonyl group of **131** from the convex face of the *cis*-hydrindane moiety. Thus, the four stereocenters, corresponding to C_{15}, C_{16}, C_{17}, and C_{18}, of reserpine were established efficiently. The remaining C_{20} stereocenter of reserpine was introduced by catalytic hydrogenation of **132** followed by DIBALH reduction and Wittig methylenation to furnish the olefin **133** with a 48% yield; the secondary hydroxyl group of **133** was then acetylated to ester **134**.

At this point, to complete the synthesis of Woodward's reserpine aldehyde ester **24** and, thus, reserpine itself, only elaboration of the *cis*-disposed methoxycarbonyl and the acetic acid side chain on the E-ring corresponding to C-15 and C-16 of reserpine remained. Acetonide deprotection of **134** followed by periodate cleavage of the resulting diol to dialdehyde, Jones oxidation to the dicarboxylic acid, and diazomethane esterification led to diester (±)-**94** in 21% yield. Finally, by taking advantage of an efficient synthetic pathway Fraser-Reid had previously reported,[53] Mehta readily converted the olefinic group in (±)-**94** into the aldehyde functionality to lead to Woodward precursor **24**, which had been previously elaborated to reserpine.

In summary, Mehta developed a conceptually simple and straightforward chiral synthesis of (±)-reserpine. Despite its unsatisfactory regioselectivity, Mehta's route demonstrates how *endo*-tricyclo[5.2.1.0]-decane can be utilized to quickly create *cis*-hydrindane derivatives possessing functionality that can be

Scheme 12. Mehta's Synthesis of Reserpine[a]



[a] Conditions: (a) OsO_4, Me_2CO, H_2O, *t*-BuOH; (b) Na−NH_3(*l*), THF, EtOH; (c) Me_2CO−Amberlyst-15; (d) MCPBA, DCM; (e) KOH, MeOH; (f) KOH, MeI; (g) PDC, *t*-BuOOH, Celite; (h) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; (i) H_2, PtO_2, EtOH; (j) DIBALH, DCM, −78 °C; (k) $MePPh_3^+I^-$, *n*-BuLi; (l) Ac_2O, pyridine, DMAP; (m) 30% TFA; (n) $NaIO_4$, 10% aq THF; (o) CrO_3, H_2SO_4, Me_2CO; (p) CH_2N_2, ether.

elaborated stereoselectively to that found in yohimbine-reserpine-type alkaloids.

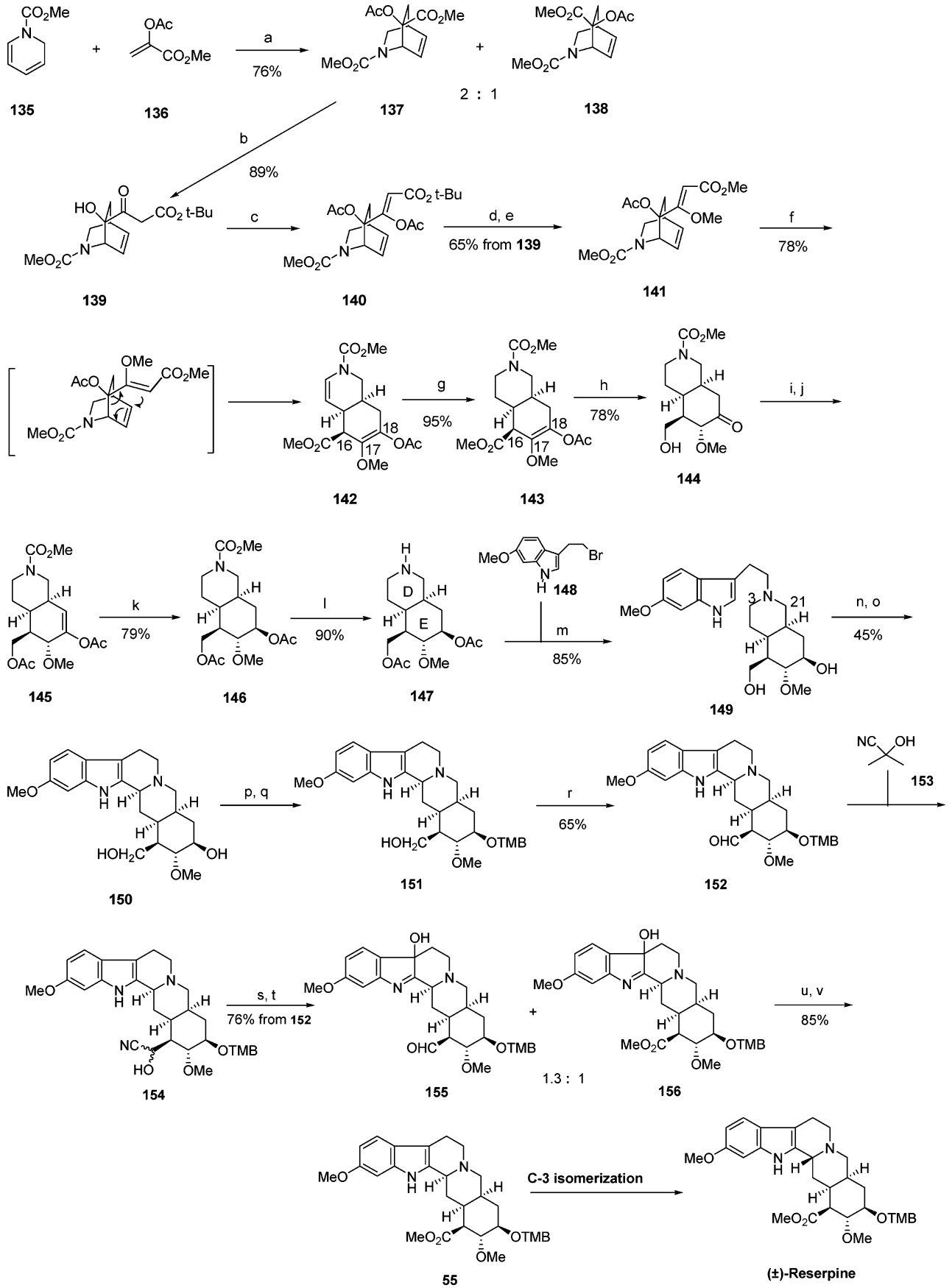
3. Syntheses Using a cis-Fused DE-Ring Core as a Precursor

3.1. Wender Approach via Cope Rearrangement

In 1980 Wender and co-workers reported the first total synthesis of (±)-reserpine[26] using a highly functionalized *cis*-fused DE-ring core as the key building block. Their strategy addressed synthesis of the *cis*-hydroisoquinoline derivatives[88] as a latent DE-ring system via an intermolecular Diels−Alder cycloaddition and a Cope rearrangement[89] sequence followed by C-ring closure to complete the synthesis of reserpine (Scheme 13).

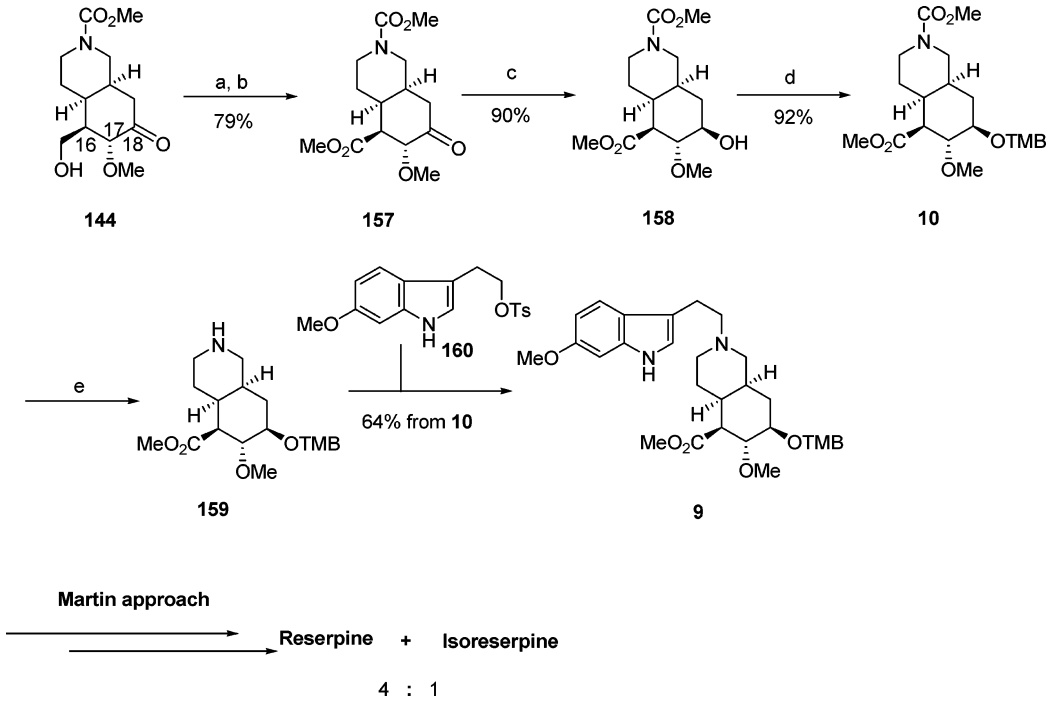
The intermolecular Diels−Alder cycloaddition of methyl 1,2-dihydropyridine-1-carboxylate (**135**)[90] with a methyl ester of 2-acetoxyacrylic acid (**136**) gave a epimeric mixture of esters **137** and **138** in a ratio of 2:1. Claisen condensation of **137** with the lithium enolate of *tert*-butyl acetate produced keto alcohol **139** with 89% yield, which was then protected as the diacetate **140** by treatment with acetic anhydride in the presence of 4-(dimethylamino)pyridine (DMAP).[91] Conversion of **140** into the desired 1,5-diene **141** was accomplished by hydrolysis of the *tert*-butylester and enol acetate moieties with trifluoroacetic acid and treatment of the resulting ketoacid with ethereal diazomethane.[92] Thermolysis of **141** at 243 °C via a Cope rearrangement gave the desired *cis*-hydroisoquinoline **142** with a 78% yield. Three of the five stereocenters of the E-ring were established in **142** by the concertedness of the rearrangement. The intermediate **142** can be envisioned as the key DE-ring precursor because cleavage of its acetate group can introduce a ketone at C-18; subsequent reduction of the C-18 ketone from the convex face can establish the fifth stereocenter of reserpine E-ring. Thus, LAH

Scheme 13. Wender's Synthesis of Reserpine[a]



[a] Conditions: (a) Δ; (b) $LiCH_2CO_2{}^tBu$, −78 °C; (c) Ac_2O; (d) TFA; (e) CH_2N_2; (f) 243 °C; (g) H_2, Pd/C; (h) LAH, 0 °C; (i) $LiN(SiMe_3)_2$, −10 °C; (j) AcCl, −78 °C; (k) H_2, 10% Pd/C; (l) Me_3SiI; (m) MeOH, K_2CO_3, reflux; (n) $Hg(OAc)_2$, HOAc; (o) $NaBH_4$; (p) 3,4,5-trimethoxybenzoyl chloride; (q) KOH, MeOH; (r) DMSO, DCC, H_3PO_4; (s) DMSO, $(COCl)_2$; (t) MeOH; (u) $NaBH_4$; (v) H^+.

Scheme 14. Wender's Improved Synthesis of Reserpine[a]



[a] Conditions: (a) CrO_3, H_2SO_4; (b) CH_2N_2; (c) $NaBH_4-CeCl_3$; (d) $(TMB)_2O$, DMAP; (e) Me_3SiI.

reduction of the diester **143**, obtained by catalytic hydrogenation of **142**, provided a 78% yield of the desired keto alcohol **144** with the required relative stereochemistry as a single isomer. Wender and co-workers attributed this high degree of stereoselectivity exhibited in the reduction of **143** to the intramolecular proton delivery from the C-16 hydroxymethyl group to the C-17 center. Acylation of the lithium enol of **144** yielded the C-18, C-19 enol acetate **145**. Stereoselective hydrogenation of **145** produced the diacetate **146** in 79% yield in which the desired reserpine C_{18} configuration was set. This result indicated that the high stereoselectivity obtained in this reduction of **145**, which presumably occurred through a syn addition, was under vicinal stereoinductive control. Deprotection of the nitrogen function in **146** by means of Me_3SiI,[93] followed by tryptophylation, produced 2,3-secoreserpinediol **149**. Wender and co-workers then subjected **149** to oxidative cyclization[94] ($Hg(OAc)_2$/HOAc) and $NaBH_4$ reduction to provide the isoreserpinediol **150**, which was accompanied by 30% of an isomeric diol, assigned as an inside reserpinediol.[95] Subsequent bi-acylation of **150** with 3,4,5-trimethoxybenzoyl chloride and then mono-hydrolysis gave the monoester **151**. Transformation of **151** into the thermodynamically more stable isoreserpine **55** was achieved with an overall yield of 16% through a lengthy sequence of steps involving Moffatt oxidation, cyanation, Swern oxidation, $NaBH_4$ reduction, and acid treatment and followed by conversion to reserpine along well-established lines.[96]

In addition, in 1987 Wender's group developed a more efficient path to reserpine from **144** via a direct stereocontrolled α-face reduction of the C-18 ketone in **144** as the key step[97] (Scheme 14). Thus, Jones oxidation of the hydroxymethyl group in **144** followed by esterification of the resultant acid with CH_2N_2 led to the methyl ester **157**, which upon reduction with $NaBH_4$–$CeCl_3$ gave the desired $C_{18}\beta$ alcohol **158** with a 90% yield.[98] Trimethoxybenzoylation of **158** produced the ester **10**, which has all of the reserpine E-ring functionality. Subsequent nitrogen deprotection and tryptophylation with 6-methoxytryptophyl tosylate **160** gave 2,3-secoreserpine **9**. Finally, completion of reserpine synthesis was achieved in 16 steps from **135** following the procedure developed by Martin and co-workers.[99]

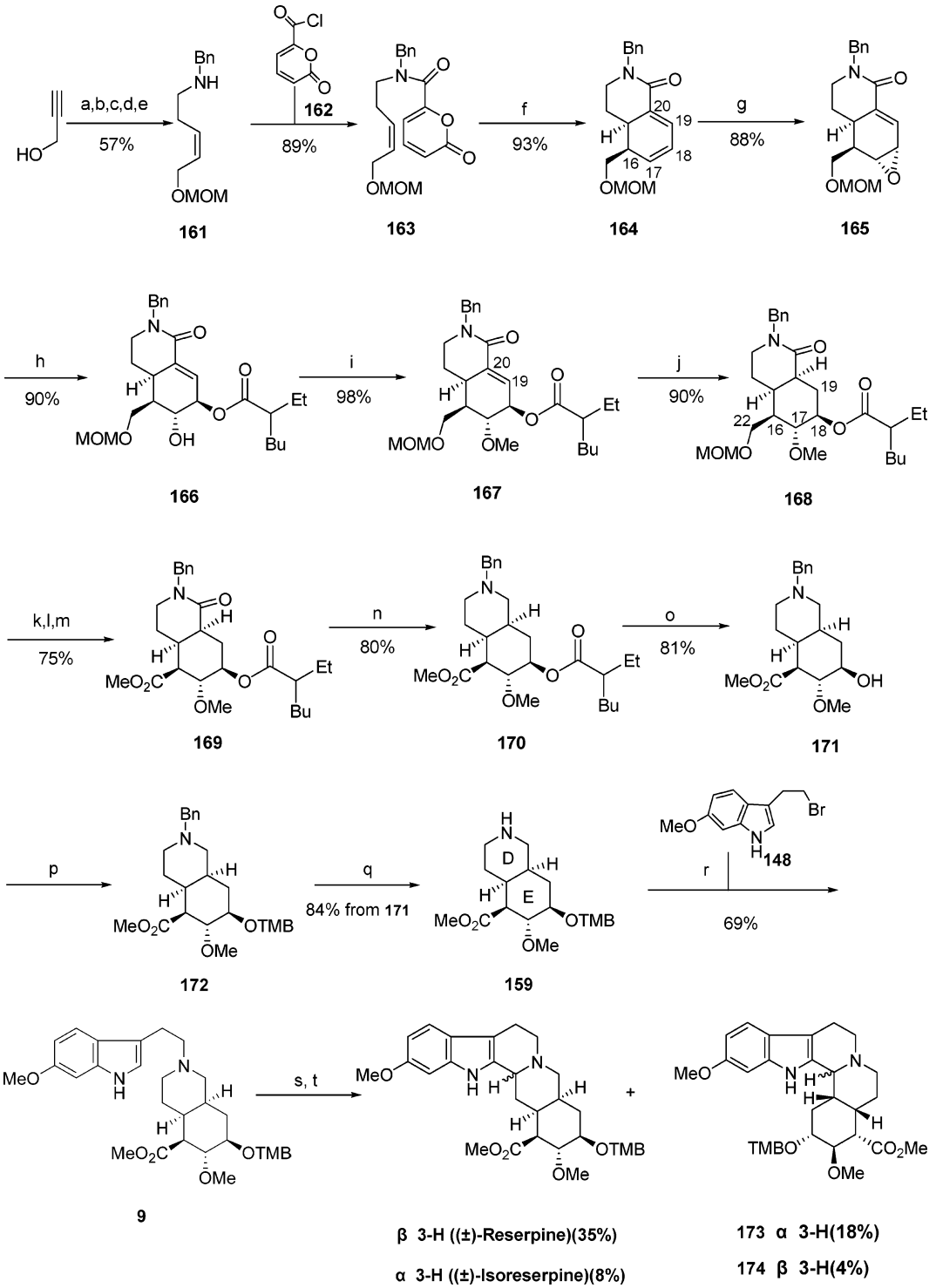
In short, Wender and co-workers contributed a formal and stereospecific synthesis of (±)-reserpine using a Cope rearrangement as a key design element. The work of Wender's group illustrates the utility of Cope rearrangement in stereoselectively constructing a DE-ring skeleton of yohimbine alkaloids and thus introduces a novel DE-ring strategy for total synthesis of reserpine.

3.2. Martin Approach via Intramolecular Diels–Alder Reaction

During their early work on the synthesis of the pentacyclic skeleton of the yohimbine alkaloids Martin and associates devised a convenient synthesis of highly functionalized hydroisoquinolines via an intramolecular [4 + 2] cycloaddition of suitable substituted azatrienes,[100] which led to a concise and efficient total synthesis of reserpine in 1985 (Scheme 15).[99]

Martin's reserpine synthesis began with the preparation of olefinic amine **161**[101] from propargyl alcohol through a straightforward five-step sequence involving protection as methoxymethyl ether, two-carbon chain extension, Lindlar catalytic hydrogenation, tosylation, and aminolysis. Coupling of **161** with 2-pyrone-6-carbonyl chloride **162**[102] resulted in the trienic amide **163**, the substrate for the key intramo-

Scheme 15. Martin's Synthesis of Reserpine[a]



[a] Conditions: (a) $MeOCH_2Br$; (b) *n*-BuLi, ethylene oxide; (c) H_2, $Pd/CaCO_3/PbO$; (d) *p*-TsCl, Py; (e) $PhCH_2NH_2$, NaI, Me_2SO; (f) xylene, reflux; (g) MCPBA; (h) BuCH(Et)COOH/BuCH(Et)COOLi, DEM, reflux; (i) MeI, Ag_2O, $CaSO_4$; (j) H_2, 20% $Pd(OH)_2/C$; (k) *p*-TsOH, MeOH; (l) PDC; (m) CH_2N_2; (n) AlH_3, THF; (o) TsOH, MeOH; (p) 3,4,5-trimethoxybenzoyl chloride; (q) H_2, 20% $Pd(OH)_2/C$, AcOH; (r) $(i\text{-}Pr)_2NEt$; (s) $Hg(OAc)_2$, HOAc; (t) Zn, aq HCl/acetone/THF, reflux.

lecular Diels–Alder reaction.[68] Subsequent thermolysis of **163** in refluxing xylene proceeded smoothly to give the cycloadduct **164** in a 93% yield. Having accomplished construction of the hydroisoquinoline skeleton, the stereoselective refunctionalization of the E-ring was undertaken. Regioselective epoxidation of the more nucleophilic C-17–C-18 double bond in **164** with MCPBA proceeded with a high degree of stereoselectivity from the less-encumbered α face to provide the α-epoxide **165** in 88% yield. The α-epoxide **165** was selectively opened with lithium 2-ethylhexanoate to produce **166** in 90% yield with the reserpine C_{15}, C_{16}, C_{17}, and C_{18} stereocenters secured. The liberated hydroxyl group in **166** was methylated with methyl iodide in the presence of Ag_2O and $CaSO_4$ to give methyl ether **167** in 98% yield. The remaining reserpine C_{20} stereocenter was introduced by catalytic hydrogenation of the Δ^{19} double bond in **167** using

Pearlman's catalyst to furnish the *cis*-hydroisoquinolone **168** in which all of the substituents on the E-ring except the one at C-15 would be in the preferred equatorial orientation. Removal of the MOM protecting group from the hydroxyl group at C-22 of **168**, followed by oxidation and esterification, gave the *cis*-decahydroisoquinoline **169** in a 75% yield. After the lactam carbonyl group in **169** was chemoselectively reduced by AlH_3, the C-18 hydroxyl group was deprotected and subsequently acylated with 3,4,5-trimethoxybenzoyl chloride to furnish the tertiary amine **172**. Removal of the *N*-benzyl protecting group in **172** by catalytic hydrogenolysis over Pearlman's catalyst in glacial acetic acid provided the secondary amine **159**. Thus, the fully intact *cis*-fused DE-ring subunit of reserpine was available in 18 steps with 13% overall yield from propargyl alcohol.

At this juncture the total synthesis of reserpine was completed by condensation of **159** with 6-methoxytryptophyl bromide **148**[103] followed by C-ring closure via a mercuric acetate-mediated oxidative cyclization and subsequent reduction of the resultant iminium species by zinc dust. It was of interest to note that under these conditions the major product was reserpine (35%) along with a modest amount of isoreserpine (8%) and two inside derivatives, **173** (18%) and **174** (4%). Compared with the observation that $POCl_3$–$NaBH_4$-mediated Bischler–Napieralski cyclization of Woodward's intermediate **26** provided only the isoreserpine stereoisomer, these results are particularly intriguing. The seemingly subtle differences in the reaction conditions are enough to result in drastic differences in the ratio of the reserpine and isoreserpine stereoisomers, although both reactions presumably proceed by generation of an iminium species, which is trapped by the indole, followed by subsequent reduction.

The work of Martin and co-workers illustrates well the utility of the intramolecular Diels–Alder reaction in the construction of the stereochemically complex DE-ring core of yohimbine alkaloids. This methodology may be applicable in an effective synthesis of yohimbine-reserpine-type alkaloids.

3.3. Shea Approach via Intramolecular Diels–Alder Reaction

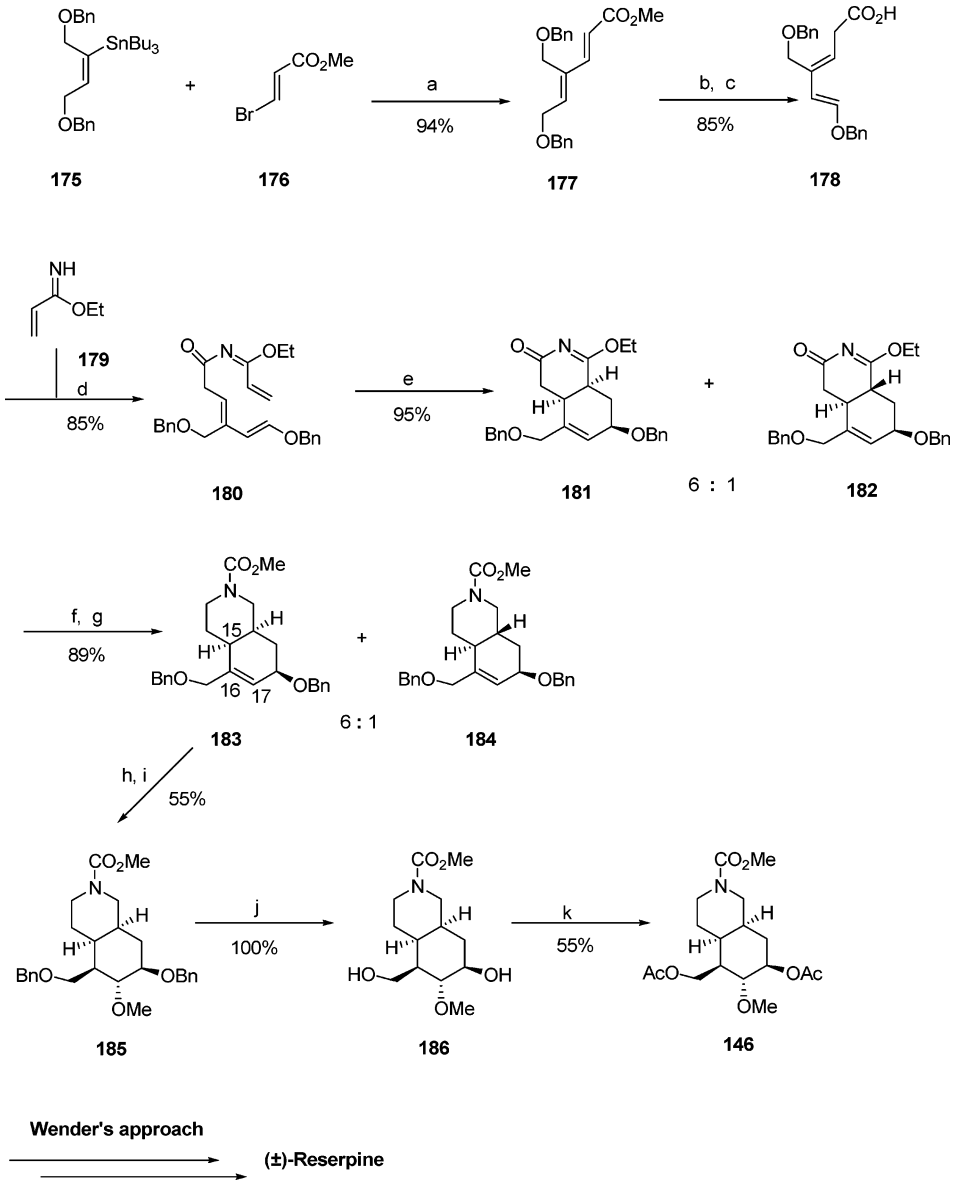
Shea and co-workers used an approach similar to that of Martin[100] in that they employed an intramolecular Diels–Alder reaction of *N*-acylvinylimidates to install the perhydroisoquinoline ring system,[104] which upon proper functionality manipulation could provide convenient access to the DE-ring subunit of reserpine.

Initially, the *N*-acylvinylimidate **180** was employed as substrate for the intramolecular Diels–Alder reaction (Scheme 16).[105] The preparation of **180** involved a straightforward four-step sequence. Stille coupling[106] of vinylstannane **175**[107] with methyl (3*E*)-bromopropenoate (**176**)[108] resulted in diene **177** in excellent yield, which was subjected to kinetic deconjugation with LDA at −78 °C followed by acidic quenching and saponification to give a single (3*E*,5*E*)-dienoic acid **178**.[109] Coupling of **178** with 1-aza-2-ethoxy-1,3-butadiene (**179**)[104b] in the presence of Mukaiyama reagent (2-chloro-1-methylpyridinium iodide)[110] provided the key substrate **180**. Heating of **180** in chloroform at 60 °C promoted the smooth intramolecular cycloaddition to produce two cycloadducts, **181** and **182**, in a 6:1 ratio.[111] This pivotal transformation not only allowed the construction of the DE-ring skeleton, but also introduced the reserpine C_{15}, C_{18}, and C_{20} stereocenters with high efficiency. After LAH reduction of the *N*-acylimidate mixtures of **181** and **182** the nitrogen was protected as separable carbamates **183** and **184**. Hydroboration–oxidation of the Δ^{16} double bond in **183**, followed by methylation with MeOTf,[112] gave the methyl ether **185** with high stereoselectivity in which the five contiguous stereocenters of reserpine were installed properly. At this point completion of the DE-ring system required only transposition of the benzyl groups for acetates. Thus, hydrogenolytic debenzylation and acetylation provided Wender's precursor **146**, from which the synthesis of reserpine was accomplished following the previously reported procedure.[26]

Later in 2003 the same group contributed an alternative approach to reserpine synthesis[113] in which the precursor **193** was used for the intramolecular Diels–Alder cycloaddition (Scheme 17). Palladium-catalyzed hydrostannylation[114] of alkynoate **187**[115] with TBTH followed by DIBALH reduction resulted in vinylstannane **188**, which was subjected to the modified Stille coupling with methyl (3*E*)-bromopropenoate (**176**) to give the conjugated ester **189** in a 94% yield. Protection of the hydroxyl group of **189** as a β-trimethylsilylethoxymethoxy ether furnished (2*E*,4*Z*)-hexadienoic ester **190**. With the preparation of (2*E*,4*Z*)-dienoic ester **190** secured, the key deconjugation was undertaken. Treatment of **190** with LDA and DMPU at −78 °C, followed by a methanolic quench, produced exclusively the (3*Z*,5*E*)-dienoic acid ester **191**, saponification of which yielded the corresponding acid **192**. In parallel with the initial synthesis, Shea prepared the crucial precursor for intramolecular Diels–Alder cycloaddition by coupling 1-aza-2-ethoxy-1,3-butadiene (**179**) with **192** in the presence of Mukaiyama reagent (2-chloro-1-methylpyridinium iodide) to produce the *N*-acylvinylimidate **193** in 85% yield. Subsequent cycloaddition occurred in refluxing chloroform to give two cycloadducts **194** and **195** in a 6:1 ratio. LAH reduction of the *N*-acylimidate functionality of the mixture followed by *N*-acylation with methyl chloroformate and chromatographic separation furnished carbamate **196** in 73% yield, which was subjected to hydroboration–oxidation to provide a single alcohol **197** with the desired stereochemistry.

From alcohol **197**, a compound incorporating the DE-ring of the alkaloid and the five required stereocenters, the synthesis of reserpine was straightforward. Methylation of the sterically congested C-17 hydroxyl group of **197** with Me_3OBF_4 in the presence of 4 Å molecular sieves gave the methyl ether **198**, followed by removal of the SEM protecting group. Oxidation of the resulting primary alcohol with PDC provided an acid, which upon esterification with CH_2N_2 yielded the methyl ester **199**. Debenzylation

Scheme 16. Shea's First Synthesis of Reserpine[a]



[a] Conditions: (a) $Pd_2(dba)_3$, TFP, CuI, NMP, 65 °C; (b) LDA, DMPU, −78 °C; (c) LiOH, H_2O; (d) 2-chloro-1-methylpyridinium iodide, Et_3N, 0 °C; (e) $CHCl_3$, 60 °C; (f) LAH, Et_2O; (g) $ClCO_2Me$, *i*-Pr_2NEt; (h) B_2H_6, 30% H_2O_2; (i) *n*-BuLi, MeOTf; (j) H_2, 10% Pd/C; (k) Ac_2O, DMAP(cat.).

and acylation of the resulting alcohol eventually led to Wender's late-stage intermediate **10**, which was transformed to reserpine following the previously documented procedure.[97]

In summary, Shea contributed two synthetic approaches to (±)-reserpine using two different *N*-acylvinylimidate derivatives as substrates for intramolecular Diels−Alder cycloaddition to construct the key DE-ring precursor. The efforts of Shea's group demonstrate the utility of *N*-acylvinylimidates in intramolecular cycloadditions for preparing a stereochemically complex perhydroisoquinoline ring system of natural yohimbine alkaloids.

4. Strategy Evaluation

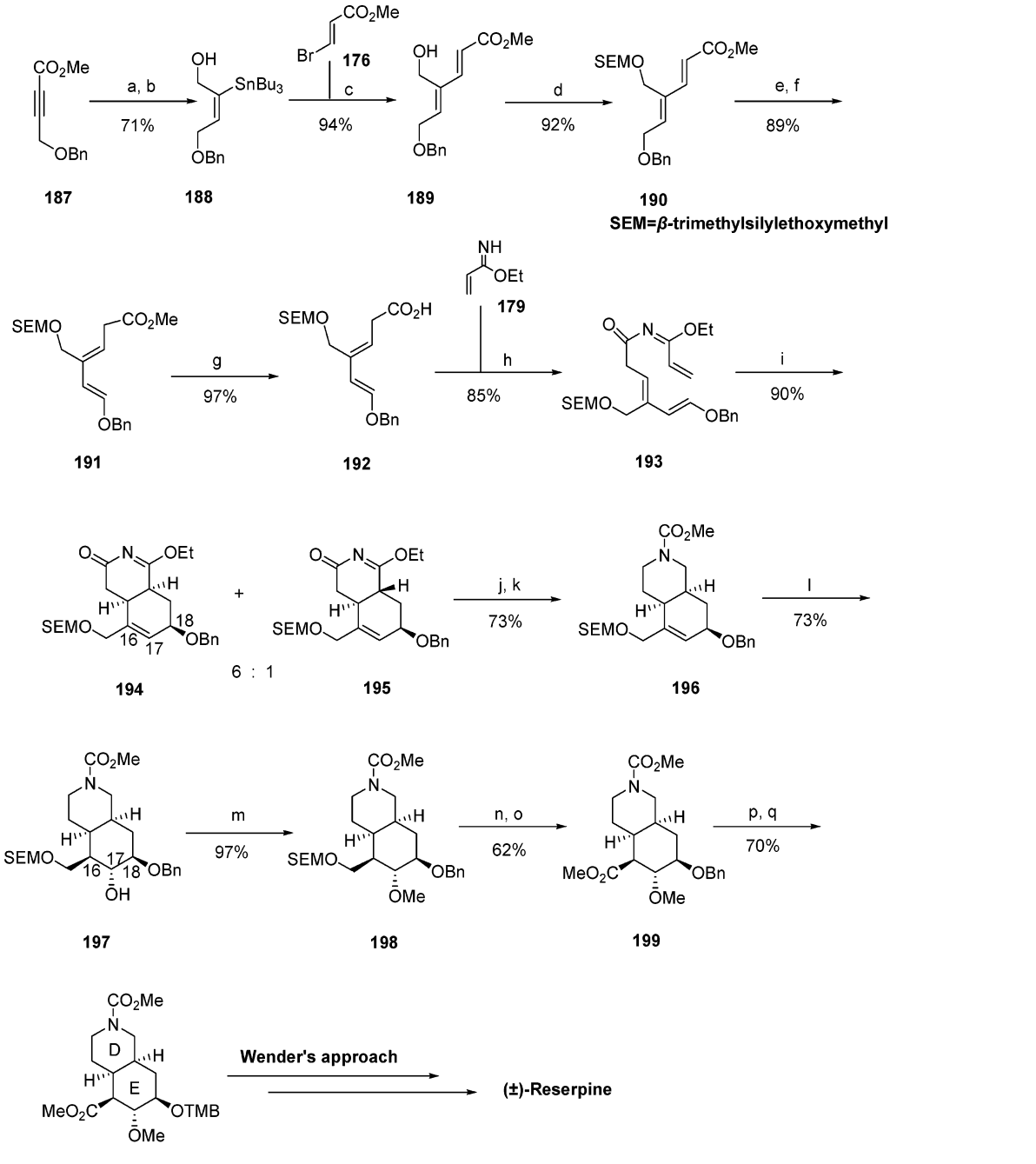
4.1. Strategy Analysis

As a prominent member of the yohimbine family, reserpine, with its imposing structure and constitution dominated by the presence of a fused pentacyclic motif and six chiral centers not all in the most stable orientation, offers a big challenge to synthetic ingenuity. The major stumbling blocks in the synthesis of the target alkaloid are the following: (a) assembling the framework of functionality rich E- or DE-ring of the alkaloid, (b) incorporation of the requisite E-ring stereogenic centers, and (c) generation of the β-H configuration at C-3. With these in mind, we summarize the elegant strategies of the successful syntheses described above with a goal of explicating the methodology for the synthetic community and opening doors to the development of new synthetic strategies.

4.1.1. Woodward's Strategy

The general features of the first total synthesis of reserpine by Woodward are shown in retrosynthetic form in Scheme 18. The last step in Woodward's

Scheme 17. Shea's Second Synthesis of Reserpine[a]



[a] Conditions: (a) $Pd(PPh_3)_4$ (2 mol %), TBTH, THF; (b) DIBALH, toluene, −78 °C; (c) $Pd_2(dba)_3$, TFP, CuI, NMP, 65 °C, 3 h; (d) SEMCl, *i*-Pr_2NEt, 0 °C; (e) LDA, DMPU, THF, −78 °C; (f) MeOH; (g) LiOH, acetone, H_2O; (h) Et_3N, CH_2Cl_2, 0 °C, 2-chloro-1-methylpyridinium iodide; (i) $CHCl_3$, 4 Å molecular sieves, 60 °C, 20 h; (j) LAH, Et_2O, 0 °C; (k) $ClCO_2Me$, *i*-Pr_2NEt, 0 °C; (l) BH_3·THF, 3 N NaOH, 30% H_2O_2; (m) Me_3OBF_4, proton sponge, 4 Å molecular sieves, CH_2Cl_2; (n) TBAF, 4 Å molecular sieves, DMPU, 80 °C; (o) PDC, DMF; CH_2N_2, Et_2O; (p) H_2, 10% Pd/C; (q) TMBCl, DMAP (cat.), NEt_3.

synthesis involved an epimerization at C-3 by intramolecular tethering to create the correct 3β-H stereochemistry. Disconnection of the key C-2−C-3 bond in methyl-*O*-acetyl-isoreserpate **28** by a retro-Bischler−Napieralski cyclization (formation of C-ring) led to the lactam intermediate **26**, which contains the ABDE-ring fragment of the target alkaloid and the C-ring in a latent form. The closure of the lactam ring (D-ring) was executed by reduction of an imine intermediate followed by lactamization. Coupling of the stereochemically and functionally rich E-ring precursor **24** with 6-methoxytryptamine **25** gave rise to the imine intermediate. Functional-group simplification of **24** led to the retrosynthetic precursor **19**, a key intermediate incorporating all five stereocenters of the E-ring of reserpine and properly disposed substitutes for elaboration of **24**. In the synthetic direction Woodward employed the Diels−Alder cycloaddition to generate a bicyclic template **31** onto which the required functionality was installed to produce **19** by taking advantage of the special stereochemical effects of the *cis*-decalin

Scheme 18. Woodward's Retrosynthetic Analysis of Reserpine

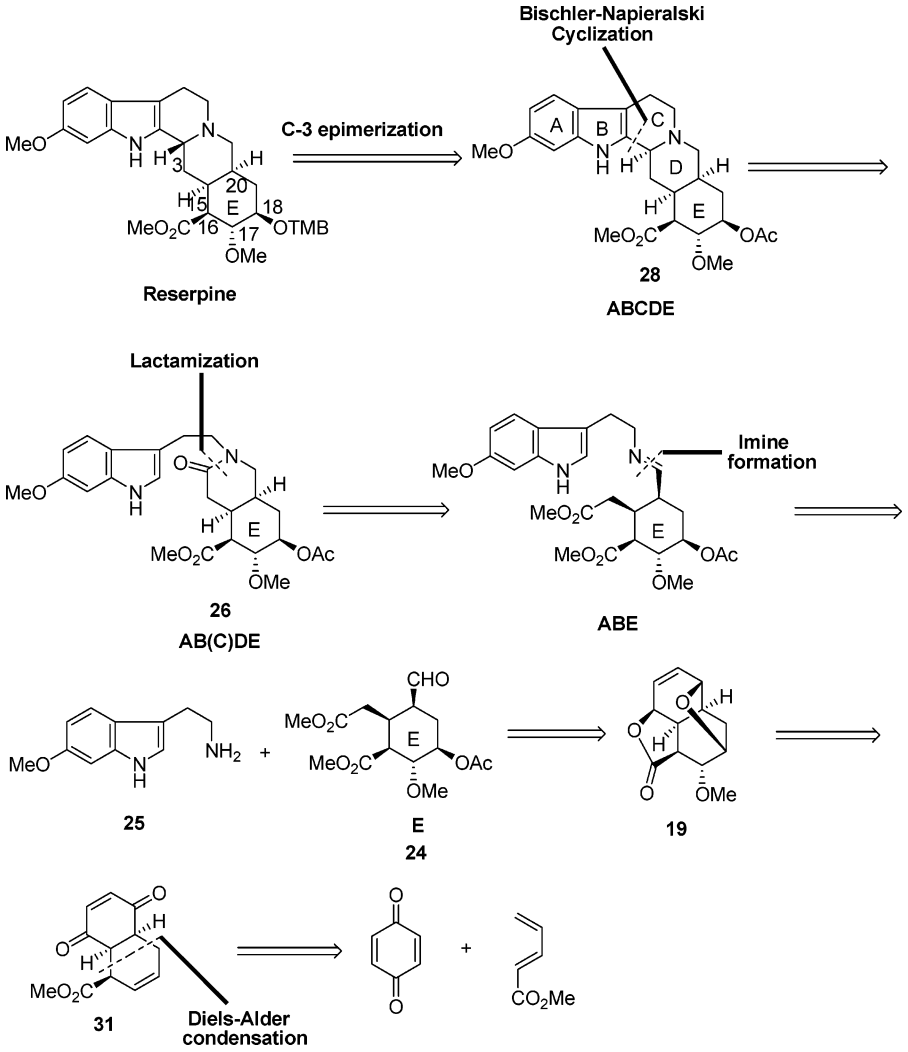


Table 2. Stereochemical Inventory for Woodward's Synthesis of Reserpine

stereocenter	control element	reaction/source
C_3	thermodynamic	equilibration
C_{15}	cyclic stereocontrol	Diels−Alder
C_{16}	cyclic stereocontrol	Diels−Alder
C_{17}	cyclic stereocontrol	bicyclo[4.4.0]decane
C_{18}	cyclic stereocontrol	Meerwein−Pondrff−Verley reduction
C_{20}	cyclic stereocontrol	Diels−Alder

Table 3. Stereochemical Inventory for Pearlman's Synthesis of Reserpine

stereocenter	control element	reaction/source
C_3	thermodynamic	equilibration
C_{15}	cyclic stereocontrol	[2 + 2] cycloaddition
C_{16}	thermodynamic	epoxidation−opening
C_{17}	thermodynamic	epoxidation−opening
C_{18}	thermodynamic	epoxidation−opening
C_{20}	cyclic stereocontrol	[2 + 2] cycloaddition

ring systems. The stereochemical inventory for Woodward's synthesis of reserpine is summarized in Table 2.

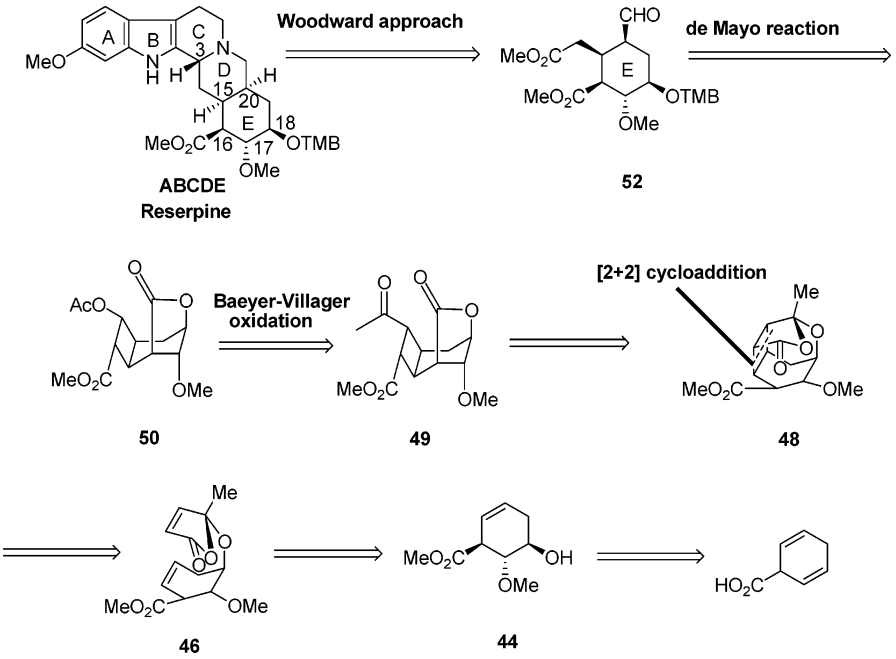
4.1.2. Pearlman's Strategy

Pearlman directed his synthesis at Woodward precursor **52**, as shown in the retrosynthetic analysis (Scheme 19). The key step in the retrosynthetic analysis is the disassembly of the polysubstituted cyclohexane ring system **52** by a retro-de Mayo reaction/Baeyer−Villager oxidation process, leading to cyclobutane **49**. In a forward sense this impressive tandem reaction would lead to the introduction of reserpine C-15/C-20 functionality. The cyclobutane ring in **49** was then disconnected by a retro-[2 + 2] cycloaddition reaction leading to the substrate **46** for cycloaddition. In the synthetic direction the intramolecular Diels−Alder reaction introduced the reserpine C_{15} and C_{20} stereocenters effectively. Further disconnection of **46** led to chiral hydroxyl−ester **44**, a compound incorporating the C_{16}, C_{17}, and C_{18} stereocenters of reserpine. The hydroxyl−ester **44** could be synthesized from 1,4-dihydrobenzoic acid via a key selective epoxidation−opening, lactonization, and methylation process. The stereochemical inventory for Pearlman's synthesis of reserpine is summarized in Table 3.

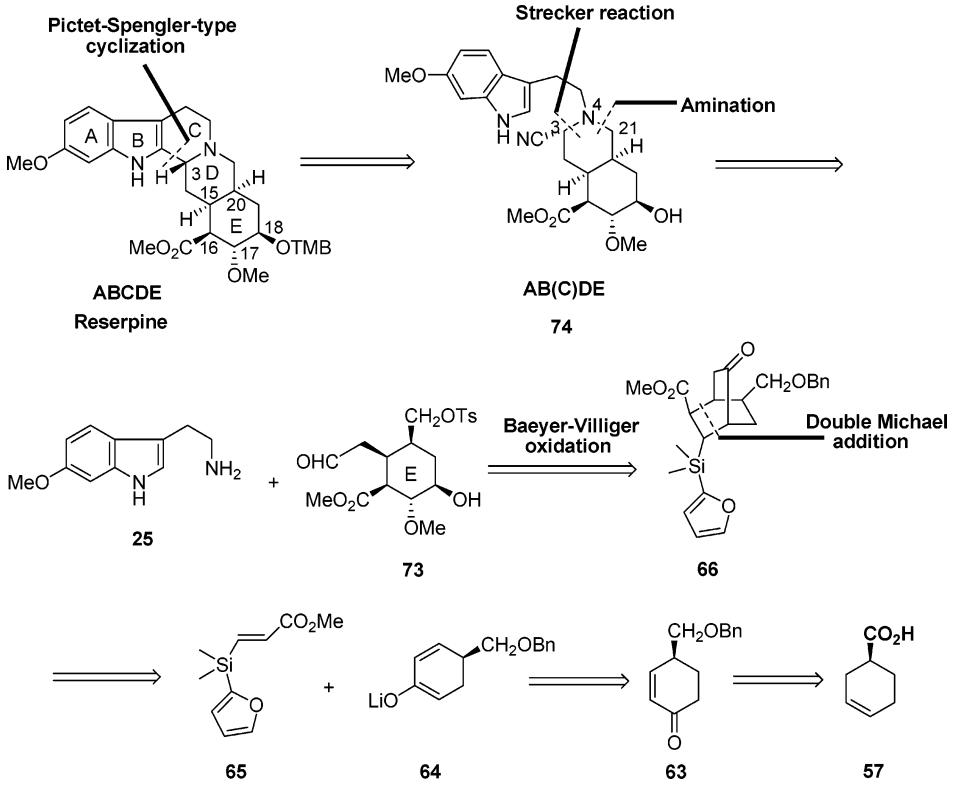
4.1.3. Stork's Strategy

The retrosynthetic analysis of reserpine by Stork is shown in Scheme 20. Stork controlled the C-3

Scheme 19. Pearlman's Retrosynthetic Analysis of Reserpine



Scheme 20. Stork's Retrosynthetic Analysis of Reserpine



configuration directly at the final C-ring closure step by employing α-amino nitrile as a masked iminium ion. Thus, retrosynthetic simplification of the target alkaloid by a retro-Pictet−Spengler-type cyclization led to the amino nitrile **74**. In the forward sense, by choosing proper solvent polarity, the amino nitrile containing a latent C-ring can give rise to a free iminium ion species which would undergo an axial indole nucleophilic attack on the cyclic iminium cation to result in the correct C-3 configuration. The amino nitrile **74** was disconnected at C-3−N-4 and N-4−C-21 by a retro-Strecker reaction/amination leading to the Stork aldehyde **73**. Stork envisioned **73** as the stereochemical outcome of the ring opening of bicyclic ketone **66** via a Baeyer−Villiger oxidation reaction. The key step in the retrosynthetic analysis is the transformation of chiral cyclohexenone **63** into bicyclic ketone **66** via the versatile double Michael addition between **64** and **65**, which assembles immediately into the cyclohexane framework with the desired five chiral centers in their proper form. Finally, functional-group simplification of **63** led to the readily available, optically pure (*S*)-3-cyclohexenecarboxylic acid (**57**). The stereochemical inventory

Scheme 21. Fraser-Reid's Retrosynthetic Analysis of Reserpine

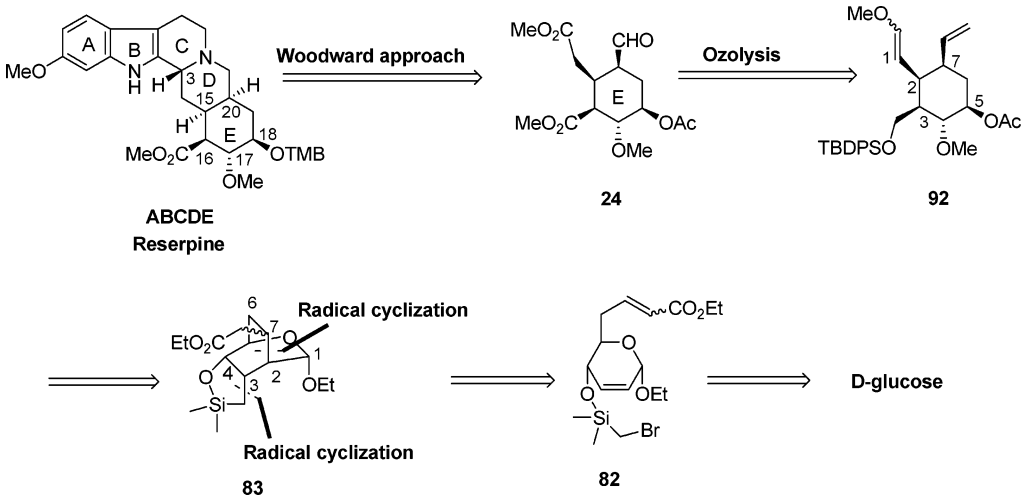


Table 4. Stereochemical Inventory for Stork's Synthesis of Reserpine

stereocenter	control element	reaction/source
C_3	stereoelectronic	nucleophilic attack
C_{15}	cyclic stereocontrol	intramolecular double Michael addition
C_{16}	cyclic stereocontrol	intramolecular double Michael addition
C_{17}	cyclic stereocontrol	intramolecular double Michael addition
C_{18}	cyclic stereocontrol	intramolecular double Michael addition
C_{20}	chiral pool	(*S*)-3-cyclohexene-carboxylic acid

Table 5. Stereochemical Inventory for Fraser-Reid's Synthesis of Reserpine

stereocenter	control element	reaction/source
C_3	thermodynamic	equilibration
C_{15}	cyclic stereocontrol	intramolecular radical cyclization
C_{16}	cyclic stereocontrol	intramolecular radical cyclization
C_{17}	stereoelectronic	hydride addition
C_{18}	chiral pool	D-glucose
C_{20}	thermodynamic	intramolecular radical cyclization

for Stork's synthesis of reserpine is summarized in Table 4.

4.1.4. Fraser-Reid's Strategy

Fraser-Reid's approach targeted the synthesis of Woodward precursor **24**. The disconnective analysis is outlined in Scheme 21. Functional-group simplification of **24** led to enol ether **92**, which incorporates the proper substituents at C-2, C-3, and C-7 for functional manipulation. Fraser-Reid envisioned its retron as the tricyclic cage molecule **83** in which three carbon branches and two oxygenated substituents for **92** are already incorporated. Retrosynthetic simplification of **83** by a retro-serial radical 5-exo/6-exo cyclization led to the silylmethylene ethers **82**. In the forward sense this impressive serial radical cyclization led to the construction of a cyclohexane skeleton and installation of reserpine C_{15} and C_{16} stereocenters simultaneously. The silylmethylene ethers **82** can be easily obtained from the readily available chiral material D-glucose. The stereochemical inventory for Fraser-Reid's synthesis of reserpine is summarized in Table 5.

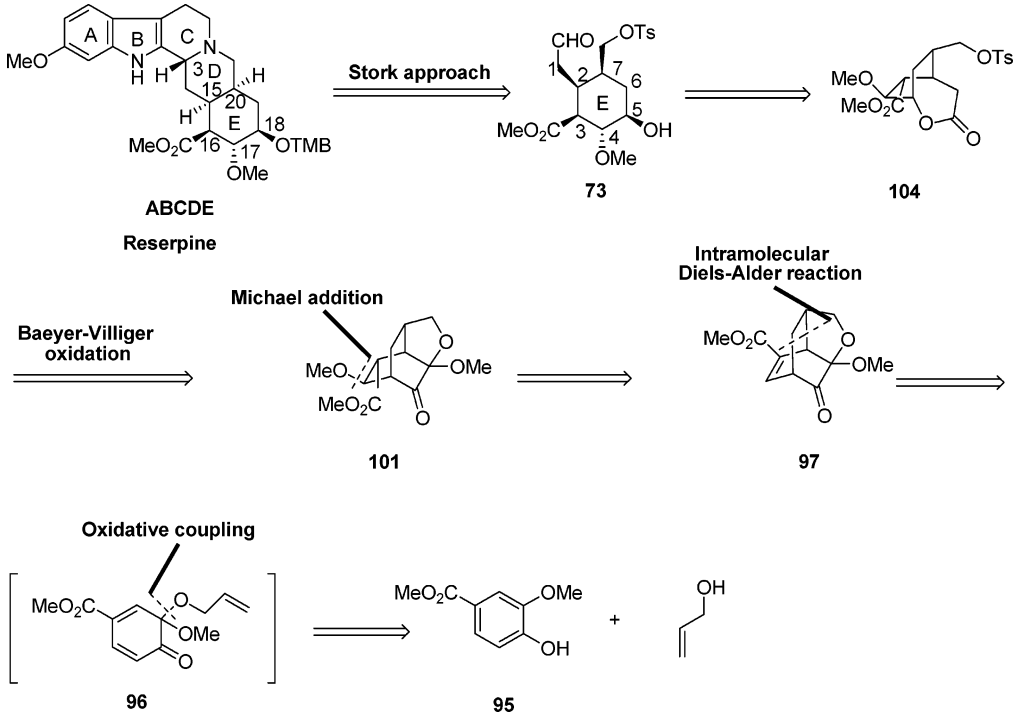
4.1.5. Liao's Strategy

The retrosynthetic pathway of Liao's reserpine synthesis is outlined in Scheme 22. The synthetic objective was the Stork aldehyde **73**. The critical design element in Liao's synthetic strategy is to use an intramolecular Diels−Alder reaction to establish the six-membered E-ring skeleton. Retrosynthetic simplification of **73** led to the lactone **104**, which can undergo a lactone ring opening to produce the complex cyclohexane framework. Functional-group simplification of **104** by a retro-Baeyer−Villiger oxidation led to ketone **101**, which can be prepared from the bicyclic ketone **97** via a key Michael addition. Finally, disassembly of the latter by a retro-intramolecular Diels−Alder cycloaddition led to the masked *o*-benzoquinone **96**. In the synthetic direction this versatile intramolecular Diels−Alder reaction allows for not only construction of the skeleton of the E-ring precursor, but also introduction of reserpine C_{15}, C_{18}, and C_{20} stereocenters. The masked *o*-benzoquinone **96** could be prepared via an in-situ oxidative coupling of the readily available methyl vanillate **95** and allyl alcohol in the presence of PhI(OAc)$_2$. The stereochemical inventory for Liao's synthesis of reserpine is summarized in Table 6.

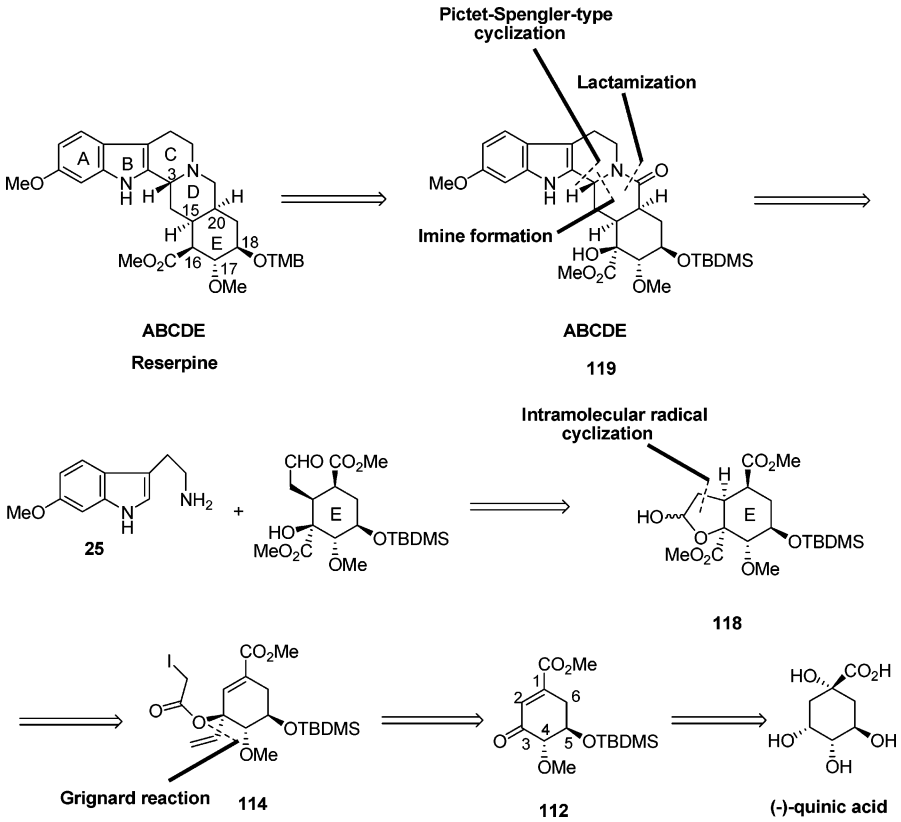
4.1.6. Hanessian's Strategy

Hanessian's reserpine synthesis employed the readily available (−)-quinic acid as a chiral template to construct the complex E-ring. The retrosynthetic pathway is outlined in Scheme 23 and starts with the simplification of reserpine to lactam **119**. Disconnection of **119** at the C-2−C-3 and N-4−C-21 bonds led to the tryptophyl unit and the E-ring precursor. In light of this, the hemiacetal **118** incorporating reserpine C_{15}, C_{17}, C_{18}, and C_{20} stereocenters was envisioned as a synthetic equivalent for the E-ring precursor. Functional-group simplification of **118** led to the α-iodoacetate ester **114**. In the synthetic

Scheme 22. Liao's Retrosynthetic Analysis of Reserpine



Scheme 23. Hanessian's Retrosynthetic Analysis of Reserpine



direction **114** incorporates an appropriate α-iodoacetate ester appendage at C-3 to introduce a two-carbon sidearm with correct steric orientation at C-2 via an intramolecular free-radical cyclization, resulting in hemiacetal **118**. The α-iodoacetate ester **114** could be prepared from (−)-quinic acid through a series of highly stereocontrolled and efficient chemical reactions via key intermediate **112**. The stereochemical inventory for Hanessian's synthesis of reserpine is summarized in Table 7.

4.1.7. Mehta's Strategy

Mehta's synthetic strategy, shown in Scheme 24, capitalized on the topology of the *endo*-tricyclo-[5.2.1.$0^{2,6}$]decane and *cis*-hydrindane system for the transfer of chirality. Following Woodward and Fraser-

Scheme 24. Mehta's Retrosynthetic Analysis of Reserpine

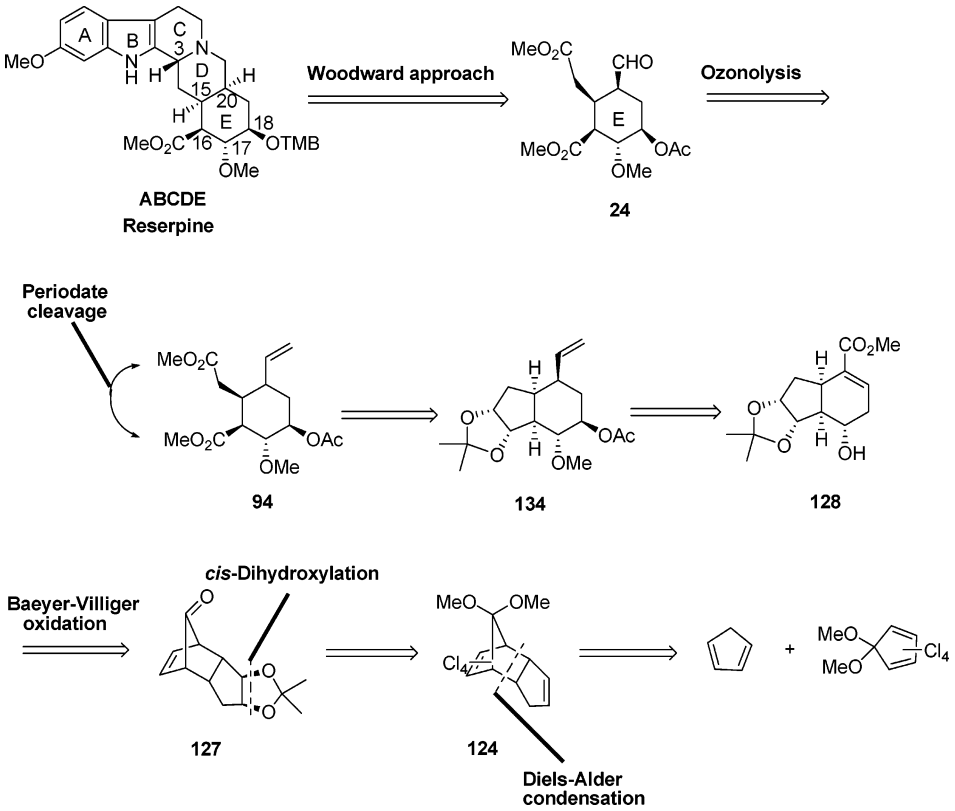


Table 6. Stereochemical Inventory for Liao's Synthesis of Reserpine

stereocenter	control element	reaction/source
C_3	stereoelectronic	nucleophilic attack
C_{15}	cyclic stereocontrol	intramolecular Diels–Alder reaction
C_{16}	stereoelectronic/ chromatographic separation	Michael addition
C_{17}	stereoelectronic/ chromatographic separation	Michael addition
C_{18}	cyclic stereocontrol	intramolecular Diels–Alder reaction
C_{20}	cyclic stereocontrol	intramolecular Diels–Alder reaction

Table 7. Stereochemical Inventory for Hanessian's Synthesis of Reserpine

stereocenter	control element	reaction/source
C_3	stereoelectronic/ chromatographic separation	nucleophilic attack
C_{15}	cyclic stereocontrol	intramolecular free-radical cyclization
C_{16}	stereoelectronic	SmI_2 deoxygenation
C_{17}	chiral pool	(−)-quinic acid
C_{18}	chiral pool	(−)-quinic acid
C_{20}	stereoelectronic	intramolecular free-radical cyclization

Reid's approaches, disassembly of the target alkaloid led to ester **134**, a compound containing aldehyde functionality and *cis*-disposed methoxycarbonyl and acetic acid sidearms in latent form. Functional-group simplification of **134** led to hydroxyl ester **128**. In the forward sense the propensity of *cis*-hydrindane **128** to react from the convex face was exploited to introduce the reserpine C_{18} and C_{20} stereocenters in a highly stereoselective manner. Hydroxyl ester **128** was then disassembled by a retro-Baeyer–Villiger oxidation, giving tricyclic keto–acetonide **127**, which could be prepared easily from readily available cyclopentadiene-based building blocks via a key Diels–Alder condensation. The stereochemical inventory for Mehta's synthesis of reserpine is summarized in Table 8.

Table 8. Stereochemical Inventory for Mehta's Synthesis of Reserpine

stereocenter	control element	reaction/source
C_3	thermodynamic	equilibration
C_{15}	cyclic stereocontrol	Diels–Alder
C_{16}	cyclic stereocontrol	Diels–Alder
C_{17}	cyclic stereocontrol	bicyclo[4.4.0]decane
C_{18}	stereoelectronic	Luche reduction
C_{20}	stereoelectronic	catalytic hydrogenation

4.1.8. Wender's Strategy

The retrosynthesis of Wender's reserpine synthesis is outlined in Scheme 25. The first key retrosynthetic disconnection was cleavage of the C-ring at the C-2–C-3 bond, which led to 2,3-secoreserpine **9**. In the synthetic direction this strategic bond was formed by a mercuric acetate-mediated oxidative cyclization protocol. Disconnection of **9** at the N-4–C-5 bond by a retro-tryptophylation led to DE-ring **159**, a precursor first used by Wender in the synthesis of reserpine. Functional-group simplification of **159** led to *cis*-hydroisoquinoline **142**, a compound incorporating the reserpine C_{15}, C_{16}, and C_{20} stereocenters and the DE-ring skeleton. In the synthetic direction the topology of the *cis*-fused hydroisoquinoline **142** was used to

Scheme 25. Wender's Retrosynthetic Analysis of Reserpine

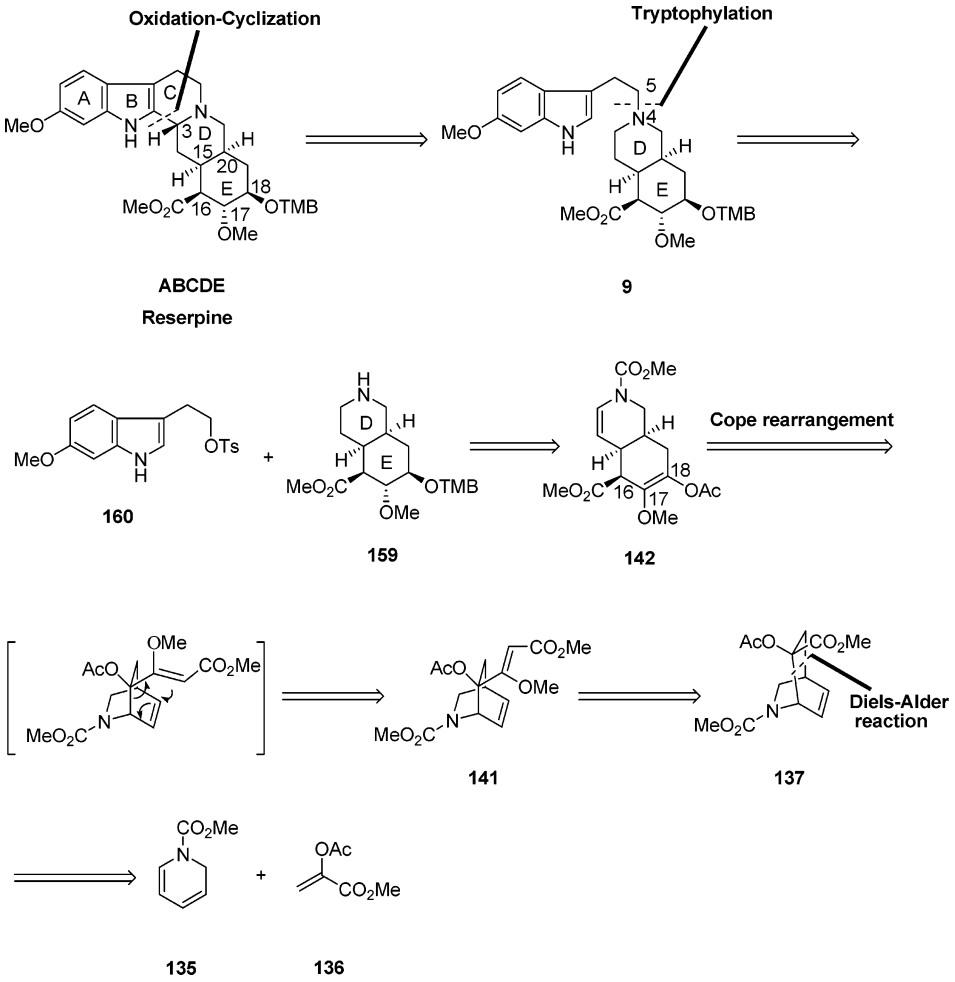


Table 9. Stereochemical Inventory for Wender's Synthesis of Reserpine

stereocenter	control element	reaction/source
C_3	stereoelectronic	nucleophilic attack
C_{15}	cyclic stereocontrol	Cope rearrangement
C_{16}	cyclic stereocontrol	Cope rearrangement
C_{17}	intramolecular proton delivery	LAH reduction
C_{18}	stereoelectronicl	Luche reduction
C_{20}	cyclic stereocontrol	Cope rearrangement

Table 10. Stereochemical Inventory for Martin's Synthesis of Reserpine

stereocenter	control element	reaction/source
C_3	stereoelectronic	nucleophilic attack
C_{15}	cyclic stereocontrol	intramolecular Diels–Alder
C_{16}	cyclic stereocontrol	intramolecular Diels–Alder
C_{17}	stereoelectronic	epoxidation–opening
C_{18}	stereoelectronic	epoxidation–opening
C_{20}	stereoelectronic	catalytic hydrogenation

install the remaining reserpine C_{17} and C_{18} stereocenters. Finally, disassembly of **142** by a retro-Cope rearrangement led to 1,5-diene **141**, which was derived from methyl 1,2-dihydropyridine-1-carboxylate (**135**) and the methyl ester of 2-acetoxyacrylic acid (**136**) via an intermolecular Diels–Alder reaction. The stereochemical inventory for Wender's synthesis of reserpine is summarized in Table 9.

4.1.9. Martin's Strategy

Martin employed the same DE-ring strategy as that of Wender to accomplish the synthesis of reserpine (Scheme 26). The final step involved a mercuric ion-induced oxidative cyclization to complete the C-ring closure. The DE-ring precursor **159** was prepared from hydroisoquinoline derivative **164** with high stereoselectivity via a selective epoxide opening and catalytic hydrogenation by taking advantage of the stereochemical propensity of the fused nitrogen heterocycle. Retrosynthetic simplification of **164** by a retro-intramolecular Diels–Alder reaction led to the trienic amide **163**, which could be synthesized from propargyl alcohol via a routine two-carbon chain extension and acylation. The stereochemical inventory for Martin's synthesis of reserpine is summarized in Table 10.

4.1.10. Shea's Strategy

Shea's reserpine synthesis also employed the DE-ring strategy using an intramolecular Diels–Alder reaction for the expeditious construction of the crucial DE-ring skeleton (Scheme 27). Functional-group simplification of DE-ring precursor **159** led to *N*-acylimidate **194**, which arose from the intramolecular cycloaddition of *N*-acylvinylimidate **193** in the tether endo mode. In the synthetic direction the *N*-acylim-

Scheme 26. Martin's Retrosynthetic Analysis of Reserpine

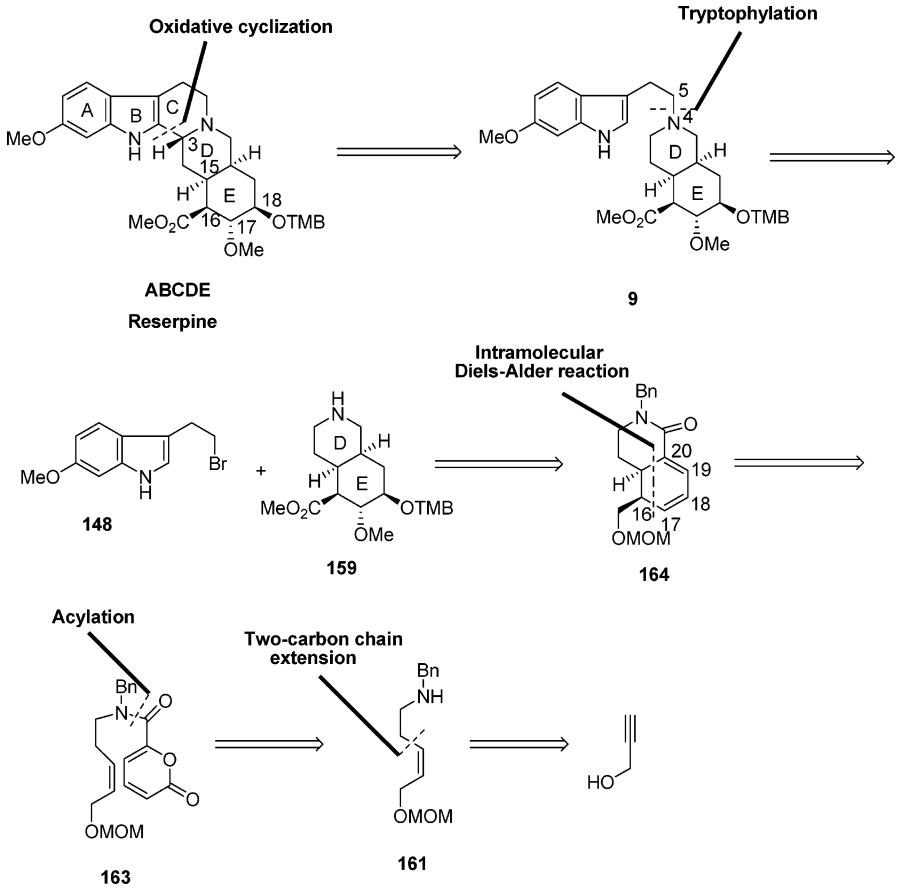


Table 11. Stereochemical Inventory for Shea's Synthesis of Reserpine

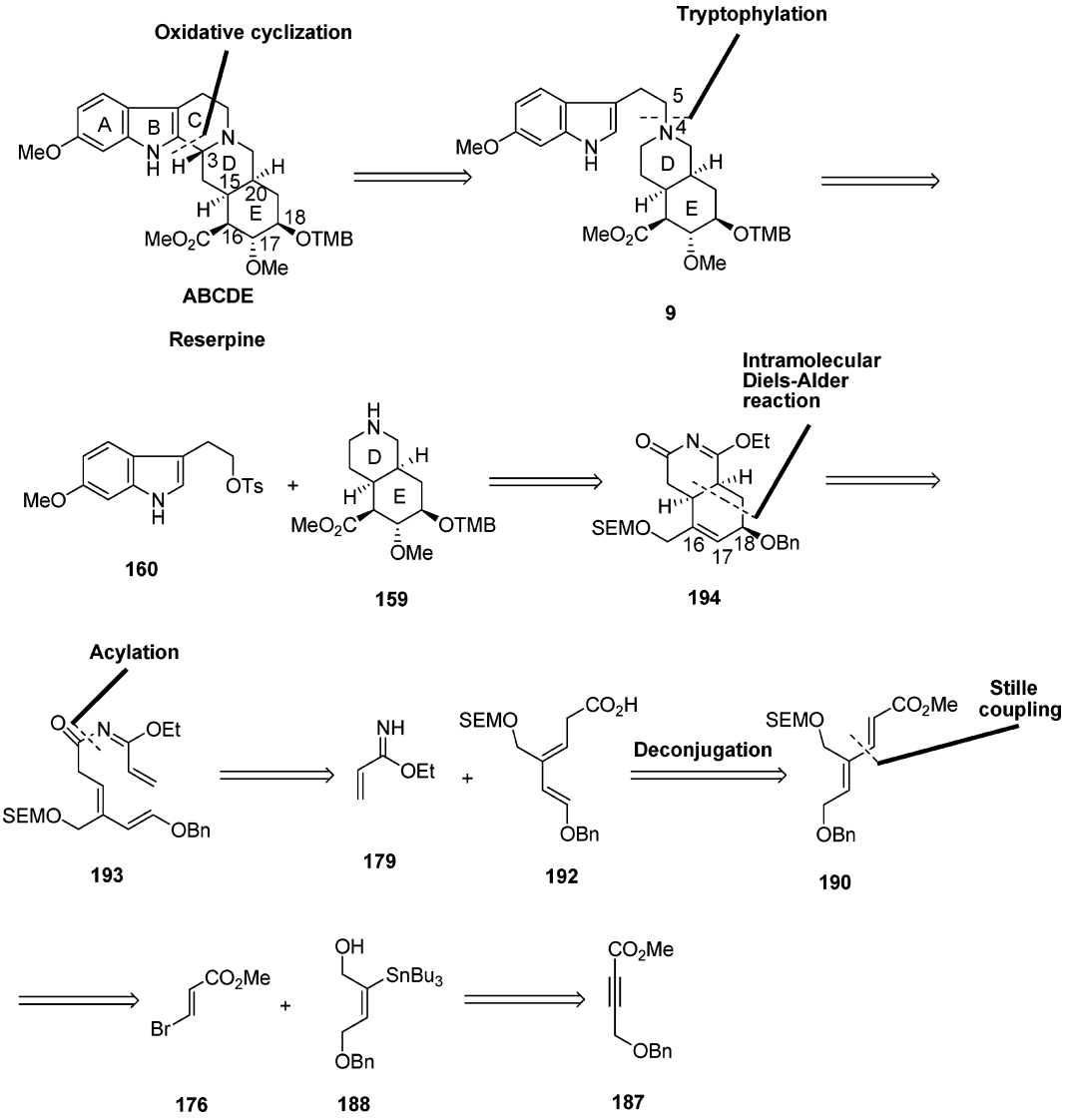
stereocenter	control element	reaction/source
C_3	stereoelectronic	nucleophilic attack
C_{15}	cyclic stereocontrol	intramolecular Diels−Alder
C_{16}	stereoelectronic	hydroboration−oxidation
C_{17}	stereoelectronic	hydroboration−oxidation
C_{18}	cyclic stereocontrol	intramolecular Diels−Alder
C_{20}	cyclic stereocontrol	intramolecular Diels−Alder

idate **194** incorporated appropriate C_{15}, C_{18}, and C_{20} stereocenters and the C-16−C-17 double bond to introduce the remaining two (C_{16} and C_{17}) stereocenters with high stereoselectivity. Retrosynthetic simplification of **193** led to (3*Z*,5*E*)-dienoic acid **192**, which was prepared from (2*E*,4*Z*)-hexadienoic ester **190** via a crucial deconjugation. Finally, functional-group simplification of **190** by a retro-Stille coupling led to the easily available alkynoate **187**. The stereochemical inventory for Shea's synthesis of reserpine is summarized in Table 11.

We just summarized the 10 successful strategies for total synthesis of reserpine. The original Woodward approach and those of Pearlman, Stork, Liao, Fraser-Reid, Hanessian, and Mehta targeted an appropriately functionalized E-ring precursor in which the requisite stereochemistry was built in. Woodward employed the Diels−Alder reaction of methyl vinylacrylate and benzoquinone to obtain the E-ring stereochemistry. Intramolecular [2 + 2] photocycloaddition in a cyclohexene derivative and cyclobutene fragmentation was the strategy employed by Pearlman in accessing the E-ring. Fraser-Reid produced the E-ring precursor via a serial 5-exo/6-exo radical cyclization of tethered pyranosyl-derived dienic carbohydrate. Stork and Liao employed the bicyclo[2.2.2]octane scaffold to deliver the desired stereochemistry of the E-ring. Hanessian employed (−)-quinic acid as a chiron in the elaboration of the E-ring. Mehta exploited the propensity of the *endo*-tricyclo[5.2.1.$0^{2,6}$]decane and *cis*-hydrindane system to react from the convex face to generate the requisite stereochemical pattern. Unlike the initial E-ring strategy of Woodward, the approaches of Wender, Martin, and Shea targeted a *cis*-fused DE-ring precursor. Wender employed Diels−Alder/Cope rearrangements as key steps, while Martin and Shea employed intramolecular Diels−Alder reaction as pivotal steps in assembling the *cis*-hydroisoquinoline framework of the DE-ring.

Among these, three enantiospecific syntheses of (−)-reserpine have been described, developed by Stork, Fraser-Reid, and Hanessian. Stork's procedure starts with a chemically resolved, enantiomerically pure (*S*)-3-cyclohexenecarboxylic acid,[46] Hanessian's approach begins with the natural (−)-quinic acid,[74] and Fraser-Reid's approach commences with ethyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside, which is derived from the readily available chiral material D-glucose.[53]

Scheme 27. Shea's Retrosynthetic Analysis of Reserpine

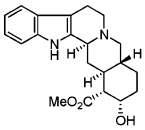
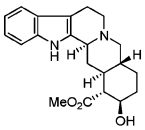
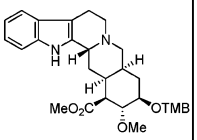
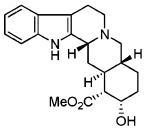


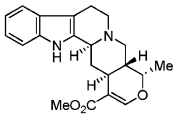
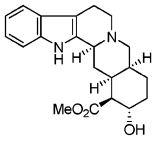
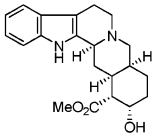
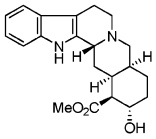
4.2. Perspectives

Does reserpine still have a future as a target for total synthesis? This question is not easy to answer because after almost 50 years of constant attention the synthetic possibilities may have been exhausted. Often the choice of different starting materials can result in different strategies, and the discovery of a new synthetic method or a new reagent in transformation may produce a new synthetic strategy; thus, the driving force behind a strategy can vary. In the context of reserpine, as a pentacyclic indole alkaloid it consists mainly of three parts: the indole (AB-ring), the trimethoxybenzene system, and the highly substituted E-ring cyclohexane. Given the simplicity of the first two fragments and their obvious attachment to the E-ring system, the main concern lies in elaboration of the stereochemically complex E-ring and solution of the stereochemical problem—isomerization at C-3—encountered in completing the architecture of the C-ring system. With respect to the latter, Woodward's and Stork's efforts provided an elegant solution. Thus, the buildup of the structurally complicated E-ring system containing five vicinal chiral centers is the strongest focus of reserpine synthesis. To the best of our knowledge, condensation of the E-ring system with the tryptophyl unit in the final stage of assembling the pentacyclic skeleton, embodied by Woodward's creative work, provides the most reliable, convergent, and efficient entry to the pentacyclic unit. Thus, the E-ring system should be constructed as an independent synthon, and selecting a natural chiral pool as the precursor of the E-ring or employing some novel synthetic technologies to construct the complex E-ring system may be a good choice. This methodology is also nicely supported by the availability of a number of elegant synthetic approaches to the E-ring or its analogue containing five contiguous chiral centers, which makes this methodology highly accessible and pragmatic.

In the pursuit of the total synthesis of reserpine, valuable general methodologies have been developed: the reliable and versatile Diels–Alder reaction in establishing the complex polysubstituted cyclohexane skeleton, the powerful Baeyer–Villiger oxidation in extracting the desired cyclic skeleton, the novel sigmatropic rearrangement in constructing the *cis*-fused bicyclic system, the interesting double Michael addition in assembling the bridged bicyclic

Table 12. Syntheses of Representive Yohimbine Alkaloids

Alkaloid	Form	Main Author	Year[a]	Ref
Normal-type Yohimbine Alkaloid				
Yohimbine 	(+)	Aube	1994	118
	(+)	Momose	1990	119
	(±)	Kuehne	1991	120
	(±)	Martin	1987	99b
	(±)	Wenkert	1982	121
	(±)	Stork	1972	122
	(+) (-)	Szantay	1986	123
	(±)	Kametani	1976	124
	(±)	Wenkert	1979	125
	(±)	Kametani	1975	126
	(±)	Szantay	1971	127
	(±)	Toke	1969	128
	(±)	Szantay	1965	129
	(±)	vanTamelen	1958	130
	(±)	Szantay	1976	131
	(±)	Ninomiya	1983	132
β-Yohimbine 	(+)	Brown	2000	133
	(+) (-)	Szantay	1986	123
	(±)	Szantay	1976	131
	(±)	Toke	1969	128
	(±)	Kuehne	1991	120
	(±)	Stork	1972	122
	(±)	Szantay	1965	129
	(±)	Wenkert	1979	125
Reserpine-type Alkaloid				
Deserpidine 	(±)	Mariano	1990	112
	(±)	Naito	1989	134
	(±)	Ninomiya	1984	116k
	(±)	Szantay	1983	116j
	(±)	Szantay	1977	135
	(±)	Weichet	1961	33
Pseudo-type Yohimbine Alkaloid				
Pseudoyohimbine 	(+)	Brown	2000	133
	(±)	Wenkert	1978	136

Alkaloid	Form	Main Author	Year[a]	Ref
Hetero-Yohimbine Alkaloid				
Ajmalicine 	(-)	Brown	2002	137
	(-)	Overman	1995	138
	(-)	Honda	1993	139
	(-)	Hanessian	1991	140
	(-)	Takano	1988	141
	(±)	Ninomiya	1986	142
	(-)	Massiot	1984	143
	(±)	Uskokovic	1981	94i
	(-)	Goutarel	1975	144
	(-)	Martin	1995	145
	(-)	Momose	1992	119b
	(-)	Takano	1985	146
	(±)	Uskokovic	1971	147
	(±)	Winterfeldt	1968	148
	(±)	Winterfeldt	1969	149
	(±)	VanTamelen	1961	150
Allo-type Yohimbine Alkaloid				
α-Yohimbine 	(±)	Martin	1985	99b
				151
	(±)	Szantay	1982	152
	(±)	Wenkert	1979	125
	(±)	Szantay	1976	131
	(±)	Toke	1973	153
Alloyohimbine 	(±)	Szantay	1976	131
	(±)	Toke	1973	153
Epiallo-type Yohimbine Alkaloid				
3-epi-α-Yohimbine 	(±)	Szantay	1982	152
	(±)	Szantay	1976	131
	(±)	Toke	1973	153a

[a] Refers to date of first communication if it exists.

system, use of the natural product as a chiral pool in producing key chiral building blocks, radical cyclization in introducing the desired stereochemistry and functionality, the novel de Mayo reaction in introducing complex functionality, and the stereochemical outcome of the *cis*-fused bicyclic system in the transfer of chirality. The power of these methods can also be applied in the total synthesis of other complex natural products.

5. Conclusions

This review has systematically summarized the existing 10 total synthesis of reserpine. The most salient feature in reserpine synthesis is the enormous endeavor to elaborate the complex six-membered E-ring system which possesses five vicinal stereocenters. As a result, reserpine has served as a testing ground for evaluating the utility of synthetic strate-

gies over the past 50 years, stimulating the development of a number of synthetic approaches leading to the culmination of both total and formal syntheses of reserpine. Development in the field of total synthesis of reserpine nicely illustrates the power of modern synthetic methods and will lead to the invention, discovery, and development of new reagents, synthetic strategies, and technologies, driving the more general field of organic synthesis forward.

Apart from the successful reserpine syntheses, there are numerous efforts devoted to different approaches and ring constructs leading to advanced intermediates.[112,116] Last but not least, the practitioners who contributed to the study of the chemical and structural relationships of yohambine alkaloids during the past century deserve great credit.

Although 10 successful total syntheses of reserpine have been developed over the past 50 years, from a practical viewpoint the approaches cited in this review are still far from satisfaction. As a result, synthetic reserpine is not competitive today in price with reserpine extracted from plant material. The original Woodward approach, although somewhat modified, is still conceptually the most attractive for commercial exploitation in our opinion owing to its feasibility and proven efficiency. The principal shortcoming of the Woodward route lies in the necessary resolution in the final step. Soon after its publication in 1958 the Woodward approach was modified by French, Czech, and Swiss chemists. It was to the credit of French workers (L. Velluz and colleagues) that reserpine's commercial production was realized in France in 1960s. In Velluz's modification the resolution was executed at the very early stage, so the cost was reduced largely compared with the original Woodward route. Despite the effectiveness of these modifications, the potential of the Woodward−Velluz approach has, however, not yet been fully realized due to the lack of an asymmetric Diels−Alder reaction between 1,4-benzoquinone and vinylacrylic acid to prepare chiral *cis*-decalin adduct **14** and hence chiral Woodward aldehyde ester **24**. Therefore, from an industrial point of view, development of an efficient asymmetric catalytic Diels−Alder reaction to synthesize enantiomerically pure Woodward aldehyde ester **24** will make the Woodward−Velluz route more practical and powerful in the total synthesis of L-reserpine.[117]

6. Tabular Survey of Total Syntheses of Representative Yohimbine Alkaloids

While the total syntheses of reserpine contribute greatly to the development of organic synthetic methodology, the syntheses of other related yohimbine alkaloids also display a similar level of accomplishment. In Table 12 the total syntheses of representative yohimbine alkaloids with distinct biological activity are compiled.

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