Communication

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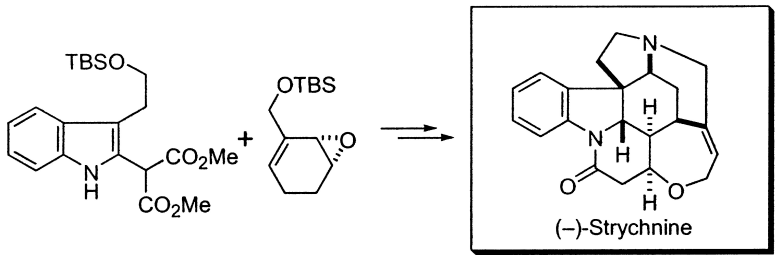

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Total Synthesis of (−)-Strychnine

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Strychnine (**1**), a well-known poison first isolated as far back as 1818,[1] has generated considerable attention among synthetic chemists mainly because of its architecturally complex structural features, including the unique heptacyclic framework as well as the six contiguous chiral centers.[2] While the first total synthesis was accomplished in 1954 by Woodward,[3a] strychnine remains a popular target for demonstrating new reactions and novel synthetic strategies.[3,4] In this communication, we report a concise stereocontrolled total synthesis of strychnine wherein efficient synthetic methodologies developed in our laboratories played crucial roles.

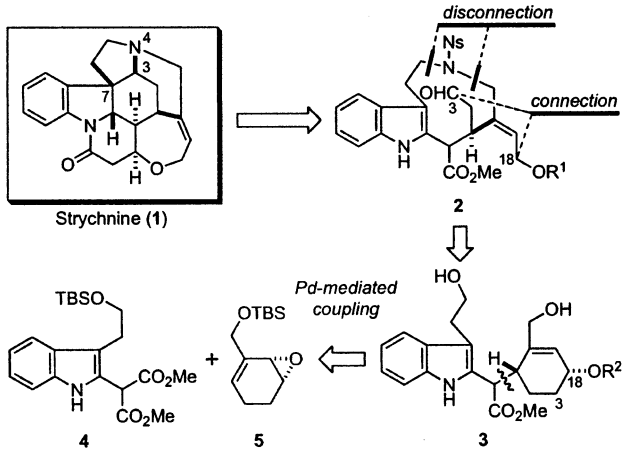
As illustrated in Scheme 1, our retrosynthesis relies upon an efficient construction of the core skeleton of **1** from the nine-membered cyclic intermediate **2**, which would be derived from the corresponding diol by means of our 2-nitrobenzenesulfonamide ($NsNH_2$) strategy.[5] To secure the geometry of the trisubstituted olefin, we planned to cleave the cyclohexene ring at the C3−18 bond of **3** to generate the two side chains. The precursor **3** should be available from the palladium-mediated coupling reaction of indolylmalonate **4** and vinyl epoxide **5**.

The synthesis of vinyl epoxide **5** commenced with methyl 1,5-cyclohexadienecarboxylate (**7**),[6] which is readily available from benzoic acid (**6**) (Scheme 2). Treatment of **9** with NBS in the presence of water gave bromohydrin **8**, which was subjected to an enzymatic resolution with lipase AYS to provide the desired chiral bromohydrin acetate **9** (46%, 99% ee) along with the unreacted enantiomer (50%, 99% ee). After reduction of **9** with DIBAL, the resultant bromohydrin **10** was treated with base to form the epoxide, and the subsequent protection of the primary alcohol as the TBS ether gave the desired vinyl epoxide **5**.

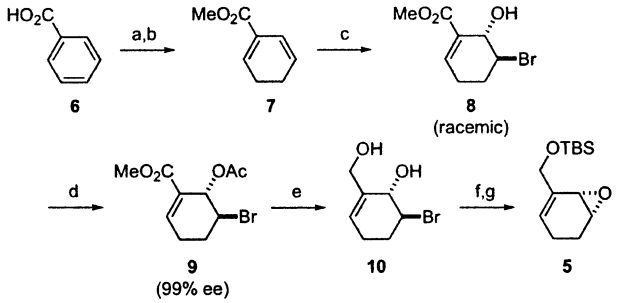
With the requisite vinyl epoxide **5** in hand, the next task was to perform the palladium-mediated coupling reaction[7] with indolylmalonate **4**,[8] which was efficiently prepared in large quantities by modification of our protocol involving radical cyclization of 2-alkenylthioanilides. While initial attempts at the coupling reaction with $Pd(PPh_3)_4$ in THF provided the desired product **11**, the yield was only 5% at best. After extensive investigation, we have found that the choice of catalyst and ligand is crucial for this process. Thus, when treated with $Pd_2(dba)_3$ and $P(2\text{-furyl})_3$ in toluene, the yield increased dramatically to afford **11** in 86% yield with complete control of regio- and stereoselectivity (Scheme 3). The coupling product **11** was then converted into diol **12** by a four-step sequence involving protection of the secondary alcohol as the MOM ether, decarbomethoxylation, installation of a Boc group on the indole nitrogen, and deprotection of the two TBS groups.

For the construction of the nine-membered cyclic amine intermediate, we devised a ring-closing double *N*-alkylation of $NsNH_2$ with diol **12** (Scheme 3).[9] Thus, upon subjection of diol **12** to the Mitsunobu reaction[10] with $NsNH_2$, the desired nine-membered Ns-amide **13** was obtained in 95% yield as the sole product. At this stage, the epimeric mixture at C16 was equilibrated to the thermodynamically more stable β-ester by treatment with DBU at

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Vinyl Epoxide[a]



[a] Reagents and conditions: (a) Na, liq NH_3−EtOH, −78 °C; (b) AcCl, MeOH, room temp; NaOMe; (c) NBS, H_2O, DMSO, room temp, 62% (three steps); (d) Lipase AYS, vinyl acetate, 40 °C, 46%, 99% ee; (e) DIBAL, CH_2Cl_2, 0 °C, 73%; (f) NaOMe, MeOH, room temp; (g) TBSCl, imidazole, CH_2Cl_2, room temp, 61% (two steps).

100 °C. Removal of the MOM group followed by Dess−Martin oxidation[11] of the resultant alcohol gave ketone **14**, which was converted into α-hydroxyketone **15** according to Rubottom's protocol.[12]

The crucial construction of the core skeleton was next achieved through a transannular formation of the iminium ion and ensuing cyclization. Oxidative cleavage of the α-hydroxyketone **15** was best performed by treatment with $Pb(OAc)_4$ in methanol benzene to furnish aldehyde **16** bearing α,β-unsaturated ester with the desired geometry. Removal of the Ns group from **16** using the standard conditions ($PhSH,Cs_2CO_3$), followed by treatment with TFA and Me_2S in one-pot induced a smooth transannular cyclization[3b,13−15] to give the pentacyclic compound **17** in 84% yield from **15**, which is an intermediate of the Kuehne's total synthesis of **1**.[3e] Finally, **17** was converted into (−)-strychnine(**1**) via the Wieland−Gumlich aldehyde (**18**)[16,17] by way of the five-step sequence reported earlier.[3d,e] All spectroscopic data of synthetic **1** were identical to those of natural strychnine.

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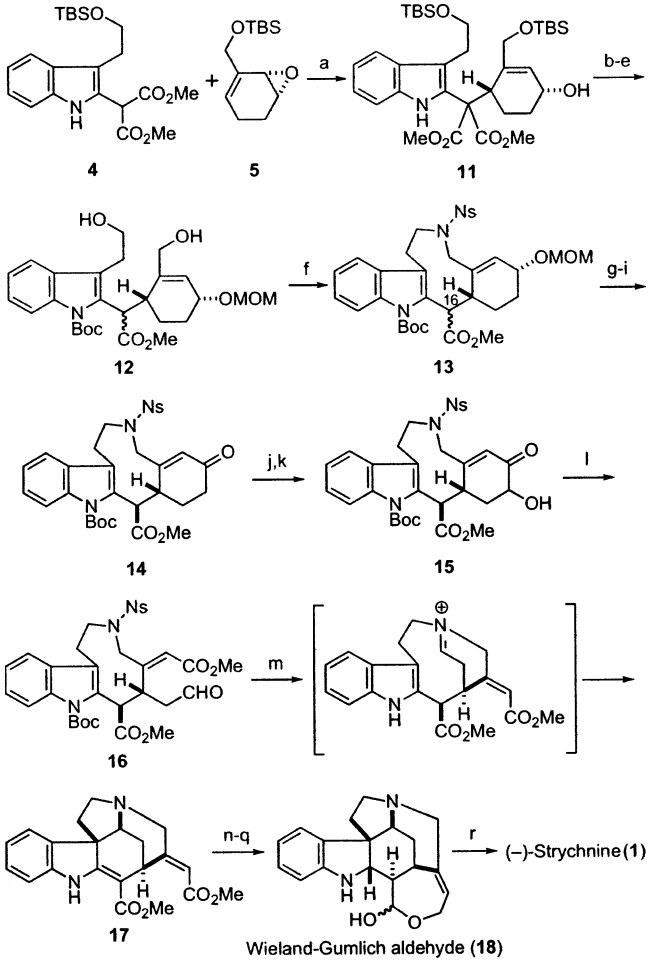
Scheme 3. Total Synthesis of (−)-Strychnine[a]



[a] Reagents and conditions: (a) $Pd_2(dba)_3$, P(2-furyl)$_3$, toluene, room temp, 86%; (b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, room temp; (c) LiI, collidine, 80 °C; (d) Boc_2O, DMAP, MeCN, room temp; (e) NH_4F·HF, DMF−NMP, room temp, 72% (four steps); (f) $NsNH_2$, PPh_3, DEAD, toluene, room temp, 95%; (g) DBU, toluene, 100 °C; (h) aq HCl, THF, 50 °C; (i) Dess−Martin periodinane, CH_2Cl_2, 0 °C, 69% (three steps); (j) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; (k) *m*CPBA, aq $NaHCO_3$−CH_2Cl_2, 0 °C; aq HCl, MeOH, room temp, 66% (two steps); (l) $Pb(OAc)_4$, MeOH-benzene, 0 °C; (m) PhSH, Cs_2CO_3, MeCN; TFA, Me_2S, CH_2Cl_2, 50 °C, 84% (two steps); (n) DIBAL, BF_3·OEt_2, CH_2Cl_2, −78 °C, 93%; (o) $NaBH_3CN$, AcOH, 10 °C; (p) NaOMe, MeOH-THF, room temp; (q) DIBAL, CH_2Cl_2, −98 °C; (r) $CH_2(CO_2H)_2$, NaOAc, Ac_2O, AcOH, 110 °C, 42% (four steps).

In conclusion, we have completed an stereocontrolled total synthesis of (−)-strychnine (**1**), demonstrating the uniqueness of the nitrobenzenesulfonamide chemistry in constructing the medium-sized cyclic amine. Finally, it should be noted that the facile construction of the polycyclic core skeleton was made possible by the removal of the nosyl group under very mild conditions. We believe that the chemistry described herein would be useful for the preparation of a variety of alkaloids.

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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323.
(2) For the structure determination, see: (a) Briggs, L. H.; Openshaw, H. T.; Robinson, R. *J. Chem. Soc.* **1946**, 903. (b) Holmes, H. L.; Openshaw, H. T.; Robinson, R. *J. Chem. Soc.* **1946**, 910. (c) Woodward, R. B.; Brehm, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 2107.
(3) (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247. (b) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403. Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116. (c) Stork, G. Presented at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, September 21, 1992. (d) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293. Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776. (e) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490. Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9427. (f) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685. (g) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 395. Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem.−Eur. J.* **2000**, *6*, 655. (h) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479. Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324. (i) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (j) Nakanishi, M.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1934. Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801. (k) Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261. (l) Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546.
(4) For reviews, see: (a) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455. (b) Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1144.
(5) (a) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353. (b) Kan, T.; Fukuyama, T. *J. Synth. Org. Chem., Jpn.* **2001**, *59*, 779.
(6) Boger, D. L.; Patel, M.; Takusagawa, F. *J. Org. Chem.* **1985**, *50*, 1911.
(7) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, 2575.
(8) (a) For the detailed experimental procedure, see the Supporting Information. (b) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791. (c) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, S.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.
(9) (a) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 1891. (b) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2003**, *59*, 8571.
(10) Mitsunobu, O. *Synthesis* **1981**, 1.
(11) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(12) Rubottom, G. M.; Gruber, J. M.; Juve, H. D., Jr.; Charleson, D. A. *Organic Syntheses*; Wiley & Sons: New York, 1990; Collect Vol. VII, 282.
(13) Haley-Mason, J. *Pure Appl. Chem.* **1975**, *41*, 167.
(14) Bonjoch, J.; Fernàndez, J-.C.; Valls, N. *J. Org. Chem.* **1998**, *63*, 7338.
(15) Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Lynch, V. *Tetrahedron Lett.* **1999**, *40*, 5135.
(16) (a) Wieland, H.; Gumlich, W. *Liebigs Ann. Chem.* **1932**, *494*, 191. (b) Wieland, H.; Kaziro, K. *Liebigs Ann. Chem.* **1933**, *506*, 60.
(17) For the conversion of Wieland−Gumlich aldehyde into strychnine, see: Anet, F. A. L.; Robinson, R. *Chem. Ind.* **1953**, 245.

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