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Total Synthesis of (±)-Strychnine via a [4 + 2]-Cycloaddition/Rearrangement Cascade

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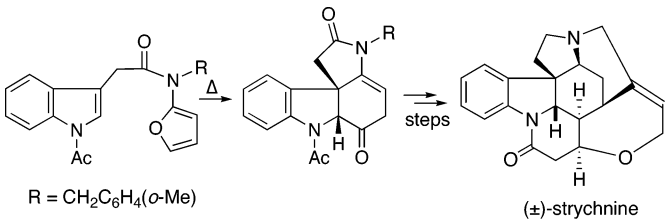
ABSTRACT



A new strategy for the synthesis of the *Strychnos* alkaloid (±)-strychnine has been developed and is based on an intramolecular [4 + 2]-cycloaddition/rearrangement cascade of an indolyl-substituted amidofuran. The critical D-ring was assembled by an intramolecular palladium-catalyzed enolate-driven cross-coupling of an *N*-tethered vinyl iodide.

Strychnos alkaloids belonging to the curane type constitute an important group of architecturally complex and widely distributed monoterpenoid indole alkaloids.[1,2] The curane 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] The synthesis of various members of the *Strychnos* family has been an area of interest ever since the structural elucidation of strychnine (**4**), the most famous of this group of alkaloids, by Robinson in 1946.[4] Strychnine was first isolated in 1818 from the Indian poison nut[5] (*Strychnos nux vomica*) and possesses highly toxic properties as a result of its interaction with the glycine receptor site, thereby blocking the flux of chloride ions and disruption of nerve-cell signaling.[6] Its complex heptacyclic structure, containing 24 skeletal atoms and six contiguous stereogenic centers, has fascinated organic chemists for the past 60 years. Nearly 40 years after Woodward's pioneering achievement of strychnine,[7] a number of other research groups have reported on its synthesis.[8]

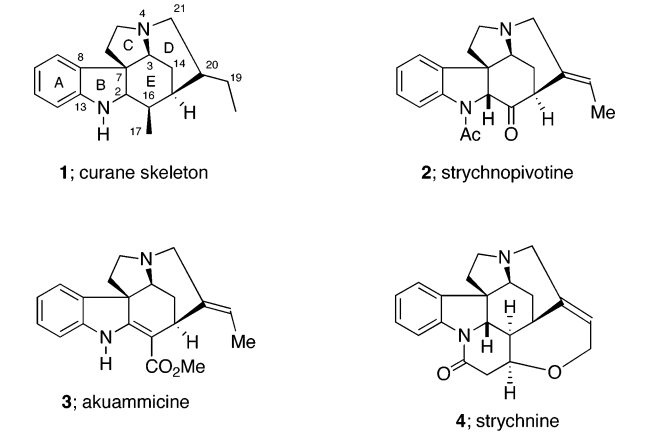


Figure 1. Some representative *Strychnos* alkaloids.

(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.

(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. (c) Openshaw, H. T.; Robinson, R. *Nature* **1946**, *157*, 438.

(5) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323.

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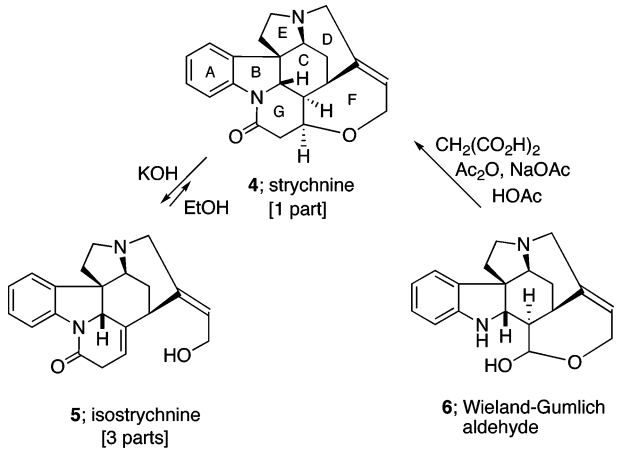
Efficient approaches toward the *Strychnos* pentacyclic framework would allow the synthesis of not only other members of this family of natural products (i.e., strychnopivotine (**2**) and akuammicine (**3**)) but also related nonnatural products possessing biological activity. Along these lines, we have recently become involved in the development and optimization of a new approach for the construction of the pentacyclic framework of the *Strychnos* system. In this paper, we report a concise stereocontrolled total synthesis of (±)-strychnine (**4**) wherein an efficient [4 + 2]-cycloaddition/rearrangement method previously developed in our laboratories plays a crucial role.[9]

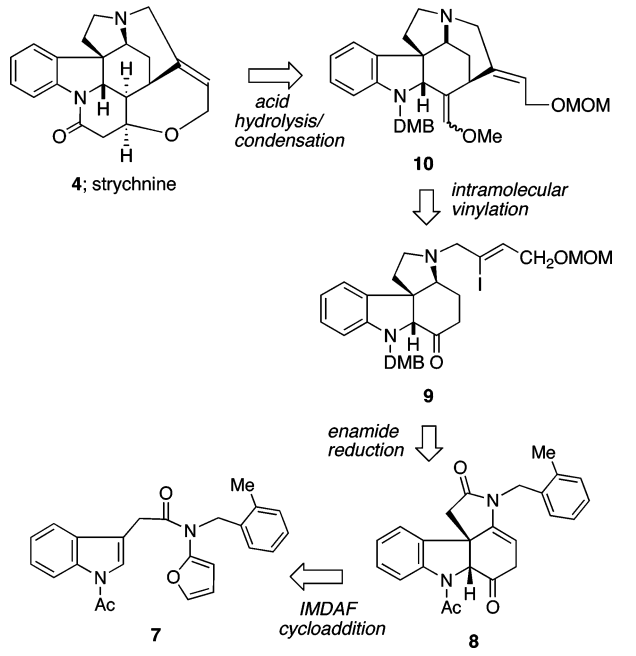
In Rawal and Iwasa's elegant synthesis of (±)-strychnine,[8e] an ingenious palladium-catalyzed intramolecular Heck reaction was used as the key step for the creation of the D-ring. As in Woodward's original approach,[7] isostrychnine (**5**) was the final critical intermediate used in this synthesis. Its Prelog−Taylor cyclization to strychnine[10] (Scheme 1), 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 (**6**) with an acetate equivalent for the formation of the G ring seemed to us to be the more attractive approach,[11] as it avoids the unfavorable equilibration ratio. As illustrated in Scheme 2, our retrosynthetic analysis of strychnine (**4**) relies upon the efficient construction of the tetracyclic substructure **8**, containing the ABCE rings of **4**, by an intramolecular [4 + 2]-cycloaddition/

Scheme 1



rearrangement cascade of 2-amidofuran **7**. The synthetic plan also involves closure of the D-ring by a palladium-catalyzed intramolecular coupling of an amido-tethered vinyl iodide with a keto enolate (i.e., **9** → **10**).[12,13]

Scheme 2



Some years ago, we commenced a program of research based on the intramolecular [4 + 2]-cycloaddition/rearrange-

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(11) Anet, F. A. L.; Robinson, R. *Chem. Ind.* **1953**, 245. See also ref 8a,c.

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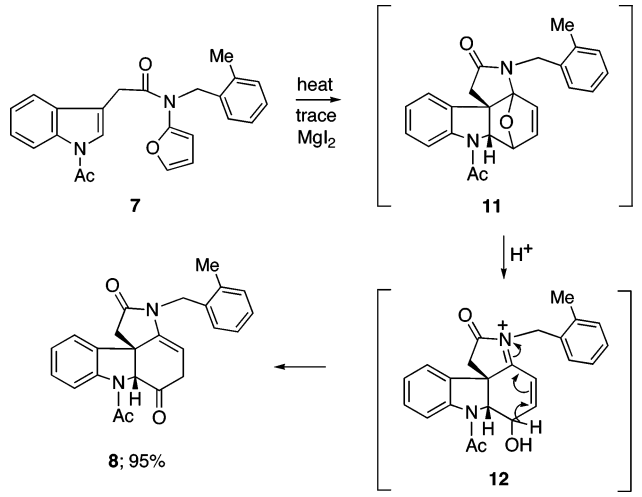
(13) For some other examples of intramolecular Pd-catalyzed vinylations, see: (a) Piers, E.; Oballa, R. M. *Tetrahedron Lett.* **1995**, *36*, 5857. (b) Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 7565.

ment cascade of 2-amidofurans as a strategy for the synthesis of different classes of alkaloids.[14] Intramolecular cycloaddition reactions often benefit from higher reactivity and greater control of stereoselectivity relative to their intermolecular counterparts. Specifically, connecting the two π-fragments via a "tether" generally facilitates the rate of the [4 + 2]-cycloaddition reaction. Our earlier experience with this domino sequence prompted us to apply the cascade approach toward (±)-strychnine. With this in mind, we prepared furanylindole **7** by acylation of the mixed anhydride of 2-(1-acetyl-1*H*-indol-3-yl)acetic acid[15] with the *N*-lithiate anion of *tert*-butyl furan-2-ylcarbamate followed by Boc deprotection[16] with $Mg(ClO_4)_2$ and subsequent *N*-alkylation using 1-(bromomethyl)-2-methylbenzene in 55% overall yield for the three-step procedure. We suspect that the presence of the large *o*-methylbenzyl group on the amido nitrogen atom causes the reactive s-trans rotamer to be more highly populated and probably helps promote the [4 + 2]-intramolecular cycloaddition. Indeed, the cycloaddition/rearrangement cascade of **7** was remarkably efficient given that two heteroaromatic systems are compromised in the reaction. Thus, heating a sample of **7** at 150 °C (toluene) in a microwave reactor for 30 min in the presence of catalytic MgI_2 afforded the desired aza-tetracycle **8** in 95% yield (Scheme 3). This reaction cascade can be rationalized by a

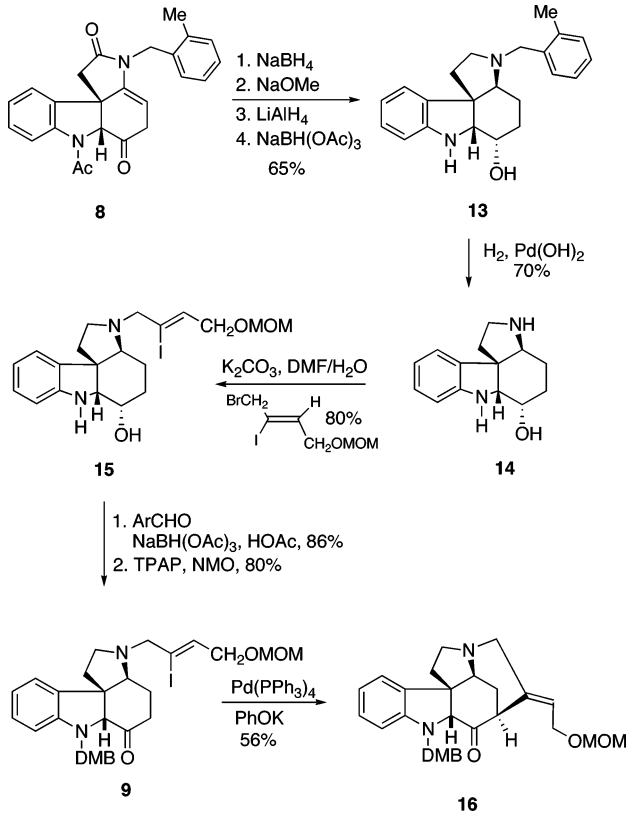
Scheme 3



nitrogen-assisted ring opening of the initially formed cycloadduct **11** to produce *N*-acyliminium ion **12**. A subsequent deprotonation followed by ketonization of the resulting enol accounts for the formation of **8**.

Our synthesis of the more advanced tetracycle **9** required for eventual D-ring cyclization of strychnine began by stereoselective reduction of the keto group of **8** with $NaBH_4$ followed by *N*-deacetylation using NaOMe (Scheme 4). The

Scheme 4



γ-lactam carbonyl group was then reduced with $LiAlH_4$, and the resulting enamine was further reduced using $NaBH(OAc)_3$ to give alcohol **13** as the major diastereomer in 65% yield over the four-step sequence.[17] Removal of the *o*-methylbenzyl group by catalytic hydrogenation furnished **14** in 70% isolated yield. This was followed by *N*-alkylation with (*Z*)-1-bromo-2-iodo-4-(methoxymethoxy)but-2-ene[18] to give alcohol **15** in 80% yield. Condensation of the indoline nitrogen present in **15** with 2,4-dimethoxybenzaldehyde in the presence of $NaBH(OAc)_3$[19] afforded the N-protected 2,4-dimethoxybenzylamine (DMB) in 86% yield.[20] Oxidation of the resulting secondary alcohol to the corresponding ketone **9** occurred smoothly in 80% yield using tetrapropylammonium perruthenate (TPAP).[21] The stage was now set for the completion of the synthesis. The critical D-ring of strychnine was constructed by a palladium-catalyzed intramolecular

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(17) Attempts to introduce the vinyl iodide moiety earlier in the synthesis were unsuccessful due to the competitive loss of the iodo group during the reduction step.

(18) The synthesis of the required allylic bromide is described in the Supporting Information.

(19) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(20) The DMP group was selected as it was readily removed under the acidic conditions employed in the hydrolysis of **10** to the Wieland−Gumlich aldehyde (**6**) (see Scheme 5).

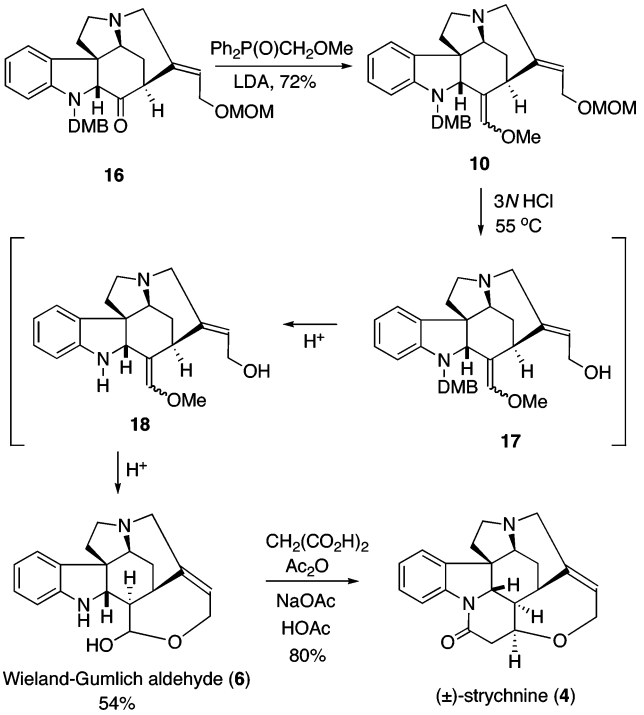
(21) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

coupling of the amino-tethered vinyl iodide with the keto enolate derived from **9**. The key palladium-catalyzed cyclization was carried out on a sample of **9** using $Pd(PPh_3)_4$ and PhOK. Gratifyingly, the reaction proceeded smoothly to furnish aza-pentacycle **16** in 56% unoptimized yield.[22]

Our initial attempts to convert the keto group of **16** into the corresponding enol ether **10** using methoxymethylenetriphenylphosphorane ($MeOCH{=}PPh_3$) were unsuccessful, probably as a consequence of steric congestion about the ketone. Consequently, we turned our attention to the phosphine oxide reagent $MeOCH_2P(O)Ph_2$ whose anion is sterically less demanding and more nucleophilic compared to the phosphorane $MeOCH{=}PPh_3$.[23,24] Thus, treatment of $MeOCH_2P(O)Ph_2$ with LDA in THF gave the lithio anion which reacted smoothly with ketone **16** at 0 °C to provide **10** as a single diastereomer in 72% isolated yield (Scheme 5). The last major hurdle involved an acid-promoted deprotection/hydrolysis of **10** into the Wieland−Gumlich aldehyde (**6**). The hydrolysis was satisfactorily accomplished by the treatment of **10** with 3 N HCl in THF at 55 °C for 10 h which gave **6** in 54% yield. By using shorter reaction times and following the reaction by NMR spectroscopy, we found that the initially formed primary alcohol **17** undergoes a subsequent deprotection of the DMB group to furnish enol ether **18**. Further stirring of **18** under the acidic conditions eventually furnished the Wieland−Gumlich aldehyde (**6**). Although the conversion of **6** into strychnine had been reported by Robinson in 1953,[11] we decided to reproduce the described protocol for the sake of a complete total synthesis. Thus, the final biomimetic condensation of **6** with malonic acid, acetic anhydride, sodium acetate, and acetic acid provided (±)-strychnine (**4**) in 80% yield and with a 4.4% overall yield for the 13-step reaction sequence starting from furanyl indole **7**.

In summary, a concise synthesis of the *Strychnos* alkaloid (±)-strychnine 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 natural product. Closure of the remaining D-ring was carried out from the aza-tetracyclic intermediate by an intramolecular palladium-catalyzed enolate-driven

Scheme 5



cross-coupling between the *N*-tethered vinyl iodide and the keto group. The short sequence used to synthesize (±)-strychnine should also provide rapid entry into other *Strychnos* alkaloid natural products and is currently under active investigation in our laboratories.

Acknowledgment. Dedicated to my colleague and friend David Goldsmith on the occasion of his 75th birthday. We appreciate the financial support provided by the National Institutes of Health (GM 059384) and the National Science Foundation (CHE-0450779). We thank Professor Larry Overman (UC Irvine) for providing a proton NMR spectrum of the Wieland−Gumlich aldehyde (**6**) for comparison purposes.

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062728B

(22) A similar approach was successfully employed in a synthesis of strychnopivotine (**2**), and this will be described at a later date.

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