Enantioselective Total Synthesis of (−)-Strychnine Using the Catalytic Asymmetric Michael Reaction and Tandem Cyclization [J. Am. Chem. Soc. 2002 , 124 , 14546−14547].

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · FEBRUARY 2003

Impact Factor: 12.11 · DOI: 10.1021/ja034038y · Source: PubMed

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Enantioselective Total Synthesis of (−)-Strychnine Using the Catalytic Asymmetric Michael Reaction and Tandem Cyclization

Takashi Ohshima,† Youjun Xu,†,‡ Ryo Takita,† Satoshi Shimizu,† Dafang Zhong,‡ and Masakatsu Shibasaki*,†

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and Laboratory of Drug Metabolism and Pharmacokinetics, Shenyang Pharmaceutical University, Wenhua Road 103, Shenyang 110016, China

Received September 7, 2002

We report a new entry for the synthesis of (−)-strychnine (**1**)[1] from easily accessible optically pure Michael adduct **5**, which is synthesized by the catalytic asymmetric Michael reaction on a greater than kilogram scale.[2c] Another key step in this entry is a novel tandem cyclization promoted by Zn for the simultaneous construction of B- and D-rings (Figure 1).[3]

(−)-Strychnine is the flagship compound of the family of *Strychnos* alkaloids and, considering its molecular weight, is one of the most complex natural products.[1] Nearly 40 years after Woodward's pioneering achievement,[4a] a number of groups have reported the total synthesis[4] and four of them have culminated in enantioselective synthesis of the natural enantiomer.[4c,e,g,i] The major stumbling blocks in the synthesis are the generation of the spirocenter at C7 and the assembling of the CDE core ring.[1] In the previous strategies, the C6−C7 bond was generated in the early stage of synthesis; thus, in many cases, the CDE ring system was assembled in the direction of C-ring to D-ring. Although an intramolecular alkylation strategy was applied for the construction of the C-ring in the synthesis of structurally simpler indole alkaloids,[2b,5] this strategy has not been utilized for the synthesis of **1**. In the present synthesis, to utilize **5** effectively in the synthesis, we assembled the CDE ring system from the D-ring to the C-ring and constructed the C7 spirocenter in the last stage by intramolecular alkylation.

Our synthesis of **1** began with the highly practical catalytic asymmetric Michael reaction.[2] Only 0.1 mol % of (*R*)-AlLibis-(binaphthoxide) (ALB) under almost neat conditions completed the Michael reaction of **6** with **7** in 24 h to afford more than a kilogram of the enantiomerically pure (>99% ee) product **5** in 91% yield without chromatographic separation.[2c] We then focused on the transformation of **5** to the key intermediate **4** (Scheme 1). First, the (*E*)-selective introduction of the hydroxylydene subunit was achieved by *anti*-selective reduction of β-keto ester **9** by $NaBH_3CN$ with $TiCl_4$ at *−55 °C* and following *syn*-elimination (Overman's method; 72%, E:Z = 15.7:1).[4c,6] DIBAL reduction of **10**, followed by silylation of the primary alcohol and conversion of the ketal to ketone afforded, after silica gel chromatography, pure (*E*)-**11**. Regioselective enol silyl ether formation was facilitated by the action of lithium 2,2,6,6-tetramethylpiperidide (C7:C16 = >6:1). Following the Saegusa-Ito reaction using $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %) provided **13** in 90% yield.[6,7] Next, mild aldol reaction[8] of enol silyl ether (α:β = ca. 3:1) followed by treatment with DBU afforded the thermodynamically more stable **14**α.[9] Subsequent iodination with DMAP and the Stille coupling produced **16** efficiently.[10]

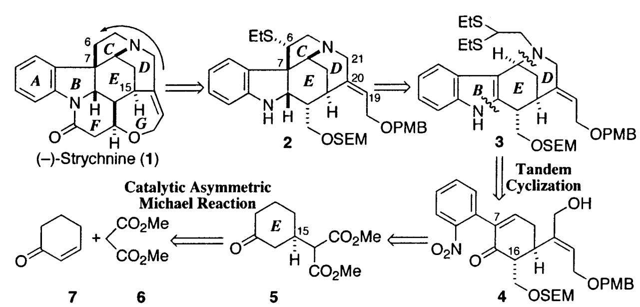


Figure 1. Retrosynthetic analysis of (−)-strychnine.

Finally, protection of the primary alcohol with SEMCl and removal of the TIPS group provided the key intermediate **4** in excellent yield.

We then focused on the construction of the BCDE-ring system. Initially, we examined 1,4-addition of the secondary amine to the enone after introduction of the amine moiety at C21 of **4**; however, it was found to be difficult due to the rapid retro reaction.[11] Numerous attempts finally led us to examine a tandem cyclization.[6] After introduction of the amine moiety, crude **17** was simply treated with Zn in MeOH−aqueous NH_4Cl to provide **3** in 77% yield. This tandem cyclization might proceed by the following sequence: (1) reduction of nitro group to amine by Zn, (2) 1,4-addition of the secondary amine, and (3) irreversible indole formation of the aniline moiety with the resulting ketone. Remarkably, the present process made it possible to skip more than eight steps in the synthesis.[6]

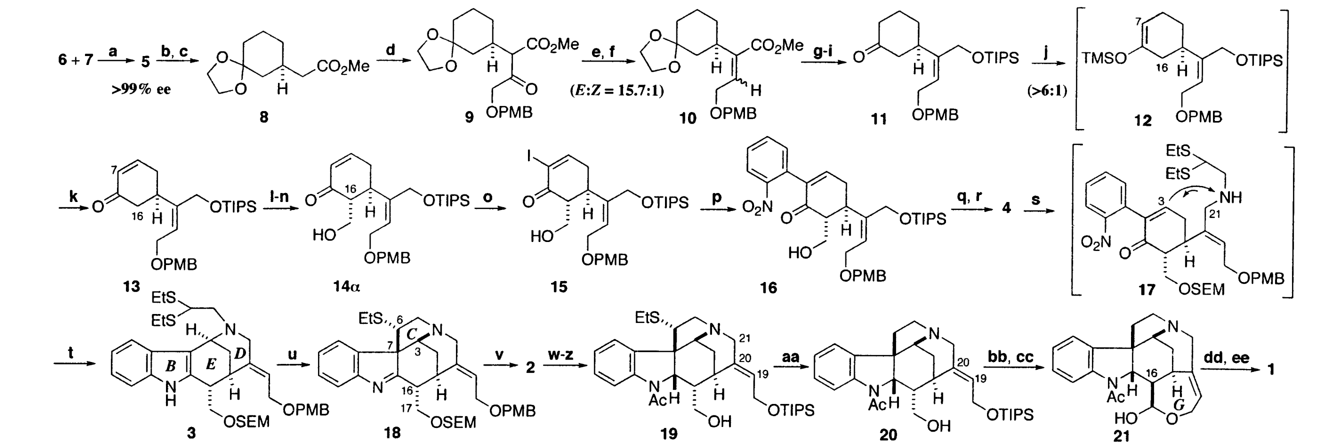
Our next goal was to construct the C-ring. We examined the intramolecular electrophilic attack of a thionium ion to generate the C7 spirocenter.[6] The reported procedure using DMTSF,[2b,5a] unfortunately, provided unsatisfactory results (<20% yield) due to generation of aldehyde, formation of an unknown dimer, and over-reaction of **18** with DMTSF. The descried condition (Scheme 1) successfully suppressed such side reactions and highly improved the yield (86%).[6] Reductions of imines in similar indole alkaloids under neutral conditions often result in the cleavage of C3−C7 bond and acidic conditions solved this problem.[4b,c,e,5] On the other hand, reduction of **18** under acidic conditions proceeded by elimination of the "SEMO" moiety to give C16−C17 exocyclic olefin. After testing numerous neutral or acidic conditions, we determined that treatment of 5 equiv of $TiCl_4$ at −78 °C before the addition of $NaBH_3CN$ effectively prevented the ring opening reaction and as a result **2** was obtained in 68% yield.

The stage was now set for the completion of the synthesis. The last major hurdle involved chemoselective reduction of the thioether (desulfurization)[12] in the presence of exocyclic olefin. The Raney Ni (W-2) reduction was the first choice for this purpose. Even

* To whom correspondence should be addressed. E-mail: mshibasa@mol.f.u-tokyo.ac.jp.
† The University of Tokyo.
‡ Shenyang Pharmaceutical University.

10.1021/ja028457r CCC: $22.00

Scheme 1 [a]



[a] Key: (a) (*R*)-ALB (0.1 mol %), KO-*t*-Bu (0.09 mol %), MS 4A, THF (49 M), 91%, >99% ee; (b) 2-ethyl-2-methyl-1,3-dioxolane, catalytic TsOH; (c) LiCl, H_2O, DMSO, 140 °C, 97% in two steps; (d) LDA, *N*-methoxy-2-(4-methoxybenzyloxy)-*N*-methylacetamide, THF, −78 °C, 72% (conversion 82%); (e) $NaBH_3CN$, $TiCl_4$, THF−CH_2Cl_2, −55 °C; (f) DCC, CuCl, benzene, reflux, 70% in two steps; (g) DIBAL, CH_2Cl_2, −78 °C; (h) TIPSOTf, Et_3N, CH_2Cl_2, −78 °C, 98% in two steps; (i) catalytic CSA, acetone, 62% (conversion 90%); (j) lithium 2,2,6,6-tetramethylpiperidide, TMSCl, THF, −78 °C; (k) $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), diallyl carbonate, MeCN, 90% in two steps; (l) LDA, TMSCl, THF, −78 °C; (m) aq. HCHO, $Yb(OTf)_3$ (20 mol %), THF; (n) DBU, CH_2Cl_2, 57% in three steps from the mixture of regioisomers **13** (conversion 80%) (o) I_2, DMAP, CH_2Cl_2, 89%; (p) 1-iodo-2-trimethylstannylbenzene, $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), Ph_3As (20 mol %), CuI (10 mol %), DMF, quantitative; (q) SEMCl, *i*-Pr_2NEt, CH_2Cl_2, quantitative; (r) 3HF·Et_3N, THF, quantitative; (s) Tf_2O, *i*-Pr_2NEt, then 2,2-bis(ethylthio)ethylamine, CH_2Cl_2, −78 °C; (t) Zn, MeOH−aqueous NH_4Cl, 77% in two steps; (u) DMTSF (5 equiv), MS 4A, CH_2Cl_2 (0.005 M), 86%; (v) $NaBH_3CN$, $TiCl_4$, THF−CH_2Cl_2, −78 °C, 68%; (w) 1.0 N HCl in MeOH, 55 °C; (x) Ac_2O, pyridine; (y) NaOMe, MeOH; (z) TIPSCl, imidazole, DMF−CH_2Cl_2, 4 °C, 51% in four steps; (aa) $NiCl_2$, $NaBH_4$, EtOH/MeOH (4:1), 61% isolated yield after 3 times process; (bb) SO_3·Py, Et_3N, DMSO; (cc) 3HF·Et_3N, THF 83% in two steps; (dd) NaOMe, MeOH, 40 °C; (ee) malonic acid, NaOAc, Ac_2O, AcOH, 110 °C, 42% in two steps.

deactivated Raney Ni in acetone, however, promoted considerable migration of exocyclic olefin (C19−C20) to endocyclic olefin (C20−C21).[12] Eventually, Ni boride[14] emerged as a promising candidate. Although a conventional protocol caused over-reduction instead of migration, by changing the solvent (*EtOH:MeOH = 4:1*) and addition order, **20** was obtained in 91% yield based on consumed starting material with high selectivity (>10:1).[6] Consecutive SO_3·Py oxidation of the primary alcohol and deprotection of the TIPS group afforded (+)-diaboline (**21**)[15] through epimerization of the C16 stereocenter. Finally, removal of the acetyl group provided the crude Wieland−Gumlich aldehyde, which was converted to (−)-strychnine (**1**)[6] by the established method.[4]

In conclusion, an enantioselective total synthesis of (−)-strychnine was accomplished through the use of the highly practical catalytic asymmetric Michael reaction as well as a tandem cyclization that simultaneously constructed B- and D-rings. Moreover, newly developed reaction conditions for thionium ion cyclization, reduction of the imine moiety, and desulfurization were pivotal to complete the synthesis. The described chemistry paves the way for the synthesis of more advanced *Strychnos* alkaloids for chemical biology studies.

Acknowledgment. This work was supported by RFTF and Encouragement of Young Scientists (A) of Japan Society for the Promotion of Science.

Supporting Information Available: Experimental details for the preparation of all new compounds and complete characterization with copies of their ^{1}H, ^{13}C, and DEPT NMR spectra (PDF). This material is available free of charge via Internet at http://pubs.acs.org.

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(10) (2-Nitrophenyl)ketone moiety was selected as a latent form of the indoline based on the previous results, see ref 4g.

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JA028457R