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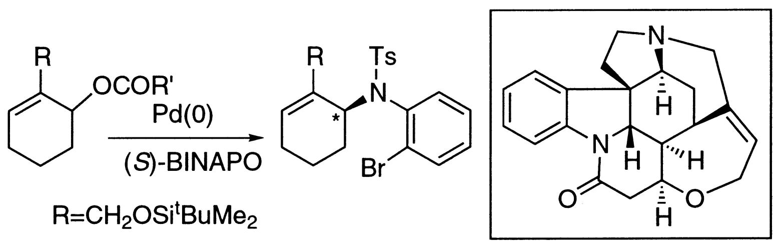

(-)-Strychnine

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# A Novel and General Synthetic Pathway to Strychnos Indole Alkaloids: Total Syntheses of (−)-Tubifoline, (−)-Dehydrotubifoline, and (−)-Strychnine Using Palladium-Catalyzed Asymmetric Allylic Substitution

Miwako Mori,* Masato Nakanishi, Daisuke Kajishima, and Yoshihiro Sato

*Contribution from the Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan*

Received November 18, 2002; E-mail: mori@pharm.hokudai.ac.jp

***Abstract:*** A method of palladium-catalyzed asymmetric allylic substitution for synthesizing 2-substituted cyclohexenylamine derivatives was established. Treatment of a 2-silyloxymethylcyclohexenol derivative with *ortho*-bromo-*N*-tosylaniline in the presence of $Pd_2dba_3 \cdot CHCl_3$ and (*S*)-BINAPO in THF afforded a cyclohexenylamine derivative with 84% ee in 80% yield. The Heck reaction was carried out to produce an indolenine derivative in good yield. Using this method, we synthesized indolenine derivative **7**, which was recrystallized from EtOH to give an optically pure compound. From this compound, tetracyclic ketone **13**, which should be a useful intermediate for the synthesis of indole alkaloids, could be synthesized. The total syntheses of (−)-dehydrotubifoline, (−)-tubifoline, and (−)-strychnine were achieved from **13**. All ring constructions for the syntheses of these natural products were achieved using a palladium catalyst.

Palladium catalysts have played an important role in recent synthetic organic chemistry, and palladium-catalyzed reactions have been used quite often in the syntheses of natural products. We have already reported an enantioselective synthesis of 2-arylcyclohexene derivatives using palladium-catalyzed asymmetric allylic substitution (Scheme 1).[1] When 2-arylcyclohexenol derivative **I** is treated with Pd(0) in the presence of a nucleophile, $\pi$-allylpalladium complex **II** is formed. Although palladium complex **II** is in a meso form, if the palladium catalyst has a chiral ligand, a nucleophile should attack from one side of $\pi$-allylpalladium complex **II**, and the chiral cyclohexene derivative **III** or *ent*-**III** would be produced. Using this method, we have synthesized cyclohexene derivative **1a** as a chiral form, which was converted into hexahydroindole derivative **2** via zirconium-promoted cyclization. From compound **2**, total syntheses of (−)-mesembrane and (−)-mesembrine[1a] were achieved. Furthermore, cyclohexene derivative **1b** was also synthesized as a chiral form using this procedure, and the total syntheses of (+)-crinamine, (−)-haemanthidine, and (+)-pretazetine were achieved via carbonyl-ene cyclization as a key step.[1b,c]

There are many alkaloids that have an aromatic ring connected to a cyclohexane ring. Even in the case of indole alkaloids, these ring systems are found in the molecule. These alkaloids could be synthesized from a 2-arylcyclohexene derivative (Scheme 2). Here, we report the construction of an indole skeleton as a chiral form using palladium-catalyzed allylic substitution[2] followed by a palladium-catalyzed Heck reaction.

(1) (a) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 5265. (b) Nishimata, T.; Mori, M. *J. Org. Chem.* **1998**, *63*, 7586. (c) Nishimata, T.; Yamaguchi, K.; Mori, M. *Tetrahedron Lett.* **1999**, *40*, 5713.

## Synthesis of Chiral 2-Substituted Cyclohexenylamine Derivatives Using Palladium-Catalyzed Allylic Substitution

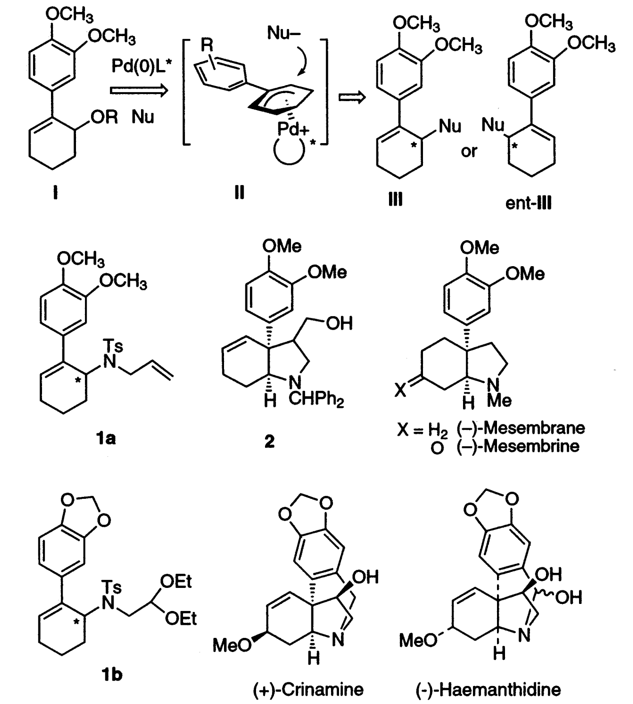
If we expect to obtain an indole derivative as a chiral form, treatment of **1a** with Pd(0) having a chiral ligand should afford **IV** as a chiral form. However, because the functional group in **IV** is only an olefin, it is difficult to synthesize indole alkaloids from **IV**. Thus, an alternative procedure was considered. If cyclohexenol derivative **V** having the functional group at the 2-position is reacted with an *ortho*-haloaniline derivative in the presence of Pd(0) with a chiral ligand, we would obtain cyclohexenylamine derivative **VI**, which should give an indoline derivative as a chiral form by treatment with a palladium catalyst (Scheme 3).

From this indoline derivative **VII**, indole alkaloids, such as tubifoline aspidospermine and strychnine, would be synthesized.

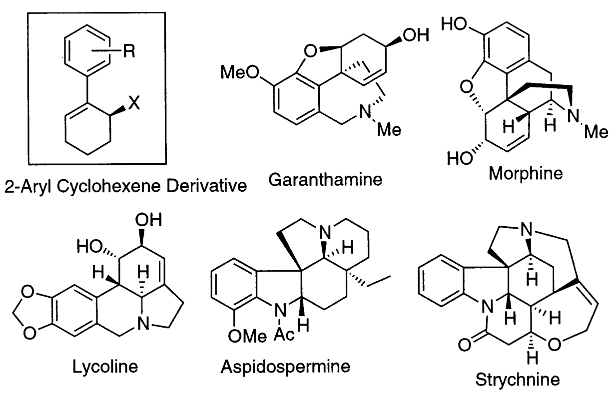
At first, 2-carboethoxy cyclohexenol derivative **3a**[3] was chosen as a substrate. When a DMF solution of **3a** and allyltosylamide **4** was stirred in the presence of 2.6 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 5.2 mol % of (*S*)-BINAPO[4] at room temperature for 3 h, cyclohexenylamine derivative **5a** was obtained in 40% yield, but the enantiomeric excess (ee) was only 5%[5] (Table 1, run 1). Compounds **3b** or **3c** having the ketal or the hydroxymethyl group as a functional group did not

(2) Recently, similar type reactions were reported by two groups: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262. (b) Hamada, Y.; Sakaguchi, K.; Hatano, K.; Hara, O. *Tetrahedron Lett.* **2001**, *42*, 1297.
(3) Graff, M.; Al Dilaimi, A.; Seguineau, P.; Rambaud, M.; Villeras, J. *Tetrahedron Lett.* **1986**, *27*, 1577.
(4) Grubbs, B. H.; DeVries, R. A. *Tetrahedron Lett.* **1977**, *18*, 1879.
(5) Conversion of **5a** into **5c** was carried out by treatment with $LiAlH_4$, and the ee of **5c** was determined by HPLC analysis using DAICEL CHIRALCEL AD (hexane/$^i$PrOH = 9:1).

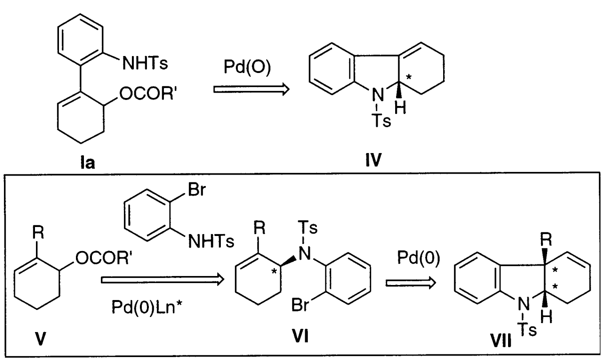
***Scheme 1.*** Asymmetric Synthesis of 2-Arylcyclohexene Derivatives



***Scheme 2.*** Natural Products Having a 2-Arylcyclohexene Moiety



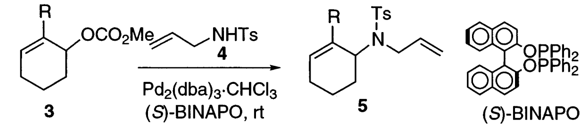
***Scheme 3.*** Our Plan for the Synthesis of an Indole Derivative



afford the desired product (runs 2 and 3). In the case of 2-benzyloxymethylcyclohexenol derivative **3d**, the desired compound **5d** was obtained in 49% yield, and the ee showed 34%[6] (run 4). Encouraged by this result, the *tert*-butyldimethylsilyloxymethyl group was chosen as a functional group, and the reaction was carried out under similar conditions in THF. After 100 h, the desired compound **5e** with 78% ee[6] was obtained in 53% yield (run 5). When the solvent was changed to DMF for this reaction, the reaction time was surprisingly shortened to 3 h (run 6). Other silyl groups afforded similar results (runs 7 and 8). Various solvents, such as $CH_2Cl_2$, DMSO, and $CH_3CN$, were used for this reaction (runs 9−11), and DMF gave the best results (run 6).

Next, to improve the ee of **5e**, the reaction was carried out at a lower temperature. When the reaction was carried out at 0 °C, the reaction rate decreased, and the desired compound **5e** was obtained in 50% yield with a slightly increased ee after 120 h (Table 2, run 2). Thus, vinyl carbonate developed by our group was used as a leaving group.[7] As expected, the reaction rate increased, and even at 0 °C the starting material disappeared on TLC after 11 h, and the same ee was obtained (run 4). At

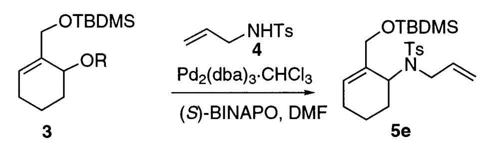
***Table 1.*** Asymmetric Allylic Substitution[a]



| run | R | | solvent | time (h) | | yield (%) | ee (%) | 3 (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | COOEt | 3a | DMF | 3 | 5a | 40 | 5 | — |
| 2 | | 3b | THF | 24 | | — | — | 84 |
| 3 | $CH_2OH$ | 3c | DMF | 13 | | — | — | 29 |
| 4 | $CH_2OBn$ | 3d | THF | 28 | 5d | 49 | 34 | 36 |
| 5 | $CH_2OTBDMS$ | 3e | THF | 100 | 5e | 53 | 78 | 23 |
| 6 | $CH_2OTBDMS$ | 3e | DMF | 3.5 | 5e | 70 | 77 | — |
| 7 | $CH_2OTES$ | 3f | DMF | 2 | 5f | 66 | 71 | — |
| 8 | $CH_2OTBDPS$ | 3g | DMF | 12 | 5g | 57 | 75 | — |
| 9 | $CH_2OTBDMS$ | 3e | $CH_2Cl_2$ | 72 | 5e | 44 | 68 | — |
| 10 | $CH_2OTBDMS$ | 3e | DMSO | 2.5 | 5e | 44 | 76 | — |
| 11 | $CH_2OTBDMS$ | 3e | $CH_3CN$ | 8 | 5e | 48 | 73 | — |

[a] All reactions were carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ (2.6 mol %) and (*S*)-BINAPO at room temperature. [b] Enantiomeric excesses were determined by HPLC using a DAICEL CHIRACEL AD (hexane:$^i$PrOH = 9:1) after debenzylation of **5d** or desilylation of **5e**.

***Table 2.*** Effect of Temperature for Allylic Substitution[a]



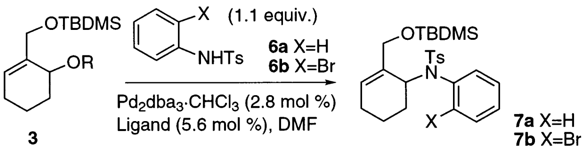
| run | R | | conditions | yield (%) | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | $CO_2Me$ | 3a | rt, 3.5 h | 70 | 77 |
| 2 | $CO_2Me$ | 3a | 0 °C, 120 h | 50 | 80 |
| 3 | $CO_2CH_2{=}CH_2$ | 3h | rt, 10 min | 76 | 77 |
| 4 | $CO_2CH_2{=}CH_2$ | 3h | 0 °C, 11 h | 50 | 80 |
| 5 | $CO_2CH_2{=}CH_2$ | 3h | −20 °C, 72 h | 49 | 82 |
| 6 | $PO(OEt)_2$ | 3i | −20 °C, 72 h | 38 | 82 |

[a] All reactions were carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ (2.6 mol %) and (*S*)-BINAPO. [b] Enantiomeric excesses were determined by HPLC using a DAICEL CHIRACEL AD (hexane:$^i$PrOH = 9:1) after desilylation of **5e**.

(6) The ee's of **5d** and **5e** were determined after conversion into **5c**.[5]

(7) (a) Mori, M.; Nishimata, T.; Nagasawa, Y.; Sato, Y. *Adv. Synth. Catal.* **2001**, *343*, 34. Palladium-catalyzed allylation using allyl vinyl carbonate was reported. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793. (c) Shimizu, I.; Minami, I.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 1797.

***Table 3.*** Reaction of **3** with a *N*-Tosylaniline Derivative[a]



| run | R | | ligand | 6 | temp (°C) | time (h) | | yield (%) | ee (%)[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1[c] | $CO_2Me$ | **3e** | dppb | **6a** | rt | 96 | **7a** | 12 | |
| 2 | $CO_2Me$ | **3e** | (*S*)-BINAPO | **6a** | rt | 3 | **7a** | 85 | 76 |
| 3 | $CO_2Me$ | **3e** | dppb | **6b** | 60 | 48 | **7b** | | |
| 4 | $CO_2Me$ | **3e** | (*S*)-BINAPO | **6b** | rt | 7 | **7b** | 78 | 80 |
| 5 | $CO_2CH_2{=}CH_2$ | **3h** | (*S*)-BINAPO | **6b** | 0 | 21 | **7b** | 64 | 84 |
| 6 | $CO_2CH_2{=}CH_2$ | **3h** | (*S*)-BINAPO | **6b** | −20 | 168 | **7b** | 67 | 83 |
| 7 | $PO(OEt)_2$ | **3i** | (*S*)-BINAPO | **6b** | 0 | 36 | **7b** | 80 | 84 |

[a] All reactions were carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ (2.6 mol %) and (*S*)-BINAPO in THF. [b] Enantiomeric excesses were determined by HPLC using a DAICEL CHIRACEL OJ after desilylation of **7**. [c] Here, dppb was used as a ligand.

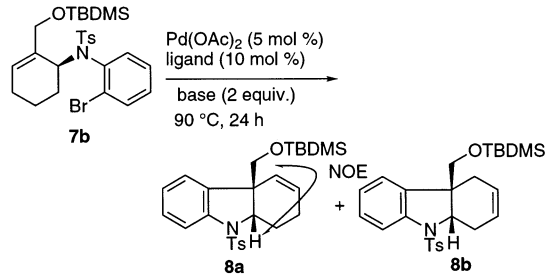
−20 °C, the ee slightly increased to 82% (run 5). When phosphate was used as a leaving group, the reaction proceeded at the same temperature, and the same ee was obtained, although the yield of **5e** slightly decreased (run 6).

To construct an indole skeleton, the nucleophile was changed to *ortho*-halo aniline derivatives. When a DMF solution of **3e** and *N*-tosylaniline **6a** was stirred in the presence of $Pd_2dba_3{\cdot}CHCl_3$ and dppb at room temperature, the desired compound **7a** was obtained in only 12% yield after 96 h (Table 3, run 1). When *ortho*-bromo-*N*-tosylaniline **7b** was used as a nucleophile, the reaction did not proceed (run 3). Surprisingly, when the reaction of **3e** with **6a** was carried out in the presence of Pd(0) and (*S*)-BINAPO as a ligand, the desired compound **7a** was obtained in 85% yield with 76% ee[8] after only 3 h (run 2). Furthermore, the use of *ortho*-bromo-*N*-tosylaniline **6b** as a nucleophile gave **7b** with 80% ee[8] in 78% yield (run 4). These results indicate that the use of (*S*)-BINAPO as a ligand accelerated the reaction rate, although the reason for this is not clear. In the case of vinyl carbonate **2h**, the reaction proceeded at 0 °C, and the desired compound with 84% ee was obtained in 64% yield (run 5). The lower reaction temperature did not affect the ee of **7b** (run 6). In the case of phosphate **2i**, the reaction rate slightly decreased as compared to that of vinyl carbonate **2h**, but **7b** with higher ee was obtained in high yield (run 7).

Because the asymmetric synthesis of a cyclohexenylamine derivative was established, the construction of an indole skeleton was next examined using the Heck reaction.[9] When a DMF solution of **7b** was stirred in the presence of 5 mol % of $Pd(OAc)_2$, 10 mol % of $PPh_3$, and $^iPr_2NEt$ (2 equiv) as a base at 90 °C for 24 h, the desired indolines **8a** and **8b** were obtained in 26% and 13% yields, respectively, along with **7b** in 31% yield (Table 4, run 1). The use of a bidentate ligand did not give a good result (run 2). When $Ag_2CO_3$[9e,f] was used as a base to prevent the formation of olefin isomer **8b**,[9g] the yield of the desired indoline **8a** increased to 42%, although **8b** was formed in 8% yield (run 3). Various ligands were examined, and $PMe_2Ph$ gave good results (runs 4 and 5). The reaction rate decreased when DMSO was used as a solvent, but only **8a** was formed (run 7). The results of NOE experiment of **8a** indicated that the stereochemistry of the ring junction of **8a** is cis.

Thus, a novel method for synthesizing chiral indoline derivative **8a** from cyclohexenol derivative **2i** using palladium-catalyzed asymmetric substitution followed by the Heck reaction was established.

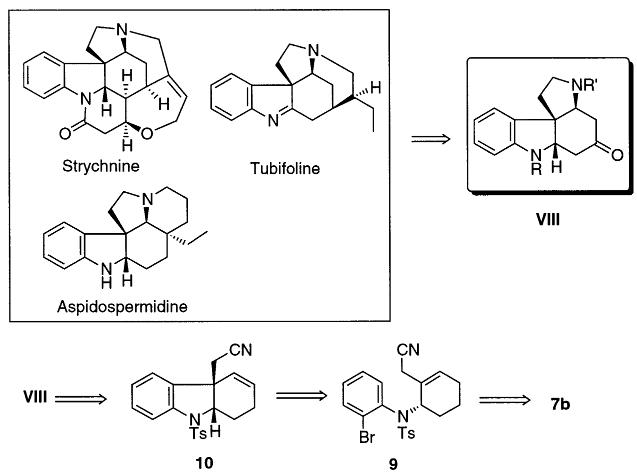
***Table 4.*** Synthesis of an Indoline Derivative by the Heck Reaction



| run | ligand | solvent | base | **8a** (%) | **8b** (%) | **7b** (%) |
|---|---|---|---|---|---|---|
| 1 | $PPh_3$ | DMF | $^iPr_2NEt$ | 26 | 13 | 31 |
| 2 | dppb | DMF | $^iPr_2NEt$ | 13 | 1 | 76 |
| 3 | $PPh_3$ | DMF | $Ag_2CO_3$ | 42 | 8 | 33 |
| 4 | $PMePh_2$ | DMF | $Ag_2CO_3$ | 52 | 13 | 29 |
| 5 | $PMe_2Ph$ | DMF | $Ag_2CO_3$ | 56 | 19 | 20 |
| 6 | $PMe_2Ph$ | $C_3H_7CN$ | $Ag_2CO_3$ | 17 | 1 | 71 |
| 7 | $PMe_2Ph$[a] | DMSO | $Ag_2CO_3$ | 47 | 0 | 38 |

[a] Reaction temp: 105 °C.

***Scheme 4.*** Retrosynthetic Analysis of Indole Alkaloids



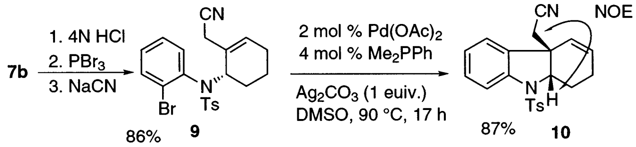
## Synthesis of a Tetracyclic Ketone as an Important Intermediate for the Synthesis of Indole Alkaloids

We next turned our attention to the total syntheses of indole alkaloids such as strychnine, tubifoline, and aspidospermine (Scheme 4). These alkaloids could be synthesized from tetracyclic ketone **VIII**, which should be an important intermediate for the synthesis of various indole alkaloids as chiral forms. Compound **VIII** would be obtained from nitrile **10**, which would be obtained from **9** by a Heck reaction. Compound **9** should be

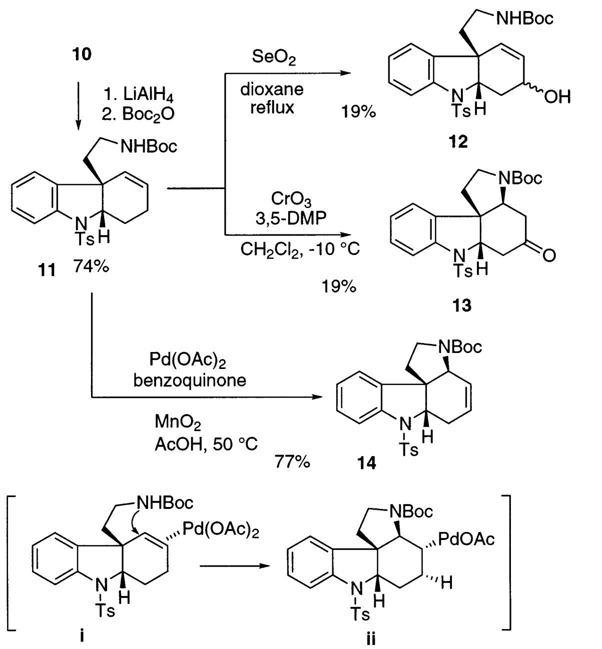
(8) The ee's of **6a** and **6b** were determined by HPLC analyses using DAICEL CHIRALCEL OJ-R ($CH_3CN/H_2O$ = 9:1) and DAICEL CHIRALCEL OJ (hexane/$^i$PrOH = 9:1) after desilylation by treatment with 4 N HCl, respectively.

(9) (a) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320. (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (c) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: New York, 1995; p 125. (d) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons: New York, 2002; Vol. I, Part IV. (e) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (f) Grigg, R.; Loganathan, V.; Santhakumar, V. *Tetrahedron Lett.* **1991**, *32*, 687. (g) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834.

*Scheme 5.* Synthesis of an Indoline Derivative



*Scheme 6.* Allylic Oxidation of a Cyclohexene



obtained from **7b** as a chiral form. Thus, the possibility of synthesizing tetracyclic ketone **VIII** from **7b** was examined.

Deprotection of **7b** with 4 N HCl followed by treatment with $PBr_3$ and then NaCN in DMSO gave nitrile **9** in good yield. The palladium-catalyzed Heck reaction of **9** proceeded smoothly under previous reaction conditions to give **10** in high yield (Scheme 5). The results of an NOE experiment of **10** indicated that the ring junction of the fused 5,6-membered ring is also cis.

To obtain tetracyclic ketone **VIII**, the Michael addition of amine, which would be obtained from nitrile **10**, to $\alpha,\beta$-unsaturated ketone was examined. Treatment of **10** with $LiAlH_4$ followed by protection of the primary amine with $Boc_2O$ afforded compound **11**. Allylic oxidation of **11** with $SeO_2$ gave allyl alcohol **12** in low yield. On the other hand, treatment of **11** with $CrO_3$ in the presence of 3,5-DMP at −10 °C afforded the desired tetracyclic ketone **13**, but the yield was only 19%. Various attempts to improve the yield of **13** were made, but the results were fruitless. Thus, palladium-catalyzed allylic oxidation of **11** was carried out. When an acetic acid solution of **11** was stirred in the presence of 10 mol % of $Pd(OAc)_2$, 40 mol % of benzoquinone, and 2 equiv of $MnO_2$[10] at 50 °C for 15 min, we surprisingly obtained compound **14** in 77% yield. Probably, the double bond of **11** coordinates to the palladium catalyst, and then amide nitrogen attacks olefin to give palladium complex **ii**. $\beta$-Hydrogen elimination from **ii** then occurs to give **14** (Scheme 6).

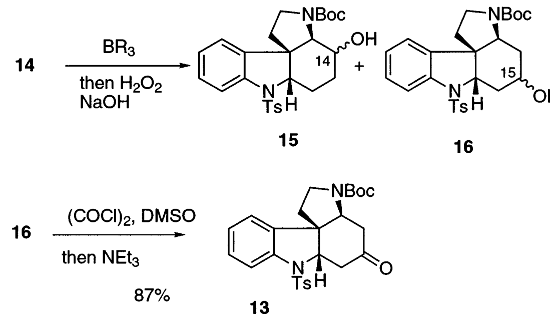
Subsequently, conversion of the olefin of **14** into ketone was carried out. On the basis of the results of a modeling study, it

(10) Hansson, S.; Heumann, A.; Rain, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975.

*Table 5.* Hydroboration of **14**

| run | $BR_3$ | temp (°C) | **15** (%) | **16** (%) | **14** (%) |
|---|---|---|---|---|---|
| 1 | $BH_3$·THF | 0 | 51 | 49 | |
| 2 | $BH_3$·THF | −20 | 44 | 49 | |
| 3 | 9-BBN | rt | 9 | 34 | 41 |
| 4 | 9-BBN | 50 | 5 | 80 | |

*Scheme 7.* Synthesis of Tetracyclic Ketone **13**



was thought that the C-15 position is less hindered than the C-14 position. Thus, it was expected that the hydroxyl group would be introduced at the C-15 position by hydroboration. Hydroboration of **14** using $BH_3$·THF followed by treatment with $H_2O_2$ in aqueous NaOH gave alcohols **15** and **16** in 49% and 51% yields, respectively (Table 5, run 1). The same results were obtained even at a lower reaction temperature (run 2). The use of a large hydroboration reagent, 9-BBN, afforded the desired alcohols **16** as a major product, and an elevated temperature gave alcohols **16** in 80% yield (runs 3 and 4). Swern oxidation of **16** was carried out to give the desired tetracyclic ketone **13** in high yield.

Thus, we achieved the synthesis of tetracyclic ketone **13** from cyclohexenol derivative **7b** (Scheme 7).

## Total Syntheses of (−)-Dehydrotubifoline and (−)-Tubifoline and Determination of the Absolute Configuration of a 2-Silyloxymethylcyclohexenylamine Derivative

As target molecules for the synthesis of indole alkaloids, we focused on *Strychnos* alkaloids, (−)-dehydrotubifoline and (−)-tubifoline,[11] which have been synthesized by several groups,[12] as racemic[12a−d] or chiral[12e] forms.

A retrosynthetic analysis of (−)-tubifoline is shown in Scheme 8.[13] (−)-Tubifoline would be synthesized from dehydrotubifoline, which would be obtained from **IX** using the Heck reaction. Compound **IX** would be obtained from **X**, which would be synthesized from tetracyclic ketone **13**. Thus, the possibility of conversion of the keto-carbonyl group of **13** into olefin using a palladium catalyst was examined.

At first, we tried to convert ketone **13** (84% ee) regioselectively into an enol triflate. Treatment of **13** with LDA followed by the addition of $PhNTf_2$ at −78 °C afforded enol triflates **17**

(11) For the isolation and structural elucidation of this alkaloid, see: Kump, W. G.; Patel, M. B.; Rowson, J. M.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1497.

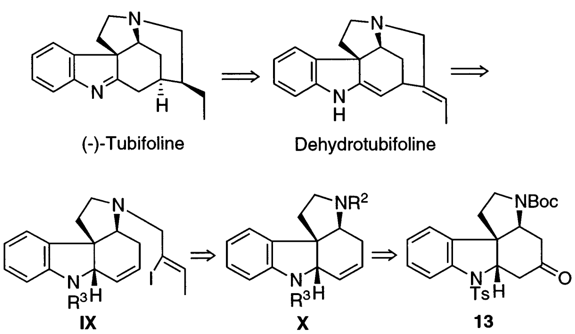
(12) (a) Danson, B. A.; Harley-Mason, J.; Foster, G. H. *Chem. Commun.* **1968**, 1233. (b) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881. (c) Ban, Y.; Yoshida, K.; Goto, I.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657. (d) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299. (e) Amat, M.; Coll, M.-D.; Bosch, J.; Espinosa, E.; Molins, E. *Tetrahedron: Asymmetry* **1997**, *8*, 935.

(13) Preliminary report: Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. *Org. Lett.* **2001**, *3*, 1913.

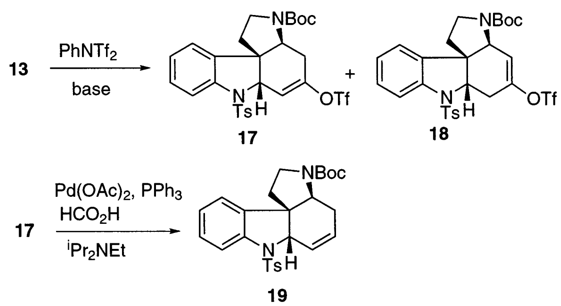
***Table 6.*** Conversion of Ketone into Enol Triflate

| run | base | temp (°C) | **17** (%) | **18** (%) | **13** (%) |
|---|---|---|---|---|---|
| 1 | LDA | −78 | 8 | 14 | 55 |
| 2 | KHMDS | −78 | 21 | 44 | 24 |
| 3 | KHMDS | −50 | 53 | trace | 11 |
| 4 | KHMDS | −35 | 64 | | |
| 5 | KHMDS | 0 | 54 | | |

***Scheme 8.*** Retrosynthetic Analysis of (−)-Tubifoline




***Scheme 9.*** Conversion of Ketone **13** into Olefin **19**




and **18** in 8% and 14% yields, respectively (Table 6, run 1). The base was changed to potassium hexamethyldisilazamide (KHMDS),[14] and the reaction was carried out at −78 °C to give **17** and **18** in 65% yield (ratio of 1 to 2, run 2). Because **17** was considered to be a thermodynamic product, the reaction temperature was raised to −50 °C. As a result, the yield of **17** improved to 53%, and only a small amount of **18** was formed. At −35 °C, the desired compound **17** was obtained as a sole product in 64% yield (runs 3 and 4). Treatment of enol triflate **17** with $HCO_2H$ and $PPh_3$ in the presence of $Pd(OAc)_2$ and $PPh_3$[15] gave the desired olefin **19** in quantitative yield (Scheme 9).

Deprotection of the tosyl group of **19** with sodium naphthalenide followed by treatment with $CF_3CO_2H$ gave diamine. Monoalkylation with **21**[16a] in the presence of $K_2CO_3$ gave **20** in 49% yield from **19**. An intramolecular Heck reaction[16a,17] using a palladium catalyst gave a pentacyclic compound in 59% yield, whose $^1$H and $^{13}$C NMR spectra agreed with those of (−)-dehydrotubifoline reported in the literature.[16] However, the $[\alpha]_D$ value of (−)-dehydrotubifoline is not known. Thus, hydrogenation of (−)-dehydrotubifoline with $PtO_2$ in EtOH was carried out (Scheme 10). The $[\alpha]_D$ value[18] and $^1$H and $^{13}$C NMR spectra of the hydrogenation product agreed with those of (−)-tubifoline reported in the literature.[11,19]

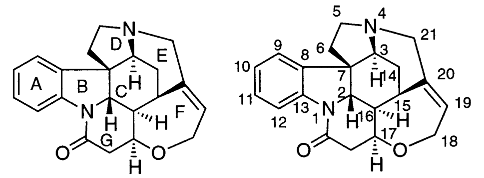
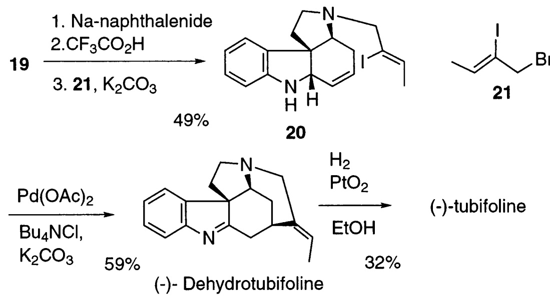



***Figure 1.*** (−)-Strychnine.

***Scheme 10.*** Synthesis of (−)-Tubifolin



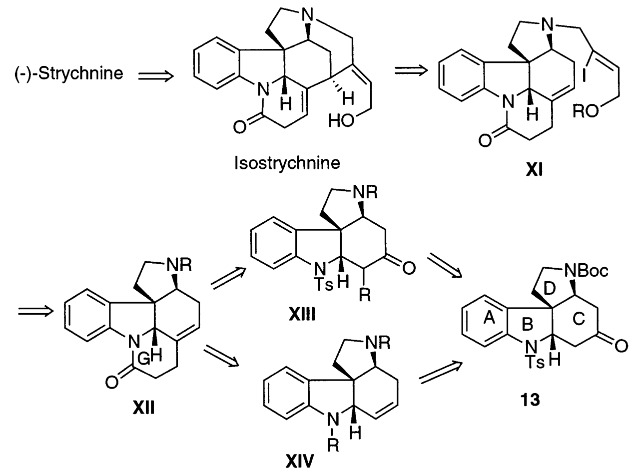

The results indicated that the absolute configuration of **7b** obtained by asymmetric allylic substitution was *S*. Thus, we succeeded in the total syntheses of (−)-dehydrotubifoline and (−)-tubifoline from allylamine derivative **7b**, which was synthesized by palladium-catalyzed asymmetric allylic substitution by 16 steps. All of the steps for the ring constructions were achieved using palladium catalysts.

## Total Synthesis of (−)-Strychnine

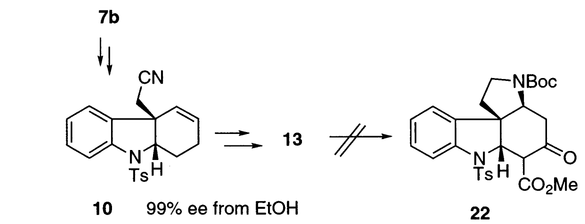
(−)-Strychnine,[20] which is the most well-known of the *Strychnos* alkaloid, has seven rings and six asymmetric centers in the molecule and is one of the most complex natural products in its size (Figure 1). Although Woodward succeeded in the total synthesis of (−)-strychnine in 1954,[21] there were no other reports on the total synthesis of strychnine for about 40 years. However, tremendous progress has been made recently in synthetic organic chemistry using organometallic complexes, and the total syntheses of complicated natural products have been achieved using novel procedures. In 1992, Magnus[22] reported the total synthesis of strychnine, and Overman succeeded in the first asymmetric total synthesis of (−)- and (+)-strychnine in 1993.[23] Following these reports, several groups succeeded in the total synthesis of (−)- or (±)-strychnine.[24,25] Rawal's synthetic process is particularly remarkable, although strychnine obtained by his process is in a racemic form.[25e] Very recently, Vollhardt succeeded in the total synthesis of (±)-strychnine using an ingenious cobalt-catalyzed [2+2+2]cycloaddition as a key step.[26] In the past decade, eight synthetic

(14) (a) Stang, P. J.; Dueber, T. E. *Org. Synth.* **1974**, *54*, 79. (b) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(15) Cacchi, S.; Morera, E.; Orter, G. *Tetrahedron Lett.* **1984**, *25*, 4821.
(16) (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030. (b) Crawley, G. C.; Harley-Mason, J. *Chem. Commun.* **1971**, 685. (c) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966.
(17) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.
(18) 84% ee, $[\alpha]^{22}_D$ −311° (*c* 0.236, AcOEt).
(19) Schumann, D.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 1996.
(20) Isolation: (a) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323. Structural elucidation: (b) Briggs, L. H.; Openshaw, H. T.; Robinson, R. *J. Chem. Soc.* **1946**, 903. (c) Woodward, R. B.; Brehm, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 2107.
(21) (a) Woodward, R. B.; Cave, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. J. *J. Am. Chem. Soc.* **1954**, *76*, 4749. (b) Woodward, R. B.; Cave, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. J. *Tetrahedron* **1963**, *19*, 247.
(22) Magnus, P.; Giles, M.; Bonnet, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, A. *J. Am. Chem. Soc.* **1993**, *115*, 8116.
(23) (a) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293. (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776.
(24) For a review of the total synthesis of strychnine, see: Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455.

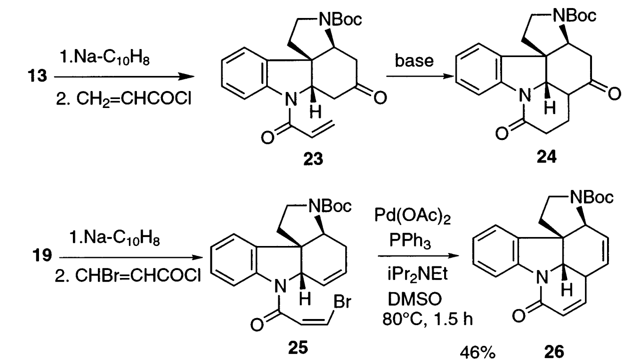
***Scheme 11.*** Retrosynthetic Analysis of (−)-Strychnine



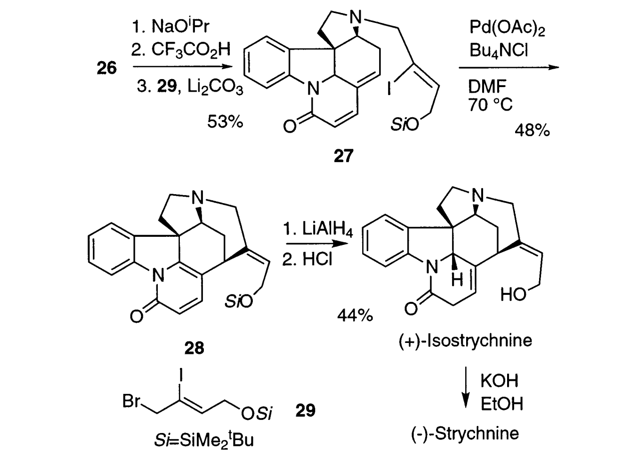
***Scheme 12.*** Introduction of an Esterl Group at the α-Position of a Keto-Carbonyl Group



***Scheme 13.*** Construction of a G-Ring



***Scheme 14.*** Total Synthesis of (−)-Strychnine



approaches[25f] to strychnine have been successful. Among them, four enantiospecific syntheses of (−)-strychnine have been reported. Magnus succeeded in the total synthesis using a relay compound obtained from (−)-strychnine.[22] Overman prepared the starting material by an enzymatic desymmetrization.[23] Kuhne[25a] succeeded in the total synthesis of (−)-strychnine from a chiral pool, L-tryptophane, and Bosch[25b] used diastereoselective reductive double amination for the synthesis of perhydroindolole derivative as an intermediate. However, there has been no report on the total synthesis of (−)-strychnine from an enantiomerically pure compound obtained by a transition metal-catalyzed asymmetric synthesis.

We have succeeded in the total synthesis of (−)-dehydrotubifolin and (−)-tubifoline from an optically active cyclohexene derivative synthesized by palladium-catalyzed asymmetric allylic substitution as a key step. The next target molecule that we focused on is (−)-strychnine,[27] which should be synthesized from tetracyclic ketone **13**. Our retrosynthetic analysis of (−)-strychnine is shown in Scheme 11. We have already constructed the ABCD rings of strychnine as a tetracyclic ketone.[13] Thus, construction of the G-ring is important for the synthesis of (−)-strychnine from tetracyclic ketone **13**. Two pathways should be considered. One is the introduction of an alkyl group at the α-position of the carbonyl group of **13** to give **XII** followed by the formation of a carbon−nitrogen bond for construction of the G-ring. The other is the introduction of an acyl group on nitrogen to form **XIV** and then construction of the G-ring. Synthesis of cyclohexene derivative **7b** was carried out using palladium-catalyzed asymmetric allylic substitution.

At first, we chose the former reaction pathway to construct **XII** by introduction of an acyl group at the α-position of the carbonyl group in **13**, which was obtained from **10**. Compound **7b** was converted into compound **10**, which was recrystallized from EtOH to give optically pure **10** ($[\alpha]_D$ −46.7°, 99% ee,[28] 73% recovery). However, many attempts to introduce an acyl group to the α-position of the keto-carbonyl group of **13** were fruitless due to steric hindrance of the large protecting group on aniline nitrogen (Scheme 12).

Thus, we next tried to introduce an acyl group on nitrogen to form a carbon−carbon bond (Scheme 13). Deprotection of the tosyl group of **13** followed by acylation with acryloyl chloride gave compound **23**. Michael addition was carried out by treatment with *t*-BuOK, but a low yield of **24** was obtained, and the reproducibility was not good. Thus, we tried construction of a G-ring by the Heck reaction. Detosylation followed by treatment with 3-bromoacryloyl chloride in the presence of $K_2CO_3$ gave **25**, which was treated with 10 mol % of $Pd(OAc)_2$ and 20 mol % of $PPh_3$ in the presence of $^iPr_2NEt$ in DMSO at 80 °C for 1.5 h. We were very pleased to find that pentacyclic compound **26** was obtained in 46% yield.

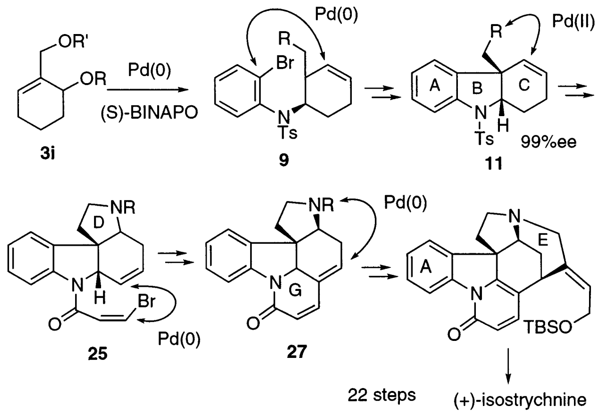
(25) Enantioselective syntheses: (a) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9427. (b) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 395. Racemic syntheses: (c) Stork, G. Reported at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, September 21, 1992. (d) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490. (e) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685. (f) Very recently, Bodwell reported the total synthesis of (±)-strychnine: Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261.

(26) (a) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479. (b) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324.

(27) Preliminary report: Nakanishi, M.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1934.

(28) The enantiomeric purty of **13** was determined by HPLC analysis (DAICEL CHIRALPAK AD, hexane/$^iPrOH$ 95/5).

***Scheme 15.*** Summary of Total Synthesis of (−)-Strychnine




Isomerization of the double bond of **26** by NaO$^i$Pr in $^i$PrOH followed by deprotection of the Boc group and then alkylation with **29** afforded compound **27**, which is an intermediate for the synthesis of (±)-strychnine reported by Vollhardt. Although the spectral data of **24** agreed with those of the intermediate reported by Vollhardt, the $[\alpha]_D$ value has not been known because it is in a racemic form in this case. Thus, compound **27** was converted into (−)-strychnine (Scheme 14). Treatment of **27** with $Pd(OAc)_2$, $Bu_4NCl$, and $K_2CO_3$ in DMF afforded hexacyclic compound **28**, which was treated with $LiAlH_4$ followed by deprotection of the silyl group to give (+)-isostrychnine, whose spectral data and $[\alpha]^{20}_D$ value [+23.7° (*c* 0.59, EtOH)] agreed with those of (+)-isostrychnine reported by Woodward.[21] (+)-Isostrychnine was converted into (−)-strychnine by treatment with KOH in EtOH by the known method.[29]

In our total synthesis of (−)-strychnine, the starting cyclohexenol derivative **7b** was synthesized from **3i** by palladium-catalyzed allylic substitution, and all cyclizations for synthesis of (+)-isostrychnine were performed using a palladium catalyst. Compound **7b** obtained from cyclohexenol derivative **3i** was converted into **9**, and a palladium-catalyzed Heck reaction afforded compound **10**, which has the A−B−C ring system. The D-ring was constructed from compound **11**, which was obtained from **10**, using palladium-catalyzed allylic oxidation. The G-ring was formed by palladium-catalyzed cyclization of **25**. The E-ring was constructed by Heck reaction of **27**. From **28**, (+)-isostrychnine was synthesized. The total synthesis of (−)-strychnine was achieved by 22 steps from **3i** (Scheme 15).

The fact that all rings of (−)-tubifoline and (+)-isostrychnine were constructed using a palladium catalyst indicates the importance of a palladium catalyst in modern synthetic organic chemistry.

**Supporting Information Available:** Experimental procedure and spectral data of **3h**,**i**, **5a**, **5d−f**, **7a**,**b**, **8a**, **9−11**, **13**, **14**, **17**, **19**, **20**, **25−28**, (−)-dehydrotubifoline, (−)-tubifoline, (+)-isostrychnine, and (−)-strychnine (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA029382U

(29) Prelog, V.; Battegay, J.; Taylor, W. I. *Helv. Chim. Acta* **1948**, *31*, 2244.