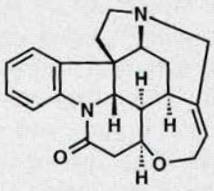

1: strychnine

2

R. B. Woodward (1954)

Strychnine

2.1 Introduction

The *Strychnos* species, indigenous to the rain forests of the Southeast Asian archipelagos and the Coromandel Coast of India, harbor the notorious poison strychnine (**1**). The poisonous properties of the *Strychnos* species were recognized in Europe as early as the sixteenth century, and in 1818 Pelletier and Caventou reported the isolation of strychnine, in pure form, from the beans of *Strychnos ignatii*.[1] Before the advent of modern spectroscopic techniques and due principally to the independent and brilliant researches of Sir Robert Robinson and Herman Leuchs, a forty-year period of extensive study culminated in the elucidation of strychnine's structure in 1946.[2] In the early 1950s, two independent X-ray crystallographic investigations confirmed the gross structure of strychnine,[3] and in 1956 X-ray crystallographic results revealed that the absolute configuration of strychnine is that shown in structure **1**.[4]

Strychnine, the most celebrated member of the *Strychnos* alkaloids, possesses a complex polycyclic structure which is assembled from only twenty-four skeletal atoms. In addition to its obvious architectural complexity, strychnine's structure contains a contiguous array of six unsymmetrically substituted tetrahedral (asymmetric) carbon atoms of which five are included within one saturated six-membered ring. The intimidating structure of the strychnine molecule elicited the following remark by Sir Robert Robinson in 1952: "For its molecular size it is the most complex substance known."[5]

The strychnine molecule presented an unparalleled challenge to anyone interested and skilled in the art of constructing complex molecules in the 1950s. The establishment of strychnine's exceed-

ingly complex structure through chemical degradation is an outstanding achievement of classical structural chemistry which is equalled by the landmark chemical synthesis of strychnine by R. B. Woodward and his colleagues at Harvard.[6] Only eight years intervened between the disclosure of strychnine's structure in 1946 and the first chemical synthesis of this substance by Woodward *et al.*[7] The employment of only the simplest of reagents to carry out impressive structural transformations is perhaps the most distinguishing feature of Woodward's elegant and instructive strychnine synthesis.

2.2 *Retrosynthetic Analysis and Strategy*

The general features of Woodward's strychnine synthesis are outlined retrosynthetically in Scheme 1. It was known at the time that *isostrychnine I* (**3**), a strychnine degradation product, could be reconverted to strychnine in a single step. In the synthetic direction, *the action of potassium hydroxide* on **3** induces its conversion to the corresponding α,β-unsaturated isomer (**2**) with concomitant creation of the stereogenic center at C-13. Once formed, intermediate **2** can either revert back to isostrychnine I or it can participate in an intramolecular Michael addition reaction to give strychnine. With this precedent in hand, it was logical to defer the assembly of the seven-membered ether ring to the last stage in the synthesis. The synthetic objective now becomes isostrychnine I (**3**), and it was anticipated that this substance could be derived from intermediate **4** through a straightforward isomerization or allylic rearrangement reaction. Removal of the vinyl appendage from intermediate **5**, the projected precursor of **4**, furnishes dehydrostrychnone (**6**). With adjacent carbonyl groups at positions 20 and 21, intermediate **6** would be expected to react readily with nucleophilic species at C-21. Moreover, the two diastereotopic faces of the C-21 ketone carbonyl are significantly different, and a nucleophilic attack on the C-21 ketone carbonyl should proceed in a highly diastereoselective manner from the much less hindered convex face of **6** (see insert, Scheme 1).

Retrosynthetic simplification of intermediate **6** is rather straightforward, furnishing *cis*-glyoxal **7** as a potential precursor. In the forward sense, an attack of N^b upon the C-20 aldehyde carbonyl could occur to give ring VI of strychnine in the form of a cyclic hemiaminal which can then undergo oxidation to **6**. *cis*-Glyoxal **7** could be formed through oxidation of methyl ketone **8**, followed by epimerization at C-14. Through some straightforward functional group manipulations, amino ketone **8** could conceivably be derived from carboxylic acid **9**.

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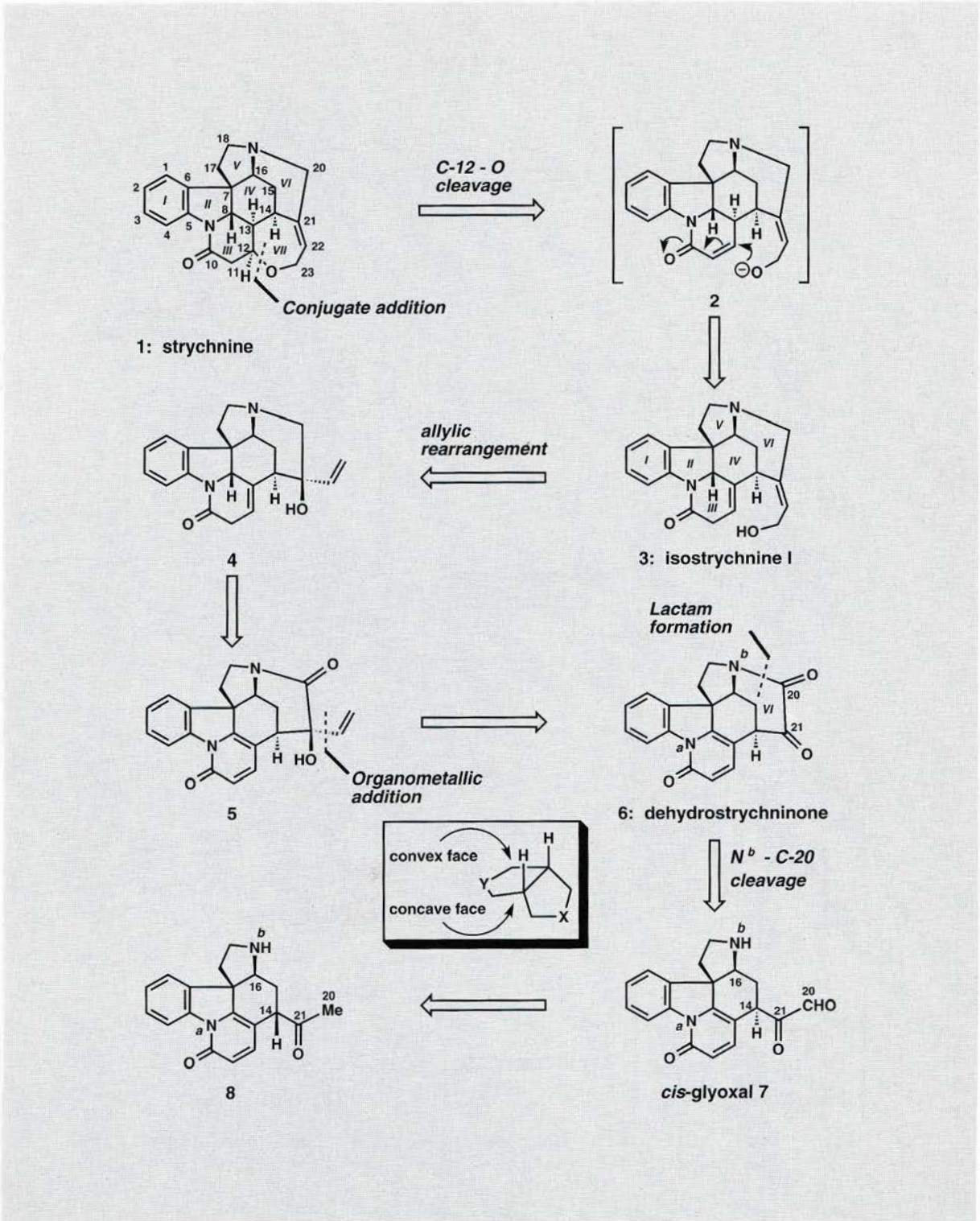
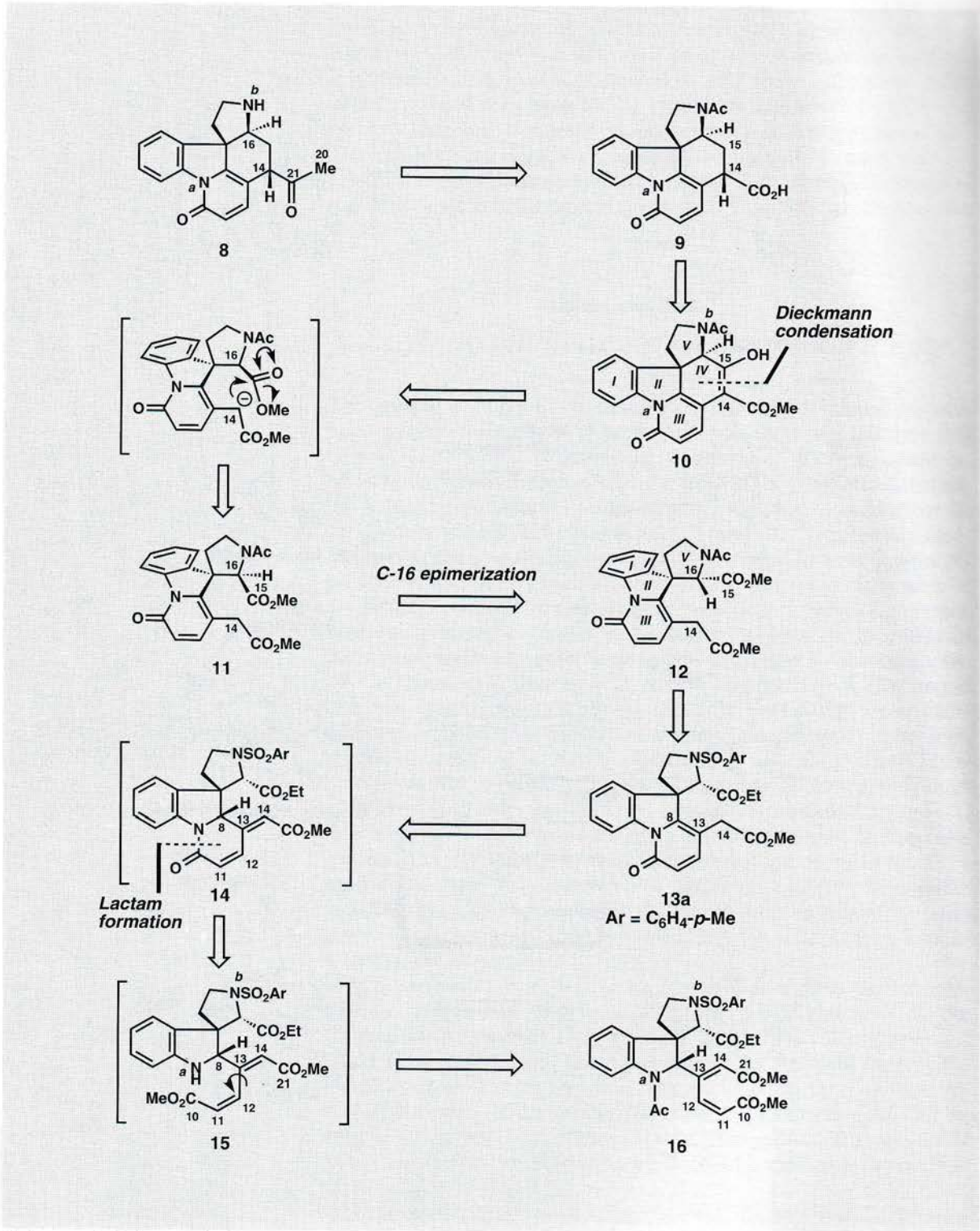
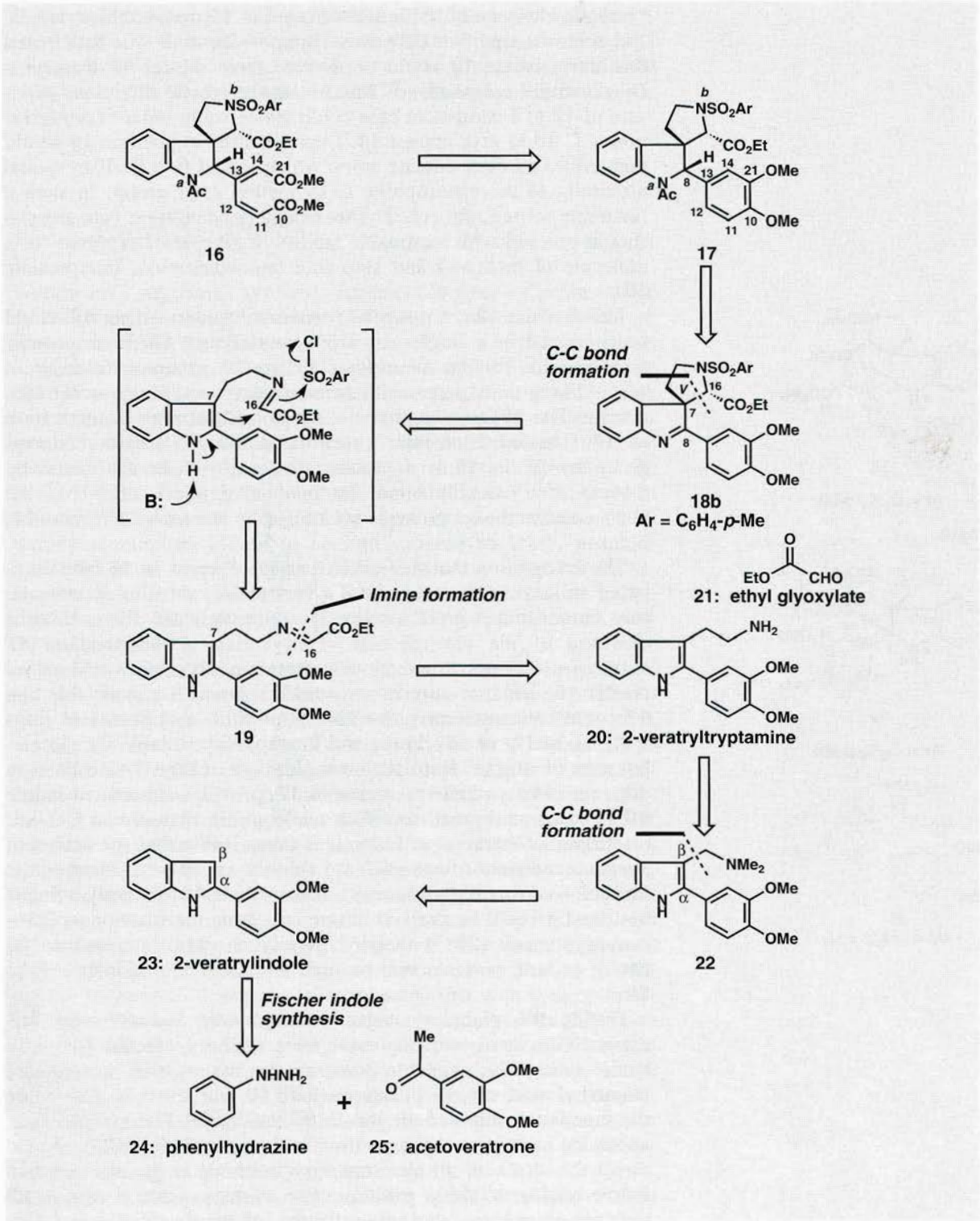


Scheme 1. Retrosynthetic analysis of strychnine (**1**).

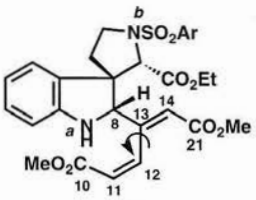


Scheme 1. Retrosynthetic analysis of strychnine (**1**) (continued).



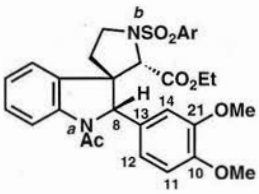
Scheme 1. Retrosynthetic analysis of strychnine (**1**) (continued).

synthetic cleavage of the indicated bond in **10** disassembles ring IV and achieves significant structural simplification. It was anticipated that intermediate **10** could be derived from diester **12** through a Dieckmann condensation.[8] Thus, in the synthetic direction, exposure of **12** to a competent base could conceivably induce epimerization at C-16 to give epimer **11**. Deprotonation at position 14 would then afford an ester enolate anion which would find itself in spatial proximity to the electrophilic C-15 methyl ester group. In such a favorable setting, the crucial Dieckmann condensation (see arrows) should proceed with reasonable facility to give, after expulsion of a molecule of methanol and keto-enol tautomerization, intermediate **10**.



15

Ar = C_6H_4-*p*-Me



17

Ar = C_6H_4-*p*-Me

Intermediate **13a**, a potential precursor of intermediate **12**, could be fashioned in a single step from intermediate **16**. Under conditions suitable for the removal of the acetate grouping from N^a, it seems likely that spontaneous lactamization would also occur (see intermediate **15**) to give aromatic pyridone **13a**, after isomerization of **14**. The intramolecular attack upon the C-10 carbomethoxyl group by N^a in **15** is a process that ought to be facilitated by the *cis* $\Delta^{11,12}$ double bond. Intramolecular attack of N^a on the C-21 carbomethoxyl group is prohibited by the *trans* $\Delta^{13,14}$ double bond.

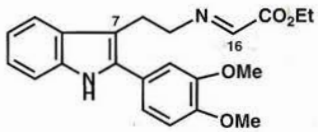
The recognition that the reactive array of atoms in **16** (see numbered atoms) could evolve from a very stable, substituted aromatic ring demonstrates great insight. It was anticipated that oxidative cleavage of the electron-rich veratryl ring in intermediate **17** between positions 10 and 21 (strychnine numbering) would afford diester **16**. Thus, in only two synthetic steps, it is conceivable that **17** could be transformed into **13a**, a molecule that possesses rings I, II, III, and V of strychnine and functionality suitable for the elaboration of ring IV. Retrosynthetic cleavage of the C7-C16 bond in **18b**, the retrosynthetic precursor of **17**, provides substituted indole **19** as a potential precursor. With nucleophilic character at C-7 and electrophilic character at C-16, it is conceivable that the action of pyridine and *para*-toluenesulfonyl chloride on **19** would lead to the formation of ring V (see arrows). Intermediate **19** is simply a Schiff base and it could be derived in one step from the reaction of 2-veratryltryptamine (**20**) with ethyl glyoxylate (**21**). Intermediate **20** could, in turn, be fashioned through homologation of intermediate **22**.

During the planning stages, the aromatic veratryl ring was expected to serve two important roles in the synthesis. Not only would it serve as as stable precursor for the reactive, unsaturated bismethyl ester moiety in intermediate **16**, but it would also guide the functionalization of the indole nucleus in **23**. The veratryl ring, appended as it is to the α position in 2-veratrylindole (**23**), should direct the attack of an electrophilic species upon the electron rich indole nucleus to the β position. The aromatic veratryl ring in **23** thus serves as a masking group for the inherently reactive indole α carbon and yet it could conceivably be modified, at some later

stage, in a manner that will permit the elaboration of rings III, IV, and VI of strychnine. 2-Veratrylindole (**23**) thus provides a logical starting point for the synthesis and it could be prepared from simple building blocks (intermediates **24** and **25**) through a Fischer indole synthesis.[9]

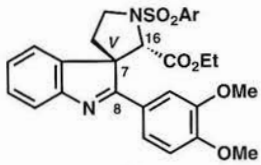
2.3 *Total Synthesis*

Woodward's strychnine synthesis commences with a Fischer indole synthesis using phenylhydrazine (**24**) and acetoveratrone (**25**) as starting materials (see Scheme 2). In the presence of polyphosphoric acid, intermediates **24** and **25** combine to afford 2-veratrylindole (**23**) through the reaction processes illustrated in Scheme 2. With its α position suitably masked, 2-veratrylindole (**23**) reacts smoothly at the β position with the Schiff base derived from the action of dimethylamine on formaldehyde to give intermediate **22** in 92% yield. *N*-Methylation of the dimethylamino substituent in **22** with methyl iodide, followed by exposure of the resultant quaternary ammonium iodide to sodium cyanide in DMF, provides nitrile **26** in an overall yield of 97%. Condensation of 2-veratryltryptamine (**20**), the product of a lithium aluminum hydride reduction of nitrile **26**, with ethyl glyoxylate (**21**) furnishes Schiff base **19** in a yield of 92%.



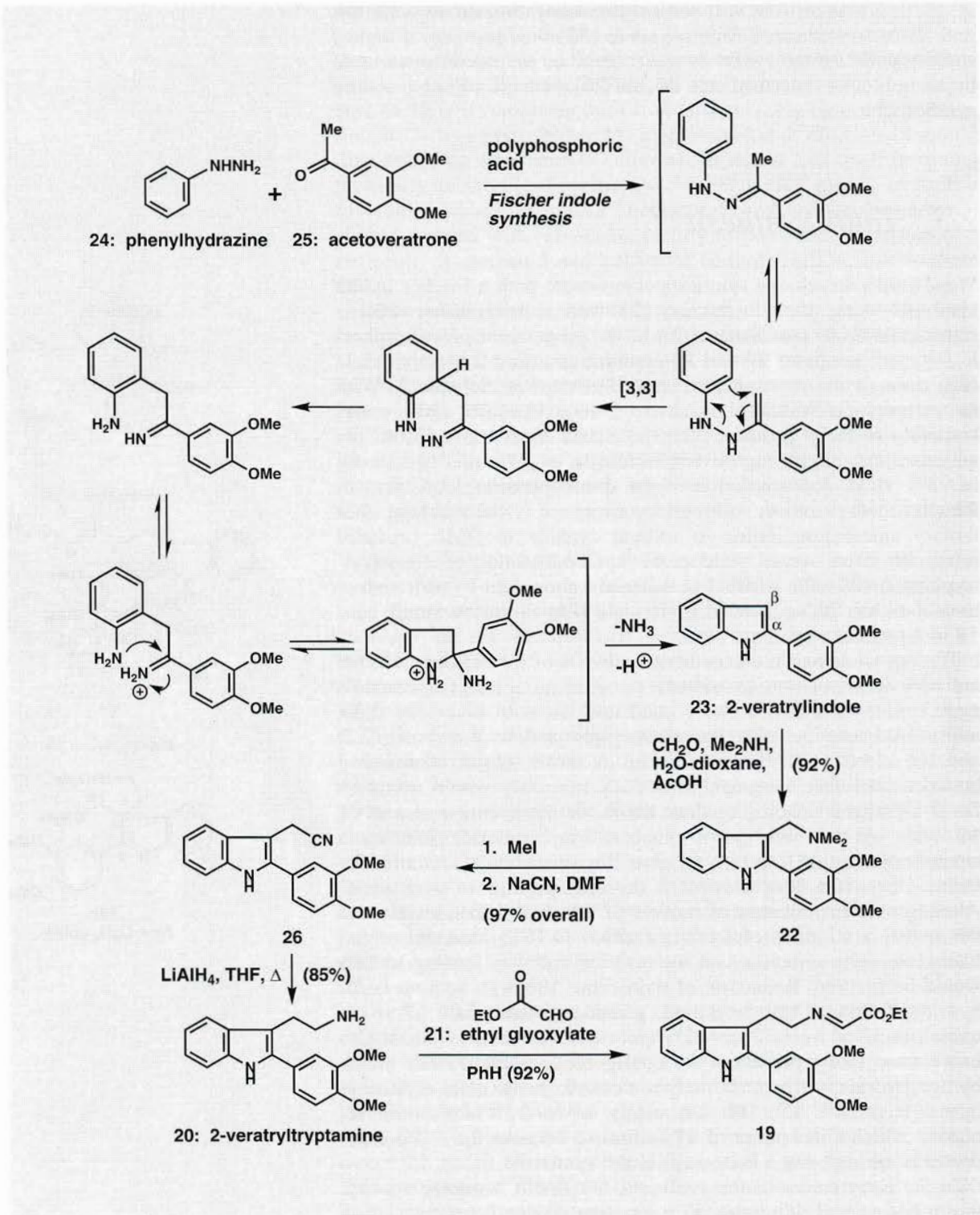
19

Having witnessed the expedient synthesis of intermediate **19**, we are now in a position to address the construction of strychnine's ring V (see Scheme 3). It is interesting to note that only three atoms intervene between the nucleophilic indole β-carbon (C-7) and the electrophilic C-16 position. A close spatial relationship between sites that have complementary reactivity would normally favor a pathway leading to their union. In the event, treatment of **19** with pyridine and *para*-toluenesulfonyl chloride induces a smooth cyclization reaction to give the spiroannulated molecule, intermediate **18b** (see arrows), as the only product in 64% yield. Although an examination of models of **18a** and **18b** certainly did not reveal a strong preference for either C-16 epimer, it seemed likely, on steric grounds, that the reaction pathway leading to **18b** would be favored. Reduction of indolenine **18b** with sodium borohydride, followed by acetylation, provides intermediate **17** in an overall yield of 84%. The newly created stereogenic center at C-8 in **17** most likely possesses the configuration shown, since attack by borohydride ion is most likely to occur from the more accessible face of trigonal C-8 in **18b**. Ultimately, however, it is of no consequence which C-8 epimer of **17** is formed because the C-8 stereocenter is destroyed at a later stage in the synthesis.

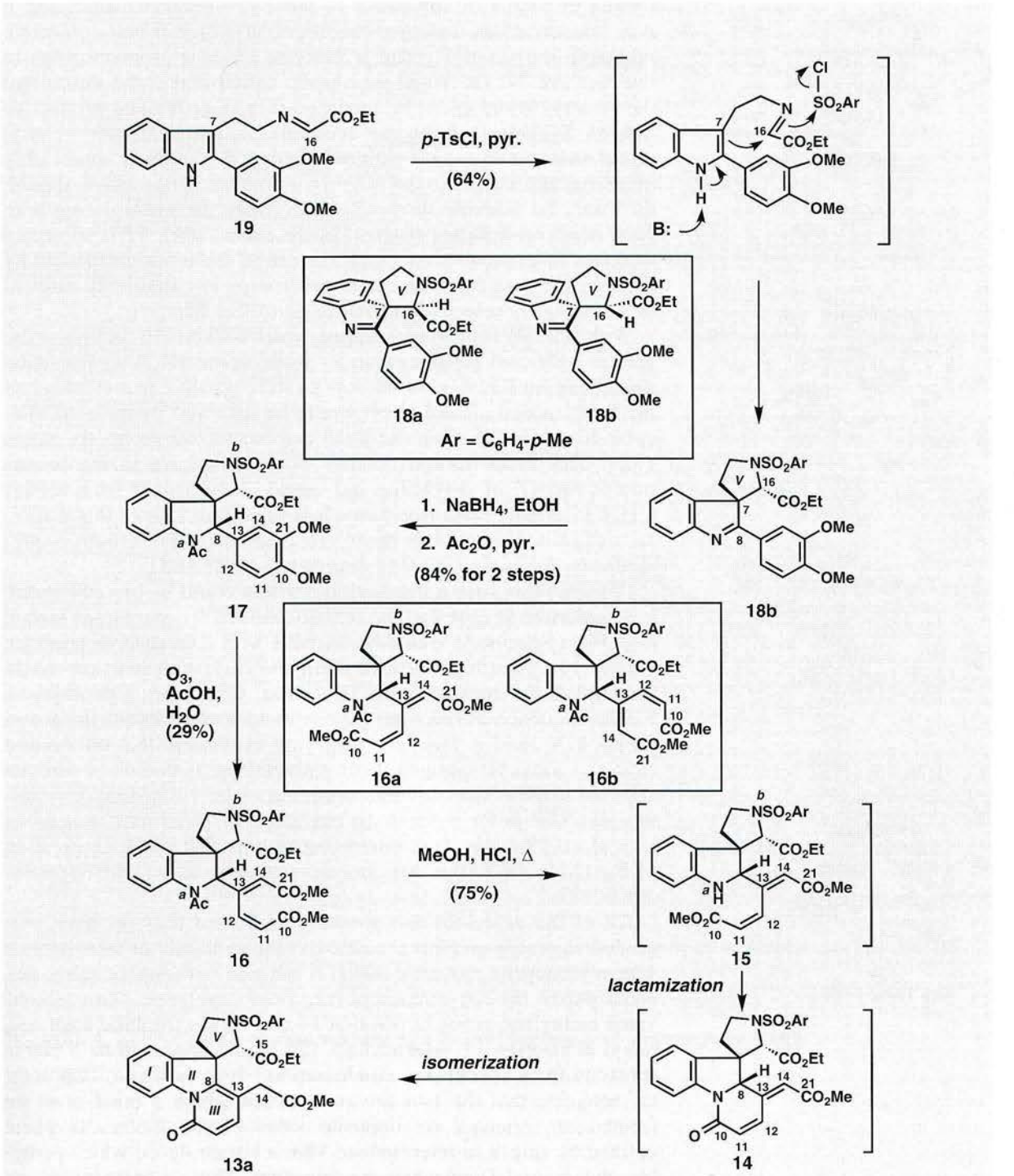


18b
Ar = C_6H_4-*p*-Me

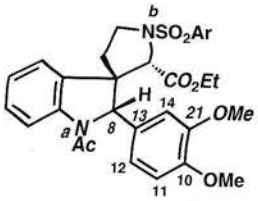
In the early stages of the synthesis, the stable, aromatic veratryl group had served admirably as a masking device for the α-carbon of the indole nucleus. It permitted the processes leading to the for-



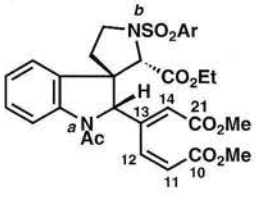
Scheme 2. Synthesis of intermediate **19**.



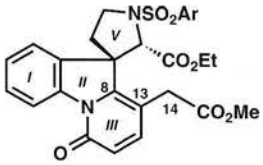
Scheme 3. Synthesis of intermediate **13a**.



17



16



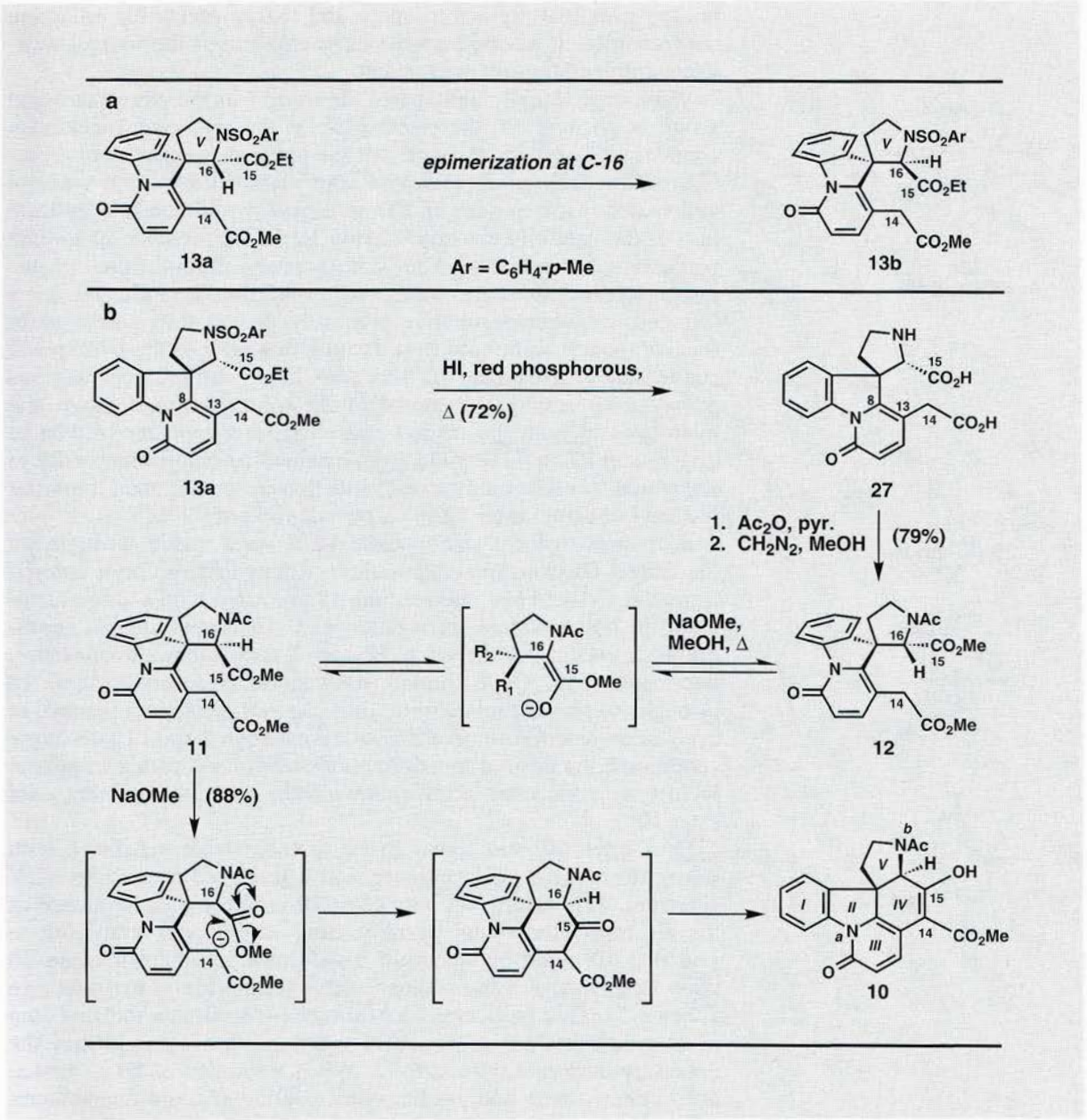
13a
Ar = C_6H_4-*p*-Me

mation of ring V of strychnine to proceed without incident, and it was tolerant of the reaction conditions to which it was subjected. Although the veratryl group is just one of three aromatic rings in intermediate **17**, the Woodward group anticipated at the outset that the veratryl group could be modified in a selective and productive fashion at some stage in the synthesis. In particular, the veratryl group, substituted as it is with two methoxyl groups, is appreciably more electron rich than the other two aromatic rings and it should, therefore, be possible to modify selectively the veratryl ring with some electron-deficient reagent. In the event, when **17** is subjected to ozone in aqueous acetic acid, the site of unsaturation flanked by the two electron-donating methoxyl groups is oxidatively cleaved in a completely selective manner to give ester **16**.

With its veratryl ring cleaved, intermediate **16** enjoys even greater rotational freedom than its predecessor **17**. With free rotation about the C12-C13 bond, it is entirely possible that cleavage of the acetyl group affixed to N^a would be followed by an intramolecular attack by N^a upon the C-10 carbomethoxyl group six atoms away. This lactamization process would culminate in the formation of ring III of strychnine and would likely benefit from the *cis* C11-C12 double bond (see **16a**). It is important to note that a similar cyclization involving the C-21 carbomethoxyl group is precluded by the *trans* C13-C14 double bond (see **16b**).

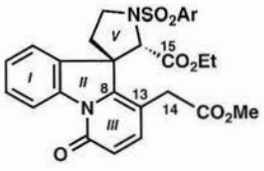
Provided that such a cyclization reaction could be brought about, it is important to note that the initially formed six-membered lactam (see **14** in Scheme 1) would be unstable with respect to its aromatic isomer **13a**. A straightforward olefin isomerization reaction would accomplish the conversion of **14** to **13a**. Of course, a prerequisite for the sequence of reactions just outlined is cleavage of the acetyl group at N^a, and it was very gratifying to observe that the desired cleavage could be brought about with boiling methanolic hydrogen chloride to give, after lactamization and olefin isomerization, intermediate **13a** in 75 % yield. In one step, all three transformations take place smoothly. It is interesting to note that transesterification of the C-15 ethyl ester does not occur under these rather vigorous conditions.

All of the processes that we have addressed thus far have proceeded smoothly and have resulted in the synthesis of intermediate **13a**, a tetracyclic molecule which is adorned with functionality that could permit the construction of ring IV of strychnine. With an activated methylene group at position 14 and an electrophilic ester carbonyl at position 15, intermediate **13a** would appear to be a viable substrate for a Dieckmann condensation.[8] It is, however, important to recognize that the two groups between which a bond must be formed are oriented on opposite sides of the molecular plane defined by ring V in intermediate **13a**, a circumstance which prohibits the desired Dieckmann condensation. Thus, a prerequisite for the desired bond-forming event is inversion of the stereogenic center at C-16 to give the epimer **13b** (Scheme 4a). In **13b**, the activated methylene at C-14 and the electrophilic C-15 ester carbonyl



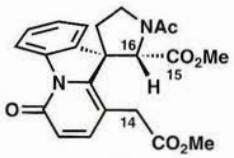
Scheme 4. Epimerization of intermediate **13a** (a) and synthesis of intermediate **10** (b).

occupy proximal regions of space and the prospects for achieving the formation of a bond between these two groups through a Dieckmann condensation seem excellent.



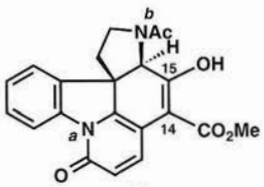
13a
Ar = C_6H_4-*p*-Me

Woodward actually anticipated all along that the ethoxycarbonyl group at position 15, the electrophile in the projected Dieckmann condensation, could, through a base-induced epimerization reaction, allow such an inversion to take place. However, it was not anticipated that exposure of **13a** to a base would result in destruction of the carefully constructed ring V! In the presence of sodium methoxide, intermediate **13a** suffers ready *β*-elimination of the stable toluene sulfinate anion, an event that is followed by a sequence of other destructive processes. It was thus necessary to remove the offending toluenesulfonyl group prior to the Dieckmann condensation. Treatment of **13a** with hot hydriodic acid and red phosphorous results in removal of the toluenesulfonyl group and hydrolysis of both the methyl and ethyl ester moieties of **13a** to give diacid **27** in 72% yield (see Scheme 4b). Subjection of **27** to sequential acetylation and esterification reactions then provides *N*-acetyl dimethyl ester **12** in an overall yield of 79%.



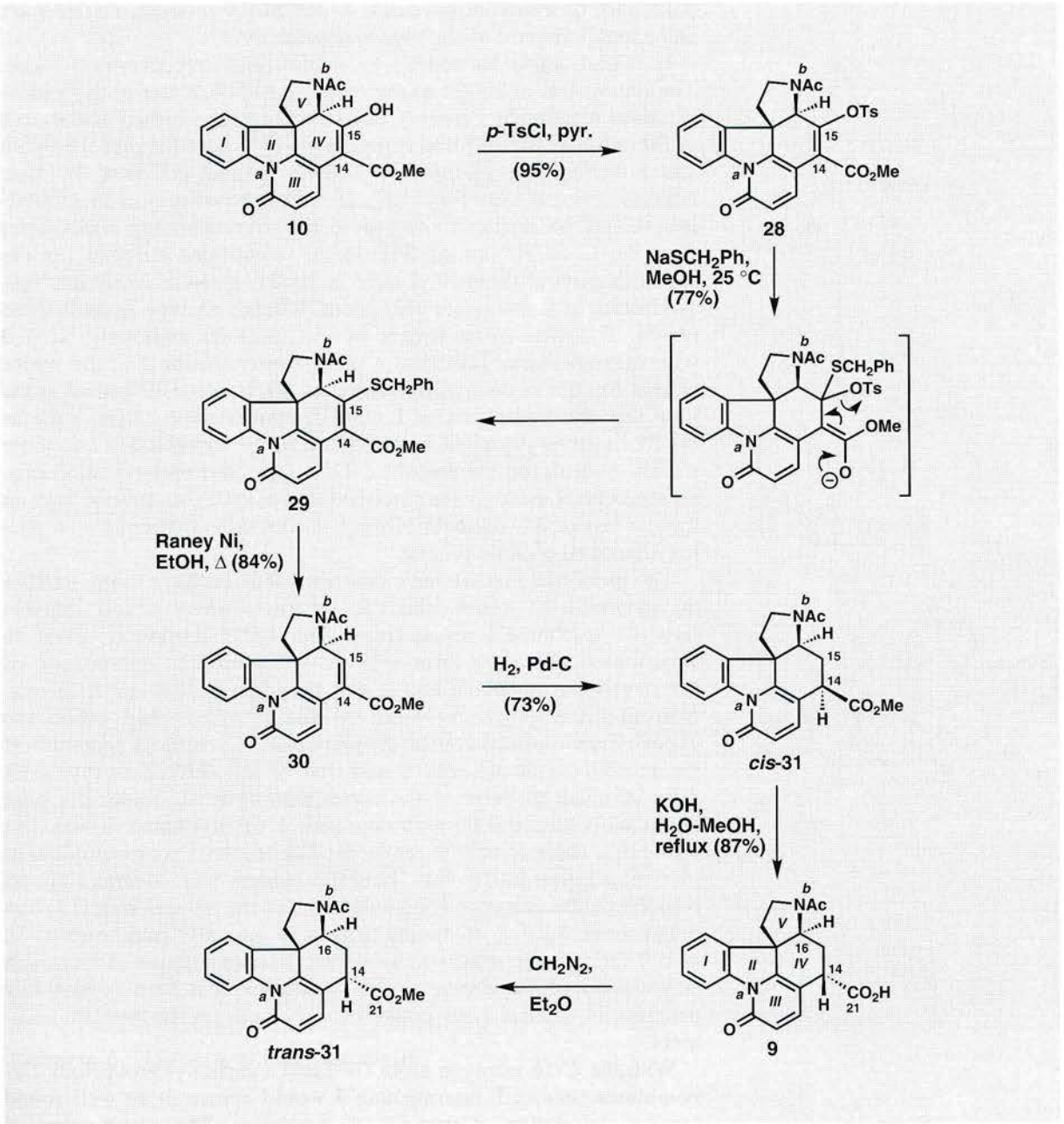
12

In its present form, intermediate **12** is not a viable substrate for the crucial Dieckmann condensation; it must undergo prior epimerization at C-16. When intermediate **12** is treated with sodium methoxide in hot methanol, enolization at C-16 occurs and an equilibrium is established between **12** and a diastereomeric substance, intermediate **11**. Once formed, **11** can either revert back to **12** through the planar enolate form, or it can participate in a productive cyclization reaction to give a new six-membered ring. Under these conditions, the desired transformations take place with exceptional facility to give, after acidification of the reaction medium, enol ester **10**.



10

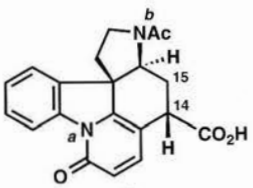
Enol ester **10** was found to be a very stable substance with respect to its keto ester tautomer, and it produced a distinctive UV spectrum. The stability of enol ester **10** is likely a consequence of the electron-withdrawing pyridone ring, and it was gratifying to find that **10** could be smoothly transformed into enol tosylate **28** upon treatment with *para*-toluenesulfonyl chloride in pyridine (see Scheme 5). This particular transformation constitutes the first step of a straightforward sequence of reactions that accomplishes the necessary deoxygenation at C-15. When a solution of **28** in methanol is treated with sodium benzylmercaptide at room temperature, *β*-benzylmercaptoester **29** forms smoothly through a transformation that can be formulated as an addition/elimination reaction. That is to say, benzylmercaptide ion initiates the event by adding in a Michael fashion to unsaturated ester **28** to give an ester enolate which subsequently collapses with concomitant *β*-elimination of the toluenesulfonyloxy group. The final step in the C-15 deoxygenation sequence requires a reduction of the carbon-sulfur bond in **29**. This objective is achieved easily with deactivated Raney nickel in hot ethanol to give unsaturated ester **30**. Saturation of the electron-deficient $\Delta^{14,15}$ double bond in **30** with hydrogen in the presence of



Scheme 5. Synthesis of intermediate **9**.

palladium on charcoal provides, as the major product, *cis* ester **31** and a small amount of the isomeric *trans* ester.

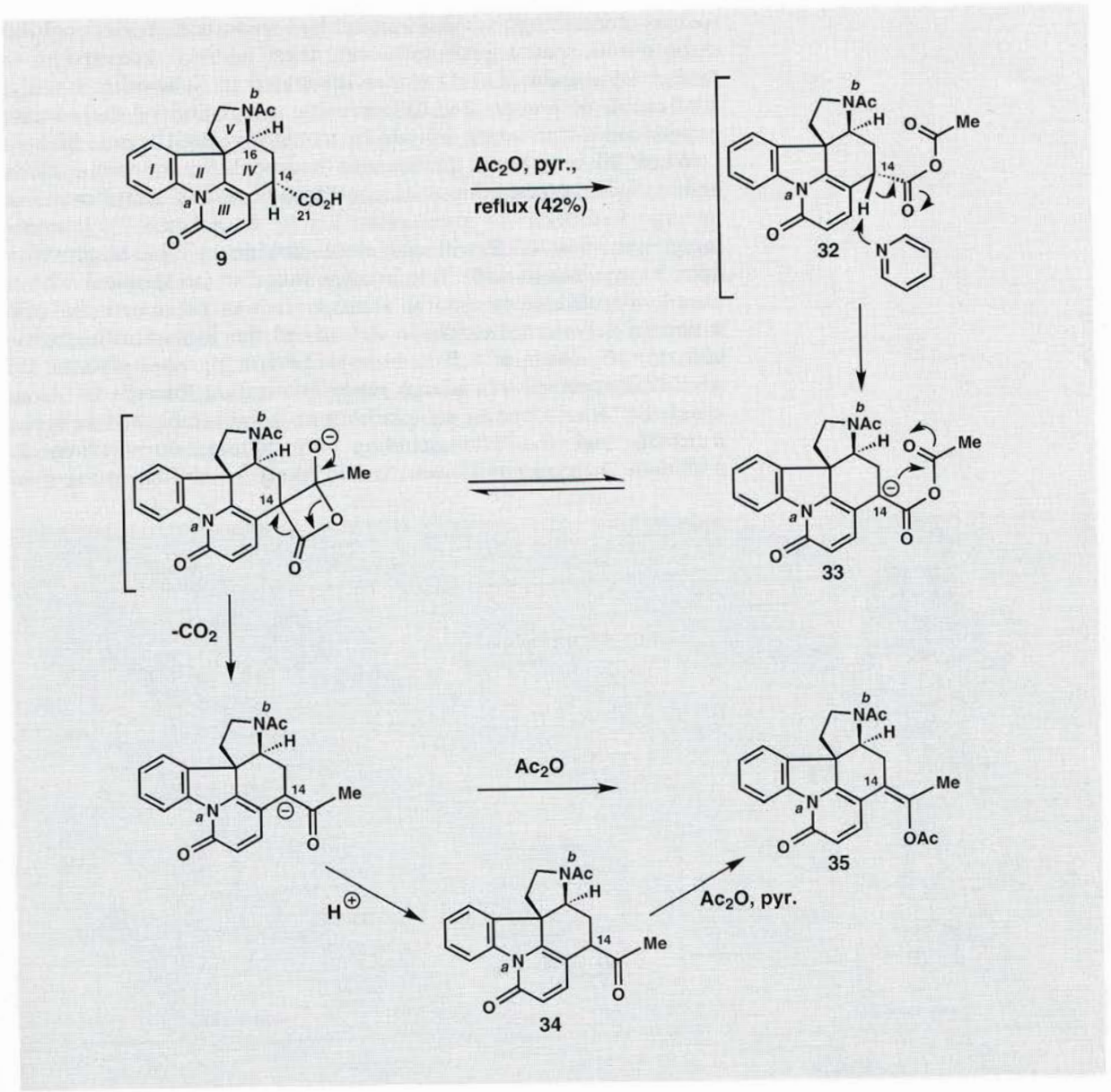
It is instructive to address an interesting stereochemical issue. The production of *cis*-**31** as the major diastereoisomer in the hydrogenation reaction is certainly not surprising; the biased framework of **30** enforces the addition of hydrogen to proceed across the much less hindered face of the $\Delta^{14,15}$ olefin to give *cis* ester **31**. But, nevertheless, *cis* ester **31**, with a crowded disposition of functionality, should be unstable relative to the corresponding *trans* ester (i.e. the C-14 epimer of **31**). Under conditions suitable for the saponification of the methyl ester in *cis*-**31**, it seems likely that epimerization at C-14 would also occur. Indeed, alkaline hydrolysis of *cis*-**31**, followed by treatment of the resultant carboxylic acid **9** with diazomethane, furnishes a methyl ester identical to the minor isomer formed in the hydrogenation of **30**. It was well known at the time that the hydrolysis of hindered, epimerizable esters, such as *cis*-**31**, is often preceded by inversion to the more stable and more readily hydrolyzed stereoisomer. Of course, the epimerization process proceeds through the intermediacy of an ester enolate and, in the context of **31**, removal of the C-14 methine hydrogen as a proton should be a facile process.



9

The processes that we have described thus far have culminated in the synthesis of racemic acid **9**, an intermediate which contains five of strychnine's seven rings. The same substance, albeit in enantiomerically pure form, was available through degradation of the strychnine molecule and it was possible, at this stage, to confirm that the preceding steps in the synthesis had taken the expected and desired course. In particular, the infrared spectrum of the racemic synthetic acid **9** and that of the derived methyl ester were identical to those of the corresponding enantiomerically pure compounds obtained through degradation of strychnine. It was also found that racemic acid **9** can be readily resolved with quinidine to give enantiomerically pure material which was identical in all respects to the corresponding substance in the natural series. A fortunate consequence of having access to optically pure carboxylic acid **9** through the synthetic sequence described above and through degradation of strychnine is that sufficient quantities of this key pentacyclic intermediate could be procured for further advancement.

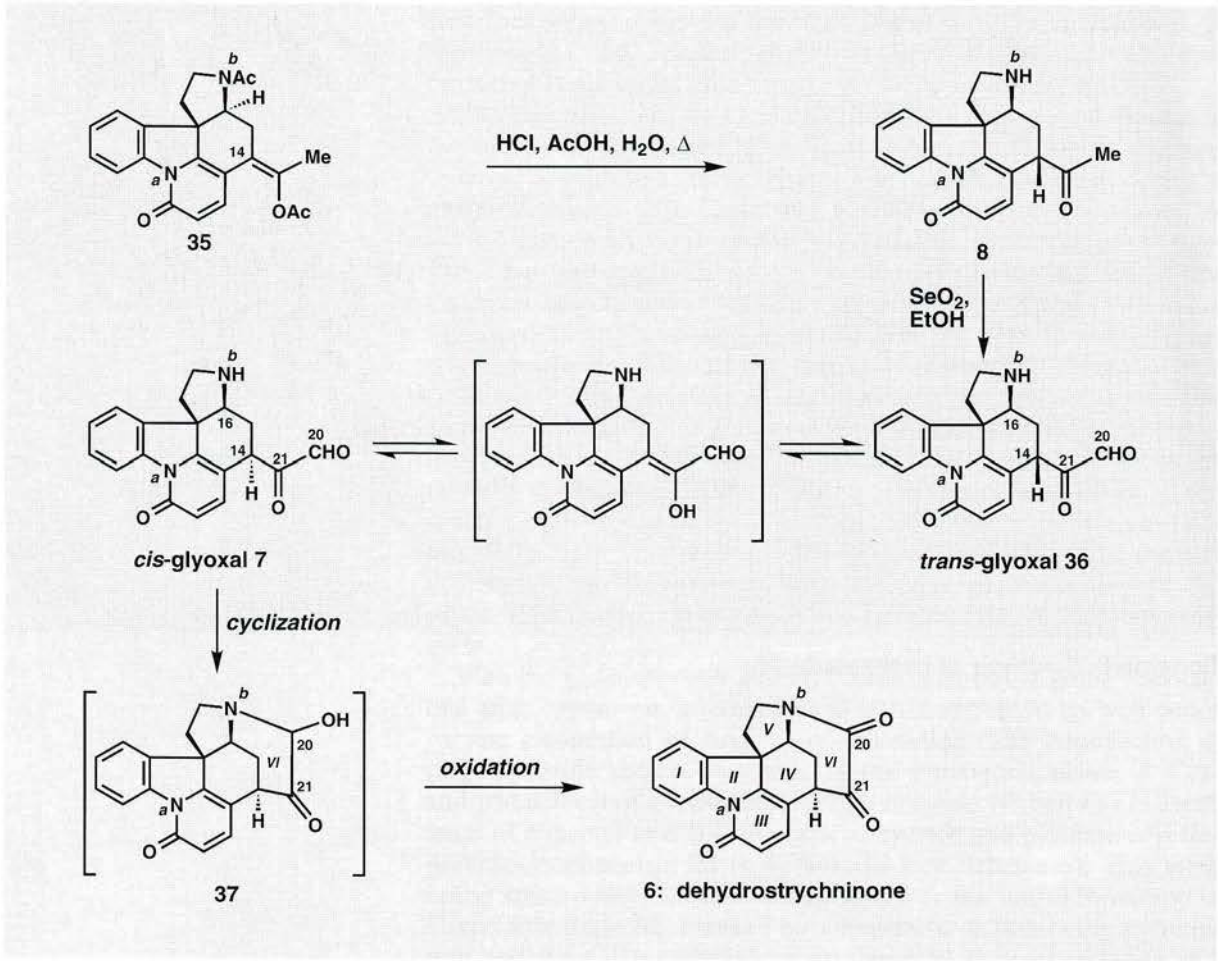
With the C-16 nitrogen atom (N^b) and a carboxyl group four carbon atoms removed, intermediate **9** would appear to be well suited for the elaboration of ring VI of strychnine. The construction of ring VI would require inversion of the stereogenic center at C-14 and installation of a methylene bridge between N^b and C-21. Treatment of *N*-acetyl acid **9** with acetic anhydride and pyridine at reflux provides enol acetate **35** in 42% yield (see Scheme 6). This interesting transformation undoubtedly involves the initial formation of mixed anhydride **32**. Flanked by the electron-withdrawing pyridone ring and the C-21 carbonyl group, the C14-H bond is labile and, under these conditions, deprotonation can occur to give **33**. This



Scheme 6. Synthesis of intermediate **35**.

species, containing as it does an enolate anion and an electrophilic carbonyl in spatial proximity, can then undergo conversion to methyl ketone **34** in the manner illustrated in Scheme 6. Finally, enolization of ketone **34**, followed by acetylation of the enolate oxygen atom with acetic anhydride, would give enol acetate **35**.

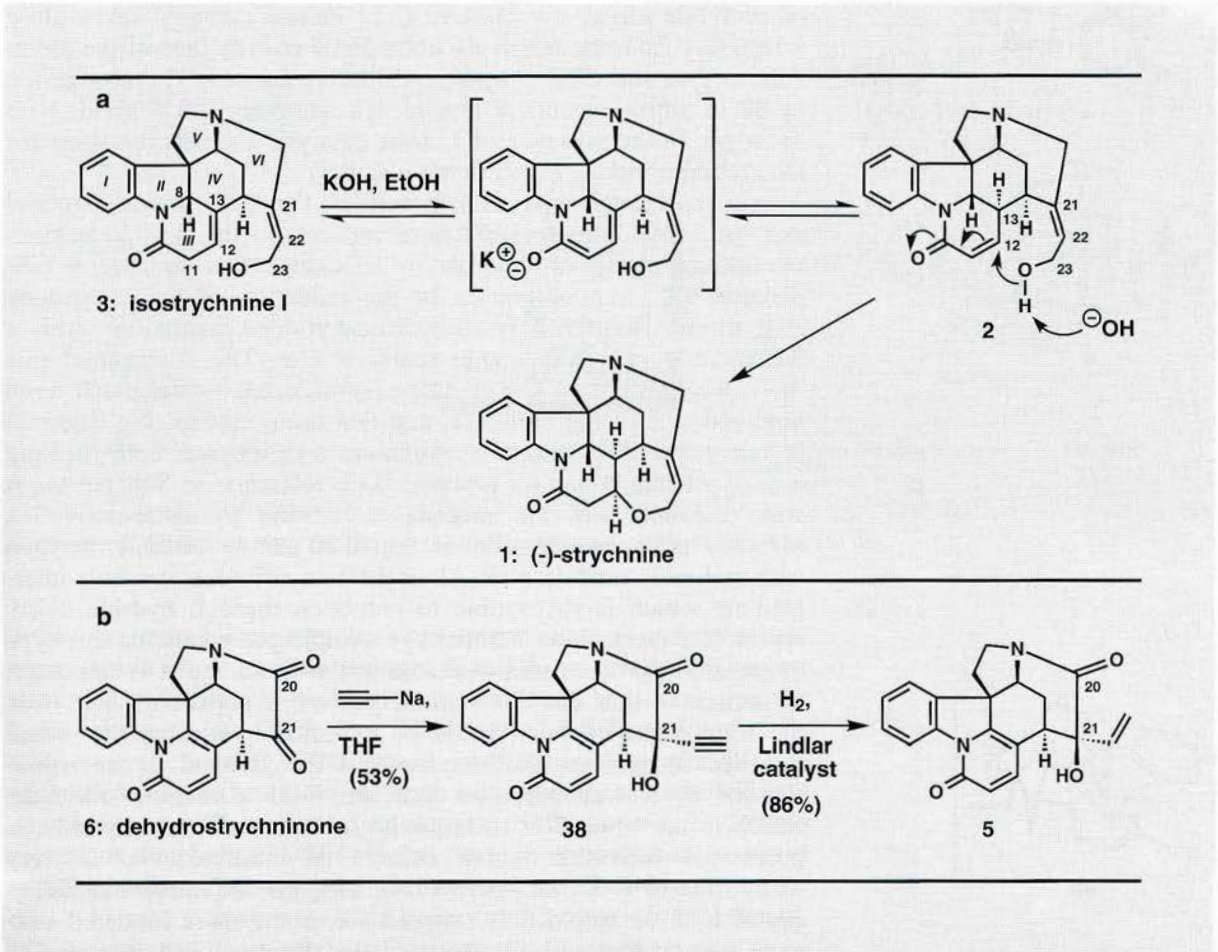
When **35** is exposed to aqueous hydrochloric and acetic acids under vigorous conditions, its enol acetate and *N*-acetyl moieties undergo hydrolysis to give amino ketone **8** (Scheme 7). Interestingly, oxidation of **8** with selenium dioxide in ethanol provides dehydrostrychninone (**6**), a substance found to be identical with a sample derived from natural sources. It was presumed that the action of selenium dioxide on **8** leads to the formation of *trans*-glyoxal **36**. With a 1,2-dicarbonyl grouping, *trans*-glyoxal **36** would be expected to undergo ready enolization towards C-14, an event that would permit an equilibrium to be established between *trans*-**36** and the corresponding *cis* epimer, intermediate **7**. Although such an equilibrium would likely be shifted in favor of



Scheme 7. Synthesis of intermediate **6**.

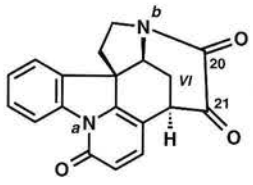
the less crowded *trans*-glyoxal stereoisomer (**36**), it is important to note that *cis*-glyoxal **7** can, once formed, participate in a productive cyclization reaction to give **37**. The close spatial relationship between N^b and the aldehydic C-20 carbonyl in **7**, and the tendency of 1,2-dicarbonyl systems to achieve the tetrahedral condition would drive the cyclization event. Finally, under the reaction conditions, oxidation of **37** occurs to give dehydrostrychninone (**6**).

We have reached an advanced stage in Woodward's synthesis. We have retraced the elegant and straightforward sequences of reactions that have led to the synthesis of intermediate **6**, a molecule possessing six rings and functionality suitable for the elaboration of the seventh and final ring of strychnine. It is important to note that when Woodward's synthesis began, it was already known that the strychnine degradation product, isostrychnine I (**3**), could be reconverted to strychnine (**1**) upon treatment of the former substance with potassium hydroxide in ethanol (see Scheme 8a).[10] Ethanolic



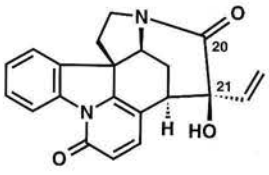
Scheme 8. Base-induced conversion of **3** to **1** (a) and synthesis of intermediate **5** (b).

potassium hydroxide initiates an equilibration of isostrychnine I (**3**) with its α,β-unsaturated isomer (**2**). With an electrophilic carbon atom at position 12 and with a nucleophilic alkoxide ion confined to a neighboring region of space by the $\Delta^{21,22}$ double bond, **2** is poised for an intramolecular Michael addition reaction to give strychnine (**1**). The overall process accomplishes the stereoselective creation of the vicinal stereocenters at C-12 and at C-13, and the formation of the seven-membered ether ring. The synthetic problem is thus reduced to the preparation of isostrychnine I (**3**) because the path to strychnine from this substance had already been laid down in 1948.[10]



6: dehydrostrychninone

In order to achieve the goal of synthesizing isostrychnine I (**3**) from dehydrostrychninone (**6**), the C-20 lactam carbonyl and the aromatic α-pyridone ring must both be reduced, and the C-21 ketone must be homologated (see Scheme 8b). With respect to the latter objective, it was found that treatment of a solution of **6** in THF with sodium acetylide results in the formation of propargylic alcohol **38** (53 % yield) (see Scheme 8b). As expected, the addition of acetylide ion to the reactive C-21 ketone carbonyl takes place selectively from the relatively unhindered convex face of the molecule to give the C-21 β-hydroxyl diastereoisomer. The conversion of **38** to allylic alcohol **5** is achieved smoothly (86 % yield) with hydrogen in the presence of Lindlar catalyst, and sets the stage for the crucial pyridone ring reduction step.



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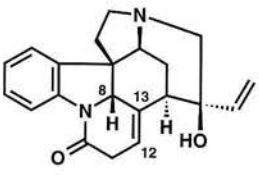
In a most impressive transformation, the C-20 amide carbonyl and the α-pyridone ring are both reduced in the desired manner by lithium aluminum hydride in refluxing ether to give **4** (see Scheme 9b). A consequence of the reduction of the α-pyridone ring to the desired $\Delta^{12,13}$-dihydro-α-pyridone oxidation level is the creation of a stereogenic center at C-8. The observation that the newly introduced C-8 hydrogen atom occupies the much more hindered side of the molecule, and that the pyridone ring carbonyl is not reduced by lithium aluminum hydride are both striking aspects of this reduction process. With reference to Scheme 9a, it was reasoned that the mechanism of the pyridone reduction involves prior coordination of the C-10 amide carbonyl oxygen with a Lewis acid (i.e. R_3Al or Li^+) to afford a cationic intermediate which is susceptible to reduction through hydride delivery at C-8 (strychnine numbering). Ample precedent for this type of reduction process was available at the time, and it is important to recognize that the C-10 amide carbonyl, protected as it is in the form of an enolate, would be expected to survive the reduction. To account for the stereoselectivity exhibited in the reduction of **5**, it was proposed that the C-21 aluminum alkoxide, which forms when **5** is treated with lithium aluminum hydride, is positioned such that it can enforce an intramolecular delivery of hydride to C-8 (see intermediate **39**); the intramolecular delivery of hydride would thus proceed across the more hindered concave face of the molecule to give the observed and desired C-8 epimer.



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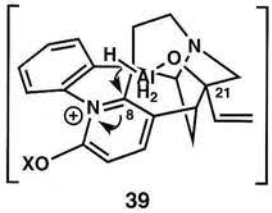

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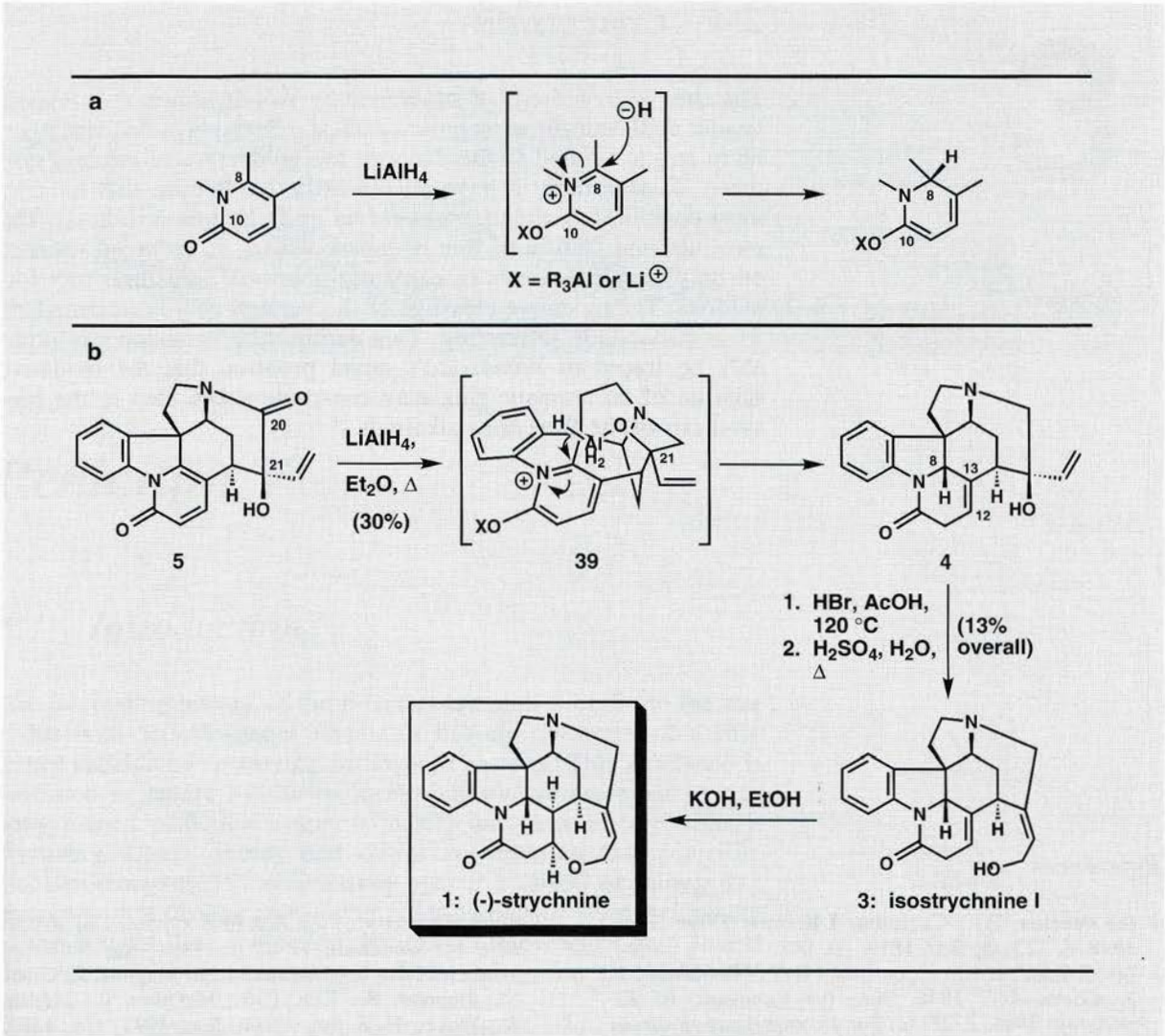

Scheme 9. Pyridone ring reduction (a) and synthesis of (–)-strychnine (**1**) (b).

The structural homology between intermediate **4** and isostrychnine I (**3**) is obvious; intermediates **3** and **4** are simply allylic isomers and the synthetic problem is now reduced to isomerizing the latter substance into the former. Treatment of **4** with hydrogen bromide in acetic acid at 120 °C results in the formation of a mixture of isomeric allylic bromides which is subsequently transformed into isostrychnine I (**3**) with boiling aqueous sulfuric acid. Following precedent established in 1948[10] and through the processes outlined in Scheme 8a, isostrychnine I (**3**) is converted smoothly to strychnine (**1**) upon treatment with potassium hydroxide in ethanol. Woodward's landmark total synthesis of strychnine (**1**) is now complete.

2.4 Conclusion

The chemical synthesis of strychnine by Woodward *et al.* is a spectacular achievement of organic synthesis. It displays brilliant ingenuity and it ushered in the dawn of the golden era of organic synthesis. Furthermore, it gave chemists the confidence that nature's most complicated molecules *could* be made by total synthesis. The most striking feature of this landmark feat is its enforced reliance on only simple reagents to carry out nontrivial structural transformations. The oxidative cleavage of the veratryl ring in intermediate **17** is particularly interesting. This daring transformation can probably be traced to Woodward's novel proposal that the oxidative scission of an aromatic ring may constitute a key step in the biosynthesis of the *Strychnos* alkaloids.[11]

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