Chapter 4
A Short Synthesis of Strychnine from Pyridine

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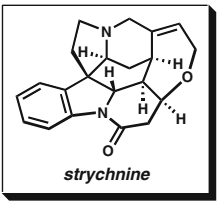

4.1 Introduction

The synthesis of complex natural products serves as a source of great inspiration and challenge for organic chemists. The synthesis of strychnine is no exception. With six contiguous stereocenters, five of which adorn the central cyclohexane ring, a stereodefined trisubstituted olefin, and seven rings, strychnine (**1**, Fig. 4.1) presents a significant challenge for synthesis. In 1952, Sir Robert Robinson said "for its molecular size strychnine is the most complex substance known" [1].

Clearly, our increasingly powerful methods for chemical synthesis, as well as improved methods for natural product isolation and structural elucidation, have changed our definitions of complexity, and Robinson's statement no longer holds true. Still, beginning as early as the 1830s, it took the efforts of countless chemists terminating with a "decades-long chemical degradative assault" to elucidate the full structure of strychnine [2–5]. That some of organic chemistry's greatest minds of the time were engaged in this pursuit is as much a testament to the challenge of structural determination in that era as it is to the possibility for new discoveries along the way. With the advent of modern spectroscopic and X-ray crystallographic

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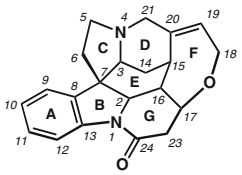


Fig. 4.1 The biogenetic numbering system used throughout this chapter (C22 has been biochemically excised)

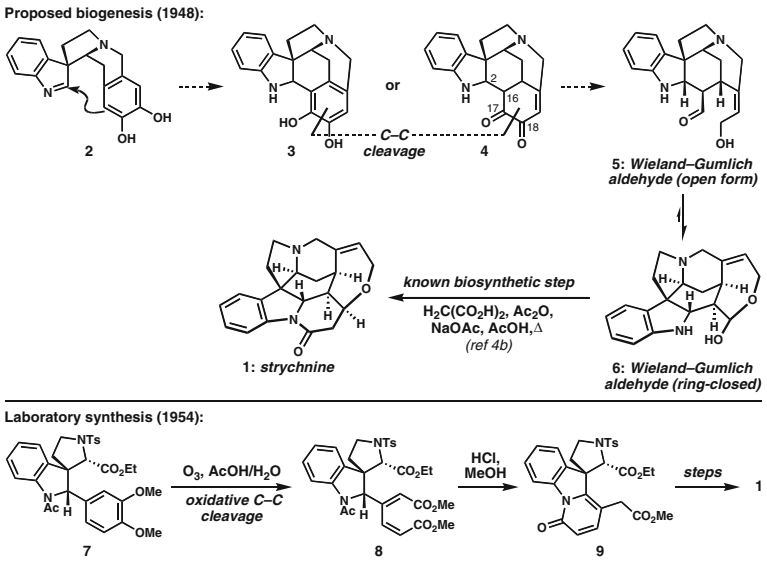
methods in the decades following strychnine's structural elucidation, clever degradation experiments were gradually marginalized. As Woodward foresaw and elegantly stated when describing in detail his group's inaugural synthesis of strychnine, the field of natural product synthesis would effectively replace structure elucidation as the major source of serendipitous discovery in organic chemistry:

> Of course, men make much use of excuses for activities which lead to discovery, and the lure of unknown structures has in the past yielded a huge dividend of unsought fact, which has been of major importance in building organic chemistry as a science. Should a surrogate now be needed, we do not hesitate to advocate the case for synthesis.
>
> R.B. Woodward, 1963 [6].

The field of complex molecule synthesis has grown tremendously since Woodward prophetically wrote these words, and one cannot overstate the contributions in terms of new methods, new strategies, and new reactivity that have arisen either deliberately or fortuitously through the exercise of natural product synthesis [7]. In the relatively short time that our laboratory has been engaged in the synthesis of natural products, we, like many other research groups, have uncovered unexpected reactivity and unusual molecular rearrangements [8]. These serendipitous discoveries have led to useful new reactions and inspired approaches to new natural product targets. In the narrative that follows, we describe our efforts directed toward the *Strychnos* family of indole alkaloids using Zincke aldehydes (5-amino-2,4-pentadienals, available from the ring opening of pyridinium salts) as key intermediates, and we highlight some of the unforeseen adventures that have kept things interesting along the way [9].

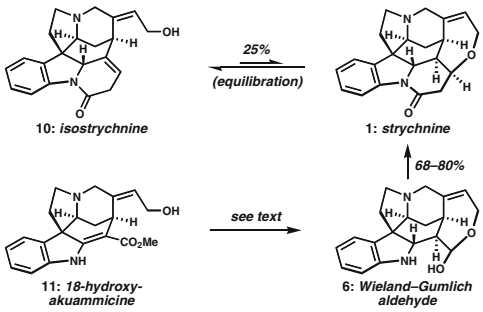
4.2 Synthesis of Strychnine: A Historical Perspective

The most famous and recognizable member of the *Strychnos* family, strychnine is thought to be the first indole alkaloid ever isolated in pure form, as reported by Pelletier and Caventou in 1818 [2]. Its elemental composition would be determined by Regnault a mere 20 years later [3], but the correct structure would not be put forth in the literature until 1946 by Robinson, and confirmed 2 years later by Woodward [4, 5]. With its moderate level of structural complexity, diverse possibilities for constructing its polycyclic ring system and an intriguing history, it is no wonder that strychnine has attracted substantial interest as a target for synthesis despite its lack of important biological activity. Over the past 60 years, 18 groups have reported



Scheme 4.1 Oxidative cleavage of an electron-rich aromatic ring was a key component of Woodward's proposal for a biogenesis of the *Strychnos* alkaloids and a key step in his subsequent synthesis of strychnine

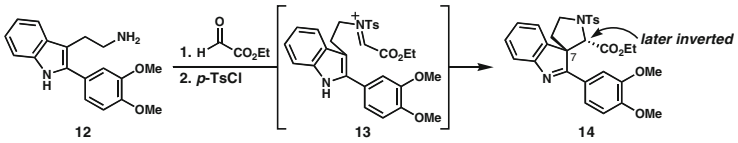
syntheses of this heptacyclic alkaloid, each reporting a unique approach to its construction [10]. The first such achievement was reported by Woodward and co-workers in 1954, a mere 6 years after the correct structure of strychnine had been rigorously established. Woodward took advantage of many lessons learned from degradation studies in the planning and execution of this synthesis and was equally inspired by his early thoughts on the biogenesis of the *Strychnos* alkaloids, incorporating elements of his proposal into the synthesis. For example, an early biogenetic proposal is outlined in Scheme 4.1, wherein intermediate **2** might be formed by successive Pictet–Spengler reactions of tryptamine with two different aldehydes (3,4-dihydroxyphenylacetaldehyde and formaldehyde) [11]. One further nucleophilic attack of the electron-rich arene could forge the C16–C2 bond [12], providing a structure (**3** or **4**) that "contains striking similarities to many of the features of the strychnine molecule." Cleavage of the C17–C18 bond and minor redox adjustments would yield the Wieland–Gumlich aldehyde (**5**/**6**), which could be converted to strychnine by incorporation of an N_a–Ac group, followed by another simple condensation reaction. With respect to this proposal, Woodward wrote: "On the whole, the possibility of building up so complicated a structure as (strychnine) by a series of simple reactions from plausible starting materials *is so striking that it is difficult to believe that the scheme lacks significance*." While these early musings were mistaken with regard to the origins of the Wieland–Gumlich aldehyde [13], the thought process of successive, simple reactions leading to a rapid buildup of complexity was compelling, and a similar oxidative cleavage of a catechol derivative (**7** → **8**) was used in Woodward's successful synthesis [10a].



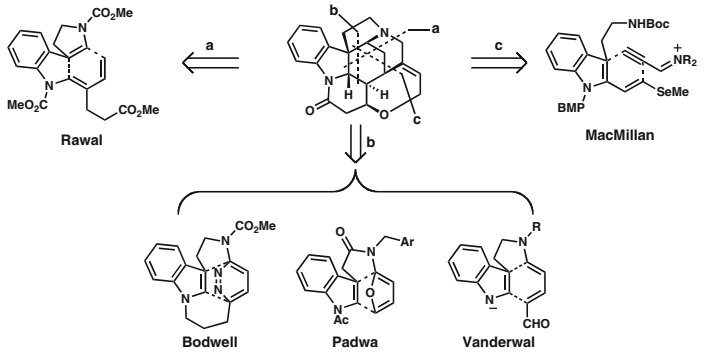
Scheme 4.2 Strychnine is readily accessed via isostrychnine or the Wieland–Gumlich aldehyde using chemistry discovered during structural elucidation/degradation studies

Following Woodward's inaugural achievement, it would take nearly 40 years before the next synthesis of strychnine would appear in the literature, although the intervening time saw substantial achievements in the synthesis of other *Strychnos* alkaloids and members of the related *Aspidosperma*, *Iboga*, and *Vinca* families [14]. The reported syntheses of strychnine since 1990 have included milestones such as the first asymmetric synthesis by Overman [10c], the first biomimetic synthesis by Martin [10h], and particularly concise syntheses by Kuehne [10d], Rawal [10e], Bodwell [10k], Reissig [10p], and MacMillan [10r]. The reported syntheses to date are all creative and instructive, many relying on new technologies that have arisen since the days of Woodward and some of which were clearly inspired by the challenge of the target alkaloid itself. In this context, strychnine continues to serve as a benchmark target against which organic chemists may measure the state-of-the-art of natural product synthesis strategy.

Although each synthesis of strychnine has been accomplished using unique methods or strategic disconnections, they share certain elements. All reported syntheses have proceeded via either isostrychnine (**10**) or the Wieland–Gumlich aldehyde (**6**) as the penultimate intermediate (Scheme 4.2) [15]. Both of these molecules are themselves naturally occurring alkaloids; isostrychnine is, as the name suggests, a constitutional isomer of strychnine, and the Wieland–Gumlich aldehyde is a biogenetic precursor of strychnine [4]. Part of the reason for this commonality is that there exist well-established procedures for the conversion of each precursor to strychnine. The equilibration of isostrychnine and strychnine favors the former, providing a 70:30 mixture that can be resolved by chromatography [16]. The conversion of the Wieland–Gumlich aldehyde to strychnine was reported by Robinson and Anet and is reported to proceed in a much higher 68–80 % yield [4c]. In addition, many of the syntheses proceeding via the intermediacy of the Wieland–Gumlich aldehyde have also employed 18-hydroxyakuammicine (**11**) as an earlier precursor, as first described by Overman and co-workers [10c, f, h, k, m, o, p]. The reliable introduction of the final ring and three stereocenters are attractive reasons for this endgame, and within 18-hydroxyakuammicine and isostrychnine remain most of the structural challenges that attract chemists to this class of alkaloids.



Scheme 4.3 Formation of the C7 quaternary center by C7–C3 bond formation by Woodward and co-workers

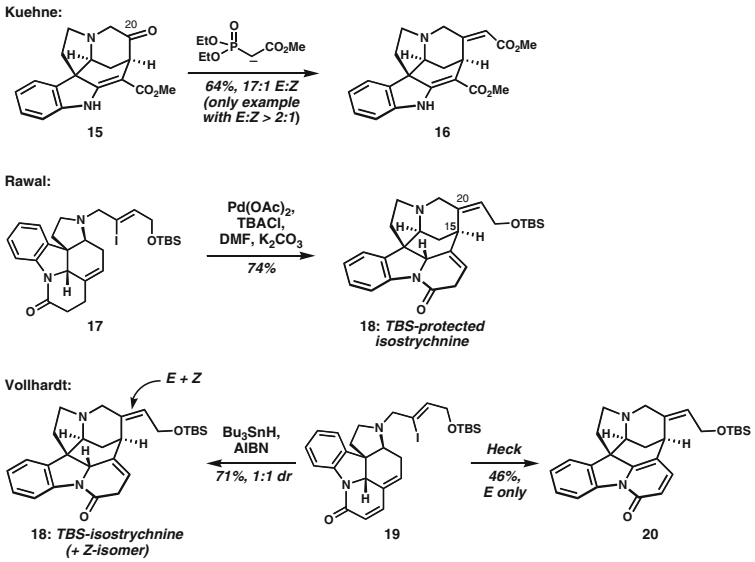


Scheme 4.4 Diels–Alder disconnections used in the synthesis of strychnine

4.3 Structural Challenges

Among the many rings and stereogenic elements that contribute to strychnine's challenge as a target for synthesis, two key structural features have inspired unique chemical solutions and deserve some comment. One important challenge is the C7 quaternary stereogenic center (see Fig. 4.1 for atom and ring labeling). At the junction of three separate rings, this center has inspired a number of clever strategies for its construction, including sigmatropic rearrangements, cycloadditions, and transition metal-catalyzed reactions. The most widely adopted strategy involves cyclization of a C7 nucleophile onto an iminium ion to forge the C7–C3 bond, often taking advantage of the inherent nucleophilicity of the indole group's 3-position. This strategy was used at an early stage in Woodward's inaugural synthesis (Scheme 4.3), and figured prominently in the syntheses of Magnus, Overman (as part of the key aza-Cope/Mannich sequence), and others [10a–c, d, f, m].

Another prominent solution makes use of the Diels–Alder cycloaddition, a reliable reaction for the construction of quaternary centers. Rawal pioneered this strategy in an intramolecular Diels–Alder reaction that constructed both the indoline B-ring and the E-ring (Scheme 4.4, disconnection a), allowing for the controlled formation of three contiguous stereocenters [10e]. Two approaches previous to ours have enlisted the indole as the 2π component in an intramolecular Diels–Alder reaction with either a pyridazine [10k], or an amidofuran [10n], as the

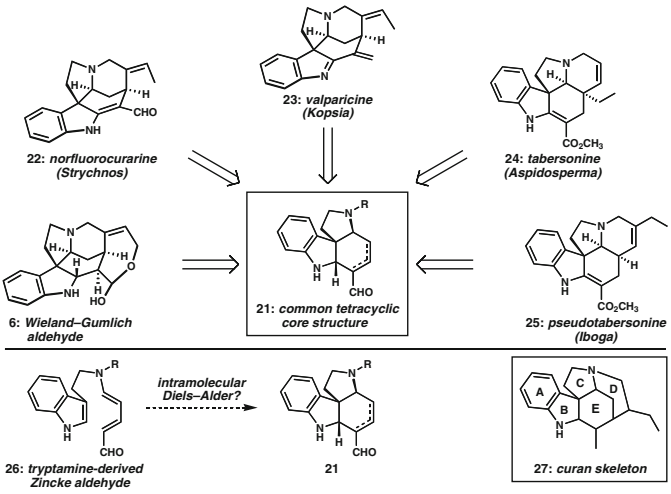


Scheme 4.5 Previous methods for formation of *E*-hydroxyethylidene functional group

4π component (disconnection b, for details, see section below). Finally, the recent synthesis reported by MacMillan and co-workers established the viability of incorporating a vinyl indole as the 4π component in an application of their enantioselective catalysis via chiral iminium ions (disconnection c) [10r]. Notably, three of the four distinct Diels–Alder disconnections that allow direct construction of the C7 quaternary center have been successfully employed in the synthesis of strychnine.

Another challenge associated with the synthesis of strychnine, as well as other *Strychnos* alkaloids, is the stereoselective construction of the *E*-hydroxyethylidene side chain (Scheme 4.5). Strategies that rely on a late-stage olefination reaction of a C20 ketone often suffered from low diasterocontrol for the newly formed alkene, with the best exception provided by Kuehne (**15** → **16**) [10a, b, d, f]. Overman, Martin, and Shibasaki took advantage of highly selective β-elimination reactions of β-hydroxy esters or amides at earlier stages of the synthesis, the products of which would be later elaborated into the Wieland–Gumlich aldehyde (not shown) [10c, h, l]. Arguably the most general of the approaches is the stereospecific closure of the D-ring piperidine using a vinylmetal species derived from a precursor vinyl halide (C20–C15 bond formation). This strategy has taken the form of a Cu/Mn-, Ni- or Pd-mediated conjugate addition, a Pd-catalyzed enolate vinylation, and an intramolecular Heck reaction [10g, e, i, j, n, r][1]. The Heck approach first reported by Rawal in

[1] A synthesis of strychnine by the Stork group was apparently disclosed in lecture form, and some of the details are provided in the review by Bonjoch and Solé from 2000 [15a]. While we prefer not



Scheme 4.6 The common core structure of many indole monoterpene alkaloids might be accessed through a tetracyclic Zincke aldehyde-derived building block

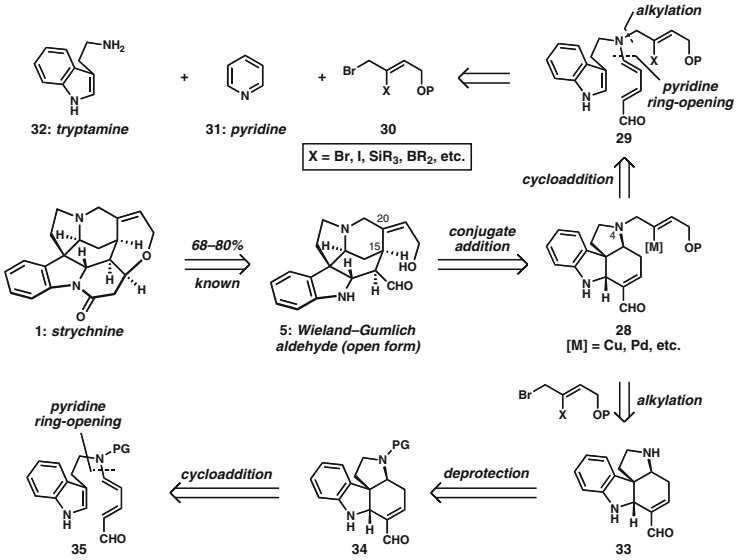
1994 (**17** → **18**) was so successful that it has been applied to closely related substrates by Vollhardt, Mori, Andrade, and MacMillan and has featured in many other alkaloid syntheses [10e, i, j, k, o, p, r, 17–21]. This versatile approach has also been used to great effect for the synthesis of simpler Strychnos alkaloids, as we will elaborate later. Vollhardt and co-workers reported an effective radical-mediated ring closure (**19** → **18**), but the product was isolated as a 1:1 mixture of alkene isomers, owing to the known rapid isomerization of vinyl radical intermediates; these workers also eventually used a Heck cyclization for this bond formation (**19** → **20**) [10i].

In our efforts toward strychnine, we have integrated an intramolecular Diels–Alder approach to its tetracyclic core with an organometallic D-ring closure. Both of these key reactions were certainly inspired by the previous accomplishments of others as described above.

4.4 Background: Zincke Aldehydes

We became particularly interested in strychnine when we noticed that the tetracycle **21** (Scheme 4.6), which might be readily available by an intramolecular Diels–Alder cycloaddition of a tryptamine-derived aminodiene, contains much of the complexity of this popular alkaloid target. In fact, this tetracycle is common to many indole monoterpene alkaloids including members of the *Strychnos*, *Aspidosperma*, and

to cite a synthesis that is not available in the primary literature, based on the account provided in [15a], the Stork group utilized a vinyl carbanionic D-ring-closure by C15–C20 bond formation that presumably proceeded via conjugate addition onto an α,β-unsaturated ester.



Scheme 4.7 Retrosynthetic options considered for strychnine

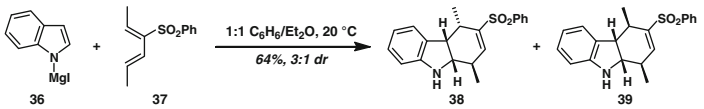
Iboga families (see **22**–**25**), comprising the ABCE rings of the curan skeleton **27**. It was our interest in the particular class of 1-amino-2,4-dienes called Zincke aldehydes (5-amino-2,4-pentadienals) [22], which derive readily from the ring-opening reactions of pyridinium salts, that caused us to recognize an opportunity for a particularly direct approach to strychnine and related alkaloids. Intramolecular cycloaddition of a tryptamine-derived Zincke aldehyde such as **26** could generate tetracycle **21** directly with probable conjugation of the unsaturated aldehyde. This line of thinking encouraged our in depth studies of Zincke aldehydes and inspired other efforts within our research group to engage Zincke aldehydes in Diels–Alder reactions (see below) [8].

Our retrosynthesis is presented in more detail in Scheme 4.7. Our objective was the Wieland–Gumlich aldehyde (shown in its hydroxy-aldehyde tautomeric form, **5**) because it can be efficiently converted to strychnine (68–80 % yields reported). Furthermore, the C17 aldehyde would be derived without redox manipulations from the Zincke aldehyde, further streamlining the synthesis and highlighting the utility of Zincke aldehydes. No previous synthesis of the Wieland–Gumlich has made direct use of a C17 aldehyde; instead previous efforts have relied on more robust esters or other surrogates, necessitating an eventual oxidation state adjustment. We envisioned that the Wieland–Gumlich aldehyde could be obtained by a conjugate addition of a vinyl nucleophile onto an α,β-unsaturated aldehyde to forge the C20–C15 bond and close the D-ring (**28** → **5**). This disconnection was pioneered by Rawal in his synthesis of dehydrotubifoline where he used an intramolecular Heck reaction (as discussed in Scheme 4.5) [18], which has proven to be a robust and strategically advantageous disconnection in several subsequent syntheses. α,β-Unsaturated aldehyde **28** (or its unconjugated isomer) would be the product of

our proposed intramolecular cycloaddition of a fully functionalized Zincke aldehyde **29** or could potentially be derived from an *N*-protected tetracycle **34**. The exact nature of intermediate **28** would depend on the precise method of D-ring closure, the functional group tolerance of the cycloaddition reaction, and the success of accessing unsubstituted tetracycle **33**. In addition to providing the framework for a particularly concise approach to strychnine, we envisioned that judicious choice of the N4-substituent and manipulation of the aldehyde group would enable the synthesis of many alkaloids of this class by a unified strategy.

4.5 Background: Intramolecular Cycloadditions of Indoles

There are two major challenges in the proposed intramolecular Diels–Alder reaction: first, the C2–C3 indole π bond is part of a stable aromatic system and is a notoriously poor dienophilic partner for [4 + 2] cycloadditions. As a result, most of the reported examples, although they are intermolecular reactions, involve electronic perturbation of the indole system. For example, triplet photosensitization [23], stoichiometric generation of an indole radical cation [24], or deprotonation to give the indole anion [25] are methods that successfully led to formal cycloaddition outcomes. For selected examples, see Eqs. (4.1) and (4.2). In many cases, the reaction proceeds in a stepwise fashion with radical and/or charged intermediates rather than via concerted cycloaddition. The lack of stereospecificity [e.g., Eq. (4.1)] is a telltale sign of a stepwise process, in this case an anionic Michael/Mannich sequence. Intramolecular examples of indole Diels–Alder reactions include the work of Bodwell and Padwa, both used in approaches to strychnine, where an *N*-acyl or *N*-alkyl indole reacts with a tethered amidofuran or pyridazine (see disconnection b, Scheme 4.4, specific reactions not shown) [10k, n]. Despite the lowered entropy of activation afforded by tethering the two reaction partners, both of these reactions occur only at elevated temperature (150–215 °C) and benefit from a subsequent irreversible fragmentation of the bicyclic [4 + 2] product.



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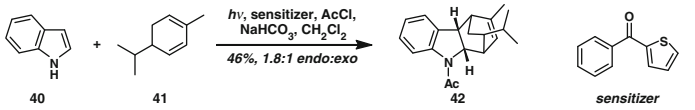
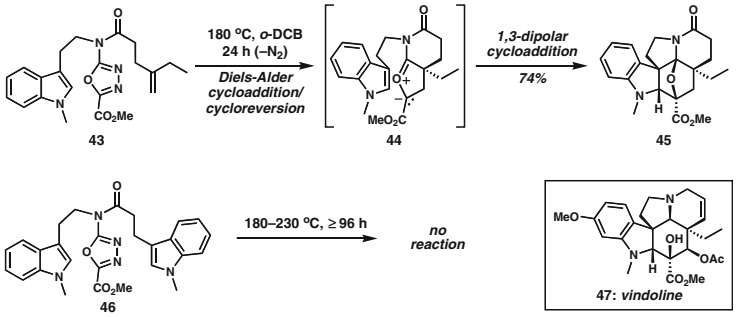


(4.2)

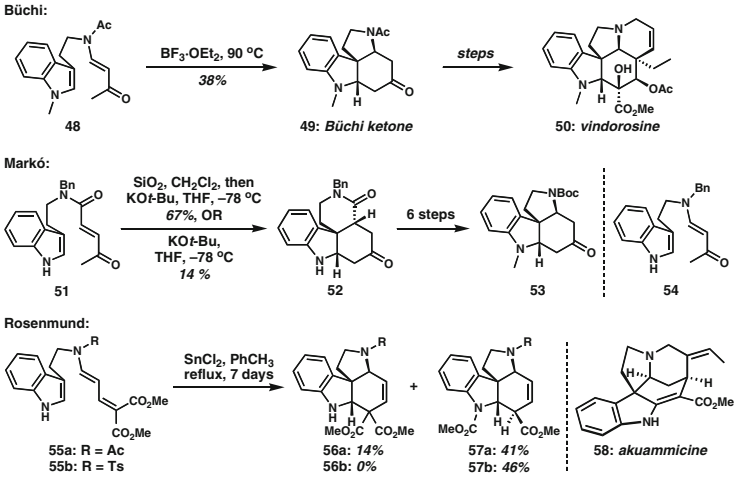
In contrast to the failure of Diels–Alder reactions, dipolar cycloadditions of indoles are much more successful, and the Boger group has reported a fascinating [4+2]/1,3-dipolar cycloaddition cascade involving indole as the dipolarophile in their impressive synthesis of vindoline (Scheme 4.8) [26]. After the initial



Scheme 4.8 Boger's cascade cycloaddition chemistry to access indole alkaloids features dipolar cycloaddition to indole, and not Diels–Alder cycloaddition

Diels–Alder reaction of the 1,3,4-oxadiazole with the pendant olefin and loss of N_2, the C2–C3 π bond participates in a subsequent 1,3-dipolar cycloaddition with the carbonyl ylide to generate complex polycycles such as **45** as single diastereomers with up to six new stereocenters. That the cascade reaction is initiated by a Diels–Alder reaction with the alkene rather than with the indole is supported by the lack of reaction even under forcing conditions with substrate **46**, in which a Diels–Alder reaction with the indole C2–C3 π bond would be required [26a].

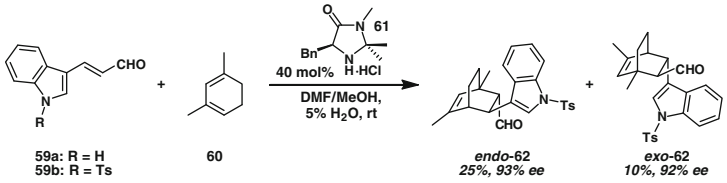
A number of stepwise indole annulations of tryptamine derivatives can be found in the literature that bear a resemblance to our proposed transformation. Early reports from Büchi and co-workers detail the synthesis of **48** and treatment with $BF_3{\cdot}OEt_2$ at elevated temperatures to give tetracycle **49**, which has become known as the Büchi ketone (Scheme 4.9) [27]. This reaction presumably arises from conjugate addition of indole C3 onto the Lewis-acid-activated electron-deficient vinylogous amide, followed by enolate equilibration and final Mannich cyclization. Tetracycle **49** was carried on to complete a concise synthesis of vindorosine (**50**). A related reaction catalyzed by $TiCl_4$ was reported by Pandit and co-workers, directly incorporating a C17 ester (not shown) [28]. More recently, Markó and co-workers reported a different method to access a similar tetracyclic ketone [29]. They found that exposure of tryptamine derivative **51** to KO*t*-Bu at low temperature gave rise to tetracyclic ketone **52**, albeit in low yield [29c]. They also reported a higher-yielding stepwise procedure using SiO_2 to catalyze the initial spirocyclization, followed by subsequent base-mediated Mannich reaction. Interestingly, the product bears a trans-fused heterodecalin system. The tetracyclic product was further processed to eventually produce the five-membered pyrrolidine **53**. Vinylogous amide substrate **54**, which closely resembles the Büchi substrate and would directly produce the desired five-membered pyrrolidine, was found to be unreactive. Rosenmund and co-workers reported the successful Lewis acid-catalyzed bicyclization reactions of diesters **55a/b** which also deliver the desired pyrrolidine C-rings, but these harsh conditions led to mixtures of products in only modest yields [30]. Nonetheless, reactions of these doubly activated diene substrates directly yield full-fledged ABCE tetracycles, with C17 in an appropriately oxidized form relevant to most curan alkaloids. That the



Scheme 4.9 Some bicyclization reactions relevant to our desired transformation

Rosenmund group never applied this reaction to the *Strychnos* alkaloids (e.g., akuammicine, **58**) is somewhat surprising.

Beyond the reluctance of indoles to participate in Diels–Alder reaction, the second challenge of our proposed intramolecular cycloaddition is that Zincke aldehydes are also known to be poor dienes in [4 + 2] cycloadditions [31]. To the best of our knowledge, there are no reported examples of successful Diels–Alder reactions with Zincke aldehydes serving as the 4π component, almost certainly owing to their high donor–acceptor stabilization. In the most closely related example that we have found, Zincke aldehyde-like compound **59a** [Eq. (4.3)] was found to be unreactive as the 2π component in an enantioselective organocatalytic Diels–Alder cycloaddition until the donor nature of the indole nitrogen was attenuated by *N*-tosylation (see **59b**) [32]. While excellent enantioselectivity was achieved, this intermolecular reaction remained inefficient, although it did serve as a key step in Kerr's synthesis of (+)-hapalindole Q.



(4.3)

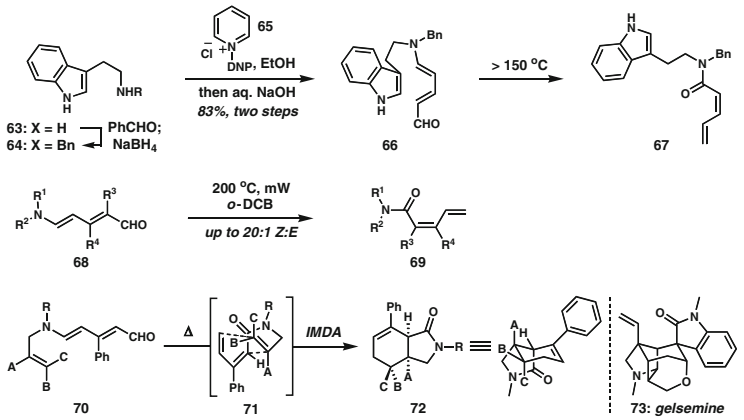
While we were concerned by the potential problems with our desired reaction, particularly the poor dienophilicity of indoles and the failure of **54** to cyclize under stepwise cyclization conditions, we were nonetheless inspired to pursue this potentially direct strategy. The successes of Markó and Rosenmund in related systems (**51** → **52** and **55** → **56**, respectively), the ease of substrate synthesis, and the significant utility of the reaction products compelled us to evaluate Zincke

aldehydes in the proposed transformation [29, 30]. Given the intramolecular setting and the possibility of electronic perturbation of the indole fragment, we remained optimistic. As we detail below, this pursuit not only provided access to several *Strychnos* alkaloids (and one *Kopsia* alkaloid) in very few steps, but we have also uncovered a wealth of unexpected reactivity potentially applicable to the stereocontrolled synthesis of completely unrelated molecules.

4.6 Development of the Intramolecular Diels–Alder Cycloaddition of Tryptamine-Derived Zincke Aldehydes

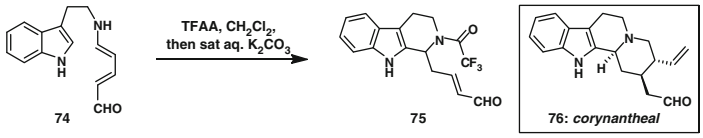
We began our investigations with the synthesis of model substrate **66** (Scheme 4.10), which is readily available on multigram scale in 83 % overall yield from tryptamine, benzaldehyde, and pyridinium salt **65** via Zincke pyridinium ring opening [9]. We first attempted thermal Diels–Alder reactions in a variety of solvents. At lower temperatures, the starting material remained unchanged, but above 150 °C in aromatic solvents, we observed the clean formation of a new product. Examination of ^{1}H-NMR spectra of the crude products showed that the indole resonances remained, while the salient resonances of the Zincke aldehyde were replaced with a new set of signals in the alkene region. The product was determined to be *Z*-α,β,γ, δ-unsaturated amide **67** [8b]. This completely unexpected reaction turned out to be quite general (see **68** → **69**) and has been observed in all of our attempts to initiate thermal Diels–Alder reactions with other Zincke aldehydes. This interesting chemistry has been further explored in our group in terms of scope and mechanism and has resulted in a new synthesis of polycyclic lactams from allyl-substituted Zincke aldehydes (**70** → **71** → **72**) [8b, d, f]. Examination of the structure of these products led us to ponder a new synthesis of gelsemine (**73**), another polycyclic alkaloid that has been a popular target over the last 20 years [33]. A Zincke aldehyde precursor **70** with suitable substitution (A = vinyl, B = H, etc.) should lead to a lactam that maps nicely with respect to substitution and stereochemistry onto three of the six rings of gelsemine. This ongoing project aims to highlight the rapid buildup of complexity provided by this cascade reaction.

After being sidetracked by the unexpected rearrangement of Zincke aldehydes under thermal conditions, we looked into encouraging the desired cycloaddition with various additives. A range of Lewis and protic acids did not promote the desired process and, in many cases, resulted in indole degradation or apparent Pictet–Spengler-like reactivity. Nuhant, Marazano, and co-workers have since reported a method for performing Pictet–Spengler-type reactions of similar Zincke aldehydes using TFAA [Eq. (4.4)], giving access to tetrahydro-β-carboline products such as **75** which could serve as useful intermediates for the synthesis of natural products such as corynantheal (**76**) [34]. We also briefly examined the use of aminium catalysis through the use of the commercially available radical cation



Scheme 4.10 Unexpected thermal rearrangement of Zincke aldehydes leads to some interesting reactivity (DNP = 2,4-dinitrophenyl)

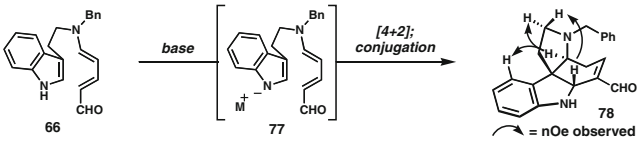
salt $N(4\text{-}BrC_6H_4)_3SbF_6$ [24]. We anticipated that an indole radical cation might engage the Zincke aldehyde; however, productive reactivity was never observed.



(4.4)

The final strategy that we explored to induce cycloaddition was indole metallation. Inspired by the anionic bicyclization of Markó that eventually led to tetracycles related to the Büchi ketone (**49** in Scheme 4.9), we examined a variety of organic and inorganic bases, and promising results were quickly obtained. Exposure of Zincke aldehyde **66** to a stoichiometric quantity of KO*t*-Bu in THF at 50 °C for 4 h led to 40 % conversion to a new isomeric product (Scheme 4.11). We identified the product as tetracyclic α,β-unsaturated aldehyde **78**; not surprisingly, the basic conditions of the reaction resulted in conjugation of the alkene with the aldehyde. The relative configuration of the product was readily discerned by nOe experiments and matched that found in the ABCE ring systems of the majority of known indole alkaloids that share that skeleton. Optimization led to a simple and reliable protocol: treatment of Zincke aldehyde **66** in THF (0.06 M) with KO*t*-Bu (commercially available 1 M solution in THF) at 80 °C in a sealed tube routinely afforded tetracycle **78** in 85 % yield.

A particularly interesting aspect of the reaction is its apparent counter-cation dependence. Our initial screen of bases included inorganic bases with a variety of counterions, including Li^+, Na^+, K^+, and MgX^+, but only potassium bases were effective. The precise role of the counterion is not completely understood, but it is critical for success. To date, the use of KO*t*-Bu or KH have consistently provided the best results, with KHMDS used as a lower-yielding alternative if absolutely necessary (in cases where the substrate was unstable to alkoxide bases).



Conditions	Result
DBU, phosphazine bases, Na_2CO_3, K_2CO_3, Cs_2CO_3, variety of solvents/temperatures	NR
MeLi, NaH or EtMgBr, THF, 0 to 50 °C	NR
EtMgBr, THF, 80 °C μW	NR
KO*t*-Bu, THF, 50 °C, 4 h	40% conversion
KO*t*-Bu, THF, 80 °C (sealed tube), < 2 h	**85% yield**

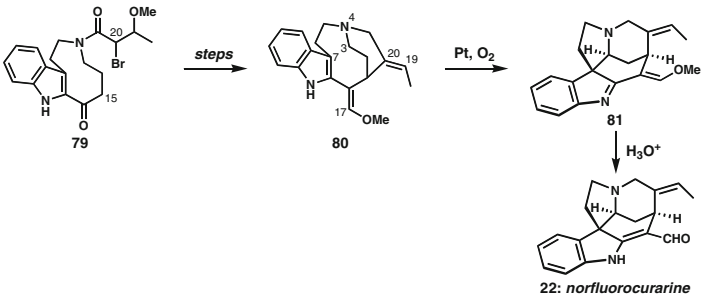
Scheme 4.11 Selected results in the base-mediated cycloaddition reaction

4.7 Synthesis of Norfluorocurarine

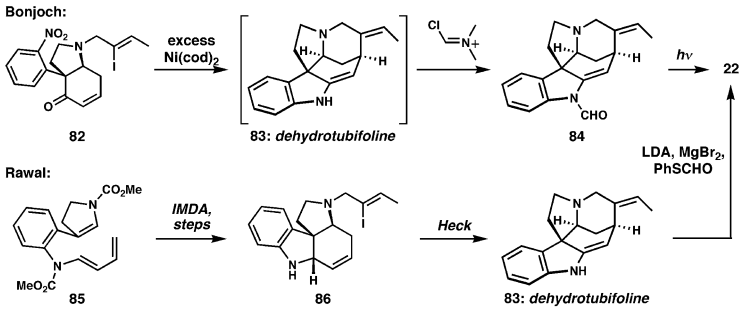
With the success of our new stereoselective cycloaddition, we turned our attention to its application in the synthesis of *Strychnos* alkaloids. Rather than immediately tackle the heptacyclic structure of strychnine itself, we initially chose to validate our methodology in the context of a less complex member of the family. We hoped to gain further insight into the advantages as well as the limitations of our bicyclization reaction, and we could then apply this knowledge to a fully optimized approach to strychnine. In this context, we targeted the *Strychnos* alkaloid norfluorocurarine (**22**, Schemes 4.6 and 4.12) that possesses the curan skeleton and includes a C17 aldehyde group, providing an ideal target for our studies. This relatively simple *Strychnos* alkaloid was first reported in 1961 by Stauffacher and was later isolated from a second source as a racemate [35].

Norfluorocurarine has been previously synthesized by the groups of Harley-Mason, Bonjoch, and Rawal [36]. The first synthesis by Crawley and Harley-Mason (1971) begins with the synthesis of macrocyclic ketone **79** (Scheme 4.12) [36a]. Closure of the D-ring and formation of the exocyclic C19–C20 alkene occurs in a base-mediated, one-pot process of **79**; presumably, attack of an enolate onto the alkyl bromide forges the C15–C20 bond, which is followed by elimination of the β-methoxyamide (giving a 1.4:1 mixture of alkene isomers). Incorporation of C17 is accomplished by a Wittig reaction to give **80**. A late-stage oxidation (Pt and O_2) forms a C3–N4 iminium ion which undergoes transannular attack by the indole (C7) to give **81**. This oxidative approach was later applied by Magnus in his synthesis of strychnine [10b].

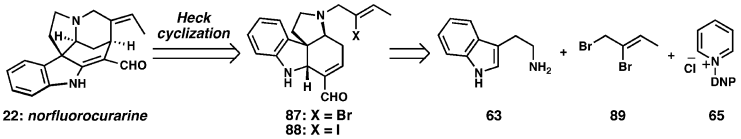
The synthesis reported by Bonjoch and co-workers utilizes a Ni-mediated reductive cyclization of vinyl iodide **82** with concomitant reductive indolenine formation; quenching of the presumed intermediate (dehydrotubifoline, **83**) with the Vilsmeier reagent affords *N*-formyl derivative **84** [36b]. Photoisomerization gives norfluorocurarine (**22**) in low yield. Similarly, Rawal and He produce



Scheme 4.12 First synthesis of norfluorocurarine by Harley-Mason and Crawley



Scheme 4.13 Norfluorocurarine syntheses by Bonjoch and Rawal groups both proceed via dehydrotubifoline



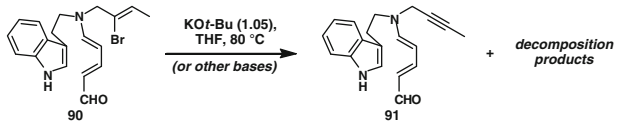
Scheme 4.14 Plan for the synthesis of norfluorocurarine

norfluorocurarine via the intermediacy of dehydrotubifoline [36c], but they reported new conditions that favor a direct *C*-formylation in preference to *N*-formylation [36b, 37]. This synthesis of dehydrotubifoline involved a Diels–Alder reaction of triene **85** and closure of the D-ring using a Heck reaction of vinyl iodide **86** (Scheme 4.13).

We reasoned that an intramolecular Heck reaction of vinyl halide **87**/**88** (Scheme 4.14), inspired by the work of Rawal, would serve as the final key step to close the D ring and deliver the natural product [18]. Based on previous reports outlined above, we anticipated that this strategy could efficiently effect closure of the D-ring with complete control of alkene geometry. This Heck-based strategy would also directly generate the vinylogous amide of norfluorocurarine by alkene

transposition from the α,β-unsaturated aldehyde, taking full advantage of the functionality in our cycloaddition products.

As anticipated, our initial studies toward norfluorocurarine yielded a number of important insights into the limitations of our bicyclization reaction. We planned to prepare cycloadduct **87** bearing the vinyl bromide appendage directly from the corresponding Zincke aldehyde, which would be prepared by alkylation of tryptamine with known dibromide **89** (Scheme 4.14) [38a], followed by Zincke aldehyde formation. Unfortunately, but the standard reaction conditions for anionic bicyclization led exclusively to decomposition of substrate **90** [Eq. (4.5)] and we were unable to isolate any of the desired tetracyclic product. The major product isolated was the corresponding alkyne **91**, presumably formed via base-mediated dehydrohalogenation. This process was observed by Solé and co-workers in a Pd-catalyzed enolate vinylation to give bridged, bicyclic products that proceeded under similar conditions [1.5 equiv KO*t*-Bu, THF, reflux; Eq. (4.6)] [20a]. Not surprisingly, more elimination was observed in substrates with *trans*-disposed H–I and H–Br (this configuration is found in our substrate **90**) and with substrates for which oxidative addition to Pd was slow. In our case and the Solé example, dehydrohalogenation could also afford an unstable allenamine, which could decompose further. As a result, we were forced to find a suitable vinyl halide surrogate that could be carried through the strongly basic bicyclization reaction.



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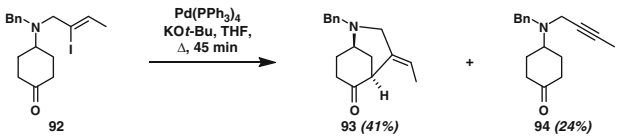
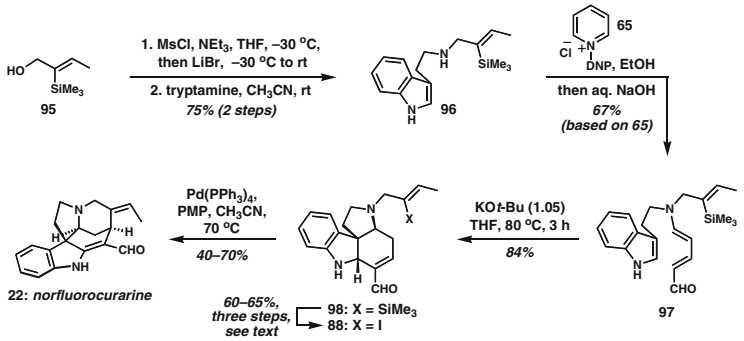


(4.6)

The most obvious vinyl halide surrogate, and one that ultimately proved useful, was a vinylsilane. Several methods are available for the stereocontrolled synthesis of vinylsilanes, including alkyne hydrosilylation, addition of vinyl nucleophiles to chlorosilanes, and reduction/functionalization of alkynylsilanes. Using the latter method, and according to the protocol of Metz and Linz [39], 1-(trimethylsilyl)-propyne was converted in one step into vinylsilane **95** via hydroalumination and reaction with paraformaldehyde. The allylic alcohol was converted to a leaving group and subsequently treated with tryptamine to afford **96** (Scheme 4.15). Zincke aldehyde **97** was produced by treatment of two equivalents of **96** with pyridinium salt **65** followed by hydrolysis of the resulting conjugated iminium ion. The second equivalent of amine liberated in the hydrolysis step was easily recovered in high yield. As we anticipated, the standard reaction conditions for cycloaddition produced tetracycle **98** in 84 % yield, once again as a single diastereomer, and without any decomposition of the vinylsilane. At this point, stereospecific conversion of the



Scheme 4.15 Synthesis of norfluorocurarine (PMP = 1,2,2,6,6-pentamethylpiperidine)

vinylsilane to the corresponding vinyl iodide was required to provide Heck substrate **88**. Unfortunately, many attempts using known iododesilylation conditions led to complex reaction mixtures in which only small quantities of the desired vinyl iodide could be observed [40][2]. This reaction was primarily complicated by undesired halogenation of the electron-rich aromatic ring. This problem could be circumvented using a three-step sequence that featured transitory *N*-trifluoroacetylation of the indoline, and the desired iodide **88** was obtained in good yield. Exposure of this substrate to a catalytic quantity of $Pd(PPh_3)_4$ and a hindered amine base instigated an intramolecular Heck reaction to yield norfluorocurarine (**22**) directly. The successful route proceeds via a longest linear sequence of seven steps from 1-(trimethylsilyl)propyne using the poorly efficient direct iodination protocol, and nine steps using the optimal three-step iodination sequence. Our synthesis of norfluorocurarine served to validate our Zincke aldehyde strategy as an efficient method to access tetracyclic intermediates with well-positioned functionality for subsequent D-ring formation [9a].

In the course of our successful synthesis, we identified several limitations of our new method and associated strategy: (1) the harsh conditions of the bicyclization reaction do not tolerate base-sensitive functionality such as vinyl halides; (2) post-cyclization manipulations such as iododesilylation reactions are complicated by the sensitive/reactive functionality of the products (α,β-unsaturated aldehyde, indoline, etc.); and (3) the incorporation of the required functionality into the Zincke aldehyde requires the synthesis of a complex tryptamine derivative, resulting in a lengthy, non-convergent route. In order to develop a concise route to strychnine, we would have to address each of these issues, and a straightforward solution to obviate all of these is described below.

[2] Although bromide **87**, could also be suitable, we spent most of our efforts on accessing iodide **88**, which would presumably be more reactive in the final Heck cyclization.

4.8 Protecting Groups Are Not Always Evil

Reexamination of our synthesis of norfluorocurarine identified a number of limitations, as outlined above. The harsh reaction conditions of the Zincke aldehyde bicyclization prevented the use of a number of useful functional groups; many of which we felt would be indispensible for the full exploration of endgame possibilities toward the Wieland–Gumlich aldehyde and thence strychnine. We discovered that, in addition to vinyl halides, functional groups that were not tolerated included propargyl groups, free alcohols, and Lewis acidic silanes (Fig. 4.2). The most attractive solution to this problem appeared to be the introduction of these motifs by *N*-alkylation after construction of the tetracyclic core. This strategy would allow for the incorporation of virtually any group and would also enable a more convergent approach. Synthesis of the tetracyclic core and the key D-ring precursor reagent in parallel followed by convergent coupling of the two pieces would result in a shorter linear sequence and more importantly would allow for late-stage divergent synthesis of many substrates via a common intermediate. The pursuit of this common tetracyclic intermediate therefore became our primary goal.

The common intermediate we sought was tetracycle **33**, which bears a free secondary amine. This goal structure could not be synthesized directly by our cycloaddition chemistry, owing to the limited stability of Zincke aldehydes derived from primary amines, which are known to readily convert to pyridinium salts [22a]. What we required was a precursor incorporating a removable substituent—in essence, a protecting group. The virtues of protecting-group free synthesis hardly need to be emphasized. It is clear that unnecessary protection and deprotection steps can lengthen a synthetic sequence and detract from the underlying chemistry. Nonetheless, protecting groups have a long-standing history in organic chemistry, and the synthesis of many classes of complex natural product (e.g., polyketides, polypeptides, carbohydrates) is often not feasible without the incorporation of strategic blocking groups. Given the advantages that a protecting group would provide in our case (greater convergency and divergent access to more complex substrates), we began to evaluate Zincke aldehydes bearing commonly used protecting groups on the nitrogen atom.

The century-old method for the synthesis of Zincke aldehydes placed certain limitations on our choice of substrates: strongly electron-withdrawing groups (Boc, Ts, Ac, etc.) are precluded because formation of Zincke aldehydes is only efficient for relatively electron-rich secondary amines. Furthermore, as vinylogous imides, these particularly electron-deficient systems were expected to be labile to basic conditions. Having established efficient three-step access to *N*-benzyl-type substrates such as **78** (Scheme 4.11), we initially aimed to convert these substrates to our desired common intermediate via amine deprotection. A survey of reaction conditions typically used for the removal of these groups led largely to undesired side reactions of the other functional groups. Cleavage of benzyl-type protecting groups under reductive conditions was precluded by the reactive α,β-unsaturated aldehyde group. Oxidative removal of the electron-rich PMB and DMB

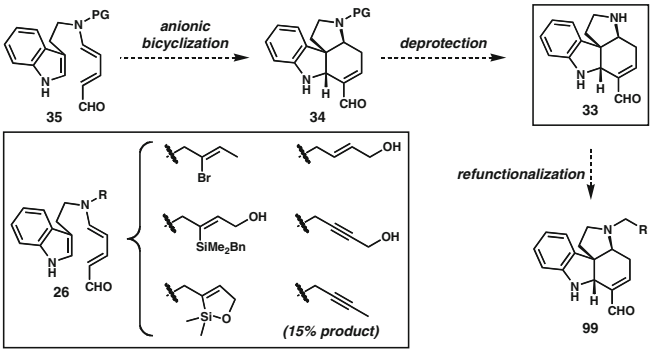
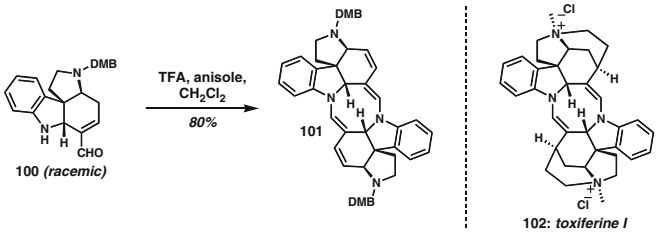


Fig. 4.2 Problematic functional groups (*inset*) and protecting group strategy to alleviate problems caused by the harsh cycloaddition conditions

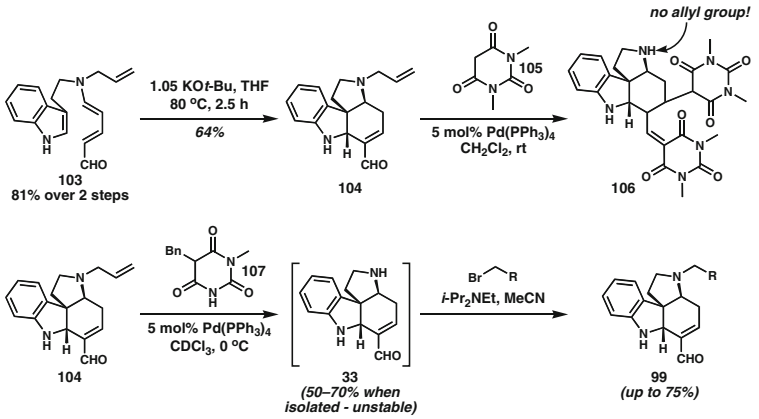
(2,4-dimethoxybenzyl) groups was similarly unsuccessful owing to complications from the electron-rich indoline. Treatment of DMB-protected amines with a strong acid such as TFA in the presence of a sacrificial nucleophile such as anisole is also known to cleave the C–N bond [41]. Under these conditions, we observed clean dimerization of our starting material to give **101** (Scheme 4.16) containing a central eight-membered diazocine ring. This product is produced by the mutual condensation of the secondary amino and aldehyde groups to give a single diastereomer of product, which we presume is the homodimer[3]. Our identification of the product was guided by the knowledge that dimers such as toxiferine I (**102**) are themselves natural products. Natural and semisynthetic analogs of toxiferine I have been investigated because of their allosteric modulation of the muscarinic acetylcholine receptor [42]. A similar biomimetic dimerization of *Strychnos* alkaloids has been reported to occur under acidic conditions (AcOH, NaOAc, 70 °C); it is interesting to note that in our case a single diastereomer of the dimer is produced from the racemic mixture of starting material.

After evaluation of several other potential protecting groups (including methyl, trimethylsilylethyl, phenylselenenylethyl) and multiple different means for their removal [9c], we turned our attention to the allyl group [41]. We began with N_b-allyl tryptamine, a known compound that is most efficiently prepared by reaction of tryptophyl bromide with allylamine, which was converted to the corresponding Zincke aldehyde **103** in good yield (Scheme 4.17) [43]. The cycloaddition reaction of **103** was particularly sensitive to concentration, giving the highest yield (64 %) of

[3] Our efforts to concretely determine the relative stereochemistry of this dimer have been met by failure. We have made attempts to resolve several of the monomeric tetracyclic aminoaldehydes of type **100** by HPLC using chiral stationary phase, in order to know for sure the structure of the homodimer. The poor solubility of these compounds in typical HPLC solvents hampered these efforts to access enantiopure monomer. A few attempts at diastereomeric salt formation from compounds of type **101** using chiral carboxylic acids were also unsuccessful. Computational analysis corroborates the assumption that the homodimer should be formed preferentially.



Scheme 4.16 Facile biomimetic dimerization of tetracyclic amino aldehyde **100**



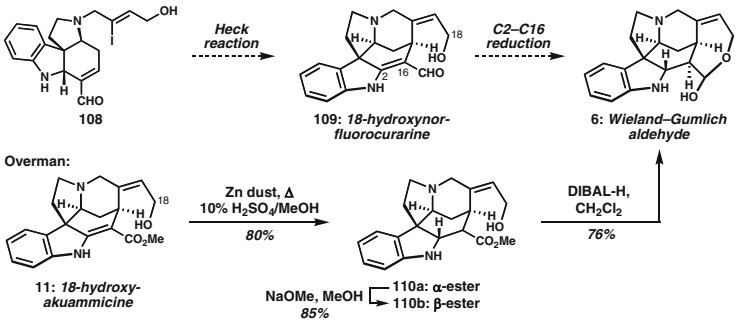
Scheme 4.17 Generation of secondary amine **33** by deprotection of *N*-allyl group enables access to functionalized core structures

tetracycle **104** at 0.02 M. Pd-catalyzed deallylation was effective under very mild conditions (0 °C, <1 h) using *N*,*N*′-dimethylbarbituric acid as the nucleophilic allyl scavenger [44]; however, this deallylation was accompanied by a Knoevenagel condensation of the barbituric acid derivative with the aldehyde, followed by Michael addition of a second equivalent of this nucleophile. This undesired process could be suppressed by incorporation of an alkyl group on the barbituric acid derivative to prevent the dehydration step of the Knoevenagel reaction. *C*-Benzylated derivative **107** or commercially available 5-methyl Meldrum's acid were used for all our subsequent investigations, and either reagent enabled the isolation of tetracycle **33** in reasonable yield. However, the presence of two nucleophilic amines and two electrophilic carbon atoms resulted in poor stability upon purification and storage. We soon found that in situ realkylation of the liberated secondary amine provided the desired products in good yields (up to 75 %). Fortunately, and surprisingly, the residual palladium did not appear to cause side reactions of the allylic, propargylic, and vinyl halides present in the electrophiles we explored. The excess barbituric acid/Meldrum's acid derivatives likewise did not interfere. Using this approach, we explored a number of endgame strategies, some of which are detailed in the sections that follow.

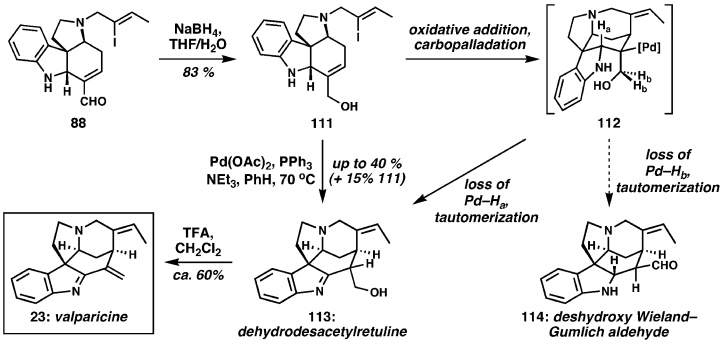
4.9 Strategies for D-Ring Formation for Strychnine

At this stage of our investigation, we had only begun to consider the multitude of possibilities for completion of the synthesis of strychnine. Based on their established success in closely related systems, we considered different strategies involving the cyclization of vinylmetal species onto the α,β-unsaturated aldehyde. Inspired by the previous work of others, we contemplated Pd-catalyzed Heck reactions, Ni-mediated reductive Heck/conjugate additions, and Cu-mediated conjugate additions, all of which required a vinyl halide precursor [15]. A Heck reaction, as we and others had demonstrated, would lead to β-hydride elimination toward nitrogen, installing an unwanted alkene at C2–C16 (**108** → **109**, Scheme 4.18). While used to advantage in our synthesis of norfluorocurarine and Rawal's synthesis of dehydrotubifoline (among others) [9a, 15, 18, 32c], such a result is not advantageous for the synthesis of strychnine via the Wieland–Gumlich aldehyde. As mentioned above, several previous syntheses of the Wieland–Gumlich aldehyde have proceeded via the analogous unsaturated ester 18-hydroxyakuammicine (**11**). Reduction of the alkene of this vinylogous carbamate has been accomplished by Zn/H_2SO_4 or $NaBH_3CN$ (**11** → **110**), leaving the ester group intact for further reduction to give the Wieland–Gumlich aldehyde [10c, f, h, k, m, o, p]. At the outset of our studies, it seemed unlikely that the potentially delicate functional group arrangements in **109** would allow for a selective reduction of the C–C π bond. We later learned that Rawal and He had in fact accomplished this transformation using Li/NH_3 in reasonable yield, completing a second synthesis of strychnine by this group that was only published in thesis form [36c]. At the time, however, we were attracted to an alternative possibility that would potentially avoid this post-cyclization redox adjustment and would probe an interesting question of reactivity.

Our hypothesis centered on a question of inherent selectivity in the β-hydride elimination step of the Heck reaction. Allylic alcohol **111** was readily obtained by reduction of norfluorocurarine precursor **88** (Scheme 4.19) and was envisioned as a model system for this approach. A Heck reaction of this substrate could have two possible outcomes: β-hydride elimination from intermediate **112** could occur in the direction of N1 (as it did in the case of norfluorocurarine) to give an enamine that should tautomerize to imine **113**, a natural product named dehydrodesacetylretuline [45]. Alternatively, β-hydride elimination could take place toward the hydroxyl group to give, after tautomerization, aldehyde **114** (deshydroxy-Wieland–Gumlich aldehyde, also a natural product) [46]. Some related systems had been reported to give variable selectivity and could in at least one case be tuned by reaction conditions (see below) [18a]. We saw this as an opportunity to probe such selectivity further, and as it turned out, either result would prove advantageous for alkaloid synthesis. If the aldehyde product predominated, then extension to a C18-hydroxylated vinyl iodide could provide a means to access the Wieland–Gumlich aldehyde. If the allylic alcohol product predominated, we envisioned a short synthesis of the recently reported alkaloid valparicine. This curan alkaloid was isolated from *Kopsia arborea* by Kam and co-workers and exhibits pronounced



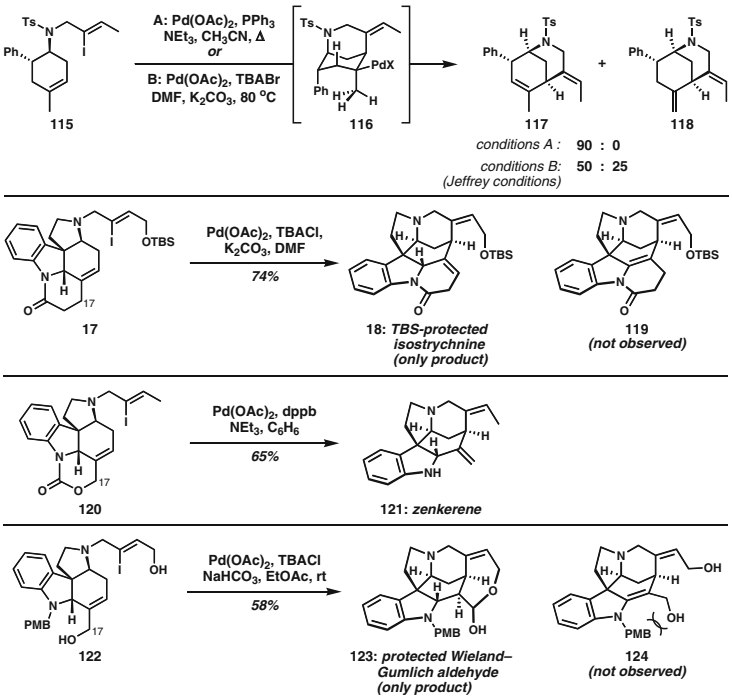
Scheme 4.18 Potential Heck-based endgames for strychnine



Scheme 4.19 Synthesis of dehydrodesacetylretuline and valparicine via Heck reaction

cytotoxicity toward drug-sensitive and drug-resistant KB cells as well as Jurkat cells [47, 48]. Under all Heck conditions examined with **111**, we never observed any aldehyde products of type **114**; dehydrodesacetylretuline **113** was the major product of successful cyclizations. We later learned that allylic alcohol **111** had been previously synthesized by Rawal and He via a different route and that they observed similar selectivity in the Heck reaction [36c]. When we treated **113** with trifluoroacetic acid, it was converted to valparicine in good yield by dehydration. The spectral data of synthetic valparicine were identical to those reported by Kam and co-workers [47].

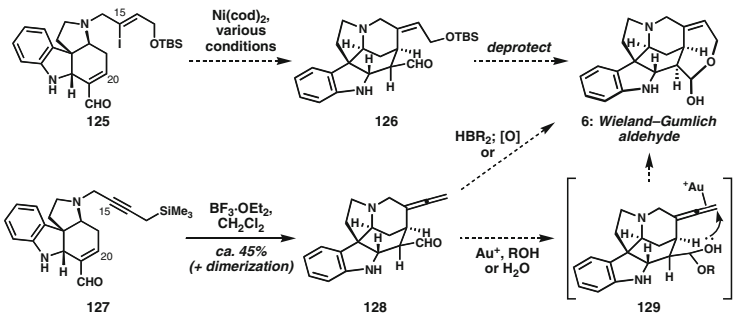
The selectivity in the Heck reaction of allylic alcohol **111** is interesting, and the factors that lead to the observed preference for β-hydride elimination toward nitrogen in this system are unclear, although a combination of steric effects and stereoelectronic factors (i.e., alignment of C–H and C–Pd bonds, $n_N \rightarrow \sigma^*_{C-H}$ interactions) is likely involved. Examination of related examples from the literature (Scheme 4.20) reveals no clear trend. Rawal and Michoud examined substrate **115**, which lacks the influence of both the amine and hydroxyl substituents and also seems to favor β-hydride elimination within the six-membered ring over formation of the exocyclic olefin under standard Heck conditions [18a]. However, under



Scheme 4.20 β-H elimination selectivity in relevant Heck cyclizations by the Rawal group and in the MacMillan strychnine synthesis

Jeffery's conditions (with a tetrabutylammonium halide additive) a change in selectivity is observed and a substantial amount of the exocyclic olefin is produced [49]. Rawal and Iwasa reported that pentacyclic substrate **17** undergoes selective β-hydride elimination toward C17 using Jeffery's conditions to give TBS-protected isostrychnine (**18**) in 74 % yield [10e]. Attempts by the Rawal group to favor β-hydride elimination toward a hydroxylated C17 to access the Wieland–Gumlich aldehyde included a Heck reaction of cyclic carbamate **120**, which underwent an unexpected Pd(II)-carboxylate elimination to give zenkerene (**121**) [36c]. To our knowledge, the only example of selective β-hydride elimination toward a C17-hydroxyl group to give an aldehyde product is found in MacMillan's recent synthesis of strychnine (**122** → **123**) [10r]. They report the use of an N_a-PMB group to disfavor formation of a C2–C16 alkene, which would introduce substantial $A_{1,3}$-strain between C17 and the substituent on nitrogen (see **124**).

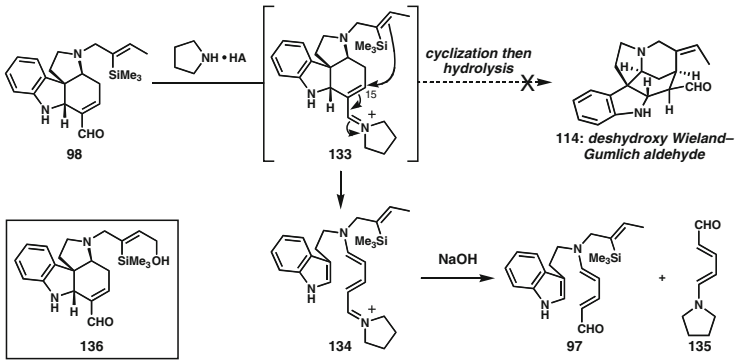
Having established that the inherent selectivity of the Heck reaction would not readily allow us to access aldehyde products related to the Wieland–Gumlich aldehyde, we considered a number of other possible reaction manifolds for C20–C15 bond formation. Each substrate was accessed by deallylation of cycloadduct **104** followed by alkylation with the appropriate allylic or propargylic halide. Inspired by the extensive studies of Bonjoch, Bosch, Solé, and co-workers,



Scheme 4.21 Efforts toward D-ring formation via nickel-mediated reductive cyclization and Sakurai allenylation

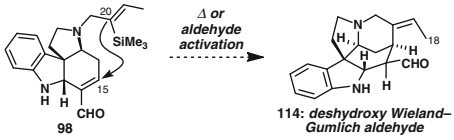
we explored the use of a reductive, Ni-mediated cyclization from vinyl iodide **125** (Scheme 4.21) [10g, 36b]. Using stoichiometric $Ni(cod)_2$ with various ligands, we did not observe productive reactivity, although an exhaustive exploration of conditions was not undertaken. Promising reactivity was observed with propargylsilane **127**, from which we successfully forged the C20–C15 bond and closed the D-ring under Sakurai conditions. Unfortunately, complete conversion could never be achieved, the yield of this transformation was low and unreliable, and varying amounts of dimeric diazocine products were also produced. A similar Sakurai product to **128** had been selectively hydrogenated by Bonjoch and coworkers in a synthesis of akuammicine; however, rather than reduction, we required a hydration of the allene terminal double bond [36b, 50]. Initially we envisioned hydration via hydroboration/oxidation; this hydroboration would need to be chemo-, regio-, and stereoselective and would need to leave the aldehyde untouched. An alternative method would be a gold-catalyzed hydration or 7-endo cyclization event of the allene and aldehyde (or hemiacetal/hydrate thereof). Given our limited access to allene **128**, these two conceptually intriguing strategies were only briefly examined with no obvious success, and we soon turned to alternative strategies for D-ring formation.

Another option that presented itself was cyclization by the direct conjugate addition of our previously synthesized vinylsilane substrate **98** to form 18-deshydroxy-Wieland–Gumlich aldehyde [Eq. (4.7)]. Again, this reaction was meant to serve as a model for the eventual approach to the Wieland–Gumlich aldehyde itself. Vinylsilanes are not particularly nucleophilic; however, they do benefit from stereospecificity in electrophilic desilylation reactions [51]. We began by simply heating vinylsilane **98** but no reaction was observed, except for decomposition at very high temperature (>200 °C). We next treated **98** with Lewis acids to activate the α,β-unsaturated aldehyde toward nucleophilic attack. A variety of Lewis acids ($TiCl_4$, $Sc(OTf)_3$, etc.) were ineffective in generating any cyclization products, although in some cases dimerization occurred to give diazocine products, as we had observed earlier with protic acids.

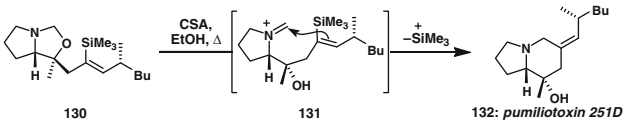


Scheme 4.22 An unexpected cycloreversion reaction

Another method of activation we considered was the use of a secondary amine to generate a more electrophilic iminium species, examples of which have been used in vinylsilane-terminated cyclization reactions, particularly by Overman and co-workers [Eq. (4.8)] [51]. In our case, the unsaturated iminium ion would be activated for



(4.7)



(4.8)

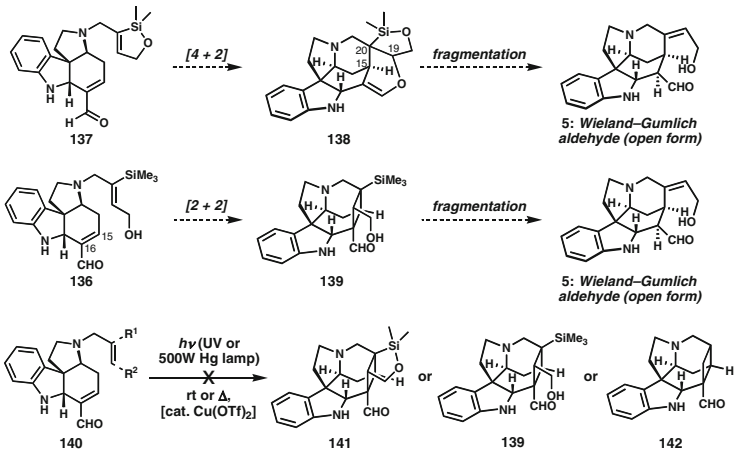
intramolecular attack at C15, analogous to the iminium activation popularized by MacMillan and others [52]. Using pyrrolidine with acid catalysis, we observed the formation of the iminium species **133** from **98** by mass spectrometry (Scheme 4.22). Even after substantial heating (up to 140 °C), no cyclization was observed, but a new product with the same mass as the iminium species was eventually observed. After aqueous work-up, we isolated a familiar product: Zincke aldehyde **97**. We also observed Zincke aldehyde **135**, as well as the secondary amines derived from hydrolysis of the intermediate iminium ion. Similar results were obtained using different secondary amines, in different solvents, and using the C18-hydroxylated silane **136** (see below for its synthesis). Apparently, iminium species **133** undergoes cycloreversion by a stepwise mechanism [53] to give the fully conjugated iminium species **134** rather than engaging the pendant vinylsilane as a nucleophile and leading to **114**. Contrasting with the successful cycloaddition, in which the formation of the tetracyclic product—as its corresponding enolate—is clearly favored,

this unexpected cycloreversion is likely favored by restoration of aromaticity of the indole and the generation of the stable, highly conjugated iminium ion. This dichotomy is remarkable [53].

4.10 Some Unusual Approaches to C15–C20 Bond Formation

Desperate times called for desperate measures. At this point, we were inspired to try a number of nonobvious strategies for C15–C20 bond formation, with an eye toward engaging the α,β-unsaturated aldehyde and the side-chain alkene in cycloaddition reactions. Cycloaddition reactions are particularly well suited to forming hindered bonds in complex systems, and the lower entropy of activation for intramolecular processes provides an additional advantage [54]. First, we imagined that if the α,β-unsaturated aldehyde could act as a heterodiene in a [4 + 2] reaction with the side-chain alkene, for example, the vinylsiloxane in **137**, the product would contain the required C15–C20 bond. This product would likely exhibit strain and might undergo a subsequent fragmentation to reintroduce the C19–C20 alkene with loss of silicon. Although the alignment of the orbitals in question did not appear ideal for a concerted fragmentation, stepwise processes involving either a silicon-stabilized carbocation or a siliconate complex could also be envisioned. Under a number of conditions, including prolonged heating under microwave irradiation, we were unable to identify any cycloadducts of type **138** or fragmentation products, and degradation began to take over (Scheme 4.23).

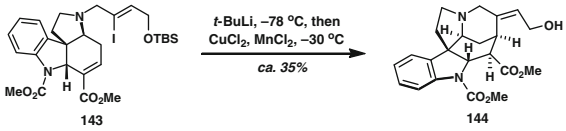
Similarly, we envisioned that a [2 + 2] cycloaddition of the C15–C16 olefin with a pendant alkene could deliver a similar product containing the required C15–C20 bond (**136** → **139**) [55]. This cycloadduct would contain a strained four-membered ring that could be viewed as a type of donor–acceptor cyclobutane. Subsequent fragmentation with loss of silicon would reintroduce the C19–C20 olefin and potentially reveal the Wieland–Gumlich aldehyde. The [2 + 2] cycloaddition was explored under a variety of conditions including photoirradiation with UV light or full-spectrum light using a mercury-vapor lamp. Reactions were performed at various temperatures and in some cases with catalytic copper(II) salts, which are known to catalyze [2 + 2] cycloadditions of unactivated systems [56]. Once again, we were unable to identify any desired products, even using the less-hindered allyl substrate that would have provided **142**. The strain in the desired hexacyclic products might be sufficiently high that the barrier to cycloaddition cannot be overcome, and decomposition becomes the dominant process under forcing conditions. We also note the paucity of literature examples of photochemical [2 + 2] cycloadditions of α,β-unsaturated aldehydes. Although decarbonylation might appear to be a concern, one of the most detailed studies on the intramolecular enal–olefin photocycloaddition suggests that post-cyclization rearrangements represent the bigger problem [57].



Scheme 4.23 Some unusual cycloaddition approaches to forge the C15–C20 bond

4.11 A Successful Route to Strychnine

Given our failure to engage the α,β-unsaturated aldehyde using the C19–C20 π bond in a direct cyclization or a cycloaddition reaction, we reexamined the opportunities presented by reactive vinylmetal intermediates. A conjugate addition reaction of a suitable vinylmetal species was the most attractive option to directly deliver the Wieland–Gumlich aldehyde without the need for other redox manipulations. Most often, vinylmetal species are generated by lithium–halogen exchange of the precursor vinyl halides, and reactivity can be tempered with catalytic or stoichiometric quantities of copper salts [58]. A specific example of this approach is found in Stork's unpublished synthesis of strychnine, some details of which are available in the literature [15a, 17]. Exposure of protected vinyl iodide **143** to *t*-BuLi followed by a mixture of $CuCl_2$ and $MnCl_2$ at −30 °C is reported to give rise to pentacyclic ester **144** in moderate yield [Eq. (4.9)]. This reaction demonstrated the feasibility of a copper-mediated ring closure via conjugate addition.



(4.9)

The conjugate addition substrate that we were considering bore an obvious resemblance to Stork's; however, it would incorporate a free NH and OH, as well as a more sensitive aldehyde. In this light, an approach involving reactive organolithium species seemed unlikely to be successful, and a few experiments quickly validated this surmise. We therefore sought a precursor that could

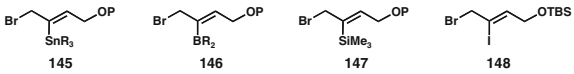
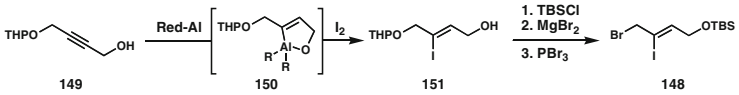


Fig. 4.3 Potential useful reagents for *N*-alkylation prior to D-ring formation

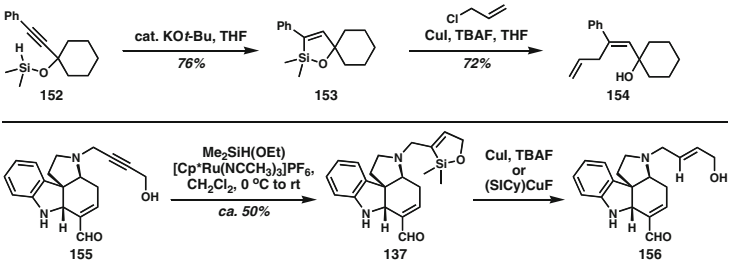


Scheme 4.24 Rawal's synthesis of vinyl iodide **155**

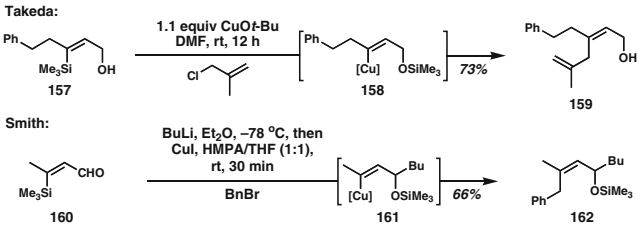
potentially be directly transmetallated to a transition metal such as copper, without the use of organolithium reagents and the explicit generation of highly reactive vinyllithium intermediates. While a vinyltin or vinylboron species would be ideal for this purpose, the stereoselective synthesis of vinylstannane **145** or vinylborane **146** (Fig. 4.3), to be incorporated by *N*-alkylation of tetracycle **33**, appeared challenging. In addition, β-bromostannanes related to **145** were found to be unstable with respect to allene formation and loss of R_3SnBr [59]. Based on our previous experience, we expected that the corresponding silane would be quite stable. The challenge became to find a concise and stereoselective synthesis of vinylsilane **147**.

Vinyl iodide **148**, used by Rawal and others, was made using a *trans*-hydroalumination of propargylic alcohol **149** with Red-Al (sodium bis(2-methoxyethoxy)-aluminum hydride) followed by an iodine quench to afford stereodefined, trisubstituted alkene **151** (Scheme 4.24) [10e]. This method is one of the reliable ways to access a trisubstituted olefin of this type with Z stereochemistry, but this reaction depends upon the presence of the propargylic alcohol. Most alkyne hydrometallations occur in a syn manner (see, e.g., the synthesis of vinylsilane **95**), and we are not aware of any syn-difunctionalization (or hydrometallation/functionalization) reactions that would provide any of the substrates shown in Fig. 4.3 from readily available materials in very few steps. Regardless of the methods used, we sought to uncover a more direct synthesis to maximize convergency. For comparison, iodide **148** is made in a total of six steps from propargyl alcohol, including three protecting group manipulations. Because we could gain access to our pivotal *N*-allyl substrate **104** in only three steps, we felt compelled to advance a new and more direct solution.

We recognized that a KO*t*-Bu- or ruthenium-catalyzed *trans*-hydrosilylation of alkynes (e.g., for KO*t*-Bu: **152** → **153**, Scheme 4.25) could serve as a pivotal reaction for the stereoselective construction of a suitable four-carbon fragment [60]. These mild methods for *trans*-hydrometallation of alkynes are directed by nearby hydroxyl groups and tolerate a broader range of functionality than the *trans*-hydroalumination reaction. Each reaction manifold can be used to give access to siloxacyclopentenes such as **153**, and this functional group has previously been directly transmetallated to copper and used for C–C bond formation (**153** → **154**) [60a]. With complex propargylic alcohol **155**, we found the most success with the method of Trost and Ball that uses $[Cp^*Ru(NCCH_3)_3]PF_6$ as the catalyst and $Me_2SiH(OEt)$ as the silane. The presumed initial product undergoes loss of EtOH



Scheme 4.25 Cyclic siloxane as a potential precursor to C15–C20 bond formation

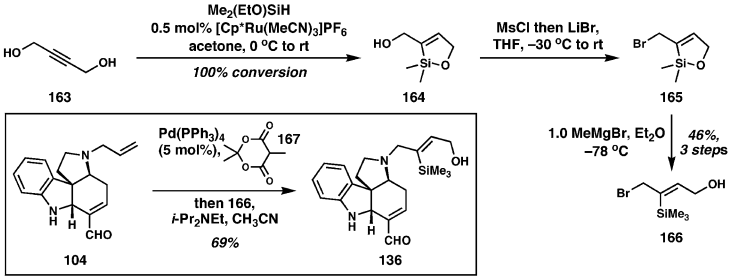


Scheme 4.26 Precedent for Brook rearrangement/transmetallation of vinylsilanes bearing allylic alcohols

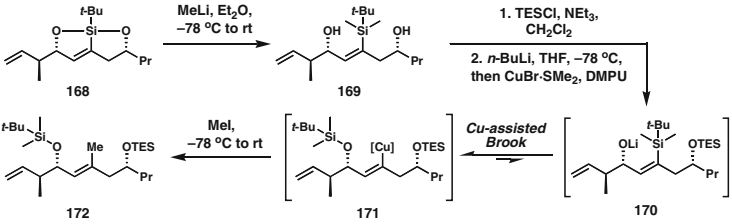
after the hydrosilylation event to give rise to siloxacyclopentene **137** [60b]. Unfortunately, when we attempted to effect the transmetallation/conjugate addition reaction in this challenging setting, we observed only protodesilylation product **156**. The protodesilylation of silacycle **137** occurs in the presence of TBAF without a copper source, suggesting that under rigorously anhydrous conditions, protodemetallation might be avoided. Using anhydrous conditions, including an NHC·CuF complex (SICy)CuF designed and supplied to us by Ball and Herron [61], we still observed only protodemetallation; the rate of cyclization was simply too slow to compete with premature quenching of the reactive organocopper intermediate under these conditions.

Further examination of the literature led us to a report by Takeda and co-workers that demonstrated the generation of vinylcopper species from vinyltrimethylsilanes, followed by C–C bond formation (**157** → **158** → **159**, Scheme 4.26) [62]. Although tetraalkylsilanes generally transmetallate quite slowly, the *cis*-disposed alcohol can participate in activation of the silicon toward transmetallation to copper in what might be described as a copper-assisted Brook rearrangement [63]. This general reaction type has been further expanded by Smith and co-workers to include different preparations of the key alkoxide (**160** → **161**) and a variety of uses of the resultant vinyl copper, including transmetallation to Pd and subsequent cross-coupling (not shown) [64].

As a result of the excellent precedent from the Takeda and Smith groups, we targeted vinylsilane **136** as a key intermediate in a Brook rearrangement/conjugate

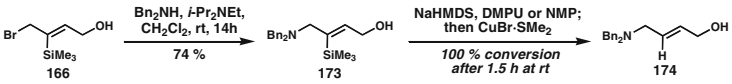


Scheme 4.27 Synthesis of Brook rearrangement substrate **136** featuring a three-step synthesis of polyfunctional building block **166**



Scheme 4.28 Leighton's precedent for siloxacycle ring opening and Brook rearrangement/C–C bond formation

addition strategy to build the D-ring of strychnine. The synthesis of **136** (Scheme 4.27) begins with the ruthenium-catalyzed *trans*-hydrosilylation of 1,4-butynediol using the method of Trost and Ball, providing silane **164** in high yield with complete control of alkene geometry [60b]. This reaction is scalable, proceeds with low catalyst loadings, and converts inexpensive 1,4-butynediol into the required *Z*-vinylsilane, while at the same time differentiating the two hydroxyl groups. With one of the hydroxyl groups internally protected as part of the siloxacycle, the other could be converted to the bromide (**165**). Subsequent treatment with methylmagnesium bromide chemoselectively opened the siloxacycle and provided the desired **166** in 46 % yield over three steps. A related example of ring opening of a siloxacycle with methyllithium is found in Leighton's synthesis of dolabelide D, revealing a vinyl-TBS group (see Scheme 4.28) [65]. The efficient sequence leading to silane **166** provides rapid access to significant quantities of this polyfunctional, stereodefined trisubstituted alkene and may prove useful for the synthesis of related vinylsilanes. Fortunately, the free alcohol in **166** did not readily suffer alkylation, and it could be stored neat (at −20 °C), allowing for easy handling of this important intermediate. When bromide **166** was added to the reaction mixture after complete deallylation of **104** using methyl Meldrum's acid (**167**), refunctionalized core **136** was isolated in 69 % yield. The alkylation was chemoselective for N_b-alkylation, and the ability to work with the free hydroxyl group eliminated the need for further protecting group manipulations.

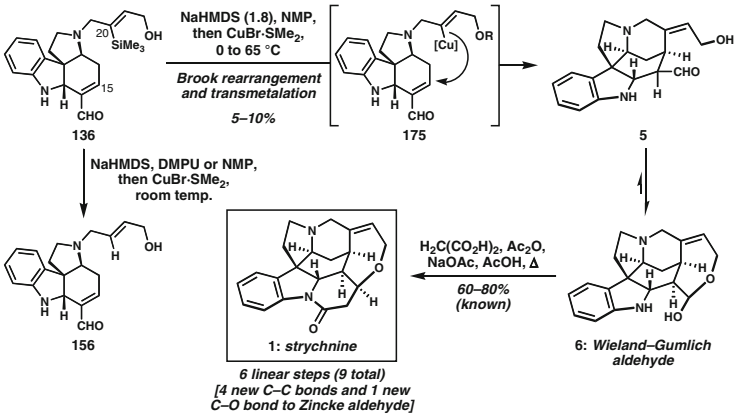


Scheme 4.29 Synthesis and Brook rearrangement of model system **173**

With convenient access to vinylsilane **136**, we again investigated the C15–C20 bond formation. Application of conditions reported by Takeda (CuO*t*-Bu, THF or DMF) [62] and co-workers resulted in recovery of starting materials at lower temperature and decomposition at elevated temperature. Similarly, conditions inspired by Smith and co-workers (*n*-BuLi or NaHMDS, then CuI, THF/HMPA or THF/DMPU) [64] did not result in C–C bond formation in the real system or model system **173** (Scheme 4.29) which also incorporates the potentially problematic allylic tertiary amine. Smith had demonstrated that the addition of a polar cosolvent was necessary to trigger the Brook rearrangement of the alkoxide (see Scheme 4.26). Similarly, a Brook rearrangement in Leighton's synthesis of dolabelide D proceeded with addition of $CuBr{\cdot}SMe_2$ in DMPU to trigger the migration event (Scheme 4.28) [65]. In our case also, it was not until DMPU (or NMP) was used as the sole solvent that the Brook rearrangement/protonolysis product was observed in the model system, cleanly generating **174**.

When these optimized conditions were applied to **136**, Brook rearrangement could be triggered in the presence of excess base, but again cyclization did not occur. When the reaction mixture was heated to 40 °C, partial cyclization was observed, and <5 % of the Wieland–Gumlich aldehyde was painstakingly isolated from the mixture of reaction products. Apparently, the free alcohol present in **136** had indeed enabled a Brook rearrangement with transmetallation to copper, followed by intramolecular conjugate addition to afford the Wieland–Gumlich aldehyde, albeit in low yield. Further optimization identified NMP as a better solvent, NaHMDS and KHMDS as preferred bases (Li prevents Brook rearrangement), and 65 °C as the best temperature for cyclization, yielding the Wieland–Gumlich aldehyde in up to 10 % yield. While the yield of this final bond construction is certainly lower than desired, there are several other reports that highlight the difficulty in forging this type of bond in related settings[4]. With the known conversion of the Wieland–Gumlich aldehyde to strychnine [4c], the adoption of this Brook rearrangement-based strategy enabled the completion of the synthesis in only six linear steps from commercially available starting materials because of the rapid, convergent assembly of vinylsilane **136**. Although the brevity of our synthesis of strychnine is certainly noteworthy, the rapid buildup of complexity using the reactivity options provided by the Zincke aldehyde is at the heart of this accomplishment. In the course of only four chemical steps, four new

[4] (a) For a relevant discussion of the difficulty of C15–C20 bond construction, see [10i] and [65a]. (b) For a discussion of D-ring formation in related pyrroloindoline natural products, see [20d].



Scheme 4.30 Completion of a six-step linear synthesis of strychnine using a Brook rearrangement/conjugate addition to generate the Wieland–Gumlich aldehyde

carbon–carbon bonds and one carbon–oxygen bond are forged to the five carbons of the Zincke aldehyde, exploiting much of the latent functionality present in this type of donor–acceptor diene (Scheme 4.30).

4.12 Conclusions

The synthesis of natural products continues to be an exciting and tremendously fulfilling pursuit and one that regularly uncovers unexpected and interesting reactivity. Our goal of synthesizing members of the *Strychnos* alkaloids was initiated by our interest in using Zincke aldehydes as starting points for the rapid generation of molecular complexity, and the wealth of interesting reactivity encountered, both anticipated and unexpected, surpassed our expectations. In our early efforts toward these alkaloids, an unusual pericyclic cascade rearrangement was found that has inspired studies toward unrelated alkaloids. Eventually, a base-mediated cycloaddition reaction of tryptamine-derived Zincke aldehydes was developed, and the synthesis of several *Strychnos* alkaloids could be achieved, including a short synthesis of strychnine. With nature's seemingly limitless capacity to create complex molecules that challenge our understanding of what can be made from a few simple elements, natural product synthesis will continue to be a source of inspiration for many years to come, especially as the emphasis continues to shift from syntheses that are minimally productive to those that are short and efficient.

Acknowledgment We dedicate this account to the memory of David Gin, a wonderful person and truly inspiring scientist. We thank the NSF (CAREER Award CHE-0847061) for support of our work. This project also benefited from support through graduate fellowships to D.B.C.M. from Eli Lilly, the NSERC of Canada, and Bristol–Myers Squibb, as well as an Amgen Young Investigator

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