# A General Synthetic Entry to the Pentacyclic *Strychnos* Alkaloid Family, Using a [4 + 2]-Cycloaddition/Rearrangement Cascade Sequence

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$R_1 = CH_2C_6H_4(o\text{-Me})$

versatile intermediate for the preparation of various *Strychnos* alkaloids
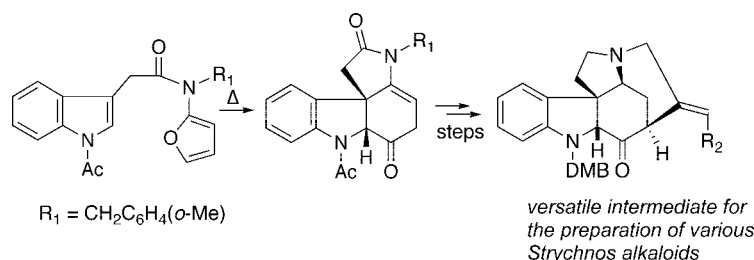
The total synthesis of (±)-strychnopivotine, (±)-tubifolidine, (±)-strychnine, and (±)-valparicine is reported. The central step in the synthesis consists of an intramolecular [4 + 2]-cycloaddition/rearrangement cascade of an indolyl-substituted amidofuran that delivers an aza-tetracyclic substructure containing the ABCE-rings of the *Strychnos* alkaloid family. A large substituent group on the amide nitrogen atom causes the reactive *s-trans* conformation of the amidofuran to be more highly populated, thereby facilitating the Diels–Alder cycloaddition. The reaction also requires the presence of an electron-withdrawing substituent on the indole nitrogen for the cycloaddition to proceed. The cycloaddition/rearrangement cascade was remarkably efficient given that two heteroaromatic systems are compromised in the reaction. Closure to the remaining D-ring of the *Strychnos* skeleton was carried out from the aza-tetracyclic intermediate by an intramolecular palladium-catalyzed enolate-driven cross-coupling between the *N*-tethered vinyl iodide and the keto functionality. The cycloaddition/rearrangement approach was successfully applied to (±)-strychnopivotine (**2**), the only *Strychnos* alkaloid bearing a 2-acylindoline moiety in its pentacyclic framework. A variation of this tactic was then utilized for a synthesis of the heptacyclic framework of (±)-strychnine. The total synthesis of (±)-strychnine required only 13 steps from furanyl indole **18** and proceeded in an overall yield of 4.4%.

Introduction

Strychnos alkaloids belonging to the curan type constitute an important group of architecturally complex and widely distributed monoterpenoid indole alkaloids.[1,2] The curan family is characterized by the presence of a pentacyclic 3,5-ethanopyrrolo[2,3-*d*]carbazole framework (i.e., **1**) bearing a two-carbon appendage at C-20 and an oxidized one-carbon substituent (C-17) at the C-16 position (Figure 1).[3] During the past two decades, the *Strychnos* alkaloid family has been the subject of

intensive study from the synthetic community. A great deal of this continuing interest has focused on the synthesis of the heptacyclic alkaloid strychnine (**3**).[4,5] The related pentacyclic curan family, however, has received far less attention.

Although there are many reports dealing with the preparation of individual members of this genus, general approaches to the core pentacyclic framework are limited.[6–12] The several different known strategies can be classified into those that form the crucial

(3) The biogenetic numbering is used for pentacyclic structures such as **1**, see: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(4) (a) Robinson, R. *Experientia* **1946**, *2*, 28. (b) Holmes, H. L.; Openshaw, H. T.; Robinson, R. *J. Chem. Soc.* **1946**, 908.

(5) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749.

(6) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966.

(1) For leading reviews of *Strychnos* alkaloids, see: (a) Bosch, J.; Bonjoch, J.; Amat, M. *Alkaloids* **1996**, *48*, 75 and references cited therein. (b) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455.

(2) Creasey, W. A. In *The Monoterpene Indole Alkaloids*; Saxton, J. E., Ed.; Interscience: New York, 1983; p 800.
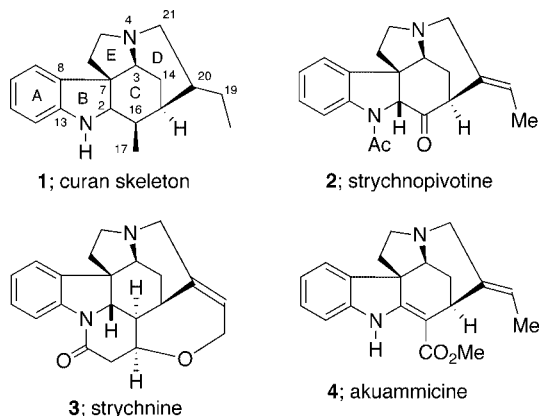
FIGURE 1. Some representative *Strychnos* alkaloids.

quaternary center at C-7 in the last synthetic steps[9–12] and those in which the strategic bonds around C-7 are preformed at the initial stages of the synthesis.[6–8] The Overman group has established a unique approach centered on an *aza-Cope rearrangement/Mannich cyclization cascade* that they successfully used for the synthesis of akummicine, dehydrotubifoline, and strychnine depending on the particular precursor employed in the key cascade sequence.[6] The Bonjoch group has made use of *cis*-3a-(2-nitrophenyl)octahydroindol-4-ones as particularly useful building blocks for assembling the pentacyclic ABCDE ring system of the *Strychnos* alkaloids.[7] Several *Strychnos* alkaloids were prepared by Kuehne starting from a tryptophan derivative that was employed in a *condensation–sigmatropic rearrangement–cyclization cascade* to form the ABCE core structure. The D-ring was then introduced *via* an S_N2 reaction.[8] Despite these earlier efforts, new and efficient approaches toward the *Strychnos* pentacyclic framework are still important as they would allow not only the synthesis of other members of this family of natural products (i.e., strychnopivotine (**2**)) but also related non-natural analogues possessing biological activity. Along these lines, we have recently become involved in the development and optimization of a new approach for the construction of the pentacyclic framework present in the *Strychnos* system.[13] In this paper, we report a concise stereocontrolled approach toward the total synthesis of several *Strychnos* alkaloids wherein an efficient [4
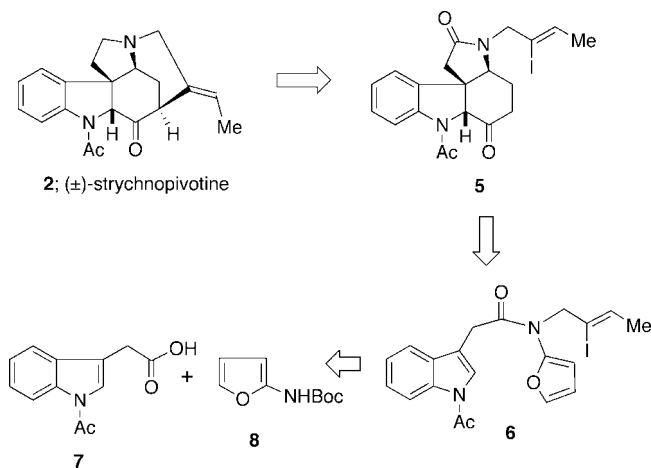
+ 2]-cycloaddition/rearrangement sequence previously developed in our laboratory plays a crucial role.[14]

Results and Discussion

Our synthetic approach toward the pentacyclic core found in the *Strychnos* alkaloids was guided by a long-standing interest in developing new applications of the intramolecular [4 + 2]-cycloaddition/rearrangement cascade of 2-amidofurans toward the synthesis of complex natural products.[14] Our recently completed syntheses of (±)-erysotramidine[15] and (±)-lycoricidine[16] nicely demonstrate the utility of this process for the construction of various alkaloids. On the basis of our earlier work, we felt that we could also use this methodology for the synthesis of strychnopivotine (**2**) and related alkaloids and this is illustrated in Scheme 1. Strychnopivotine (**2**) was isolated from the root bark of *Strychnos Variabilis* and its structural elucidation was reported by Angenot and co-workers in 1980.[17,18] As illustrated in Scheme 1, our retrosynthetic analysis of strychnopivotine (**2**) involves closure of the D-ring in the final step of the synthesis by a Bonjoch/Solé palladium-catalyzed intramolecular coupling of the amido-tethered vinyl iodide **5** with a keto–enolate generated anion.[19,20] A critical step of our synthetic plan relies upon the efficient construction of the tetracyclic substructure found in **5** by an intramolecular [4 + 2]-cycloaddition/rearrangement cascade of 2-amidofuran **6**.

While the furan ring of **6** provides the 4π-constituent, the dienophilic partner corresponds to an indole moiety. Previous

(7) (a) Solé, D.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 7803. (b) Solé, D.; Bonjoch, J.; García-Rubio, S.; Suriol, R.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 5213. (c) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230.

(8) (a) Kuehne, M. E.; Xu, F.; Brook, C. S. *J. Org. Chem.* **1994**, *59*, 7803. (b) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1997**, *62*, 7950. (c) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9434. (d) Kuehne, M. E.; Wang, T.; Seraphin, D. *J. Org. Chem.* **1996**, *61*, 7873.

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(10) Amat, A.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299.

(11) (a) Kuehne, M. E.; Frasier, D. A.; Spitzer, T, D. *J. Org. Chem.* **1991**, *56*, 2696. (b) Kuehne, M. E.; Brook, C. S.; Frasier, D. A.; Xu, F. *J. Org. Chem.* **1994**, *59*, 5977.

(12) Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. *J. Am. Chem. Soc.* **1996**, *118*, 9804.

(13) For a preliminary report, see:(a) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279.

(14) (a) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304. (b) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515. (c) Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643. (d) Wang, Q.; Padwa, A. *Org. Lett.* **2004**, *6*, 2189. (e) Padwa, A.; Ginn, J. D. *J. Org. Chem.* **2005**, *70*, 5197. (f) Padwa, A.; Bur, S. K.; Zhang, H. *J. Org. Chem.* **2005**, *70*, 6833.

(15) Padwa, A.; Wang, Q. *J. Org. Chem.* **2006**, *71*, 7391.

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(17) Tits, M.; Tavernier, D.; Angenot, L. *Phytochemistry* **1980**, *19*, 1531.

(18) For some synthetic studies, see:(a) Teuber, H.-J.; Tsaklakidis, C.; Bats, J. W. *Liebigs Ann. Chem.* **1992**, 461. (b) Solé, D.; Urbaneja, X.; Cordero-Vargas, A.; Bonjoch, J. *Tetrahedron* **2007**, *63*, 10177.

(19) (a) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225. (b) Solé, D.; Diaba, J.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746. (c) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387. (d) Solé, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal.* **2004**, *346*, 1646. (e) Solé, D.; Urbaneja, X. *J. Org. Chem.* **2005**, *7*, 5461.

(20) For some other examples of intramolecular Pd-catalyzed vinylations, see:(a) Piers, E.; Oballa, R. M. *Tetrahedron Lett.* **1995**, *36*, 5857. (b) Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 7565. For an example of a Ni(0) promoted intramolecular coupling of ketone enolates with aryl halides, see:(c) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507.

SCHEME 2

9; R^2 = small group 10; R^2 = large group
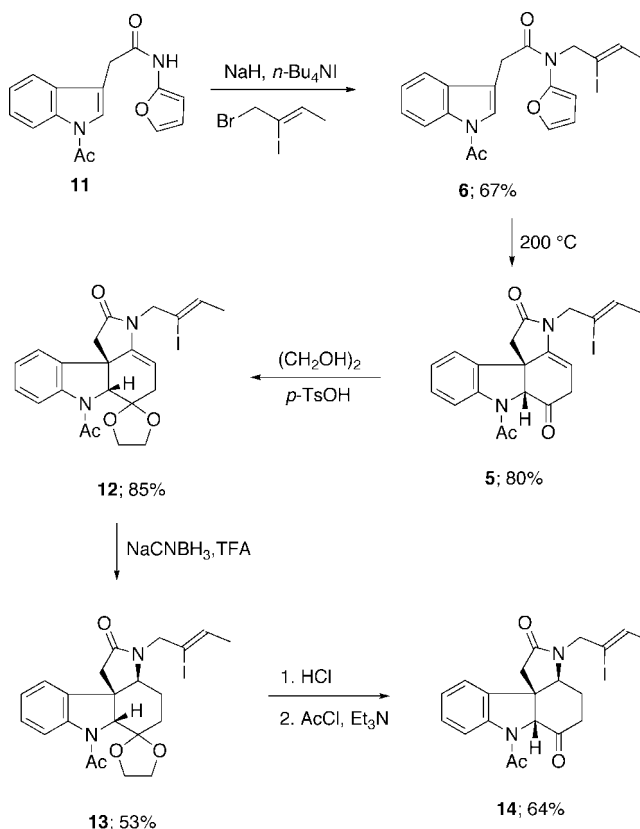
SCHEME 3

SCHEME 4
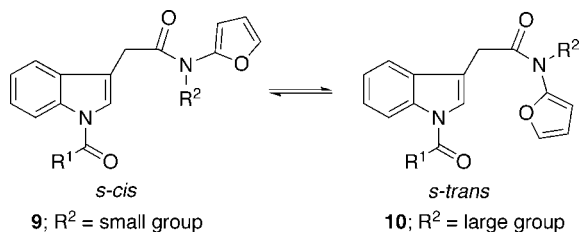
studies revealed that the 2,3-double bond of the indole ring could serve as a dienophile in the IMDAF reaction only when the indole nitrogen atom possessed an electron-withdrawing substituent.[21] Further, to increase the efficiency of the cycloaddition process, it was found that incorporation of a sp^2 center within the tether was beneficial and this was routinely accomplished by using an amide linkage.[21] However, when a secondary amide was utilized, no cycloaddition occurred due to the propensity of these amides to adopt the *s-cis* conformation **9**.[22] This unfavorable conformation could be overcome by replacing the amide hydrogen with a larger group, which caused the reactive *s-trans* conformation **10** to be more highly populated, and therefore the cycloaddition would be more prone to occur (Scheme 2).
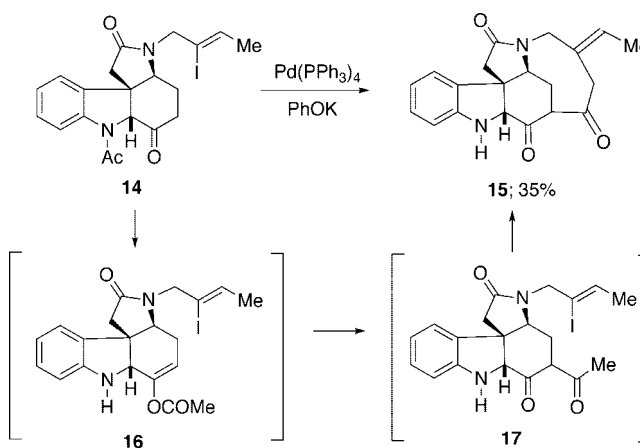
First Approach toward (±)-Strychnopivotine (2). With this background in mind, our synthetic endeavors toward strychnopivotine (**2**) began by the *N*-alkylation of indole **11** with *Z*-1-bromo-2-iodobut-2-ene, which afforded furanyl amide **6** in 58%.[23] The presence of the 2-iodo-2-butenyl side chain would serve not only in the contemplated D-ring closing reaction, but also to bias the amide into the desired *s-trans* conformation. Indeed, heating a sample of **6** in toluene at 200 °C in a sealed tube initiated the desired cycloaddition/rearrangement cascade to give **5** in 80% yield and the stereospecificity of the cascade process ensured that a *cis*-BC ring fusion was formed (Scheme 3). Reduction of the enamido π-bond present in **5** was achieved via a three-step sequence.

This involved (a) protection of the keto group with ethylene glycol to give ketal **12**, (b) exposure of **12** to NaCNBH$_3$ in the presence of TFA to give **13**, and (c) hydrolysis of the ketal to the corresponding carbonyl group. Most surprisingly, our attempts to induce D-ring closure by subjecting tetracycle **14** to the Bonjoch/Solé cyclization conditions[19] (Pd(PPh$_3$)$_4$/PhOK) provided the unexpected β-diketone **15** in 35% yield as the only isolable product from the reaction mixture. A possible mechanism for this unusual reorganization is outlined in Scheme 4 and involves an initial migration of the acetyl group from the indoline nitrogen onto the oxygen atom of the enolate anion. The transient enol-ester **16** so formed then undergoes a subsequent acyl group shift[24] to furnish β-diketone **17**. The acetyl group present in the newly formed diketone **17** is close enough in proximity to the vinyl center to undergo the enolate cross-coupling reaction. It would appear as though coupling at

the more acidic position is seriously retarded as a consequence of severe nonbonded interactions in its transition state for this insertion.

Second Generation Approach toward (±)-Strychnopivotine (2). Considering the difficulty we encountered with the palladium-catalyzed intramolecular coupling reaction of the tetracyclic keto-lactam **14**, we decided to slightly modify our approach toward (±)-strychnopivotine (**2**). Comparison of the geometry of **14** with the various systems studied by Bonjoch and Solé[19] led us to speculate that the presence of the amido carbonyl group in the E-ring significantly increased the rigidity of the skeleton thereby creating an element of strain in the transition state for the critical coupling reaction. We reasoned that by reducing the lactam carbonyl group to the corresponding pyrrolidine, the source of strain in the transition state would be

(21) Padwa, A.; Brodney, M. A.; Lynch, S. M.; Rashatasakhon, P.; Wang, Q.; Zhang, H. *J. Org. Chem.* **2004**, *69*, 3735.

(22) Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517. See also: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 620.

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(24) (a) Young, F. G.; Frostick, F. C.; Sanderson, J. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1950**, *72*, 3635. (b) Mao, C.-L.; Frostick, F. C.; Man, E. H.; Manyik, R. M.; Wells, R. L.; Hauser, C. R. *J. Org. Chem.* **1969**, *34*, 1425.

SCHEME 5

18

heat

19; 95%

1. NaBH₄
2. NaOMe
3. LiAlH₄
4. NaBH(OAc)₃

21; 56%

1. H₂, Pd(OH)₂
2. BrCH₂

20; 65%

1. ArCHO
   NaBH(OAc)₃, HOAc
2. TPAP, NMO

22; 79%

Pd(PPh₃)₄

PhOK

1. HCl **23**; R = DMB, 61%
2. Ac₂O **2**; R = Ac, 65%
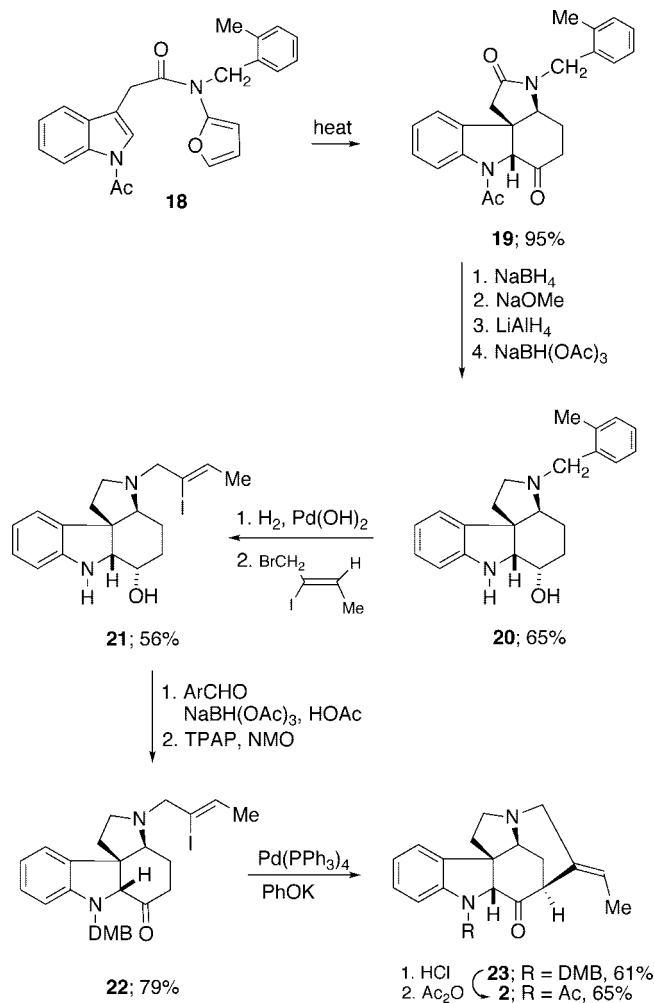
relieved and the desired coupling reaction would occur. Unfortunately, all of our attempts to prepare the necessary pyrrolidine by lactam reduction also resulted in the simultaneous loss of the iodo group on the side chain. To circumvent this over-reduction problem, we opted to reduce the lactam carbonyl group prior to the installation of the vinyl iodide side chain. For this purpose, furanyl indole **18** was prepared from indole acetic acid (**7**) in a manner analogous to that used for the synthesis of **6**. The presence of the large *o*-methylbenzyl group on the amido nitrogen atom causes the reactive *s-trans* conformer to be more highly populated thereby promoting the intramolecular cycloaddition. Indeed, the cycloaddition/ rearrangement cascade of **18** was quite facile given that two aromatic systems are compromised in the reaction. Thus, heating a sample of **18** at 150 °C in a microwave reactor in the presence of a trace amount of MgI₂ for 30 min afforded the desired aza-tetracycle **19** in 95% yield (Scheme 5).

Our synthesis of the more advanced tetracycle **22** required for eventual D-ring cyclization began by stereoselective reduction of the keto group in **19** with NaBH₄ followed by *N*-deacetylation using NaOMe. The lactam carbonyl group was then reduced with LiAlH₄ and the resulting enamine was further reduced using NaBH(OAc)₃ to give alcohol **20** as the major diastereomer in 65% yield for the four-step sequence (Scheme 5). Removal of the *o*-methylbenzyl group by catalytic hydrogenation followed by *N*-alkylation with *Z*-1-bromo-2-iodobut-2-ene furnished alcohol **21** in 56% overall yield. Condensation

of the indoline nitrogen present in **21** with 2,4-dimethoxyben-zaldehyde in the presence of NaBH(OAc)₃[25] afforded the nitrogen-protected 2,4-dimethoxybenzylamine (DMB) derivative in 94% yield. Oxidation of the resulting secondary alcohol to the corresponding ketone **22** occurred smoothly in 79% yield with tetrapropylammonium perruthenate (TPAP).[26] The stage was now set for the completion of the synthesis. The key palladium-catalyzed cross-coupling was carried out on a sample of **22** with Pd(PPh₃)₄ and PhOK. Gratifyingly, the reaction proceeded smoothly to furnish aza-pentacycle **23** in 61% yield. Finally, removal of the 2,4-dimethoxybenzyl group by reaction with HCl followed by *N*-acetylation with acetic anhydride gave (±)-strychnopivotine (**2**) in 65% yield for the last two steps. The synthetic sample obtained was identical with the reported spectral properties of (±)-strychnopivotine (**2**).[17]

(±)-Tubifolidine (25). The synthesis of (±)-tubifolidine (**25**), a *Strychnos* alkaloid isolated by Schmid and co-workers in 1964,[27] was chosen as the next synthetic target to further highlight the methodology. Before its isolation, this alkaloid was a known compound that had been obtained by a partial synthesis in the context of a chemical correlation effected for the structural elucidation of a more complex member of the *Strychnos* family.[28,29] Our synthesis of (±)-tubifolidine (**25**) was readily realized by the sequential reduction of intermediate **23** that had been prepared earlier. Thus, treatment of **23** under Wolff–Kishner type conditions (Na, hydrazine in ethylene glycol)[30] served to remove the carbonyl group as well as the dimethoxybenzyl protecting group in 62% yield to furnish alkene **24**. Next, reduction of the C-20 appendage was attempted (Scheme 6). The reaction solvent was found to be critical for successful reduction, as was the necessity to buffer the hydrogenation reaction with Na₂CO₃. By carrying out the catalytic reduction of **24** with Pd/C as the catalyst in THF, the sole product obtained in 50% yield corresponded to (±)-tubifolidine (**25**).[9,29]

(±)-Valparicine (29). Kam and co-workers reported in 2006 on the isolation of the alkaloid valparicine (**29**) from the stem-bark extracts of *K. arborea*, a member of the *Kopsia* family.[31] Initial studies indicated that this alkaloid shows pronounced cytotoxic activity against KB and Jurkat cells.[32] It has been proposed that valparicine (**29**) is biogenetically related to pericine (**26**) by means of a Polonovski reaction wherein the E-ring of the alkaloid is formed by cyclization of the indole ring onto the resulting iminium ion as indicated in Scheme 7.[31] Although strictly not a member of the *Strychnos* family, the structural similarity with strychnopivotine (**2**) triggered our interest in a synthesis of (±)-valparicine (**29**). Having a sample of **23** on hand, we treated this intermediate with trimethyl-

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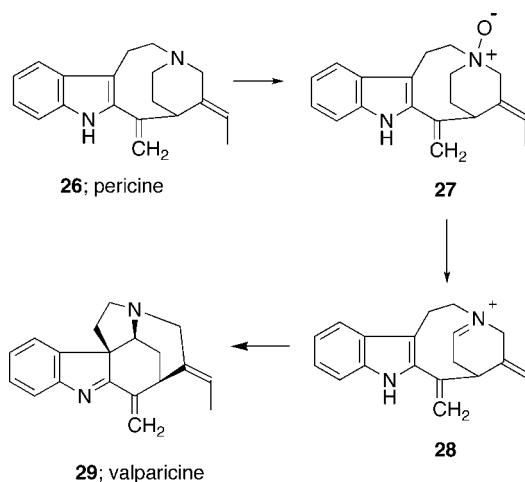
(31) Lim, K.-H.; Low, Y.-Y.; Kam, T.-S. *Tetrahedron Lett.* **2006**, *47*, 5037.

(32) Lim, K.-H.; Hiraku, O.; Komiyama, K.; Koyano, T.; Hayashi, M.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1302.
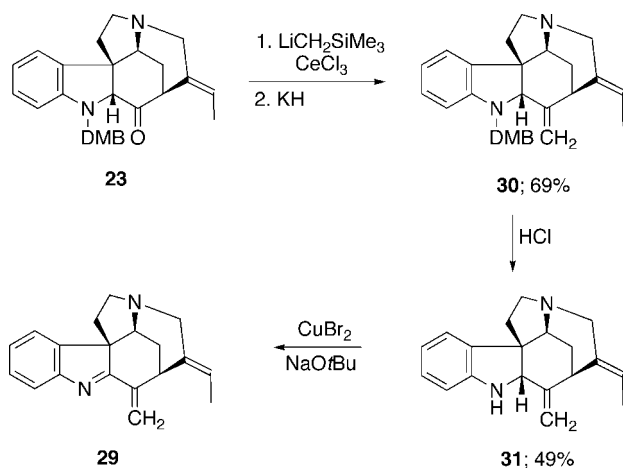
SCHEME 6
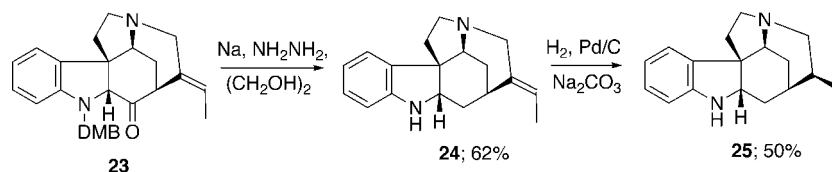
SCHEME 7

SCHEME 8

silylmethyl lithium and cerium(III) chloride[33] and this was followed by heating the resulting alcohol with potassium hydride in THF, which delivered the C-16 methylene unit of **30** in 69% yield. The DMB protecting group was then removed by warming **30** with 1.0 M HCl/MeOH to produce **31** in 49% yield (Scheme 8). To complete the synthesis, all that remained was an oxidation of the C−N single bond between the C$_2$ and N$_1$ position. A number of different oxidizing conditions were evaluated including IBX,[34] TPAP,[35] Swern oxidation,[36] and MnO$_2$.[37] However, each of these reactions failed to deliver the expected product. Eventually, it was found that stirring a sample of **31** with copper

bromide and sodium *tert*-butoxide[38] for 40 min at 25 °C resulted in the formation of (±)-valparicine (**29**) together with recovered starting material thereby completing the first total synthesis of this alkaloid. The spectral data for the mixture obtained was perfectly consistent with that reported by Kam and co-workers.[31]

(±)-Strychnine (3). Strychnine, a well-known poison found in large amounts in the Indian poison nut, has a long and rich history as one of the more notorious members of the *Strychnos* alkaloid family.[1,2] Over the years, strychnine has attracted considerable attention from the synthetic community mainly due to its complex heptacyclic structure, containing 24 skeletal atoms and six contiguous stereogenic centers. The alkaloid was first isolated in 1818[39] and its highly toxic properties result from its interaction with the glycine receptor site, thereby blocking the flux of chloride ions, which results in disruption of nerve-cell signaling.[40] Extensive degradative and structural studies culminated in the elucidation of strychnine's structure by Robinson in 1946.[4,41] The relative and absolute configurations were later confirmed by X-ray crystallographic analysis.[42] Nearly 40 years after Woodward's pioneering achievement of strychnine,[5] a number of other research groups have reported on its synthesis.[43,44] Strychnine still remains a popular target for demonstrating new reactions and novel synthetic strategies.

Most of the reported syntheses of strychnine employ either isostrychnine (**32**) or the Wieland−Gumlich aldehyde **33** as an advanced intermediate. The Prelog−Taylor cyclization of iso-

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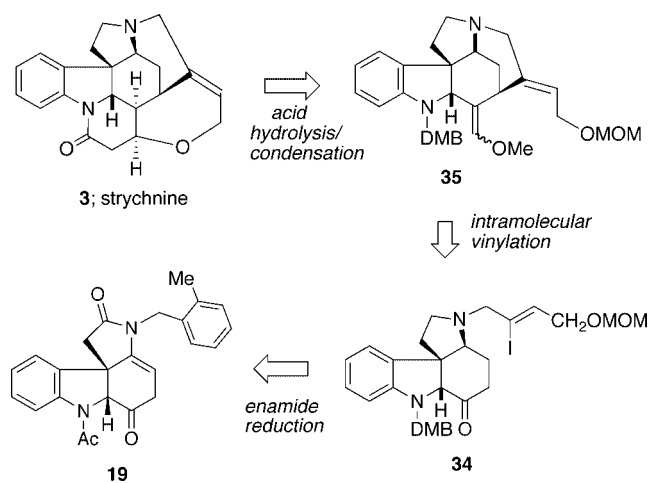(35) Yamaguchi, J.; Takeda, T. *Chem. Lett.* **1992**, *21*, 1933.
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SCHEME 9

**3**; strychnine [1 part]

32; isostrychnine [3 parts]

33; Wieland-Gumlich aldehyde

SCHEME 10

3; strychnine

acid hydrolysis/ condensation

35

intramolecular vinylation

34

enamide reduction

19

SCHEME 11

20

H₂, Pd(OH)₂

36; 70%

BrCH₂ / CH₂OMOM

K₂CO₃, DMF/H₂O

37; 80%

1. ArCHO NaBH(OAc)₃ HOAc

2. TPAP, NMO

34; 69%
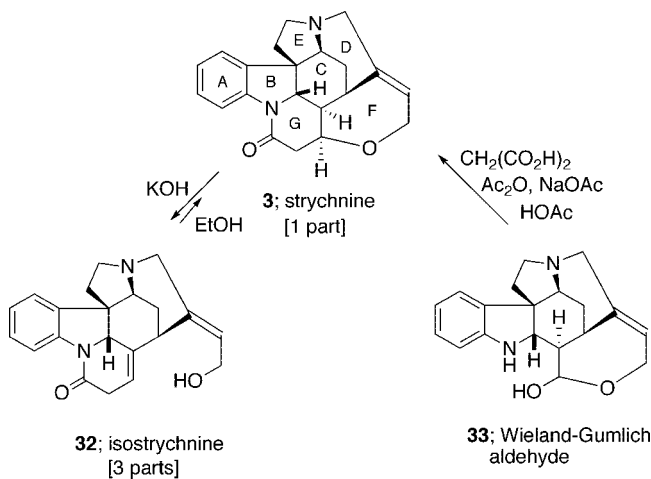
strychnine (**32**) to strychnine (**3**)[45] (Scheme 9), however, suffers from an unfavorable 3:1 equilibration ratio of these two compounds. From this perspective, the alternative biomimetic route to strychnine involving condensation of the Wieland–Gumlich aldehyde **33** with an acetate equivalent for the formation of the G ring seems to be the more attractive approach,[46] as it avoids the unfavorable equilibrium mixture. With this in mind, we set out to prepare the Wieland–Gumlich aldehyde **33** using the above IMDAF cascade/rearrangement methodology.

As illustrated in Scheme 10, our retrosynthesis of strychnine (**3**) relies upon the efficient construction of the pentacyclic intermediate **35**, which in turn would be derived from the previously prepared tetracycle **19** used in the earlier strychnopivotine (**2**) synthesis. As before, we planned to generate the D-ring of **35** by a palladium-catalyzed intramolecular coupling of the amido-tethered vinyl iodide **34** with its keto–enolate.[19,20]

Intermediate **34** should be available from **19** by reduction of the enamido group followed by amide deprotection and a subsequent N-alkylation. The synthesis of tetracycle **34** began from the previously prepared pyrrolidinyl substituted alcohol **20** as was outlined in Scheme 5. Removal of the o-methylbenzyl group by catalytic hydrogenation furnished **36** in 70% isolated
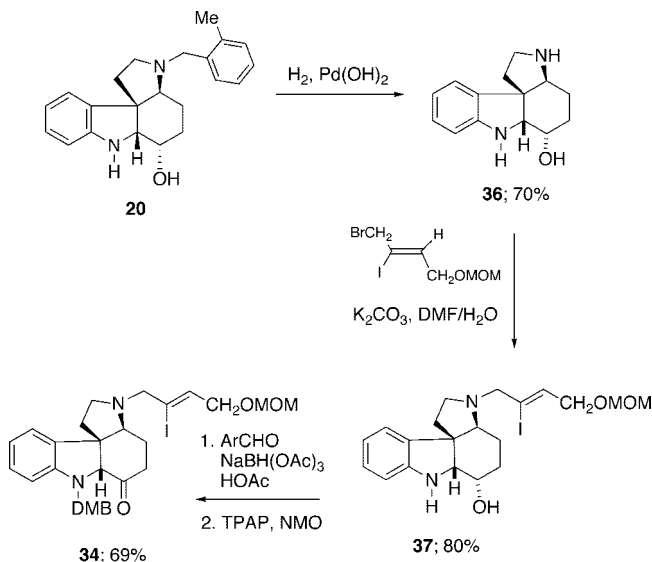
yield. This was followed by N-alkylation with Z-1-bromo-2-iodo-4-(methoxymethoxy)but-2-ene to give alcohol **37** in 80% yield. Condensation of the indoline nitrogen present in **37** with 2,4-dimethoxybenzaldehyde in the presence of NaBH(OAc)₃[25] afforded the N-protected DMB derivative in 80% yield. Oxidation of the resulting secondary alcohol to the corresponding ketone **34** occurred smoothly in 69% yield with use of tetrapropylammonium perruthenate (TPAP) (Scheme 11).[26]

We were pleased to find that the critical D-ring of strychnine could be readily constructed by a palladium-catalyzed intramolecular coupling of the amino-tethered vinyl iodide with the keto–enolate derived from **34**. The critical palladium-catalyzed cyclization was carried out on a sample of **34** with Pd(PPh₃)₄ and PhOK. The reaction proceeded smoothly to furnish the aza-pentacycle **38** in 56% yield (Scheme 12). Our initial attempts to convert the keto group of **38** into the corresponding enol ether **35** using methoxymethylene–triphenylphosphorane (MeOCH=PPh₃) were unsuccessful, probably as a consequence of steric congestion about the ketone. Consequently, we turned our attention to the phosphine oxide reagent MeOCH₂P(O)Ph₂, whose anion is sterically less demanding and more nucleophilic compared to the phosphorane MeOC=PPh₃.[47,48] Thus, treatment of MeOCH₂P(O)Ph₂ with LDA in THF gave the lithio anion, which reacted smoothly with ketone **38** at 0 °C to provide **35** as a single diastereomer in 72% isolated yield. The last major hurdle involved an acid-promoted deprotection/hydrolysis of **35** into the Wieland–Gumlich aldehyde **33**. The hydrolysis was satisfactorily accomplished by the treatment of **35** with 3 N HCl in THF at 55 °C for 10 h, which gave **33** in 54% isolated yield. By using shorter reaction times and following the reaction by NMR spectroscopy, we found that the initial reaction involved sequential deprotection of the MOM group followed by hydrolysis of the DMB group to give **39** as a transient species. The resulting enol ether portion of **39** was subsequently converted into the Wieland–Gumlich aldehyde **33** (Scheme 12). Although the conversion of **33** into strychnine had been reported by Robinson in 1953,[46] we decided to reproduce the described protocol for the sake of a complete synthesis. Thus, the final biomimetic condensation of **33** with malonic acid, sodium acetate, and acetic acid provided (±)-strychnine (**3**) in 80% yield

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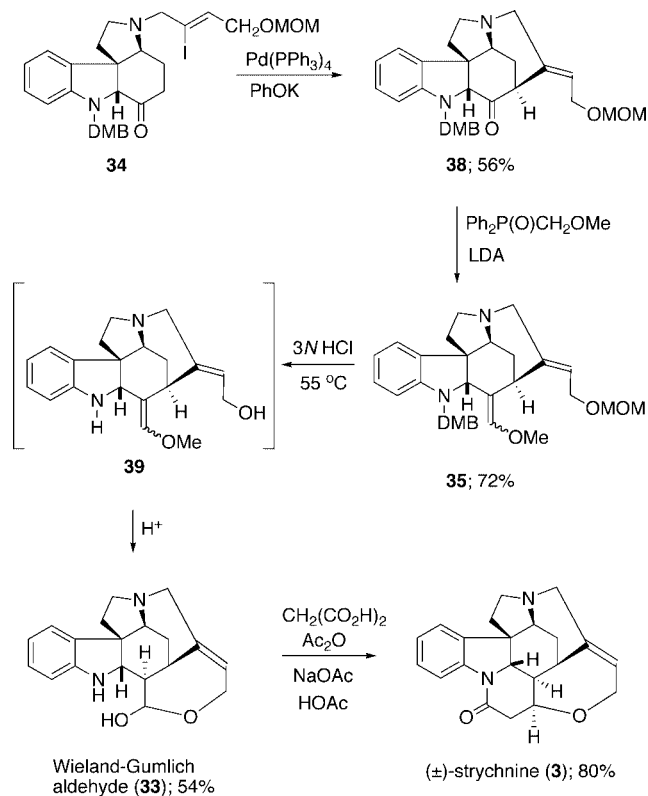
and with a 4.4% overall yield for the 13-step reaction sequence starting from furanyl indole **18**.

In conclusion, a concise synthesis of several members of the *Strychnos* family of alkaloids is reported. A central step in the synthesis consists of an intramolecular [4 + 2]-cycloaddition/rearrangement cascade of an indolyl-substituted amidofuran, which delivers an aza-tetracyclic substructure containing the ABCE-rings of the *Strychnos* alkaloid family. Closure of the remaining D-ring was carried out from the aza-tetracyclic intermediate by an intramolecular palladium-catalyzed enolate-driven cross-coupling between the *N*-tethered vinyl iodide and the keto group. We believe that the chemistry described herein will be useful for the preparation of a variety of other alkaloids.

Experimental Section

2-(1-Acetyl-1H-indol-3-yl)-N-furan-2-yl-N-(2-iodobut-2-enyl)-acetamide (6). To a 4.0 g (8.6 mmol) solution of indole **11**[21] in 35 mL of DMF at 0 °C was added 0.38 g (9.4 mmol) of NaH in small portions and the resulting mixture was stirred at 0 °C for 2 h. A solution of 2.7 g (10.3 mmol) of *cis*-1-bromo-2-iodobut-2-ene[23] in 20 mL of DMF was added at 0 °C and this was followed by the addition of 0.6 g (1.7 mmol) of tetrabutylammonium iodide. The reaction mixture was stirred at 0 °C for 2 h and was then slowly quenched with an aqueous NaHCO$_3$ solution and extracted with EtOAc. The organic layer was dried over Na$_2$SO$_4$ then filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 3.7 g (67%) of **6** as a pale yellow oil: IR (thin film) 3124, 2914, 1701, 1450, and 1388 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.70 (d, 3H, *J* = 6.0 Hz), 2.58 (s, 3H), 3.62 (s, 2H), 4.59 (s, 2H), 5.72

(q, 1H, *J* = 6.4 Hz), 6.18 (dd, 1H, *J* = 3.6 and 1.2 Hz), 6.39 (dd, 1H, *J* = 3.2 and 2.0 Hz), 7.20–7.42 (m, 5H), and 8.40 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.6, 23.9, 30.7, 58.5, 102.7, 106.0, 111.2, 115.4, 116.5, 118.7, 123.4, 123.7, 125.2, 130.0, 134.1, 135.5, 140.2, 147.1, 168.4, and 170.9.

7-Acetyl-3-(2-iodobut-2-enyl)-3,5,6a,7-tetrahydropyrrolo[2,3-d]carbazole-2,6-dione (5). A solution containing 0.40 g (0.87 mmol) of furanyl indole **6** in 1.3 mL of toluene was heated in a sealed tube at 200 °C for 2 h. The reaction mixture was cooled to rt and then concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.32 g (80%) of **5** as a pale yellow oil: IR (thin film) 3416, 3030, 2971, 2904, 1721, 1685, 1470, and 1388 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.84 (d, 3H, *J* = 6.4 Hz), 2.37 (s, 3H), 2.72 (d, 1H, *J* = 16.8 Hz), 2.89 (dd, 1H, *J* = 16.8 and 2.8 Hz), 3.00 (d, 1H, *J* = 16.8 Hz), 4.49 (d, 1H, *J* = 15.2 Hz), 4.49 (s, 1H), 4.69 (d, 1H, *J* = 15.2 Hz), 5.13 (dd, 1H, *J* = 6.0 and 2.8 Hz), 6.03 (q, 1H, *J* = 6.4 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 7.25–7.32 (m, 2H), and 8.16 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.8, 23.9, 36.6, 45.7, 49.7, 51.8, 71.3, 94.6, 101.2, 117.9, 121.7, 125.2, 129.5, 134.0, 134.6, 140.6, 140.9, 169.6, 171.6, and 202.7; HRMS calcd for [(C$_{20}$H$_{19}$IN$_2$O$_3$) + H]$^+$ 463.0513, found 463.0516.

7-Acetyl-3-(2-iodobut-2-enyl)-6-(1,3-dioxolane)-3,5,6a,7-tetrahydropyrrolo[2,3-d]carbazole-2-one (12). To a solution containing 0.20 g (0.31 mmol) of ketone **5** in 6 mL of benzene was added 0.35 mL (6.2 mmol) of ethylene glycol followed by 0.06 g (0.3 mmol) of *p*-toluenesulfonic acid. The solution was heated at reflux for 1 h, cooled to rt, and then poured into an aqueous NaHCO$_3$ solution and extracted with EtOAc. The combined organic layer was dried over Na$_2$SO$_4$ then filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.18 g (85%) of **12** as an orange solid: mp 192–193 °C; IR (thin film) 1726, 1680, 1655, 1476, and 1388 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.70 (dd, 1H, *J* = 15.6 and 3.2 Hz), 1.80 (dt, 3H, *J* = 6.4 and 1.6 Hz), 2.25 (br s, 4H), 2.53 (d, 1H, *J* = 17.2 Hz), 3.03 (d, 1H, *J* = 17.2 Hz), 3.80–3.90 (m, 1H), 3.90–4.07 (m, 3H), 4.40 (d, 1H, *J* = 15.6 Hz), 4.45 (br s, 1H), 4.64 (dt, 1H, *J* = 15.6 and 1.6 Hz), 5.03 (dd, 1H, *J* = 7.6 and 3.2 Hz), 6.10 (qd, 1H, *J* = 6.4 and 1.2 Hz), 7.10 (td, 1H, *J* = 7.6 and 1.2 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), and 7.94 (br s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 17.6, 22.6, 24.8, 32.1, 45.9, 47.0, 50.3, 52.8, 64.5, 65.8, 66.3, 73.9, 96.8, 97.5, 103.1, 109.6, 117.7, 123.1, 125.7, 129.7, 136.2, 142.0, and 173.2. Anal. Calcd for C$_{22}$H$_{23}$IN$_2$O$_4$: C, 52.19; H, 4.58; N, 5.53, found C, 51.82; H, 4.70; N, 5.27.

7-Acetyl-3-(2-iodobut-2-enyl)-6-(1,3-dioxolane)-3,5,6a,7-hexahydropyrrolo[2,3-d]carbazole-2-one (13). To a solution containing 0.20 g (0.3 mmol) of enamide **12** in 2 mL of CH$_2$Cl$_2$ at 0 °C was added 1 mL of TFA followed by 0.09 g (1.4 mmol) of NaCNBH$_3$ in small portions over 30 min at 0 °C. The mixture was stirred for 1 h at 0 °C, diluted with CH$_2$Cl$_2$, and then quenched with an aqueous NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$. The combined organic layer was dried over Na$_2$SO$_4$ then filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.11 g (53%) of **13** as a pale yellow oil: IR (thin film) 3416, 2960, 2914, 2873, 1701, 1655, and 1199 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.4–1.64 (m, 2H), 1.76–2.00 (m, 2H), 1.83 (d, 3H, *J* = 6.4 Hz), 2.35 (s, 3H), 2.42 (d, 1H, *J* = 16.8 Hz), 2.66 (d, 1H, *J* = 16.8 Hz), 3.51–3.60 (m, 1H), 3.68–3.82 (m, 3H), 3.93–4.12 (m, 2H), 4.23 (s, 1H), 4.57 (d, 1H, *J* = 14.8 Hz), 5.98 (q, 1H, *J* = 6.4 Hz), 7.04–7.17 (m, 2H), 7.21–7.28 (m, 1H), and 8.02 (br d, 1H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.5, 21.8, 23.4, 27.5, 46.6, 50.3, 50.8, 55.5, 64.5, 65.9, 70.8, 103.1, 108.5, 117.1, 120.4, 124.3, 128.5, 133.3, 134.8, 143.7, 169.8, and 173.0; HRMS calcd for [(C$_{22}$H$_{23}$IN$_2$O$_4$) + H]$^+$ 509.0932, found 509.0929.

7-Acetyl-3-(2-iodobut-2-enyl)-3,3a,4,5,6a,7-hexahydropyrrolo[2,3-d]carbazol-2,6-dione (14). To a solution of 0.04 g (0.08 mmol) of acetal **13** in 2.0 mL of THF was added 3.0 mL of 6 N

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HCl and the resulting mixture was heated at 55 °C for 3 h. After cooling to rt, the reaction mixture was quenched with solid NaHCO$_3$ and then diluted with H$_2$O and EtOAc. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H$_2$O and brine, dried over MgSO$_4$, and filtered. After concentration under reduced pressure, the residue was taken up in 1.5 mL of CH$_2$Cl$_2$ and cooled to 0 °C. To this solution was added 50 μL of triethylamine followed by 13 μL of acetyl chloride. The reaction mixture was stirred at rt for 2 h and then quenched by the addition of a saturated NaHCO$_3$ solution. The organic layer was separated and the aqueous phase was extracted with CH$_2$Cl$_2$. The combined organic layer was washed with H$_2$O then brine and dried over MgSO$_4$. After removal of the solvent under reduced pressure, the residue was purified by flash silica gel chromatography to give 24 mg (64%) of ketone **14** as a colorless oil: IR (neat) 1728, 1698, 1666, and 1398 cm^{-1}; ^{1}H NMR (600 MHz, CD$_3$CN) δ 1.79 (d, 3H, J = 6.0 Hz), 1.97–2.01 (m, 1H), 2.03 (s, 3H), 2.21–2.26 (m, 1H), 2.29–2.34 (m, 1H), 2.42 (d, 1H, J = 16.8 Hz), 2.66–2.72 (m, 1H), 3.04 (d, 1H, J = 16.8 Hz), 4.09–4.12 (m, 1H), 4.11 (d, 1H, J = 15.0 Hz), 4.76 (d, 1H, J = 15.0 Hz), 4.85 (s, 1H), 6.10 (q, 1H, J = 6.0 Hz), 7.07 (t, 1H, J = 7.5 Hz), 7.26 (t, 1H, J = 7.5 Hz), 7.36 (d, 1H, J = 7.5 Hz), and 8.14 (d, 1H, J = 7.5 Hz); ^{13}C NMR (150 MHz, CDCl$_3$) δ 22.1, 23.7, 24.3, 33.6, 46.9, 51.8, 53.6, 57.5, 74.1, 102.6, 118.2, 121.5, 124.8, 130.0, 131.1, 136.0, 142.6, 169.9, 172.8, and 204.1.

Pentacyclic Diketone 15. To a solution containing 24 mg (0.052 mmol) of the above compound in 2.0 mL of THF at rt was sequentially added 15 mg (0.16 mmol) of phenol, 0.13 mL of 1 M t-BuOK in t-BuOH, and 6.0 mg (0.016 mmol) of Pd(PPh$_3$)$_4$. The reaction mixture was heated at reflux under an argon atmosphere for 4 h and then cooled to rt. The mixture was then diluted with 1 N NaOH and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with 1 N NaOH, H$_2$O, and brine, then dried over MgSO$_4$. After concentration under reduced pressure, the residue was purified by flash silica gel chromatography to give 7 mg (35%) of the pentacyclic ketone **15** as a pale yellow solid: IR (neat) 3488, 1690, 1484, and 1413 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.66 (dd, 3H, J = 7.2 and 2.0 Hz), 1.77 (dd, 1H, J = 15.6 and 3.6 Hz), 1.94 (ddd, J = 15.6, 5.6, and 2.4 Hz), 2.45 (d, 1H, J = 16.0 Hz), 2.65 (s, 1H), 2.68 (d, 1H, J = 16.0 Hz), 3.21 (s, 1H), 3.23 (d, 1H, J = 16.0 Hz), 3.48 (d, 1H, J = 16.0 Hz), 3.47–3.55 (m, 1H), 3.85 (d, 1H, J = 5.6 Hz), 4.44 (s, 1H), 4.55 (d, 1H, J = 16.0 Hz), 5.85 (q, 1H, J = 7.2 Hz), 7.15 (td, 1H, J = 7.6 and 0.8 Hz), 7.29 (d, 1H, J = 7.6 Hz), 7.34 (td, 1H, J = 7.6 and 0.8 Hz), and 7.65 (d, 1H, J = 7.6 Hz); HRMS calcd for [(C$_{20}$H$_{21}$N$_2$O$_3$) + H]$^+$ 337.1547, found 337.1556.

2-(1-Acetyl-1*H*-indol-3-yl)-*N*-furan-2-yl-*N*-(2-methylbenzyl)-acetamide (18). To a solution containing 5.7 g (20 mmol) of furanyl indole **11** in 100 mL of DMF at 0 °C was added 0.8 g (20 mmol) of NaH. The mixture was stirred for 2 h at 0 °C, and then a solution of 5.6 g (24 mmol) of α-iodo-o-xylene in 30 mL of DMF was added at 0 °C. The reaction mixture was stirred for 3 h and was then quenched with H$_2$O and extracted with EtOAc. The combined organic layer was dried over NaHCO$_3$ and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 4.7 g (61%) of **18** as a yellow solid: mp 96–97 °C; IR (neat) 1695, 1674, 1601, 1442, 1368, 1258, and 739 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.11 (s, 3H), 2.58 (s, 3H), 3.65 (s, 2H), 4.90 (s, 2H), 5.63 (d, 1H, J = 2.4 Hz), 6.32 (dd, 1H, J = 3.6 and 2.4 Hz), 7.14–7.44 (m, 10H), and 8.43 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.9, 23.9, 30.6, 49.4, 105.5, 111.2, 115.5, 116.5, 118.7, 123.4, 123.6, 125.3, 125.8, 127.6, 128.9, 130.0, 130.2, 134.3, 135.5, 136.5, 140.1, 147.6, 168.4, and 170.9. Anal. Calcd for C$_{24}$H$_{22}$N$_2$O$_3$: C, 74.59; H, 5.74; N, 7.25, found C, 74.35; H, 5.81, N, 7.11.

7-Acetyl-3-(2-methylbenzyl)-3,5,6a,7-tetrahydropyrrolo[2,3-*d*]carbazole-2,6-dione (19). To a solution of 0.3 g (0.8 mmol) of indoyl furan **18** in 4 mL of toluene in a CEM Discover microwave 10 mL tube equipped with a magnetic stir bar was added 0.007 g

(0.16 mmol) of MgI$_2$. The vessel was charged with nitrogen and sealed with a microwave rubber cap. The sample was then placed in microwave reactor and irradiated at 200 W at 150 °C for 30 min. After the mixture was cooled to rt, the solvent was removed under reduced pressure. The resulting residue was purified by flash silica gel column chromatography with a40% EtOAc/hexane mixture as the eluent to provide 0.29 g (95%) of **19** as a pale yellow solid: mp 184–186 °C; IR (thin film) 1716, 1657, 1594, 1467, 1384, 353, and 749 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.34 (s, 3H), 2.42 (s, 3H), 2.71 (d, 1H, J = 16.4 Hz), 2.81 (dd, 1H, J = 20.4 and 2.4 Hz), 2.94 (dd, 1H, J = 20.4 and 5.6 Hz), 3.10 (d, 1H, J = 16.4 Hz), 4.57 (s, 1H), 4.79 (d, 1H, J = 16.0 Hz), 4.89 (d, 1H, J = 16.0 Hz), 4.98 (dd, 1H, J = 5.6 and 2.4 Hz), 6.92–7.05 (m, 2H), 7.12–7.28 (m, 5H), and 8.15 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.3, 23.8, 36.6, 42.1, 45.7, 49.9, 71.2, 94.7, 117.9, 120.8, 125.1, 126.2, 126.7, 127.7, 129.5, 130.8, 132.7, 134.2, 135.5, 140.7, 140.9, 169.6, 171.9, and 202.9; HRMS calcd for [(C$_{24}$H$_{22}$N$_2$O$_3$) + H]$^+$ 387.1703, found 387.1715.

3-(2-Methylbenzyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (20). To a solution containing 1.0 g (2.6 mmol) of enamide **19** in 24 mL of a 1:1 mixture of EtOH/THF at 0 °C was added 0.098 g (2.6 mmol) of NaBH$_4$ in one portion. The mixture was stirred for 30 min at 0 °C, then quenched with an aqueous NaHCO$_3$ solution and extracted with EtOAc. The combined organic phase was dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude residue was taken up in 50 mL of THF and 5.2 mL (2.6 mmol) of 0.1 N NaOMe in MeOH solution was added. After being stirred for 15 min, the reaction was quenched with an aqueous NH$_4$Cl solution and extracted with EtOAc. The combined organic phase was dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude residue was taken up in 50 mL of THF and 7.8 mL (7.8 mmol) of a 1 M LiAlH$_4$ in THF solution was added dropwise. The mixture was heated at reflux for 3 h, cooled to 0 °C, and quenched by the dropwise addition of 0.3 mL of H$_2$O followed by 0.3 mL of a 15% aqueous NaOH solution and 0.87 mL of H$_2$O. The mixture was filtered through Celite and then washed with EtOAc. The filtrate was dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude residue was taken up in 50 mL of 1,2-dichloroethane, then cooled to −20 °C, and 2.2 g (10.4 mmol) of NaBH(OAc)$_3$ was gradually added over a 1 h interval. The reaction mixture was stirred for an additional 2 h, diluted with CHCl$_3$, and quenched with an aqueous NaHCO$_3$ solution and extracted with CHCl$_3$. The combined organic layer was dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.56 g (65%) of **20** as a pale yellow oil: IR (thin film) 3367, 3293, 1720, 1650, 1605, 1401, and 739 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.46–2.00 (m, 6H), 2.21 (ddd, 1H, J = 13.6, 9.2 and 4.4 Hz), 2.42–2.50 (m, 1H), 2.81 (td, 1H, J = 9.6 and 4.0 Hz), 3.42 (d, 1H, J = 12.8 Hz), 3.78 (d, 1H, J = 12.8 Hz), 3.82 (d, 1H, J = 4.0 Hz), 4.16–4.23 (m, 1H), 6.67 (d, 1H, J = 8.0 Hz), 6.78 (t, 1H, J = 7.6 Hz), 7.07 (td, 1H, J = 7.6 and 1.2 Hz), 7.12–7.18 (m, 4H), and 7.26–7.28 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.1, 19.6, 25.9, 35.9, 50.9, 54.4, 54.7, 67.8, 68.6, 69.1, 109.5, 119.0, 123.3, 125.5, 126.8, 127.6, 129.2, 130.0, 137.1, 137.6,137.7, and 149.4; HRMS calcd for [(C$_{22}$H$_{26}$N$_2$O) + H]$^+$ 335.2118, found 335.2114.

2,3,3a,4,5,6,6a,7-Octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (36). To a 0.06 g (0.09 mmol) sample of Pd(OH)$_2$/C (Pearlman's catalyst) in a sealed tube was added a solution of 0.1 g (0.3 mmol) of pyrrolidine **20** in 1 mL of MeOH. The mixture was repeatedly flushed with H$_2$ and was then stirred at rt under 60 psi for 2 days. At the end of this time, the mixture was filtered through Celite and washed with 30 mL of MeOH, 30 mL of a 1:1 mixture of MeOH/CH$_2$Cl$_2$, and 30 mL of triethylamine/MeOH/CH$_2$Cl$_2$ (5:25:70). The combined organic solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography to give 0.56 g (68%) of the titled compound as a pale yellow oil: IR (thin film) 3321, 3045, 1602, 1487, 1467, 1057, and

726 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 1.38–1.51 (m, 1H), 1.65–1.74 (m, 1H), 1.79–1.90 (m, 2H), 2.14–2.32 (m, 2H), 3.04–3.12 (m, 1H), 3.36–3.46 (m, 1H), 3.55 (ddd, 1H, J = 12.0, 9.2, and 8.0 Hz), 3.80 (d, 1H, J = 4.4 Hz), 3.88 (dt, 1H, J = 10.8 and 4.4 Hz), 6.64 (d, 1H, J = 8.0 Hz), 6.66 (t, 1H, J = 7.2 Hz), 6.99 (td, 1H, J = 8.0 and 1.2 Hz), and 7.03 (d, 1H, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 26.2, 27.1, 32.5, 44.2, 56.4, 64.6, 68.5, 69.0, 111.3, 120.1, 122.6, 129.7, 136.7, and 151.1.

3-(2-Iodobut-2-enyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (21). To a solution of 25 mg (0.11 mmol) of the above compound in 1.0 mL of DMF at rt was added 0.2 mL of H$_2$O and 75 mg (0.55 mmol) of K$_2$CO$_3$. The resulting solution was cooled to 0 °C and was treated with a solution of 31 mg (0.12 mmol) of Z-1-bromo-2-iodobut-2-ene[23] in 0.6 mL of DMF. The reaction mixture was stirred at 0 °C for 12 h, quenched with H$_2$O, and extracted with Et$_2$O. The combined organic layer was washed with H$_2$O and brine, then dried over MgSO$_4$. After concentration under reduced pressure, the residue was purified by flash silica gel chromatography to give 35 mg (79%) of **21** as a colorless oil: IR (neat) 3359, 2793, 1607, 1483, 1464, and 1049 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.42–1.49 (m, 1H), 1.56–1.73 (m, 3H), 1.77 (d, 3H, J = 6.4 Hz), 1.93–2.00 (m, 2H), 2.19–2.26 (m, 1H), 2.47 (dd, 1H, J = 7.2 and 3.6 Hz), 2.66 (ddd, 1H, J = 9.2, 9.2, and 6.8 Hz), 2.89 (ddd, 1H, J = 9.2, 9.2, and 4.4 Hz), 3.14 (d, 1H, J = 13.8 Hz), 3.44 (d, 1H, J = 13.8 Hz), 3.81 (d, 1H, J = 3.6 Hz), 4.03 (brs, 1H), 4.21–4.29 (m, 1H), 5.84 (q, 1H, J = 6.4 Hz), 6.66 (d, 1H, J = 7.6 Hz), 6.76 (td, 1H, J = 7.6 and 1.0 Hz), 7.06 (td, 1H, J = 7.6 and 1.0 Hz), and 7.21 (dd, 1H, J = 7.6 and 1.0 Hz); ^{13}C NMR (150 MHz, CDCl$_3$) δ 20.2, 21.9, 26.0, 36.2, 50.2, 54.7, 64.2, 66.7, 68.7, 69.2, 109.6, 110.4, 119.2, 123.8, 127.9, 130.9, 137.1, and 149.8; HRMS calcd for [(C$_{18}$H$_{23}$N$_2$OI) + H]$^+$ 411.0928, found 411.0925.

7-(2,4-Dimethoxybenzyl)-3-(2-iodobut-2-enyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol. To a solution of 0.1 g (0.26 mmol) of **21** in 6.0 mL of 1,2-dichloroethane at 0 °C was added 52 mg (0.3 mmol) of 2,4-dimethoxybenzaldehyde and 0.14 g (65 mmol) of NaBH(OAc)$_3$, followed by the dropwise addition of 44 µL (0.8 mmol) of acetic acid. The reaction mixture was stirred at 0 °C for 10 min and then at rt for 12 h. The solution was quenched with a saturated K$_2$CO$_3$ solution and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with H$_2$O and brine, then dried over MgSO$_4$. After concentration under reduced pressure, the residue was purified by flash chromatography to give 0.14 g (94%) of the titled compound as a pale yellow oil: IR (neat) 3500, 1606, 1485, 1259, and 1036 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.52–1.65 (m, 4H), 1.72–1.78 (m, 1H), 1.79 (d, 3H, J = 6.3 Hz), 1.92–1.97 (m, 1H), 1.99–2.08 (m, 2H), 2.32–2.37 (m, 1H), 2.74 (t, 1H, J = 3.0 Hz), 3.01 (d, 1H, J = 13.5 Hz), 3.05–3.10 (m, 1H), 3.47 (d, 1H, J = 3.6 Hz), 3.61 (d, 1H, J = 13.5 Hz), 3.80 (s, 3H), 3.82 (s, 3H), 4.26–4.30 (m, 1H), 4.32 (d, 1H, J = 16.2 Hz), 4.50 (d, 1H, J = 16.2 Hz), 5.86 (q, 1H, J = 6.3 Hz), 6.43 (d, 1H, J = 8.4 Hz), 6.45 (d, 1H, J = 8.4 Hz), 6.49 (s, 1H), 6.68 (t, 1H, J = 7.2 Hz), 7.03 (d, 1H, J = 8.1 Hz), 7.05 (d, 1H, J = 7.2 Hz), and 7.25 (t, 1H, J = 8.1 Hz); ^{13}C NMR (150 MHz, CDCl$_3$) δ 18.8, 21.9, 24.8, 39.8, 48.1, 51.2, 53.7, 55.5, 55.6, 65.5, 65.6, 68.2, 73.8, 98.7, 104.2, 107.1, 110.4, 118.0, 119.8, 121.8, 128.2, 129.2, 131.0, 135.3, 152.9, 158.3, and 160.2; HRMS calcd for [(C$_{27}$H$_{33}$N$_2$OI) + H]$^+$ 561.1609, found 561.1623.

7-(2,4-Dimethoxybenzyl)-3-(2-iodobut-2-enyl)-1,2,3,3a,4,5,6,6a,7-octahydropyrrolo[2,3-*d*]carbazol-6-one (22). To a solution containing 0.12 g (0.21 mmol) of the above compound and 0.1 g of 4 Å molecular sieves in 9.0 mL of CH$_3$CN at 0 °C was added 38 mg (0.31 mmol) of *N*-methylmorpholine-*N*-oxide and 22 mg (0.06 mmol) of tetrapropylammonium perruthenate. After the solution was stirred at 0 °C for 20 min, the cooling bath was removed and the mixture was stirred at rt for an additional 3 h. The reaction mixture was then filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford 0.09 g (79%) of **22** as a

pale yellow oil: IR (neat) 1711, 1606, 1484, and 1208 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.77 (dd, 3H, J = 6.4 and 1.2 Hz), 1.84–1.97 (m, 2H), 2.12–2.22 (m, 2H), 2.29–2.52 (m, 4H), 2.98 (d, 1H, J = 14.0 Hz), 3.12–3.17 (m, 1H), 3.59 (s, 1H), 3.59 (dt, 1H, J = 14.0 and 1.2 Hz), 3.59 (s, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.12 (d, 1H, J = 16.2 Hz), 4.25 (d, 1H, J = 16.2 Hz), 5.83 (q, 1H, J = 6.4 Hz), 6.38–6.43 (m, 2H), 6.55 (d, 1H, J = 7.6 Hz), 6.76 (td, 1H, J = 7.6 and 0.8 Hz), and 7.03–7.12 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.4, 21.9, 32.5, 37.8, 47.8, 51.6, 55.4, 55.5, 59.1, 64.6, 67.9, 81.8, 98.6, 103.8, 107.5, 108.8, 118.4, 118.7, 122.8, 128.7, 129.5, 131.5, 132.8, 152.7, 158.4, 160.3, and 210.4; HRMS calcd for [(C$_{27}$H$_{31}$N$_2$O$_3$I) + H]$^+$ 559.1452, found 559.1445.

Pentacyclic Ketone 23. To a solution of 0.09 g (0.16 mmol) of ketone **22** in 6.0 mL of THF at room temperature was added 46 mg (0.48 mmol) of phenol, 0.4 mL of 1 M *t*-BuOK in *t*-BuOH, and 19 mg (0.016 mmol) of Pd(PPh$_3$)$_4$, respectively. The reaction mixture was heated at reflux under an argon atmosphere for 3 h and then cooled to room temperature. The mixture was diluted with 1 N NaOH and extracted with CH$_2$Cl$_2$. The combined organic extracts were washed with 1 N NaOH, H$_2$O, and brine, dried over MgSO$_4$, and filtered. After concentration under reduced pressure, the residue was subjected to silica gel chromatography to give 42 mg (61%) of pentacyclic ketone **23** as a colorless oil: IR (neat) 1713, 1606, 1485, 1462, and 1207 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.60 (d, 3H, J = 6.6 Hz), 2.01 (dd, 1H, J = 11.9 and 5.7 Hz), 2.08–2.15 (m, 2H), 2.30 (dt, 1H, J = 14.4 and 3.6 Hz), 2.80 (ddd, 1H, J = 10.8, 10.8, and 6.6 Hz), 2.97 (d, 1H, J = 15.0 Hz), 3.31 (t, 1H, J = 8.1 Hz), 3.37 (s, 1H), 3.73 (s, 1H), 3.77–3.81 (m, 8H), 4.36 (d, 1H, J = 15.6 Hz), 4.49 (d, 1H, J = 15.6 Hz), 5.51 (q, 1H, J = 6.6 Hz), 6.39 (dd, 1H, J = 8.4 and 1.8 Hz), 6.44 (d, 1H, J = 1.8 Hz), 6.46 (d, 1H, J = 8.4 Hz), 6.69 (t, 1H, J = 7.5 Hz), 7.00 (d, 1H, J = 7.5 Hz), 7.08 (t, 1H, J = 7.5 Hz), and 7.10 (d, 1H, J = 7.5 Hz); ^{13}C NMR (150 MHz, CDCl$_3$) δ 13.6, 24.5, 39.3, 44.6, 46.4, 52.3, 52.9, 55.4, 55.6, 58.6, 61.3, 75.0, 98.6, 103.8, 107.5, 118.0, 118.7, 122.0, 125.5, 129.0, 129.6, 130.2, 132.1, 151.3, 158.6, 160.3, and 210.8; HRMS calcd for [(C$_{27}$H$_{30}$N$_2$O$_3$) + H]$^+$ 431.2329, found 431.2325.

(±)-Strychnopivotine (2). To a flask containing 20 mg (0.047 mmol) of pentacyclic ketone **23** was added 1.4 mL of HCl (1.2 N HCl in MeOH) and the mixture was heated at 55 °C for 5 h. After cooling to room temperature, the solution was diluted with a saturated K$_2$CO$_3$ solution and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with H$_2$O and brine, dried over MgSO$_4$, and filtered. The solvent was removed under reduced pressure and the resulting residue, which contained the deprotected indoline, was used in the next step without any purification: IR (neat) 3352, 2923, 1712, 1604, 1464, and 1109 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.57 (dt, 3H, J = 6.8 and 1.6 Hz), 1.73 (d, 1H, J = 14.8 Hz), 1.90 (ddd, 1H, J = 12.4, 7.6, and 7.6 Hz), 2.18 (dd, 1H, J = 12.4 and 6.4 Hz), 2.48 (dt, 1H, J = 14.8 and 3.6 Hz), 2.91 (d, 1H, J = 15.2 Hz), 2.95–3.00 (m, 1H), 3.38 (dd, 1H, J = 10.0 and 8.0 Hz), 3.43 (br s, 1H), 3.77 (s, 1H), 3.90 (br t, 2H, J = 7.6 Hz), 4.94 (br s, 1H), 5.57 (q, 1H, J = 6.8 Hz), 6.75–6.85 (m, 2H), 6.97 (d, 1H, J = 6.8 Hz), and 7.08 (td, 1H, J = 7.6 and 1.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.2, 25.0, 39.8, 45.5, 51.9, 53.7, 59.2, 59.7, 68.7, 111.1, 120.0, 122.2, 127.1, 128.7, 129.5, 129.9, 151.3, and 210.8.

The crude residue was taken up in a mixture of 1.0 mL of pyridine and 0.5 mL of CH$_2$Cl$_2$. To this solution was added 88 µL (0.94 mmol) of Ac$_2$O and the mixture was stirred at room temperature for 48 h. The reaction mixture was quenched with a saturated NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$. The organic extracts were washed with a saturated NaHCO$_3$ solution, H$_2$O, and brine, dried over MgSO$_4$, and filtered. After concentration under reduced pressure, the residue was purified by flash silica gel chromatography to give 9 mg (65%) of (±)-strychnopivotine (**2**) as an amorphous solid: IR (neat) 2924, 1645, 1511, 1456, 1246, and 1038 cm^{-1}; ^{1}H NMR (600 MHz, CD$_3$CN) δ 1.54 (dt, 3H, J = 7.2 and 1.8 Hz), 1.60 (d, 1H, J = 9.0 Hz), 1.76–1.82 (m, 1H), 2.05 (s, 3H), 2.13 (dd, 1H, J = 13.2 and 6.0 Hz), 2.56 (dt, 1H, J = 9.0

and 3.6 Hz), 2.88 (d, 1H, J = 15.0 Hz), 3.00–3.06 (m, 1H), 3.30 (dd, 1H, J = 9.9 and 8.1 Hz), 3.45 (s, 1H), 3.83 (d, 1H, J = 15.0 Hz), 3.94 (s, 1H), 4.64 (s, 1H), 5.64 (q, 1H, J = 7.2 Hz), 7.06 (td, 1H, J = 7.2 and 1.2 Hz), 7.16 (d, 1H, J = 7.2 Hz), 7.22 (td, 1H, J = 7.2 and 1.2 Hz), and 8.13 (d, 1H, J = 7.2 Hz); ^{13}C NMR (150 MHz, CD$_3$CN) δ 13.7, 24.2, 26.6, 26.7, 41.5, 47.5, 52.4, 54.2, 59.8, 60.3, 71.2, 72.0, 117.4, 123.2, 123.4, 125.4, 127.2, 127.9, 128.3, 129.2, 129.7, 130.3, 131.8, 133.7, 144.4, 171.2, and 208.5; HRMS calcd for [(C$_{20}$H$_{22}$N$_2$O$_2$) + H]$^+$ 323.1754, found 323.1753.

(±)-19,20-Dehydrotubifolidine (24). To a solution containing 0.07 g (0.16 mmol) of the pentacyclic ketone **23** in 10 mL of ethylene glycol at rt was added 1.3 mL (41 mmol) of hydrazine hydrate followed by 0.67 g (29 mmol) of sodium metal. After the sodium metal had dissolved, the reaction mixture was heated to 160 °C for 1 h, then at 190 °C for 1 h, and finally at 210 °C for 3 h. After cooling to rt, the reaction mixture was partitioned between H$_2$O and CH$_2$Cl$_2$ and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.03 g (62%) of **24** as a white solid: mp 169–171 °C; IR (neat) 3360, 2925, 1607, 1583, 1465, and 740 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.22–1.33 (m, 2H), 1.55 (dt, 1H, J = 14.0 and 2.0 Hz), 1.64 (d, 3H, J = 7.2 Hz), 2.03–2.21 (m, 3H), 2.70–2.84 (m, 3H), 3.24 (t, 1H, J = 8.8 Hz), 3.45 (dd, 1H, J = 10.8 and 6.4 Hz), 3.52 (br s, 1H), 3.72 (d, 1H, J = 14.0 Hz), 3.81 (br s, 1H), 5.37 (q, 1H, J = 7.2 Hz), 6.65 (d, 1H, J = 7.6 Hz), 6.76 (td, 1H, J = 7.6 and 0.4 Hz), and 7.04–7.08 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.2, 25.7, 27.8, 36.0, 38.8, 52.0, 53.0, 54.9, 59.2, 60.2, 110.0, 119.0, 121.2, 122.4, 127.8, 131.1, 136.9, and 150.4; HRMS calcd for [(C$_{18}$H$_{22}$N$_2$) + H]$^+$ 267.1855, found 267.1856.

(±)-Tubifolidine (25). To a solution containing 2.0 mg (0.008 mmol) of (±)-dehydrotubifoline **24** in 1 mL of THF at rt under nitrogen was added 2.0 mg (0.023 mmol) of Na$_2$CO$_3$, followed by 1.0 mg (0.023 mmol) of 10% Pd/C. The reaction flask was flushed with hydrogen and was then stirred under a H$_2$ atmosphere overnight. The mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude residue was taken up in CH$_2$Cl$_2$ and washed with a 1 N HCl solution. The aqueous layer was neutralized with a 1 N NaOH solution and extracted with CH$_2$Cl$_2$. The combined organic layer was dried over Na$_2$SO$_4$ then filtered and concentrated under reduced pressure to give 1.0 mg (50%) of (±)-tubifolidine (**25**): IR (neat) 3359, 2924, 1653, 1606, and 1464 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 0.91 (t, 3H, J = 7.2 Hz), 1.26–1.40 (m, 4H), 1.74 (dt, 1H, J = 13.2 and 3.0 Hz), 1.78–1.80 (m, 1H), 1.86 (ddd, 1H, J = 13.2, 10.8, and 2.4 Hz), 1.90–1.94 (m, 1H), 1.98–2.03 (m, 1H), 2.08 (t, 1H, J = 12.0 Hz), 2.42 (dt, 1H, J = 13.2 and 8.4 Hz), 2.85 (t, 1H, J = 10.8 Hz), 3.02–3.11 (m, 1H), 3.13–3.12 (m, 1H), 3.37 (br s, 1H), 3.62–3.66 (m, 1H), 6.63 (d, 1H, J = 7.8 Hz), 6.77 (t, 1H, J = 7.8 Hz), and 7.03–7.06 (m, 2H); HRMS calcd for [(C$_{18}$H$_{24}$N$_2$) + H]$^+$ 269.2012, found 269.2009.

Pentacyclic Alkene 30. A sample of 0.8 g (2.2 mmol) of CeCl$_3$ hydrate was heated at 60 °C under reduced pressure for 3 h to remove the water of hydration. After cooling to rt, the solid was dissolved in 0.5 mL of THF and the solution was stirred for 1 h at rt. The mixture was cooled to −78 °C and 0.56 mL (0.56 mmol) of 1 M trimethylsilylmethyl lithium in THF was added dropwise. After being stirred at −78 °C for 30 min, a solution of the pentacyclic ketone **23** in 0.5 mL of THF was added via cannula. The solution was allowed to warm to rt, and was then heated at reflux for 12 h. After cooling to rt, 98 μL (0.65 mmol) of *N,N,N′,N′*-tetramethylethylenediamine was added in one portion. The mixture was stirred for 30 min, poured into a saturated aqueous NaHCO$_3$ solution, and extracted with CH$_2$Cl$_2$. The organic phase was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude residue was used in the next step without further purification.

A sample of 40 mg (0.38 mmol) of potassium hydride (60% in mineral oil) was washed with 5 mL of hexane and then suspended in 0.5 mL of THF. To this suspension was added the above crude residue in 0.5 mL of THF. The resulting mixture was stirred at rt for 2 h, quenched by pouring the mixture into a saturated aqueous NH$_4$Cl solution, and then extracted with CH$_2$Cl$_2$. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, then filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.04 g (69%) of **30** as a yellow solid: mp 138–142 °C; IR (neat) 2925, 1607, 1463, 1293, and 1207 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.69 (d, 3H, J = 6.4 Hz), 1.94–2.10 (m, 2H), 2.30–2.41 (m, 2H), 3.03 (dt, 2H, J = 11.6 and 7.4 Hz), 3.32 (d, 1H, J = 14.4 Hz), 3.50–3.56 (m, 1H), 3.58 (s, 1H), 3.72–3.82 (m, 2H), 3.78 (s, 3H), 3.84 (s, 1H), 4.18 (d, 1H, J = 16.4 Hz), 4.30 (d, 1H, J = 16.4 Hz), 5.14 (d, 1H, J = 8.8 Hz), 5.49 (q, 1H, J = 6.4 Hz), 6.39 (d, 1H, J = 7.6 Hz), 6.40 (d, 1H, J = 8.8 Hz), 6.46 (d, 1H, J = 2.4 Hz), 6.73 (t, 1H, J = 7.6 Hz), and 7.01–7.12 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.5, 24.1, 33.3, 36.6, 45.0, 51.8, 52.6, 54.4, 55.2, 55.3, 63.3, 73.2, 98.4, 203.7, 108.3, 117.8, 118.3, 118.6, 122.2, 125.9, 128.8, 129.4, 131.4, 145.1, 150.6, 157.9, and 160.0; HRMS calcd for [(C$_{28}$H$_{32}$N$_2$O$_2$) + H]$^+$ 429.2523, found 429.2537.

Pentacyclic Alkene 31. To a flask containing 50 mg (0.11 mmol) of **30** was added 5 mL of HCl (1.0 N HCl in MeOH) and the mixture was heated at 55 °C for 5 h. After cooling to rt, the reaction was quenched with a saturated aqueous K$_2$CO$_3$ solution and then extracted with CH$_2$Cl$_2$. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, and filtered. The solvent was removed under reduced pressure, and the crude residue was purified by flash silica gel chromatography to give 16 mg (49%) of **31** as a yellow solid: mp 139–141 °C; IR (neat) 3367, 2925, 1607, 1484, 1464, and 741 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.65 (d, 3H, J = 6.8 Hz), 1.88 (dt, 1H, J = 13.6 and 2.4 Hz), 1.95–2.09 (m, 2H), 2.16–2.23 (m, 2H), 2.80–2.93 (m, 1H), 3.00 (d, 1H, J = 14.8 Hz), 3.18–3.25 (m, 1H), 3.54–3.57 (m, 3H), 4.01 (s, 1H), 4.04 (br s, 1H), 4.98 (s, 2H), 5.38 (q, 1H, J = 6.8 Hz), 6.64 (d, 1H, J = 7.2 Hz), 6.75 (td, 2H, J = 7.2 and 1.2 Hz), and 7.04 (qd, 2H, J = 7.2 and 1.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.0, 26.4, 36.3, 38.9, 53.0, 53.7, 55.8, 62.5, 67.1, 109.2, 110.9, 119.0, 120.7, 122.3, 127.9, 132.7, 137.3, 149.9, and 150.0.

(±)-Valparicine (29). To a solution containing 4.0 mg (0.016 mmol) of CuBr$_2$ in 0.5 mL of THF was added a solution of 2.0 mg (0.016 mmol) of *t*-BuONa in 0.5 mL of THF via cannula. The resulting mixture was stirred for 15 min at rt, and then cooled to 0 °C. To this mixture was added a dropwise solution of 2.0 mg (0.007 mmol) of **31** in 0.5 mL of THF. After being stirred at 0 °C for 40 min, the mixture was quenched with an aqueous NH$_4$OH solution (3.5%) and then extracted with CH$_2$Cl$_2$. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, and filtered. The solvent was removed under reduced pressure and the crude residue was subjected to flash silica gel column chromatography to give a 1:1 mixture of **31** and (±)-valparicine (**29**). We were not able to separate the mixture into its component parts by chromatography. The NMR spectrum of (±)-valparicine (**29**) was obtained by substraction of peaks from the starting material **31** and is perfectly consistent with the NMR data reported by Kam and co-workers:[31] ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.15 −1.38 (2H, m), 1.77 (d, 3H, J = 7.2 Hz), 1.97–2.04 (m, 2H), 2.07 (dt, 1H, J = 13.8 and 3.0 Hz), 2.42 (ddd, 1H, J = 13.2, 9.0, and 6.0 Hz), 3.18 −3.24 (1H, m), 3.26 (d, 1H, J = 15.0 Hz), 3.31 (ddd, 1H, J = 11.4, 9.0, and 6.0 Hz), 3.73 (d, 1H, J = 15.6 Hz), 3.84 (br s, 1H), 5.34 (s, 1H), 5.49 (q, 1H, J = 7.2 Hz), 7.22 (t, 1H, J = 7.2 Hz), 7.33 (d, 1H, J = 7.2 Hz), 7.36 (d, 1H, J = 7.2 Hz), and 7.61 (d, 1H, J = 7.2 Hz).

Z-1-Bromo-2-iodo-4-methoxymethoxybut-2-ene. To a solution containing 1.0 g (3.4 mmol) of Z-3-iodo-4-(tetrahydropyran-2-yloxy)-2-butenol[44f] in 13 mL of CH$_2$Cl$_2$ at 0 °C was added 0.13 mL (0.81 mmol) of diisopropylethylamine followed by 0.06 mL (0.81 mmol) of chloromethyl methyl ether. The reaction mixture

was stirred at 0 °C for 5 h, diluted with CH_2Cl_2, and washed with an aqueous $NaHCO_3$ solution. The combined organic extracts were dried over Na_2SO_4, then filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.95 g (82%) of 2-(2-iodo-4-methoxymethoxybut-2-enyloxy)tetrahydropyran as a colorless oil: IR (thin film) 1654, 1450, 1447, 1201, and 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45–1.90 (m, 5 H), 3.71 (s, 3H), 3.48–3.55 (m, 1H), 3.86 (ddd, 1H, J = 12.4, 9.2, and 3.2 Hz), 4.16–4.21 (m, 3H), 4.64 (s, 2H), 4.68 (t, 1H, J = 3.2 Hz), and 6.22 (tt, 1H, J = 5.6 and 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 25.3, 30.3, 55.4, 62.0, 71.1, 74.2, 96.1, 97.1, 104.6, and 133.3.

To a solution of 1.7 g (4.9 mmol) of the above compound in 49 mL of MeOH at 0 °C was added 0.09 g (0.49 mmol) of *p*-toluenesulfonic acid. The reaction mixture was stirred at 0 °C for 1 h, quenched with an aqueous $NaHCO_3$ solution, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, then filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.76 g (60%) of 2-iodo-4-methoxymethoxybut-2-en-1-ol as a colorless oil: IR (thin film) 3403, 2934, 1655, 1446, and 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (t, 1H, J = 6.8 Hz), 3.38 (s, 3H), 4.17 (dt, 2H, J = 5.6 and 1.2 Hz), 4.23 (dd, 2H, J = 6.8 and 1.2 Hz), 4.62 (s, 2H), and 6.21 (tt, 1H, J = 5.6 and 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 70.9, 71.0, 96.0, 108.9, and 131.5.

To a solution of 0.48 g (1.9 mmol) of the above alcohol in 28 mL of CH_2Cl_2 at −30 °C was added 0.59 g (2.2 mmol) of triphenylphosphine followed by 0.46 g (2.6 mmol) of *N*-bromo-succinimide. The reaction mixture was maintained at −30 °C for 1 h, diluted with Et_2O, and washed with an aqueous $NaHCO_3$ solution. The combined organic extracts were dried over Na_2SO_4, then filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.47 g (79%) of *Z*-1-bromo-2-iodo-4-methoxymethoxybut-2-ene as a colorless oil: IR (thin film) 2929, 1633, 1448, 1211, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3H), 4.14 (d, 2H, J = 5.2 Hz), 4.33 (s, 1H), 4.64 (s, 1H), 6.28 (t, 1H, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.1, 55.5, 71.4, 96.2, 101.6, and 137.1.

7-(2,4-Dimethoxybenzyl)-3-(2-iodo-4-methoxymethoxybut-2-enyl)-2,3,3a,4, 5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol. To a solution of 0.12 g (0.54 mmol) of pyrrolidine **36** in 5.0 mL of DMF at rt was added 1.2 mL of H_2O and 0.37 g (2.7 mmol) of K_2CO_3. The resulting mixture was cooled to 0 °C, and this was followed by the addition of a solution of 0.21 g (0.65 mmol) of the above bromide in 1.0 mL of DMF. The solution was stirred at 0 °C for 12 h and then partitioned between Et_2O and H_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with H_2O and brine, dried over MgSO$_4$, and filtered. After concentration under reduced pressure, the residue was purified by flash chromatography to provide 0.2 g (80%) of vinyl iodide **37** as a pale yellow oil that was immediately used in the next step.

To a flask containing 54 mg (0.11 mmol) of **37** was added 3.0 mL of 1,2-dichloroethane. To the resulting solution at 0 °C was added 23 mg (0.14 mmol) of 2,4-dimethoxybenzaldehyde and 61 mg (0.29 mmol) of NaBH(OAc)$_3$, followed by the addition of 20 μL (0.34 mmol) of acetic acid. The reaction mixture was stirred at 0 °C for 10 min and then at rt for 12 h. The solution was quenched with a saturated K_2CO_3 solution and extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and brine, dried over MgSO$_4$, and filtered. After concentration under reduced pressure, the residue was purified by flash silica gel chromatography to give 61 mg (86%) of the titled compound as a colorless oil: IR (neat) 3456, 1673, 1606, and 1485 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.54–1.62 (m, 2H), 1.68 (d, 1H, J = 6.0 Hz), 1.74–1.79 (m, 1H), 1.93–2.06 (m, 3H), 2.38 (td, 1H, J = 9.0 and 6.6 Hz), 2.80 (t, 1H, J = 0.6 Hz), 3.06 (d, 1H, J = 13.8 Hz), 3.11 (td, 1H, J = 9.0 and 5.1 Hz), 3.40 (s, 3H), 3.46 (d, 1H, J = 3.6 Hz), 3.62

(d, 1H, J = 13.8 Hz), 3.81 (s, 3H), 3.82 (s, 3H), 4.19 (d, 1H, J = 5.4 Hz), 4.24–4.28 (m, 1H), 4.32 (d, 1H, J = 16.2 Hz), 4.50 (d, 1H, J = 16.2 Hz), 4.66 (s, 1H), 6.14 (t, 1H, J = 5.4 Hz), 6.43–6.46 (m, 2H), 6.49 (d, 1H, J = 1.8 Hz), 6.68 (t, 1H, J = 7.5 Hz), 7.02–7.05 (m, 2H), and 7.24(d, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 24.7, 39.8, 48.0, 51.3, 53.5, 55.5, 55.6, 55.7, 65.4, 65.6, 68.1, 71.7, 73.6, 96.3, 98.7, 104.1, 107.1, 109.9, 118.0, 119.7, 121.7, 128.2, 129.1, 132.7, 135.2, 152.8, 158.2, and 160.2; HRMS calcd for [($C_{29}H_{37}N_2O_5I$) + H]$^+$ 621.1820, found 621.1817.

7-(2,4-Dimethoxybenzyl)-3-(2-iodo-4-methoxymethoxybut-2-enyl)-2,3,3a,4,5,6,6a,7-octahydropyrrolo[2,3-*d*]carbazol-6-one (34). To a flask containing 0.9 g (1.5 mmol) of the above compound and 0.73 g of 4 Å molecular sieves in 50 mL of CH_3CN at 0 °C was added 0.26 g (2.2 mmol) of *N*-methylmorpholine-*N*-oxide, followed by the addition of 0.15 g (0.43 mmol) of tetra-*n*-propylammonium perruthenate in several portions. After the solution was stirred at 0 °C for 20 min, the cooling bath was removed and the mixture was stirred at rt for an additional 2 h. The mixture was then filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.72 g (80%) of ketone **34** as a pale yellow oil: IR (neat) 1707, 1601, 1479, 1209, and 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83–1.98 (m, 2H), 2.13–2.23 (m, 2H), 2.30–2.53 (m, 3H), 2.54 (d, 1H, J = 2.8 Hz), 2.99 (d, 1H, J = 14.0 Hz), 3.15–3.20 (m, 1H), 3.39 (s, 3H), 3.59 (dd, 1H, J = 14.0 and 1.6 Hz), 3.60 (s, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.12 (d, 1H, J = 16.4 Hz), 4.15–4.18 (m, 1H), 4.25 (d, 1H, J = 16.4 Hz), 4.65 (s, 2H), 6.10 (t, 1H, J = 4.2 Hz), 6.40 (dd, 1H, J = 8.2 and 2.4 Hz), 6.43 (d, 1H, J = 2.4 Hz), 6.55 (d, 1H, J = 8.2 Hz), 6.77 (td, 1H, J = 7.6 and 0.8 Hz), and 7.03–7.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 32.5, 37.8, 47.8, 51.8, 55.4, 55.5, 55.7, 59.0, 64.5, 67.9, 71.6, 81.7, 96.4, 98.6, 103.9, 107.2, 108.8, 118.4, 118.7, 122.8, 128.8, 129.5, 132.7, 133.3, 152.7, 158.4, 160.3, and 210.3.

Pentacyclic Ketone 38. To a solution of 0.35 g (0.57 mmol) of **34** in 6.0 mL of THF at room temperature was added 0.13 g (0.11 mmol) of Pd(PPh$_3$)$_4$, 0.74 mL of 1 M *t*-BuOK in *t*-BuOH, and 80 mg (0.85 mmol) of phenol in 8 mL of THF. The reaction mixture was heated at reflux under argon for 2 h, cooled to rt, diluted with a 1 N NaOH solution, and extracted with CH_2Cl_2. The combined organic extracts were washed with 1 N NaOH, H_2O, and brine, dried over MgSO$_4$, and filtered. After concentration under reduced pressure, the residue was purified by silica gel chromatography to give 0.15 g (56%) of the pentacyclic ketone **38** as a pale yellow oil: IR (neat) 1711, 1607, 1484, and 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (dd, 1H, J = 12.8, and 5.0 Hz), 2.14–2.34 (m, 3H), 2.66–2.74 (m, 1H), 3.05 (d, 1H, J = 16.0 Hz), 3.20 (t, 1H, J = 8.4 Hz), 3.33 (s, 1H), 3.35 (s, 3H), 3.65 (br s, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 3.79 (d, 1H, J = 16.0 Hz), 4.10 (dd, 1H, J = 13.2 and 4.4 Hz), 4.22–4.37 (m, 3H), 4.61 (s, 2H), 5.57 (dd, 1H, J = 8.4 and 4.4 Hz), 6.40 (dd, 1H, J = 7.8 and 2.2 Hz), 6.44 (d, 1H, J = 2.2 Hz), 6.49 (d, 1H, J = 7.8 Hz), 6.74 (td, 1H, J = 7.4 and 0.6 Hz), and 7.03–7.11 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 38.7, 43.8, 46.9, 51.8, 52.6, 55.4, 55.5, 55.6, 58.3, 62.3, 63.6, 76.8, 96.1, 98.6, 103.8, 108.5, 118.6, 118.7, 122.3, 125.8, 128.9, 129.3, 130.9, 137.5, 151.9, 158.4, 160.2, and 209.5; HRMS calcd for [($C_{29}H_{34}N_2O_5$) + H]$^+$ 491.2540, found 491.2534.

Pentacyclic Enol Ether 35. To a flask containing 0.45 mL (3.2 mol) of diisopropyl amine in 4.0 mL of THF at 0 °C was slowly added 1.2 mL (2.9 mmol) of *n*-BuLi (2.5 M in hexane). The resulting LDA solution was added dropwise to a suspension of Ph$_2$P(O)CH$_2$OMe in 6.0 mL of THF at 0 °C. The reaction mixture was stirred at this temperature for 20 min and to the resulting red solution was added a solution containing 0.14 g (0.29 mmol) of pentacyclic ketone **38** in 2.0 mL of THF. After the solution was stirred for 20 min, the cooling bath was removed and the reaction mixture was stirred at rt for 22 h. The solution was quenched with a saturated NH$_4$Cl solution and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The

residue was purified by flash silica gel chromatography to provide 90 mg (72%) of vinyl ether **35** as a pale yellow foam: IR (neat) 1607, 1485, 1121, and 1038 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.79–1.84 (m, 1H), 2.20–2.25 (m, 1H), 2.45–2.53 (m, 2H), 3.00–3.08 (m, 1H), 3.17–3.28 (m, 2H), 3.35 (s, 3H), 3.35–3.42 (m, 1H), 3.47–3.53 (m, 6H), 3.80 (s, 3H), 3.83 (s, 3H), 4.08 (dd, 1H, J = 12.0 and 6.0 Hz), 4.11 (d, 1H, J = 16.8 Hz), 4.18–4.21 (m, 2H), 4.58 (s, 1H), 4.63 (d, 1H, J = 6.6 Hz), 4.65 (d, 1H, J = 6.6 Hz), 5.38 (t, 1H, J = 6.0 Hz), 6.14 (s, 1H), 6.23 (d, 1H, J = 8.1 Hz), 6.41 (dd, 1H, J = 8.1 and 2.4 Hz), 6.47 (d, 1H, J = 2.4 Hz), 6.71 (t, 1H, J = 7.5 Hz), 6.99 (t, 1H, J = 7.5 Hz), 7.06 (d, 1H, J = 7.5 Hz), and 7.07 (d, 1H, J = 7.5 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 25.2, 29.9, 39.2, 45.6, 52.1, 54.0, 55.1, 55.4, 55.5, 55.6, 59.9, 62.7, 66.9, 67.5, 95.7, 98.4, 103.8, 108.0, 112.4, 118.3, 120.3, 122.1, 128.0, 128.4, 128.6, 132.0, 151.4, 151.9, 157.7, and 159.6; HRMS calcd for [(C$_{31}$H$_{38}$N$_2$O$_5$) + H]$^+$ 591.2853, found 591.2847.

(±)-**Strychnine (3).** To a solution containing 8.0 mg (0.015 mmol) of the pentacyclic enol ether **35** in 1.5 mL of THF was added 1.5 mL of 4 M HCl. The reaction mixture was heated at 55 °C for 10 h, cooled to 0 °C, neutralized with a saturated NH$_4$OH solution, and extracted with EtOAc. The organic extracts were washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was heated at 60 °C under vacuum overnight to remove the 1,4-diol derived from acid hydrolysis of THF under the reaction conditions. The resulting crude residue consisted of the Wieland−Gumlich aldehyde **33**: ^{1}H NMR (600 Hz, CDCl$_3$) δ 1.54 (d, 1H, J = 14.4 Hz), 1.57–1.62 (m, 1H), 1.82 (d, 1H, J = 10.8 Hz), 2.06 (dd, 1H, J = 12.6 and 6.6 Hz), 2.26–2.30 (m, 1H), 2.66 (s, 1H), 2.67 (d, 1H, J = 14.4 Hz), 2.80–2.84 (m, 1H), 3.26 (dd, 1H, J = 8.0 and 8.0 Hz), 3.75 (d, 1H, J = 14.4 Hz), 3.82 (d, 1H, J = 10.8 Hz), 3.92–3.99 (m, 2H), 4.23 (dd, 1H, J = 14.4 and 7.2 Hz), 5.00 (s, 1H), 5.81 (br s, 1H), 6.80 (d, 1H, J = 7.5 Hz), 6.88 (t, 1H, J = 7.5 Hz), 7.04 (d, 1H, J = 7.5 Hz), 7.10 (d, 1H, J = 7.5 Hz).

To the crude residue was added 0.5 mL of acetic acid, 48 mg of malonic acid, 48 mg of sodium acetate, and 10 μL of acetic anhydride, and the resulting mixture was heated at 120 °C for 2 h. The reaction mixture was cooled to rt, diluted with H$_2$O, basified with a 50% NaOH solution, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC to afford 2.3 mg (43% for the 2 steps) of (±)-strychnine (**3**) as a white solid: mp 278–283 °C (lit.[44] mp 275–285 °C) for the two-step sequence: ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.28 (dt, 1H, J = 10.4 and 3.2 Hz), 1.48 (d, 1H, J = 14.0 Hz), 1.89–1.93 (m, 2H), 2.37 (dt, 1H, J = 14.0 and 4.4 Hz), 2.67 (dd, 1H, J = 17.2 and 3.2 Hz), 2.76 (d, 1H, J = 15.2 Hz), 2.89 (dd, 1H, J = 18.4 and 10.0 Hz), 3.14 (dd, 1H, J = 17.2 and 8.4 Hz), 3.15–3.17 (m, 1H), 3.22–3.28 (m, 1H), 3.99 (br s, 1H), 4.06 (dd, 1H, J = 13.6 and 5.6 Hz), 4.16 (dd, 1H, J = 13.6 and 7.4 Hz), 4.29 (dt, 1H, J = 8.4 and 3.2 Hz), 5.94 (t, 1H, J = 5.6 Hz), 7.10 (td, 1H, J = 7.6 and 1.2 Hz), 7.17 (dd, 1H, J = 7.6 and 1.2 Hz), 7.26 (td, 1H, J = 7.6 and 1.2 Hz), 8.09 (dd, 1H, J = 7.6 and 1.2 Hz).

Supporting Information Available: ^{1}H and ^{13}C NMR data for various key compounds lacking CHN analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8003716